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 Sodium thiosulphate (prevention of ototoxicity induced by cisplatin chemotherapy, solid tumours, 1 month to < 18 years)

of 17 July 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all 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 studies the pharmaceutical company have 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.
7. Number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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

At their session on 10 December 2024, the Federal Joint Committee (G-BA) decided to initiate a benefit assessment for the active ingredient sodium thiosulphate for the prevention of ototoxicity induced by cisplatin chemotherapy according to Section 35a, paragraph 6 SGB V in conjunction with Chapter 5 Section 16, paragraph 1 VerfO.

The medicinal product Pedmarqsi, containing the active ingredient sodium thiosulphate, was first placed on the market on 1 February 2025. 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 assessment procedure for the active ingredient sodium thiosulphate 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.

The final dossier was submitted to the G-BA in due time on 30 January 2025. On 1 February 2025, the assessment procedure started.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 May 2025 on the G-BA website (www.g-ba.de), 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 sodium thiosulphate 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, 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 have 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 sodium thiosulphate.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have 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 Sodium thiosulphate (Pedmarqsi) in accordance with the product information

Pedmarqsi is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.

Therapeutic indication of the resolution (resolution of 17.07.2025):

See therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

Appropriate comparator therapy for sodium thiosulphate:

- Monitoring wait-and-see approach

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV)

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1. Apart from the active ingredient sodium thiosulphate, no medicinal products are currently approved for the prevention of ototoxicity induced by cisplatin chemotherapy.

On 2. A non-medicinal treatment option is not considered for the therapeutic indication in question.

On 3. In the present 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 of non-medicinal treatments.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic 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 therapeutic indication according to Section 35a, paragraph 7 SGB V. There are no written statements.

The evidence on treatment options for the prevention of ototoxicity induced by cisplatin chemotherapy is limited overall and no Cochrane reviews or systematic reviews were identified.

With the exception of sodium thiosulphate, the underlying guidelines do not provide any recommendations on (medicinal) therapy options for the prevention of ototoxicity induced by cisplatin chemotherapy[2,3].

In detail, treatment with amifostine and diethyldithiocarbamate as well as an adjustment of the cisplatin infusion duration or intratympanic middle ear therapy are explicitly not recommended[2]. It should also be noted that routine tinnitus testing and regular audiograms should be performed to monitor hearing loss induced by platinum-containing chemotherapy[3]. The active ingredient sodium thiosulphate, which is named as a therapy option in the guidelines, is again ruled out as an appropriate comparator therapy with regard to the research question of the benefit assessment.

Against the background of the lack of recommendations in the guidelines on (medicinal) treatment options for the prevention of ototoxicity induced by cisplatin chemotherapy, "monitoring wait-and-see approach" is determined as the appropriate comparator therapy in the overall analysis.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

<u>Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy</u>

[2] Freyer DR et al. Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline. Lancet Child Adolesc Health 2020;4(2):141-150.
[3] NCCN. Adolescent and young adult (AYA) oncology, version 2.2025 [online]. Plymouth Meeting (USA): NCCN; 2024. [Accessed: 04.02.2025]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/aya.pdf.

a) Patients 1 month to < 18 years of age with localised, non-metastatic hepatoblastoma with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

Indication of non-quantifiable additional benefit.

b) Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours other than hepatoblastoma with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company submitted the results of the two clinical studies ACCL0431 and SIOPEL 6.

ACCL0431 study

The ACCL043 study is an open-label, randomised, multicentre phase III study comparing sodium thiosulphate versus no administration of sodium thiosulphate. Patients aged ≥ 1 and ≤ 18 years with localised or metastatic tumours who received cisplatin treatment were enrolled in the cross-tumour study. They showed, among others, the following tumours: newly diagnosed, histologically confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma.

A total of 61 patients were randomly assigned to treatment with sodium thiosulphate + cisplatin and 64 patients to treatment with cisplatin. Randomisation was stratified according to previous cranial radiotherapy (yes/ no) and for patients without previous cranial radiotherapy additionally according to age (< 5/ ≥ 5 years) and duration of the planned cisplatin infusion (< 2/ ≥ 2 hours).

The study was conducted at 38 study sites in Canada and the USA from 2008 to 2019.

Sodium thiosulphate was administered in deviation from the product information. In the ACC0431 study, the patients received a dosage of 10.2 g/m^2 body surface area (BSA) or 341 mg/kg body weight. Information on the number of patients who were treated according to dosage by BSA or body weight is not available. As only 6 patients (4.8%) had a body weight ≤ 10 kg according to the authorisation documents, it is assumed that only a few young children or children with a small body height were enrolled in the study and were dosed according to body weight. It is therefore assumed that the majority of patients were dosed with 10.2 g sodium thiosulphate/m^2 BSA, which corresponds to a 20.3% lower dosage than prescribed in the product information (> 10 kg body weight with 12.8 g/m^2 BSA).

In the ACCL0431 study, audiograms were carried out at defined points in time to assess hearing impairments. The values from the baseline examination were compared with those from the follow-up examination four weeks after the end of treatment.

The primary endpoint of the study was hearing loss according to the American Speech-Language-Hearing Association (ASHA) criteria. Patient-relevant secondary endpoints were overall survival and endpoints on adverse events. The data cut-offs were made in 2015 and 2019, as well as at an additional unclear point in time between these two years.

Limitations of the ACCL0431 study

The study population includes a high percentage of patients with metastatic disease (34.4% in the intervention arm vs 40.6% in the comparator arm). However, sodium thiosulphate is only approved for patients with localised, non-metastatic disease. The evaluations of the ACCL0431 study presented by the pharmaceutical company therefore do not allow any assessment-relevant statements to be made, as a substantial proportion of the patients in the ACCL0431 study do not represent the relevant population of patients with localised, non-metastatic disease for the benefit assessment.

As a result, the ACCL0431 study is not suitable for the assessment of the additional benefit of sodium thiosulfate.

SIOPEL 6 study

The SIOPEL 6 study is an open-label, randomised, multicentre phase III study comparing sodium thiosulphate versus no administration of sodium thiosulphate. Patients aged > 1 month and ≤ 18 years with newly diagnosed, histologically confirmed hepatoblastoma who received cisplatin treatment were enrolled.

A total of 61 patients were randomly assigned to treatment with sodium thiosulphate + cisplatin and 53 patients to treatment with cisplatin. Randomisation was stratified by country (categorisation unclear), age (< 15/ > 15 months) and PRETEXT classification (I and II/ III). The study was conducted at 52 study sites in Australia, New Zealand, Europe and the USA from 2007 to 2018.

Sodium thiosulphate was administered according to the product information. To assess hearing impairment, audiograms were performed in the SIOPEL 6 study at defined time points, including after every second cisplatin cycle and at the end of treatment. Overall, the examinations carried out in the SIOPEL 6 study for the detection of hearing impairment are assessed as sufficient implementation of the appropriate comparator therapy of the monitoring wait-and-see approach.

The primary endpoint of the study was hearing loss (BROCK grade ≥ 1). Patient-relevant secondary endpoints were overall survival and endpoints on adverse events. No information on the reason for the data cut-off is available for the evaluations presented in the dossier. Based on the information available, it can however be assumed that the present analyses are the final analysis after a 5-year follow-up. The benefit assessment is based on this data cut-off.

Extent and probability of the additional benefit

Mortality

Overall survival in the SIOPEL 6 study was operationalised as the time from randomisation to death from any cause. For the endpoint of overall survival, there was no statistically significant difference between the treatment groups.

Morbidity

Failure of the curative therapeutic approach (event-free survival, EFS)

For patients with newly diagnosed hepatoblastoma, curative therapy is generally possible and the therapeutic goal. Patients are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant.

The significance of the EFS endpoint depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by the present curative therapeutic approach.

In the SIOPEL 6 study, EFS was defined as the time from randomisation to the first occurrence of one of the following events:

- Progression
- Relapse
- Secondary malignancy
- Death

In the study, 11 EFS events occurred in the intervention arm and 11 EFS events in the control arm. Information on the events qualifying for the endpoint with a corresponding breakdown of the subcomponents is not available. Furthermore, the progression subcomponent does not necessarily reflect the failure of the curative therapeutic approach in the present operationalisation. Overall, it is therefore not certain that the EFS endpoint reflects the failure of the curative therapeutic approach. No suitable data are therefore available for the endpoint of failure of the curative therapeutic approach.

Hearing loss (BROCK grade ≥ 1)

The primary endpoint of the SIOPEL 6 study was defined as the percentage of patients with hearing loss - defined as BROCK grade ≥ 1 (measured by pure tone audiometry [PTA]), with the hearing threshold to be assessed at baseline (before the start of treatment) and after completion of study treatment or at an age of at least 3.5 years, whichever occurs later.

The hearing loss results presented for the benefit assessment are based on single measurements taken 6 to 12 weeks after completion of study treatment or at an age of at least 3.5 years (whichever occurs later).

In accordance with the requirements of the regulatory authority as part of the approval process, evaluations for the primary endpoint were pre-specified, which also included patients for whom no evaluable audiometric surveys were available. The percentage of patients with missing values in relation to the ITT population was n = 2 (3.5%) for sodium thiosulphate and n = 6 (11.5%) in the control group. The replacement strategy to be used for the primary analysis was not defined by the regulatory authority. In their sensitivity analyses, the pharmaceutical company pre-specified 2 analyses for the ITT population and presented them in the dossier (imputation of missing values as hearing loss responders; imputation of missing values as hearing loss non-responders). As part of the written statement procedure, the pharmaceutical company also submitted further sensitivity analyses, which, however, leave the overall picture unchanged, as it is assumed in the present data basis that the result for the endpoint of hearing loss (BROCK grade ≥ 1) would have been between the two analyses presented in the dossier (imputation as hearing loss responder and hearing loss non-responder) if evaluable audiometric surveys had been available for all patients.

For the present assessment, the analyses "imputation as hearing loss responder" and "hearing loss non-responder" are therefore used to derive the additional benefit.

There was a clear advantage of sodium thiosulphate for imputation as hearing loss responder and a moderate advantage thereof for imputation as non-responder.

Quality of life

No endpoints on health-related quality of life data were assessed in the SIOPEL 6 study. The median age of patients was 13 months at the time of enrolment in the study.

Side effects

Adverse events (AEs)

An adverse event (AE) occurred in 96.2% of patients in the intervention arm and 87.5% thereof in the control arm. The results were only presented additionally.

Serious adverse events (SAE)

In summary, no suitable data are available for serious adverse events (SAEs) in the SIOPEL 6 study. On the one hand, AEs were collected as SAEs that are potentially not an SAE at all according to the common SAE definition (unexpected AE of grade 3 and 4). On the other, expected AEs were defined that should not be documented as SAEs per se, although they could potentially be an SAE according to the common SAE definition (e.g. expected toxicities associated with hospitalisation). In addition, the AE of transient hypernatraemia (grade 3 or 4) was only collected as an SAE in the comparator arm but not in the intervention arm.

Discontinuation due to AEs

In the SIOPEL 6 study, discontinuation due to AEs were only documented for SAEs. No suitable data are thus available for the endpoint of discontinuation due to AEs. Overall, only one discontinuation (due to hypersensitivity [PT]) was documented in the intervention arm of the SIOPEL 6 study. Furthermore, it is unclear whether discontinuation due to AEs only include discontinuation of sodium thiosulphate and were therefore only documented in the intervention arm.

Severe AEs

For the endpoint of severe AEs, there is no statistically significant difference between the treatment arms.

Specific AE

In detail, the specific AEs of vomiting (AE), hypokalaemia and hypophosphataemia (both severe AEs) each showed a statistically significant difference to the disadvantage of sodium thiosulphate.

In the overall assessment of the results on side effects, no suitable data are available for SAEs and therapy discontinuation due to AEs. For the severe AEs, there was no statistically significant difference between the treatment arms. In detail, there were disadvantages in the specific AEs.

Overall assessment

The ACCL0431 and SIOPEL 6 studies were presented for the assessment of the additional benefit of sodium thiosulfate for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic solid tumours.

The SIOPEL 6 study population comprises patients with newly diagnosed, histologically confirmed hepatoblastoma. Among others, patients with germ cell tumours, hepatoblastoma, medulloblastoma, neuroblastoma and osteosarcoma were enrolled in the ACCL0431 study.

The ACCL0431 study is not suitable for the benefit assessment, as a significant proportion of the patients do not represent the relevant population of patients with localised, non-metastatic disease.

Against this background, the G-BA conducted a separate assessment of the additional benefit for patients with localised, non-metastatic hepatoblastoma and patients with localised, non-metastatic solid tumours other than hepatoblastoma.

a) Patients 1 month to < 18 years of age with localised, non-metastatic hepatoblastoma with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

Results are available from the SIOPEL 6 study on sodium thiosulphate versus no administration of sodium thiosulfate in the endpoint categories of mortality, morbidity and side effects.

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups.

In the morbidity endpoint category, results are available for the hearing loss endpoint (BROCK grade ≥ 1; measured using the BROCK scale). In order to counteract the percentage of missing values in the evaluation, the pharmaceutical company presented various sensitivity analyses. The imputation of the missing values as hearing loss responders and the imputation of the missing values as hearing loss non-responders are used to derive the additional benefit. Both analyses showed a statistically significant difference to the advantage of sodium thiosulphate compared to the control arm. There was a clear advantage of sodium thiosulfate for imputation as hearing loss responder and a moderate advantage thereof for imputation as non-responder. With regard to the results for the endpoint of hearing loss (BROCK grade ≥ 1), it should be noted that only single measurements were carried out for the assessment of hearing loss on the basis of the BROCK scale. Furthermore, there is no data available on the speech and language development of the children concerned. Against this background and in view of the fact that the results of the underlying sensitivity analyses differ with regard to the extent of the respective effect, the overall extent of the benefit cannot be quantified with certainty.

No suitable data are available for the endpoint of failure of the curative therapeutic approach (event-free survival, EFS).

Endpoints on health-related quality of life were not assessed in the SIOPEL 6 study.

No suitable data are available for the endpoints of SAEs and discontinuation due to AEs. With regard to severe AEs (CTCAE grade ≥ 3), there was neither an advantage nor a disadvantage of sodium thiosulphate. In detail, there were disadvantages in the specific AEs.

The overall analysis showed an advantage for the endpoint of hearing loss, which cannot be quantified with certainty overall.

As a result, a non-quantifiable additional benefit of sodium thiosulphate was identified for the treatment of patients 1 month to < 18 years of age with localised, non-metastatic hepatoblastoma with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy.

b) Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours other than hepatoblastoma with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

A high percentage of patients in the ACCL0431 study had metastatic disease (34.4% in the intervention arm vs 40.6% in the comparator arm). However, sodium thiosulphate is only approved for patients with localised, non-metastatic disease. The ACCL0431 study is therefore not suitable for the assessment of the additional benefit of sodium thiosulfate.

For the group of patients with solid tumours other than hepatoblastoma, there are therefore no suitable data for an assessment of the additional benefit of sodium thiosulphate. An additional benefit is not proven.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, randomised, multicentre phase III SIOPEL 6 study. In the study, the administration of sodium thiosulphate was compared with no administration of sodium thiosulphate. The risk of bias at study level is rated as low.

The risk of bias for the endpoint of overall survival is rated as low at the endpoint level.

For the endpoint of hearing loss (BROCK grade ≥ 1), there was a risk of bias due to a potentially relevant difference in the percentage of missing values between the treatment groups.

While the risk of bias of the results for the endpoint of severe AEs (CTCAE grade ≥ 3) is assessed as low, an assessment for SAEs and discontinuation due to AEs is not possible due to the lack of assessable data.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated so high as to justify a downgrading of the reliability of data of the overall assessment. Therefore, an indication is derived for the reliability of data of the additional benefit identified.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Pedmarqsi" with the active ingredient sodium thiosulphate.

Pedmarqsi was approved as a PUMA medicinal product for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic solid tumours.

The G-BA determined the monitoring wait-and-see approach as the appropriate comparator therapy.

The pharmaceutical company presented the randomised controlled trials SIOPEL 6 and ACCL0431 comparing sodium thiosulphate + cisplatin with cisplatin.

The SIOPEL 6 study population comprises patients with newly diagnosed, histologically confirmed hepatoblastoma. The ACCL0431 study population includes, among others, patients with germ cell tumours, hepatoblastoma, medulloblastoma, neuroblastoma and osteosarcoma.

The ACCL0431 study is not suitable for the benefit assessment. Therefore, the G-BA conducted a separate assessment of the additional benefit for patients with localised, non-metastatic hepatoblastoma and patients with localised, non-metastatic solid tumours other than hepatoblastoma.

Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

a) Patients 1 month to < 18 years of age with localised, non-metastatic hepatoblastoma with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

and

b) Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours other than hepatoblastoma with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

On a)

In terms of overall survival, there was no advantage of the administration of sodium thiosulphate.

In the morbidity endpoint category, results are available for the endpoint of hearing loss (BROCK grade ≥ 1; measured using the BROCK scale) for two sensitivity analyses. There was a clear advantage of sodium thiosulfate for imputation as hearing loss responder and a moderate advantage thereof for imputation as non-responder. With regard to the results, it should be noted that only single measurements were taken to assess hearing loss on the basis of the BROCK scale. Furthermore, there is no data available on the speech and language development of the children concerned. Against this background and in view of the fact that the results of the sensitivity analyses differ with regard to the extent of the respective effect, the overall extent of the benefit cannot be quantified with certainty.

No suitable data are available for the endpoint of failure of the curative therapeutic approach (event-free survival, EFS). Furthermore, no data on health-related quality of life were collected.

No suitable data are available for the SAEs and discontinuation due to AEs. For severe AEs (CTCAE grade ≥ 3), there was neither an advantage nor a disadvantage of sodium thiosulphate. In detail, there were disadvantages in the specific AEs.

In the overall assessment, an indication of a non-quantifiable additional benefit of sodium thiosulphate over monitoring wait-and-see approach was identified.

On b)

The ACCL0431 study is not suitable for the benefit assessment, as a significant proportion of the patients do not represent the relevant population of patients with localised, non-metastatic disease for the benefit assessment. No suitable data are therefore available for an assessment of the additional benefit. 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 pharmaceutical company determined the total number of patients step-by-step from the incidences of the target populations in the therapeutic indication per tumour entity and derived the total number of SHI patients in the target population from this. For the present assessment, the total number of SHI patients in the target population is derived from the

interim results per tumour entity, only for hepatoblastoma on the one hand and for solid tumours other than hepatoblastoma on the other.

For patients with hepatoblastoma, the pharmaceutical company determined a number of 21 to 26 patients (before estimating a SHI percentage). With 87.90% of patients covered by statutory health insurance, this results in 18 to 23 patients.

Accordingly, for patients with solid tumours other than hepatoblastoma, the difference between this range and that of the total SHI target population specified by the pharmaceutical company (38 to 228 patients) represents the number of patients with solid tumours other than hepatoblastoma (20 to 205 patients).

Overall, this information is subject to uncertainty. On the one hand, the main reasons for this are the exclusive consideration of newly diagnosed patients and the lack of consideration of potentially relevant tumour diagnoses. On the other, there is an overestimation because the more appropriate, relevant age-specific incidence rates are not used as a basis. Moreover, uncertainties remain due to the missing valid data on the percentage values of localised, non-metastatic tumours and on treatment with cisplatin chemotherapy.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Pedmarqsi (active ingredient: sodium thiosulphate) at the following publicly accessible link (last access: 9 July 2025):

https://www.ema.europa.eu/en/documents/product-information/pedmarqsi-epar-product-information_en.pdf

Therapy with sodium thiosulphate should only be initiated and monitored by specialists experienced in the treatment of patients with solid tumours, specifically in the treatment of the respective tumour entity.

Sodium thiosulphate may only be used after cisplatin infusions with a duration of up to 6 hours. Sodium thiosulphate must not be used if

- the cisplatin infusion lasts longer than 6 hours or
- another cisplatin infusion is planned within the next 6 hours.

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 2025).

Treatment period:

The treatment duration with sodium thiosulphate (Pedmarsqi) depends on the number of cisplatin chemotherapy cycles carried out, according to the product information. The number of cisplatin chemotherapy cycles carried out depends in particular on the specific underlying cisplatin-containing chemotherapy protocol and is therefore different from patient to patient. The following derivation refers to the use of sodium thiosulphate (Pedmarqsi) for a single cycle of cisplatin chemotherapy.

Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Sodium thiosulphate	Single application 6 h after completion of the respective cisplatin infusion	Different from patient to patient	1[a]	1[a]
Appropriate comparator therapy				
– monitoring wait-and-see approach				
Monitoring wait-and-see approach	Not calculable			

Consumption:

Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied. The average body weight of a 1-year-old child is accordingly 7.6 kg with an average height of 0.67 m. The average weight of a 17-year-old subject is 67.0 kg with an average height of 1.74 m. This results in a body surface area of 0.36 m^2 for children below the age of one year and 1.81 m^2 for 17-year-olds (calculated according to Du Bois 1916)[4].

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ Chemotherapy cycle	Average consumption per chemotherapy cycle by potency
Medicinal product to be assessed					
Sodium thiosulphate	120 ml/m^2 = 43.2 ml	43.2 ml - 289.6 ml	1 x 100 ml - 3 x 100 ml	1	1 x 100 ml - 3 x 100 ml

[4] Federal Health Reporting. Average body measurements of the population (2017, both sexes), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ Chemotherapy cycle	Average consumption per chemotherapy cycle by potency
	- 160 ml/m² = 289.6 ml				
Appropriate comparator therapy					
– monitoring wait-and-see approach					
Monitoring wait-and-see approach	Not calculable				

Costs:

Sodium thiosulphate (Pedmarsqi) is only intended for use in hospital under specialist medical supervision in accordance with the product information. Sodium thiosulphate (Pedmarsqi) is listed in LAUER-TAXE® as a clinic pack only. Accordingly, sodium thiosulphate (Pedmarsqi) is 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.

Costs of the medicinal products:

Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

Designation of the therapy	Packaging size	Costs (purchase price of clinic pack plus value-added tax)	Value-added tax (19%)	Costs after deduction of statutory rebates
Medicinal product to be assessed				
Sodium thiosulphate 80 mg/ml	1 x 100 ml INF	€ 10,533.00	€ 2,001.27	€ 12,534.27
Appropriate comparator therapy				
Monitoring wait-and-see approach	Not calculable			
Abbreviations: INF = infusion solution in vial				

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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.

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.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section

35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain

any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for sodium thiosulphate (Pedmarqsi); Pedmarqsi 80 mg/ml solution for infusion; last revised: May 2025

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product sodium thiosulphate is a medicinal product placed on the market from 1 January 2025.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is 0 per cent (0.0%) of the total number of study participants.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

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 their session on 11 March 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 January 2025, the pharmaceutical company submitted a dossier for the benefit assessment of sodium thiosulphate to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 7 VerfO.

By letter dated 31 January 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 sodium thiosulphate.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 April 2025, and the written statement procedure was initiated with publication on the G-BA website on 2 May 2025. The deadline for submitting statements was 23 May 2025.

The oral hearing was held on 10 June 2025.

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 July 2025, and the proposed draft resolution was approved.

At their session on 17 July 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	11 March 2025	Determination of the appropriate comparator therapy
Working group Section 35a	3 June 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 June 2025	Conduct of the oral hearing
Working group Section 35a	17 June 2025 2 June 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	8 July 2025	Concluding discussion of the draft resolution
Plenum	17 July 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 17 July 2025

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

Prof. Hecken