Sodium thiosulfate (prevention of ototoxicity induced by cisplatin chemotherapy)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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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

The questionnaire on the disease and its treatment was answered by Renate Pfeifer.

IQWiG thanks the respondent and the patient organizations “Förderkreis für krebskranke Kinder und Jugendliche Bonn e. V.”, “Deutsche Leukämie- und Lymphomhilfe e. V.” und “BAG SELBSTHILFE e. V.” for participating in the written exchange and for their support. The respondent and the patient organizations were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AdEERS	Adverse Event Expedited Reporting System
AE	adverse event
AFP	alpha fetoprotein
ASHA	American Speech-Language-Hearing Association
BSA	body surface area
CHIC	Children's Hepatic Tumours International Collaboration
CTCAE	Common Terminology Criteria for Adverse Events
EFS	event-free survival
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GPOH	Gesellschaft für Pädiatrische Onkologie und Hämatologie (Society for Paediatric Oncology and Haematology)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
mITT	modified intention to treat
PRETEXT	Pre-treatment Tumour Extension
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SIOP	International Society of Pediatric Oncology
SPC	Summary of Product Characteristics
WDF	well differentiated foetal

I 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 sodium thiosulfate. 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 3 February 2025.

Research question

The aim of this report is the assessment of the added benefit of sodium thiosulfate in comparison with watchful waiting as the appropriate comparator therapy (ACT) in patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of sodium thiosulfate

Therapeutic indication	**ACT**[a]
Patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours with indication for the prevention of ototoxicity induced by cisplatin chemotherapy	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The G-BA defined watchful waiting as the ACT. The company deviated from the G-BA's specification by determining best supportive care instead of watchful waiting as the ACT. The review of the completeness of the study pool taking into account the ACT watchful waiting did not reveal any studies further to those identified by the company. Therefore, the company's deviation regarding the specification of the ACT remains without consequence. The benefit assessment was conducted in comparison with the G-BA's ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The review of the study pool identified the SIOPEL 6 study used by the company. The company additionally included the ACCL0431 study in the benefit assessment. The ACCL0431 study is unsuitable for assessing the added benefit of sodium thiosulfate. However, an adequate

analysis of the data could provide supporting information on the question of whether the results of the included SIOPEL 6 study can be transferred to other patient groups. The ACCL0431 study and its relevance for the benefit assessment are explained below.

Study ACCL0431

The ACCL0431 study is unsuitable for the assessment of the added benefit of sodium thiosulfate in comparison with the ACT watchful waiting in patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy because the dosage of sodium thiosulfate deviated from the Summary of Product Characteristics (SPC).

The ACCL0431 study is an open-label, cross-tumour RCT comparing sodium thiosulfate versus no sodium thiosulfate treatment in patients aged ≥ 1 to ≤ 18 years who had newly diagnosed, histologically confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma or other malignancy, and who were receiving cisplatin chemotherapy. Patients had to have a treatment plan with a planned cumulative cisplatin dose of ≥ 200 mg/m^2 body surface area (BSA) at enrolment.

125 patients were randomly allocated at a 1:1 ratio to treatment with sodium thiosulfate (N = 61) or cisplatin (N = 64). Randomization was stratified by prior cranial radiation (yes/no) and for patients without prior cranial radiation additionally by age (< 5/≥ 5 years) and duration of the planned cisplatin infusion (< 2/≥ 2 hours).

Cisplatin was administered according to the sites' disease-specific treatment protocols. In addition to the administration of cisplatin, a prior chemotherapy regimen was allowed to be continued. No information was available on disease-specific therapy (e.g. as monotherapy or combination therapy) including dosage.

The primary outcome of the study was hearing loss according to American Speech-Language-Hearing Association (ASHA) criteria. Patient-relevant secondary outcomes were overall survival and adverse event (AE) outcomes.

Treatment with sodium thiosulfate not in compliance with the SPC

According to the approval, patients with > 10 kg body weight should be treated with 12.8 g/m^2 BSA, patients with 5 to 10 kg with 9.6 g/m^2 BSA, and patients with < 5 kg with 6.4 g/m^2 BSA sodium thiosulfate. No patient in the ACCL0431 study was dosed in compliance with the marketing authorization. The patients received dosages of 10.2 g/m^2 BSA, or 341 mg/kg body weight for patients who received cisplatin dosed according to body weight due to their young age or small body size. No information was available on the respective numbers of patients treated based on BSA or body weight. As only 6 patients (4.8%) weighed ≤ 10 kg according to the approval documents, it was assumed that only a few young children or children with a

small body size were included in the ACCL0431 study and were thus dosed based on their body weight. It can therefore be generally assumed that the majority of patients were dosed with 10.2 g/m^2 BSA sodium thiosulfate. In comparison with the dosage recommended in the SPC, these patients received a dosage that was 20.3% too low (12.8 g/m^2 BSA for children with > 10 kg body weight). For the unknown, but presumably small proportion of patients who were dosed based on body weight, the extent of the deviation from the dosage according to the SPC is unclear. Due to the dosing of sodium thiosulfate, which deviated from the SPC, the ACCL0431 study was therefore not used to assess the added benefit of sodium thiosulfate in comparison with watchful waiting as ACT in patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours for the prevention of ototoxicity induced by cisplatin chemotherapy. The underdosing of sodium thiosulfate is important firstly because of the potential underreporting of the side effects of sodium thiosulfate. Secondly, it is of particular relevance that a possible tumour-protective effect of sodium thiosulfate with an impact on overall survival can be overlooked due to underdosing. This is due to the fact that although sodium thiosulfate prevents cisplatin-induced hearing impairment due to its interaction with cisplatin, it also harbours the risk of a possible reduction in the effectiveness of cisplatin.

Apart from the lack of suitability of the ACCL0431 study due to the non-approved dosage of sodium thiosulfate, the study had further limitations. For example, the study population included a high proportion of patients with metastatic disease (34.4% in the intervention arm versus 40.6% in the comparator arm), for whom treatment with sodium thiosulfate is not approved. In addition, no suitable data on side effects were available for the benefit assessment because the recording of AEs was incomplete and differed between the study arms, so that weighing up of benefit and harm would not be possible. Despite the limitations described above, the results on efficacy outcomes (especially hearing loss) as well as on overall survival and possibly on the failure of a curative treatment approach could provide supporting information on the question of whether the results of the included SIOPEL 6 study (see next section) can be transferred to other patient groups. This would require analyses of the subpopulation of non-metastatic patients according to entities or relevant subgroups (e.g. based on the cisplatin dose or the application interval).

SIOPEL 6 study

The SIOPEL 6 study was used for the benefit assessment. The study enrolled patients with hepatoblastoma. The study is therefore only suitable for drawing conclusions on the added benefit of sodium thiosulfate for patients with hepatoblastoma.

The SIOPEL 6 study is an open-label RCT comparing sodium thiosulfate versus no sodium thiosulfate treatment in patients aged ≥ 1 month to ≤ 18 years who had newly diagnosed, histologically confirmed standard-risk hepatoblastoma, and who were receiving cisplatin chemotherapy. In the SIOPEL 6 study, cisplatin was described as part of the study medication.

In terms of the research question, however, cisplatin was not part of the intervention or the ACT. The patients were not allowed to have received any previous chemotherapy.

114 patients were randomly allocated at a 1:1 ratio to treatment with sodium thiosulfate (N = 61) or cisplatin (N = 53). Randomization was stratified by country (categorization unclear), age (< 15/> 15 months) and Pre-treatment Tumour Extension (PRETEXT) classification (I and II/III).

The patients received 4 cycles of cisplatin preoperatively (each on Day 1 of a 14-day cycle) with an infusion duration of 6 hours. This was followed by surgery. After surgery, 2 more cycles of cisplatin were administered (each on Day 1 of a 14-day cycle). If the disease progressed after ≥ 2 cycles of preoperative cisplatin treatment, the treatment was discontinued, and treatment with 2 to 4 cycles of cisplatin + doxorubicin (without sodium thiosulfate) was recommended. If there was a sufficient response, surgery was performed followed by 2 cycles of cisplatin + doxorubicin.

The cisplatin dose was 80 mg/m^2 BSA in children > 10 kg body weight. In children ≤ 10 kg body weight, dosing was based on body weight. Patients received a mean cumulative cisplatin dose (including the administration of cisplatin + doxorubicin) of 364 mg/m^2 in the intervention arm and 363 mg/m^2 in the comparator arm. For the treatment strategy of the patients in the study, see the following section.

Dosing with sodium thiosulfate was carried out as a 15-minute infusion 6 hours after the end of the respective cisplatin infusion, in compliance with the SPC. SPC-compliant antiemetic therapy in the intervention arm was administered 30 minutes prior to sodium thiosulfate administration in addition to any cisplatin-associated antiemetic therapy.

The study's primary outcome was hearing loss (BROCK grade ≥ 1). Patient-relevant secondary outcomes were overall survival and AE outcomes.

Definition and treatment of patients with standard-risk hepatoblastoma in the SIOPEL 6 study

Against the background of the current health care context, the certainty of conclusions of the SIOPEL 6 study is limited, as patients in the SIOPEL 6 study were not categorized in accordance with current risk stratification for hepatoblastoma and thus an unclear proportion of patients were potentially not treated in line with the corresponding interim recommendations. According to the protocol, all patients received preoperative cisplatin treatment, followed by surgery and postoperative cisplatin treatment. It is unclear to what extent tumours were directly operable without preoperative chemotherapy at the time of study inclusion. Information was also lacking regarding the differentiation of the foetal tumour cells (well differentiated foetal [WDF] type), which is important for the treatment decision for or against

postoperative chemotherapy. Furthermore, according to the study documents, insufficient information was available for 2 anatomical risk factors (extrahepatic abdominal disease and involvement of the inferior vena cava and/or the hepatic veins), which are used to decide between cisplatin monotherapy (low risk) and combination chemotherapy with cisplatin and carboplatin + doxorubicin (intermediate risk). In particular, it can generally be assumed that patients were included in the study who would receive only surgery without cisplatin chemotherapy, or a much lower cumulative dose of cisplatin (only postoperative cisplatin therapy), according to current recommendations. This applies to patients at very low risk who have a good prognosis. Patients with a lower cumulative exposure to cisplatin have a lower risk of hearing impairment. Thus, the SIOPEL 6 study potentially overestimates the risk of ototoxicity and the associated protective effects of sodium thiosulfate in patients with hepatoblastoma. Patients who would not receive cisplatin according to current recommendations are not included in the given therapeutic indication. The SIOPEL 6 study can therefore at most be used to derive, for example, hints of an added benefit.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT. The comparator arm of the SIOPEL 6 study was a sufficient approximation to the ACT watchful waiting.

Classification of the patient population of the SIOPEL 6 study against the background of the therapeutic indication

With an average age of 1.5 years at diagnosis, patients with hepatoblastoma are generally a very young patient group. Patients in the therapeutic indication of localized, non-metastatic hepatoblastoma are in a potentially curative treatment situation. The patients are generally operated on to remove the liver tumour and almost always receive chemotherapy. In terms of risk factors for ototoxicity induced by cisplatin chemotherapy, these patients have a comparatively high risk, particularly due to their young age at disease onset and the single cisplatin dose per cycle, which is not administered over several days.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for the SIOPEL 6 study.

The risk of bias of the results for the outcome of overall survival was rated as low. The risk of bias for the outcome of hearing loss (Brock grade ≥ 1) was rated as high due to a potentially relevant difference in the proportion of missing values between the treatment groups. In the outcome category of side effects, the risk of bias of the results for the outcomes of severe AEs and other specific AEs (hypokalaemia [severe AEs] and hypophosphataemia [severe AEs] was rated as low in each case. The results for the outcomes of vomiting (AEs) and nausea (AEs) had a high risk of bias due to the lack of blinding in subjective outcome recording. No suitable data were available for the outcomes of failure of the curative treatment approach, serious AEs

(SAEs) and discontinuation due to AEs. Outcomes on health-related quality of life were not recorded.

Due to the limited certainty of conclusions of the SIOPEL 6 study (see above), at most hints, e.g. of an added benefit, can be derived for all outcomes.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is neither a hint of an added benefit nor a hint of lesser benefit of sodium thiosulfate in comparison with watchful waiting; an added benefit or lesser benefit is therefore not proven.

Morbidity

Failure of the curative treatment approach

No suitable data were available for the outcome of failure of the curative treatment approach. There is neither a hint of an added benefit nor a hint of lesser benefit of sodium thiosulfate in comparison with watchful waiting; an added benefit or lesser benefit is therefore not proven.

Hearing loss (BROCK grade ≥ 1)

For the outcome of hearing loss (BROCK grade ≥ 1), assessed using the BROCK scale, both analyses presented (imputation of missing values as hearing loss responders or non-responders) showed a statistically significant difference in favour of sodium thiosulfate + cisplatin compared with cisplatin. There is a hint of an added benefit of sodium thiosulfate in comparison with watchful waiting. Depending on the imputation strategy, the extent of the added benefit differs (imputation of missing values as hearing loss responders: extent considerable; imputation of missing values as hearing loss non-responders: extent minor).

Health-related quality of life

Outcomes on health-related quality of life were not recorded. There is no hint of an added benefit of sodium thiosulfate in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No suitable data were available for the outcomes of SAEs and discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from sodium thiosulfate in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs

No statistically significant difference between treatment groups was found for the outcome of severe AEs. There is no hint of greater or lesser harm from sodium thiosulfate in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Vomiting (AEs)

For the outcome of vomiting (AEs), a statistically significant difference was found to the disadvantage of sodium thiosulfate + cisplatin in comparison with cisplatin. There is a hint of greater harm from sodium thiosulfate in comparison with watchful waiting.

Nausea (AEs)

No statistically significant difference between treatment groups was found for the outcome of nausea (AEs). There is no hint of greater or lesser harm from sodium thiosulfate in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Other specific AEs

Hypokalaemia and hypophosphataemia (both severe AEs)

For each of the outcomes of hypokalaemia and hypophosphataemia (AEs), a statistically significant difference was found to the disadvantage of sodium thiosulfate + cisplatin in comparison with cisplatin. In each case, there is a hint of greater harm from sodium thiosulfate in comparison with watchful waiting.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug sodium thiosulfate in comparison with the ACT is assessed as follows:

Based on the SIOPEL 6 study, this benefit assessment can only draw conclusions on children with localized, non-metastatic hepatoblastoma with a therapeutic indication for the prevention of ototoxicity induced by cisplatin chemotherapy. Patients with localized, non-metastatic hepatoblastoma are characterized by a young patient population in a potentially curative treatment situation. Due in particular to the young age at disease onset and the single

[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].

dose of cisplatin per cycle, which is not administered over several days, these are patients with a comparatively high risk of cisplatin-induced ototoxicity.

No suitable data were available for patients 1 month to < 18 years of age with other localized, non-metastatic, solid tumours with a therapeutic indication for the prevention of ototoxicity induced by cisplatin chemotherapy. The added benefit was therefore derived separately for these 2 patient groups.

Patients with hepatoblastoma

The overall assessment showed one positive and several negative effects of sodium thiosulfate in comparison with watchful waiting. In the outcome category of serious/severe symptoms/late complications, a hint of a non-quantifiable added benefit of at most considerable extent was shown the outcome of hearing loss. In contrast, there were hints of greater harm, in each case of minor extent, in severe and non-severe side effects such as vomiting and severe hypokalaemia and hypophosphataemia. No data were available for the outcome category of health-related quality of life. The negative effects of various specific side effects, some of which were severe, do not completely call into question the positive effect regarding hearing loss.

In summary, here is a hint of a minor added benefit of sodium thiosulfate in comparison with watchful waiting for children with localized, non-metastatic hepatoblastoma with indication for the prevention of ototoxicity induced by cisplatin chemotherapy.

Patients with other solid tumours

No suitable data were available for patients 1 month to < 18 years of age with other localized, non-metastatic, solid tumours with indication for the prevention of ototoxicity induced by cisplatin chemotherapy. For these patients, there is no hint of an added benefit of sodium thiosulfate in comparison with watchful waiting; an added benefit is therefore not proven.

Table 3 shows a summary of probability and extent of the added benefit of sodium thiosulfate.

Table 3: Sodium thiosulfate – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours with indication for the prevention of ototoxicity induced by cisplatin chemotherapy	Watchful waiting	Patients with hepatoblastoma: hint of minor added benefit
		Patients with other solid tumours: added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is the assessment of the added benefit of sodium thiosulfate in comparison with watchful waiting as the ACT in patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of sodium thiosulfate

Therapeutic indication	**ACT[a]**
Patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours with indication for the prevention of ototoxicity induced by cisplatin chemotherapy	Watchful waiting
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The G-BA defined watchful waiting as the ACT. The company deviated from the G-BA's specification by determining best supportive care instead of watchful waiting as the ACT. The review of the completeness of the study pool taking into account the ACT watchful waiting did not reveal any studies further to those identified by the company. Therefore, the company's deviation regarding the specification of the ACT remains without consequence. The benefit assessment was conducted in comparison with the G-BA's ACT. For information regarding the studies identified by the company in terms of relevance and implementation of the ACT, see Sections I 3.1 and I 3.2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on sodium thiosulfate (status: 9 December 2024)
- Bibliographical literature search on sodium thiosulfate (last search on 9 December 2024)
- Search of trial registries/trial results databases for studies on sodium thiosulfate (last search on 9 December 2024)
- Search on the G-BA website for sodium thiosulfate (last search on 9 December 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on sodium thiosulfate (last search on 17 February 2025); for search strategies, see I Appendix A of the full dossier assessment

The review of the study pool identified the SIOPEL 6 study used by the company. The company additionally included the ACCL0431 study [3-6] in the benefit assessment. The ACCL0431 study is unsuitable for assessing the added benefit of sodium thiosulfate. However, an adequate analysis of the data could provide supporting information on the question of whether the results of the included SIOPEL 6 study can be transferred to other patient groups. The ACCL0431 study and its relevance for the benefit assessment are explained below.

I 3.1 Study ACCL0431

Table 20 and Table 21 in I Appendix B of the full dossier assessment describe the ACCL0431 study presented by the company.

The ACCL0431 study is unsuitable for the assessment of the added benefit of sodium thiosulfate in comparison with the ACT watchful waiting in patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy, because the dosage of sodium thiosulfate deviated from the SPC. A description of the study is provided below, followed by an explanation of why the study is not suitable for the benefit assessment.

The ACCL0431 study is an open-label, cross-tumour RCT comparing sodium thiosulfate versus no sodium thiosulfate treatment in patients aged ≥ 1 to ≤ 18 years who had newly diagnosed, histologically confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma or other malignancy, and who were receiving cisplatin chemotherapy. Patients had to have been included in the ACCL05C1 study [7] first. The ACCL05C1 study is an observational study of the same study group, which included patients

with planned cisplatin treatment aged 1 to 30 years. Hearing impairment was recorded as part of the ACCL05C1 study, including for the patients in the ACCL0431 study. The patients therefore remained in the ACCL05C1 study while participating in the ACCL0431 study.

Based on the inclusion criteria, the ACCL0431 study included patients with newly diagnosed tumours. According to the study protocol, patients were considered newly diagnosed if they were previously untreated or currently receiving cancer treatment for the tumour that made the patient eligible for the study. Patients were not allowed to have received previous platinum-based chemotherapy (cisplatin or carboplatin), but other prior chemotherapy was permitted. Patients had to have a treatment plan with a planned cumulative cisplatin dose of ≥ 200 mg/m^2 BSA at enrolment. Further inclusion criteria were normal audiometry results and a performance status score of ≥ 50 (using the Karnofsky scale for patients > 16 years of age and the Lansky scale for patients ≤ 16 years of age).

125 patients were randomly allocated at a 1:1 ratio to treatment with sodium thiosulfate (N = 61) or cisplatin (N = 64). Randomization was stratified by prior cranial radiation (yes/no) and for patients without prior cranial radiation additionally by age (< 5/≥ 5 years) and duration of the planned cisplatin infusion (< 2/≥ 2 hours).

Cisplatin was administered according to the sites' disease-specific treatment protocols. In addition to the administration of cisplatin, a prior chemotherapy regimen was allowed to be continued. No information was available on disease-specific therapy (e.g. as monotherapy or combination therapy) including dosage. See the next section for information on treatment with sodium thiosulfate.

The primary outcome of the study was hearing loss according to ASHA criteria. Patient-relevant secondary outcomes were overall survival and AE outcomes.

Treatment with sodium thiosulfate not in compliance with the SPC

According to the marketing authorization, patients with > 10 kg body weight should be treated with 12.8 g/m^2 BSA, patients with 5 to 10 kg with 9.6 g/m^2 BSA, and patients with < 5 kg with 6.4 g/m^2 BSA sodium thiosulfate [8]. No patient in the ACCL0431 study was dosed in compliance with the marketing authorization. The patients received dosages of 10.2 g/m^2 BSA, or 341 mg/kg body weight for patients who received cisplatin dosed according to body weight due to their young age or small body size. No information was available on the respective numbers of patients treated based on BSA or body weight. As only 6 patients (4.8%) weighed ≤ 10 kg according to the approval documents, it was assumed that only a few young children or children with a small body size were included in the ACCL0431 study and were thus dosed based on body weight. It can therefore be generally assumed that the majority of patients were dosed with 10.2 g/m^2 BSA sodium thiosulfate. In comparison with the dosage recommended in the SPC, these patients received a dosage that was 20.3% too low (12.8 g/m^2

BSA for children with > 10 kg body weight). For the unknown, but presumably small proportion of patients who were dosed based on body weight, the extent of the deviation from the dosage according to the SPC is unclear.

Due to the dosing of sodium thiosulfate, which deviated from the SPC, the ACCL0431 study was not used to assess the added benefit of sodium thiosulfate in comparison with watchful waiting as the ACT in patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours for the prevention of ototoxicity induced by cisplatin chemotherapy. The underdosing of sodium thiosulfate is important firstly because of the potential underreporting of the side effects of sodium thiosulfate. Secondly, it is of particular relevance that a possible tumour-protective effect of sodium thiosulfate with an impact on overall survival can be overlooked due to underdosing. This is due to the fact that although sodium thiosulfate prevents cisplatin-induced hearing impairment due to its interaction with cisplatin, it also harbours the risk of a possible reduction in the effectiveness of cisplatin. This aspect of the potential tumour-protective effects of sodium thiosulfate is discussed in detail in the European Public Assessment Report (EPAR) [9]. In patients with metastatic disease in the ACCL0431 study, for example, there was a statistically significant disadvantage for sodium thiosulfate + cisplatin versus cisplatin for the overall survival outcome (HR: 2.96 [1.08; 8.06]; p = 0.03) [9]. Accordingly, the marketing authorization was limited to patients with non-metastatic disease. In the EPAR, the uncertainty regarding the possible tumour-protective effects of sodium thiosulfate also becomes clear by the divergent position of 2 reviewers, who did not see a positive benefit/risk ratio.

High proportion of patients with metastatic disease

Irrespective of the dosing of sodium thiosulfate, which was not in compliance with the marketing authorization, the data from study ACCL0431 presented by the company were unsuitable for the benefit assessment. Sodium thiosulfate is exclusively approved for the treatment of patients with non-metastatic tumours. In the ACCL0431 study, 21 patients (34.4%) in the intervention arm and 26 patients (40.6%) in the comparator arm were not included in the population relevant for the research question, as they had metastatic disease.

Further comments on the ACCL0431 study

Weighing up of benefit and harm not possible

The recording of AEs in the ACCL0431 study was incomplete and differed between the study arms. It is therefore not possible to weigh up benefit and harm due to unsuitable data on side effects.

In the sodium thiosulfate arm, certain AEs were recorded using the Adverse Event Expedited Reporting System (AdEERS). The recording varied based on i) severity (according to the Common Terminology Criteria for Adverse Events [CTCAE]); ii) whether the AE was identified

as related to sodium thiosulfate administration; iii) whether the AE was expected and iv) whether it was associated with hospitalization. For example, grade 1 AEs were not documented at all and grade 2 AEs were only documented if they were unexpected and also assessed as associated with the study medication (possible, probable or definite association). Grade 3 AEs, on the other hand, were only documented if they were associated with hospitalization, or were unexpected in the absence of hospitalization and also assessed as being associated with the study medication (possible, probable or definite association). In the ACCL0431 study, all AEs reported using the AdEERS were also classified as SAEs. Thus, AEs that do not represent a SAE purely due to their severity may be included in the results for SAEs. In addition, SAEs were only reported for patients in the sodium thiosulfate arm.

Other than the AdEERS recording in the sodium thiosulfate arm, a routine recording was conducted for both study arms. With some exceptions (e.g. ≥ grade 1 hypernatraemia or allergic reactions of any grade), this only included the recording of non-haematological grade ≥ 3 AEs.

Discontinuations due to AEs were not systematically recorded in the ACCL0431 study.

Overall, the analyses on side effects were unsuitable for the benefit assessment due to the differing and incomplete data recording between the study arms. Regardless of the sodium thiosulfate dosing, which deviated from the SPC, it would therefore be impossible to weigh up benefit and harm using the ACCL0431 study.

Unclear information on data cut-offs

According to the clinical study report (CSR) dated 7 February 2019, the last patient was enrolled on 24 February 2012. The analysis of the primary outcome of hearing loss took place 4 weeks after the end of treatment. A follow-up on hearing loss was planned up to 1 year after the end of treatment. The tumour status of all patients was followed up for 10 years after enrolment. Analyses of 3 data cuts are available:

- The 31 March 2015 cut in the publication by Freyer et al [3]
- The data cut in the study report: The date of the data cut-off is unclear, but a comparison with the results on overall survival showed that it was after the data cut-off used in the publication by Freyer et al [3] and before the data cut-off used in the publication by Orgel et al [10].
- Data from the 31 December 2019 cut-off in the publication by Orgel et al. [10]

There is no complete information available on the reasons for the data cut-offs mentioned.

According to the 2018 statistical analysis plan, the final analysis was to take place after the last patient had completed the study. It is not clear from the documents which outcome the

final analysis refers to: whether the information relates to completion at 1 year after the end of treatment (hearing loss), or to completion after 10 years of follow-up (tumour status including overall survival). In addition, the specification for the final analysis was only made after the final analysis for the primary outcome according to the 2017 publication Freyer et al [3] had already taken place.

A final analysis at the end of the study after all patients had been observed for 10 years or were no longer available for follow-up observation for other reasons is not available.

No separate results are available for the relevant subgroups

In the present therapeutic indication for the prevention of ototoxicity induced by cisplatin chemotherapy, a number of risk factors for ototoxicity and thus potential effect modifiers are of importance. These include the following [11,12]:

- a high cumulative cisplatin dose,
- the application interval (cisplatin 100 mg/m^2 over 5 days is less toxic than over 3 days),
- young age (especially < 5 years),
- the simultaneous use of other ototoxic drugs (e.g. aminoglycosides and loop diuretics or the combination of vincristine and cisplatin),
- prior or concomitant radiotherapy to the cochlea or the vestibulocochlear nerve,
- a pre-existing hearing impairment,
- renal insufficiency and
- specific genetic variants

Depending on the tumour entity, risk factors for ototoxicity, such as the application interval, may vary. For the cross-entity ACCL0431 study, no results by entity or subgroup analyses related to the risk factors described above (with the exception of age) were available in Module 4 A of the dossier. Besides age, different entities may differ in particular with regard to the cumulative cisplatin dose and the corresponding application intervals. For example, patients with hepatoblastoma (see Section I 3.2 on studies included) are treated with a 1-day cisplatin chemotherapy block per cycle. Patients with common entities in the ACCL0431 study, such as osteosarcoma, neuroblastoma or germ cell tumours, are treated with multi-day chemotherapy blocks of up to 10 consecutive days for neuroblastoma [13-15].

Despite the limitations described above, the results on efficacy outcomes (especially hearing loss) as well as on overall survival and possibly on the failure of a curative treatment approach could provide supporting information on the question of whether the results of the included SIOPEL 6 study (see next section) can be transferred to other patient groups. This would

require analyses of the subpopulation of non-metastatic patients according to entities or relevant subgroups (e.g. based on the cisplatin dose or the application interval).

I 3.2 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: sodium thiosulfate vs. watchful waiting

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
SIOPEL 6	Yes	No[d]	Yes[d]	Yes [6,16]	Yes [17,18]	Yes [9,19,20]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. This is a clinical study conducted by the University of Birmingham. The company was not the sponsor of the study, but acquired the marketing rights for Europe, Australia and New Zealand for the drug to be assessed from the marketing authorization holder in March 2024.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The SIOPEL 6 study was used for the benefit assessment. The study enrolled patients with hepatoblastoma. The study is therefore only suitable for drawing conclusions on the added benefit of sodium thiosulfate for patients with hepatoblastoma (see Sections I 3.3 and I 5.2 below).

I 3.3 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: sodium thiosulfate + cisplatin[a] vs. cisplatin[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
SIOPEL 6	RCT, open-label, parallel	Patients (> 1 month to ≤ 18 years) with ▪ newly diagnosed, histologically confirmed hepatoblastoma[c] ▪ with cisplatin treatment	▪ sodium thiosulfate + cisplatin (N = 61)[d] ▪ cisplatin (N = 53)[d]	Screening: ND Treatment: ▪ preoperative[e]: 4 cycles of cisplatin ± sodium thiosulfate ▪ surgery ▪ preoperative: 2 cycles of cisplatin ± sodium thiosulfate Observation[f]: outcome-specific, up to 5 years after enrolment[g]	52 study centres in: Australia, Belgium, Denmark, France, Great Britain, Ireland, Italy, Japan, New Zealand, Spain, Switzerland, United States 12/2007–2/2018[h]	Primary: hearing loss (BROCK grade ≥ 1) Secondary: overall survival, AEs

a. Cisplatin was described as part of the study medication in the SIOPEL 6 study. In terms of the research question, however, cisplatin was not part of the intervention or the ACT.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. Standard-risk hepatoblastoma defined according to the 2005 PRETEXT revised staging system [21]:
   - PRETEXT I, II or III
   - serum AFP > 100 ng/mL
   - no additional PRETEXT criteria (extrahepatic abdominal disease (E1, E1a, E2, E2a), intraperitoneal haemorrhage or tumour rupture (H1), distant metastases, regardless of location (M1), lymph node metastases (N1, N2), involvement of the main portal vein (P2, P2a), involvement of the inferior vena cava and/or the hepatic veins (V3, V3a)
d. Of these, 4 patients in the intervention arm and 1 patient in the comparator arm did not start treatment.
e. If surgery was delayed, up to 2 additional cycles could be given before surgery (Days 57 and 71).
f. Outcome-specific information is provided in Table 12.
g. Follow-up observation was planned for up to 5 years after enrolment. At the end of the 5-year period, follow-up examinations were carried out as clinically indicated and in accordance with the respective national guidelines.
h. Final analysis at the end of the study, planned for the time point at which audiometry results for the primary outcome of hearing loss were available for 102 patients, or at the latest 3 years after the last patient had been enrolled. The last patient completed treatment on 14 April 2015 and the follow-up on 28 February 2018.

Table 6: Characteristics of the study included – RCT, direct comparison: sodium thiosulfate + cisplatin[a] vs. cisplatin[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
AE: adverse event; AFP: alpha fetoprotein; N: number of randomized patients; ND: no data; PRETEXT: Pre-treatment Tumour Extension; RCT: randomized controlled trial						

Table 7: Characteristics of the intervention – RCT, direct comparison: sodium thiosulfate + cisplatin[a] vs. cisplatin[a] (multipage table)

Study	Intervention	Comparison
SIOPEL 6	4 cycles preoperatively[b]: each on Day 1 of a 14-day cycle (IV): ▪ cisplatin (6-hour infusion) ▫ > 10 kg: 80 mg/m² BSA ▫ ≥ 5 kg and ≤ 10 kg: 2.7 mg/kg BW ▫ < 5 kg: 1.8 mg/kg BW ▪ sodium thiosulfate[c] (15-minute infusion, 6 hours after the end of the cisplatin infusion) ▫ > 10 kg: 12.8 g/m² BSA ▫ ≥ 5 kg and ≤ 10 kg: 9.6 g/m² BSA ▫ > 5 kg: 6.4 g/m² BSA Surgery 2 cycles postoperatively: each on Day 1 of a 14-day cycle, no later than 21 days after surgery (IV): ▪ cisplatin (6-hour infusion) ▫ For dosage, see information on preoperative administration above ▪ sodium thiosulfate (15-minute infusion, 6 hours after the end of the cisplatin infusion) ▫ For dosage, see information on preoperative administration above	4 cycles preoperatively[b]: each on Day 1 of a 14-day cycle (IV): ▪ cisplatin (6-hour infusion) ▫ > 10 kg: 80 mg/m² BSA ▫ ≥ 5 kg and ≤ 10 kg: 2.7 mg/kg BW ▫ < 5 kg: 1.8 mg/kg BW Surgery 2 cycles postoperatively: each on Day 1 of a 14-day cycle, no later than 21 days after surgery (IV): ▪ cisplatin (6-hour infusion) ▫ For dosage, see information on preoperative administration above
	Treatment or dose adjustments: ▪ If the disease progressed after ≥ 2 cycles, the treatment was discontinued, and treatment with 2–4 cycles of cisplatin + doxorubicin (without sodium thiosulfate) was recommended. If there was a sufficient response, surgery was performed followed by 2 cycles of cisplatin + doxorubicin. ▪ Sodium thiosulfate: discontinuation of treatment in case of toxicities of CTCAE grade ≥ 3[d]	
	Disallowed pretreatment ▪ Any previous chemotherapy **Premedication** ▪ Antiemetic therapy (5-HT3 receptor agonist + dexamethasone ± other antiemetics such as chlorpheniramine or metoclopramide **Allowed concomitant treatment** ▪ Ototoxic drugs: e.g. loop diuretics (e.g. furosemide), aminoglycosides and vancomycin were allowed, but were ideally to be avoided	

a. Cisplatin was described as part of the study medication in the SIOPEL 6 study. In terms of the research question, however, cisplatin was not part of the intervention or the ACT.
b. If surgery was delayed, up to 2 additional cycles could be given before surgery.
c. The dosing information provided in the study documents referred to sodium thiosulfate pentahydrate. The figures given in the table are equivalent doses of anhydrous sodium thiosulfate according to the SPC (conversion factor 0.64).
d. Discontinuation of study medication in case of toxicities of CTCAE grade ≥ 3 (metabolic, vascular, neurological, renal or other toxicities presumed to be related to the study medication).

Table 7: Characteristics of the intervention – RCT, direct comparison: sodium thiosulfate + cisplatin[a] vs. cisplatin[a] (multipage table)

Study	Intervention	Comparison
BSA: body surface area; BW: body weight; CTCAE: Common Terminology Criteria for Adverse Events; 5-HT3: 5-hydroxytryptamine; IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics		

The SIOPEL 6 study is an open-label RCT comparing sodium thiosulfate versus no sodium thiosulfate treatment in patients aged ≥ 1 month to ≤ 18 years who had newly diagnosed, histologically confirmed standard-risk hepatoblastoma, and who were receiving cisplatin chemotherapy. In the SIOPEL 6 study, cisplatin was described as part of the study medication. In terms of the research question, however, cisplatin was not part of the intervention or the ACT. The patients were not allowed to have received any previous chemotherapy. In the SIOPEL 6 study, standard-risk hepatoblastoma was defined using the PRETEXT revised staging system from 2005 [21] as follows:

- PRETEXT I (1 section of the liver involved, 3 adjoining sections free), II (1 or 2 sections of the liver involved, 2 adjoining sections free) or III (2 or 3 sections of the liver involved, and no 2 adjoining sections free)
- Serum alpha fetoprotein (AFP) > 100 ng/mL
- No additional PRETEXT criteria (extrahepatic abdominal disease [E1, E1a, E2, E2a], intraperitoneal haemorrhage or tumour rupture [H1], distant metastases, regardless of location [M1], lymph node metastases [N1, N2], involvement of the main portal vein [P2, P2a], involvement of the inferior vena cava and/or the hepatic veins [V3, V3a])

For the definition of patients with standard-risk hepatoblastoma and their treatment in the SIOPEL 6 study, see the following section.

114 patients were randomly allocated at a 1:1 ratio to treatment with sodium thiosulfate (N = 61) or cisplatin (N = 53). Randomization was stratified by country (categorization unclear), age (< 15/> 15 months) and PRETEXT classification (I and II/III).

The patients received 4 cycles of cisplatin preoperatively (each on Day 1 of a 14-day cycle) with an infusion duration of 6 hours. This was followed by surgery. After surgery, 2 more cycles of cisplatin were administered (each on Day 1 of a 14-day cycle). If the disease progressed after ≥ 2 cycles of preoperative cisplatin treatment, the treatment was discontinued, and treatment with 2 to 4 cycles of cisplatin + doxorubicin (without sodium thiosulfate) was recommended. If there was a sufficient response, surgery was performed followed by 2 cycles of cisplatin + doxorubicin.

The cisplatin dose was 80 mg/m^2 BSA in children > 10 kg body weight. In children ≤ 10 kg body weight, dosing was based on body weight. Patients received a mean cumulative cisplatin dose (including the administration of cisplatin + doxorubicin) of 364 mg/m^2 in the intervention arm and 363 mg/m^2 in the comparator arm. For the treatment strategy of the patients in the study, see the following section.

Dosing with sodium thiosulfate was carried out as a 15-minute infusion 6 hours after the end of the respective cisplatin infusion, in compliance with the SPC [8]. SPC-compliant antiemetic therapy in the intervention arm was administered 30 minutes prior to sodium thiosulfate administration in addition to any cisplatin-associated antiemetic therapy.

The study's primary outcome was hearing loss (BROCK grade ≥ 1). Patient-relevant secondary outcomes were overall survival and AE outcomes.

Definition and treatment of patients with standard-risk hepatoblastoma in the SIOPEL 6 study

The SIOPEL 6 study is an older study, which commenced in 2007. It included patients with standard-risk hepatoblastoma according to the then-valid PRETEXT criteria from 2005 [21]. This categorization provided for 2 groups: standard risk (see above for definition) and high risk (PRETEXT IV or AFP level < 100 ng/mL or additional PRETEXT criteria [see above for definition]). According to the current criteria of the Children's Hepatic Tumours International Collaboration (CHIC), which also includes the German Society for Paediatric Oncology and Haematology (GPOH), patients are now divided into 4 risk groups (very low, low, intermediate, high) (see Table 22 in I Appendix C of the full dossier assessment) [22-24]. The patients included in the SIOPEL 6 study potentially fall into the groups with very low, low and intermediate risk. Depending on the risk group, the treatment of patients differs according to interim recommendations [22]. Patients at very low risk (patients whose tumours are operable at the time of diagnosis), for example, are recommended to have surgery without preoperative chemotherapy [22]. In case of WDF tumour cells, their treatment is completed after the operation. Postoperative chemotherapy is only recommended for a different type of histology (no WDF histology). Patients at low risk (patients whose tumour is not [yet] operable at the time of diagnosis), in contrast, receive pre- and postoperative cisplatin monotherapy, which is in line with the treatment used in the SIOPEL 6 study. Patients at intermediate risk, however, are treated with a pre- and postoperative combination therapy consisting of alternating cisplatin and carboplatin + doxorubicin blocks [22]. Overall, it is unclear how the patients in the SIOPEL 6 study were distributed among the groups with very low, low and intermediate risk. It can be assumed that some patients in the SIOPEL 6 study fall into the very-low-risk group and should have received surgery directly without preoperative chemotherapy according to interim recommendations [22]. The extent to which postoperative chemotherapy was necessary in these patients is unclear as there was no

information on WDF type. In addition, patients in the SIOPEL 6 study also potentially fall into the intermediate-risk group, as patients with anatomical risk factors (involvement of the main portal vein [P1] or involvement of the inferior vena cava and/or the hepatic veins [V1, V2]) could also be enrolled in accordance with the inclusion criteria. According to current interim recommendations, these patients would receive a combination therapy of cisplatin and carboplatin/doxorubicin [22].

Irrespective of this, there is an additional uncertainty in the SIOPEL 6 study, as according to the study documents no information is available on the anatomical risk factor of extrahepatic abdominal disease (100% missing values), and information on the risk factor of involvement of the inferior vena cava and/or the hepatic veins is only available for 15% of the patients (see Table 9).

Against the background of the current health care context, the certainty of conclusions of the SIOPEL 6 study is generally limited, as patients in the SIOPEL 6 study were not categorized in accordance with current risk stratification and thus an unclear proportion of patients were potentially not treated in line with the corresponding interim recommendations. According to the protocol, all patients received preoperative cisplatin treatment, followed by surgery and postoperative cisplatin treatment. It is unclear to what extent tumours were directly operable without preoperative chemotherapy at the time of study inclusion. Information was also lacking regarding the differentiation of the foetal tumour cells (WDF type), which is important for the treatment decision for or against postoperative chemotherapy. Furthermore, according to the study documents, insufficient information was available for 2 anatomical risk factors, which are used to decide between cisplatin monotherapy (low risk) and combination chemotherapy with cisplatin and carboplatin + doxorubicin (intermediate risk) [22]. In particular, it can generally be assumed that patients were included in the study who would receive only surgery without cisplatin chemotherapy, or a much lower cumulative dose of cisplatin (only postoperative cisplatin therapy), according to current recommendations. This applies to patients at very low risk who have a good prognosis. Patients with a lower cumulative exposure to cisplatin have a lower risk of hearing impairment. Thus, the SIOPEL 6 study potentially overestimates the risk of ototoxicity and the associated protective effects of sodium thiosulfate in patients with hepatoblastoma. Patients who would not receive cisplatin according to current recommendations are not included in the given therapeutic indication. The SIOPEL 6 study can therefore at most be used to derive, for example, hints of an added benefit.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT. The comparator arm of the SIOPEL 6 study was a sufficient approximation to the ACT watchful waiting. This is explained below:

In the SIOPEL 6 study, audiograms were performed after every second cisplatin cycle and at the end of treatment to record hearing impairment. After the end of treatment, annual hearing examinations were carried out until a final measurement at the age of 3.5 years (primary outcome of the study) (see Table 8). For patients who were older than 3.5 years during treatment, the audiometry was performed 6 to 12 weeks after the last dose of cisplatin. Further follow-up observation was possible if clinically indicated and in accordance with national guidelines.

According to the consultation version of the S3 guideline "Supportive therapy for oncological patients", audiometry to assess possible ototoxicity in patients receiving cisplatin-based chemotherapy should be performed before starting treatment and if subjective symptoms occur [11]. The S1 guideline "Long-term follow-up of children, adolescents and young adults with cancer – Avoiding, recognizing and treating late effects" recommends a preoperative baseline audiogram and audiogram checks within 24 hours before each new block of cisplatin [25]. In addition, hearing tests should be carried out every 6 months for the first 2 years after the end of chemotherapy and then annually for at least 3 more years.

Overall, the patients in the SIOPEL 6 study were examined sufficiently closely and specifically for the detection of hearing impairment; the examination intervals used were thus considered to be a sufficient approximation to an adequate operationalization of watchful waiting with regard to the detection of hearing impairment.

Classification of the patient population of the SIOPEL 6 study against the background of the therapeutic indication

With an average age of 1.5 years at diagnosis [26], patients with hepatoblastoma are generally a very young patient group. Patients in the therapeutic indication of localized, non-metastatic hepatoblastoma are in a potentially curative treatment situation. The patients are generally operated on to remove the liver tumour and almost always receive chemotherapy [26]. In terms of risk factors for ototoxicity induced by cisplatin chemotherapy (for risk factors, see Section I 3.1), these patients have a comparatively high risk, particularly due to their young age at disease onset and the single cisplatin dose per cycle, which is not administered over several days (see also Section I 5.2 for the overall conclusion on the added benefit).

Data cut-off

The SIOPEL 6 study started in December 2007 and has been completed. No information on the reason for the data cut-off is available either for the analyses in the publication by Brock et al [19] or for the analyses presented in Module 4 A and the study documents. The final analysis for the primary outcome of hearing loss was planned for the time point at which audiometry results for this outcome were available for 102 patients, or at the latest 3 years after the last patient had been enrolled. For the overall survival outcome, follow-up was planned up to

5 years after inclusion of the last patient (see table below). The last patient completed treatment on 14 April 2015. The follow-up was completed with the last patient on 28 February 2018. At this time, the median observation period for overall survival was 4.6 years in the intervention arm and 4.2 years in the comparator arm (see Table 10). Irrespective of the fact that there is no information on the reason for the data cut-off, the available analyses can be presumed to be the final analysis after 5 years of follow-up. This is due to the fact that the actual observation periods were close to the planned follow-up periods of 5 years.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin

Study **Outcome category** **Outcome**	**Planned follow-up observation**
SIOPEL 6	
Mortality	
Overall survival	▪ Up to 5 years after inclusion of the last patient[a]
Morbidity	
Hearing loss (BROCK grade ≥ 1)	▪ Up to 12 weeks after completion of study treatment or until the age of at least 3.5 years, whichever was later[a]
Health-related quality of life	▪ Outcomes in this category were not recorded
Side effects	
All outcomes in the side effects category	▪ Up to 30 days after the last dose of study treatment[b]
a. Further follow-up was possible if clinically indicated and recommended by national guidelines. b. SAEs that were considered to be related to study procedures were additionally followed up for up to 5 years. RCT: randomized controlled trial; SAE: serious adverse event	

The observation period for the outcome of hearing loss was systematically shortened, as the outcome was only recorded up to 12 weeks after completion of the study treatment or up to an age of at least 3.5 years, whichever was later. The observation periods for side-effect outcomes, except for SAEs related to study procedures, were also systematically shortened because they were recorded only for the period of treatment with the study medication (plus 30 days). However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival. Outcomes on health-related quality of life were not recorded.

Study population

Table 9 shows the characteristics of the patients in the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin (multipage table)

Study Characteristic Category	Sodium thiosulfate + cisplatin N = 57	Cisplatin N = 52
SIOPEL 6		
Age [months]		
Mean (SD)	19 (17)	18 (15)
Median [min; max]	13 [1; 99]	13 [3; 70]
Sex [F/M], %	47/53	44/56
Geographical region, n (%)		
Europe	49 (86)	45 (87)
United States	1 (2)	1 (2)
Japan	2 (4)	3 (6)
Other	5 (9)	3 (6)
Family origin, n (%)		
White	32 (56)	32 (62)
Black or African American	0 (0)	2 (4)
Asian	6 (11)	7 (14)
Other	8 (14)	5 (10)
Unknown	11 (19)	6 (12)
Body weight [kg], mean (SD)	10.2 (3.8)	10.3 (3.3)
AFP at diagnosis [ng/mL]		
Mean (SD)	496 085 (888 294)	374 405 (565 679)
Median [min; max]	181 500 [273; 5 489 165]	79 252 [187; 2 632 585]
AFP category, n (%)		
< 1000 ng/mL	4 (7)	4 (8)
1000 to < 1 000 000 ng/mL	45 (79)	42 (81)
> 1 000 000 ng/mL	8 (14)	6 (12)
PRETEXT classification[a, b], n (%)		
I	11 (19)	0 (0)
II	30 (53)	31 (60)
III	16 (28)	21 (40)
Distant metastases (M[b]), n (%)		
Yes	0 (0)	0 (0)
No	55 (97)	52 (100)
Unclear	2 (4)	0 (0)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin (multipage table)

Study **Characteristic** **Category**	**Sodium thiosulfate + cisplatin** **N = 57**	**Cisplatin** **N = 52**
Lymph node metastases (N[b]), n (%)		
Yes	0 (0)	0 (0)
No	56 (98)	51 (98)
Unclear	1 (2)	1 (2)
Involvement of the inferior vena cava and/or the hepatic veins (V[b])		
Missing	50 (88)	43 (83)
Information available[c]	7 (12)[d]	9 (17)[d]
Involvement of the portal vein (P[b]), n (%)		
Yes	5 (9)	8 (15)
No	50 (88)	41 (79)
Unclear	2 (4)	3 (6)
Extrahepatic abdominal disease (E[b]), n (%)		
Missing	57 (100)	52 (100)
Tumour focality (F[b]), n (%)		
F0 (solitary tumour)	53 (93)	45 (87)
F1 (≥ 2 tumours[e])	4 (7)	7 (14)
Tumour rupture or intraperitoneal haemorrhage (H[b]), n (%)		
Yes	0 (0)	0 (0)
No	55 (97)	51 (98)
Unclear	2 (4)	1 (2)
Caudate lobe involvement (C[b]), n (%)		
Yes	4 (7)	5 (10)
No	49 (86)	40 (77)
Unclear	4 (7)	7 (14)
Treatment discontinuation, n (%)[f]	ND	ND
Study discontinuation, n (%)[g]	2 (4)	6 (12)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin (multipage table)

Study Characteristic Category	Sodium thiosulfate + cisplatin N = 57	Cisplatin N = 52
a. PRETEXT classification: I: 1 section of the liver involved, 3 adjoining sections free; II: 1 or 2 sections of the liver involved, 2 adjoining sections free; III: 2 or 3 sections of the liver involved, and no 2 adjoining sections free. b. Additional PRETEXT criteria according to the 2005 PRETEXT classification [21]. c. Including: involvement, no involvement of the inferior vena cava and/or the hepatic veins, and unclear. d. Institute's calculation. e. Regardless of nodule size or PRETEXT classification. f. 7% vs. 2% of the randomized patients never started treatment. In addition, 0 patients in the intervention arm and 2 patients in the control arm died during treatment with the study medication. g. Study completion was defined as participation in the audiometric examination after the last cisplatin treatment or reaching ≥ 3.5 years of age (whichever was later). Reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients and patients who received at least 1 dose of the study medication): other reasons (2% vs. 4%). The data additionally include patients who died during the course of the study (intervention arm: 2% vs. control arm: 8%). AFP: alpha fetoprotein; F: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients who received at least 1 dose of study medication; ND: no data; PRETEXT: Pre-treatment Tumour Extension; RCT: randomized controlled trial; SD: standard deviation		

The patient characteristics in the SIOPEL 6 study were largely balanced between the 2 treatment groups. The median age of the patients in both arms was 13 months. The majority of patients were white (56% versus 62%) and the proportion of boys and girls was largely balanced. In accordance with the inclusion criteria, they did not have any distant or lymph node metastases. For missing information on certain anatomical risk factors (involvement of the inferior vena cava and/or the hepatic veins and extrahepatic abdominal disease), see Section I 3.2. Differences, which were presumably due to the small sample size, were seen in the PRETEXT classification (19% of patients in the intervention arm versus 0% in the comparator arm had PRETEXT I hepatoblastoma).

No data are available on the proportion of patients who discontinued treatment. The proportion of patients who discontinued the study was 4% in the intervention arm and 12% in the comparator arm. The most common reason for study discontinuation was patient death.

Information on the course of the study

Table 10 shows patients' mean and median treatment durations as well as the mean and median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin

Study **Duration of the study phase** **Outcome category/outcome**	**Sodium thiosulfate + cisplatin** **N[a] = 53**	**Cisplatin** **N[a] = 56**
SIOPEL 6		
Total treatment duration[b, c] [days]		
Median [min; max]	94.0 [63; 158]	94.5 [54; 181]
Mean (SD)	97.7 (16.1)	97.5 (21.7)
Treatment duration before surgery[b, d] [days]		
Median [min; max]	44.0 [15; 88]	43.0 [14; 58]
Mean (SD)	44.6 (7.6)	42.6 (7.0)
Observation period [years]		
Overall survival[e]	N[f] = 57	N[f] = 52
Median [min; max]	4.6 [1.2; 9.3]	4.2 [0.2; 8.6]
Mean (SD)	ND	ND
Morbidity (hearing loss [BROCK grade ≥ 1])		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Health-related quality of life	Outcomes in this category were not recorded	
Side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a. Number of patients who received at least 1 dose of the study medication. The patients were analysed according to the treatment they actually received.
b. From first dose in first cycle to last dose in last cycle, or to date of surgery, if no postoperative chemotherapy was given.
c. Including cisplatin + doxorubicin administration in case of treatment discontinuation due to disease progression.
d. From first dose in first cycle to last dose in last cycle prior to surgery.
e. No information is available on how the observation period was calculated.
f. Number of randomized patients who received at least 1 dose of the study medication.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The median and mean total treatment duration including preoperative chemotherapy, surgery and postoperative chemotherapy was just under 100 days in both study arms (median: 94.0 versus 94.5 days; mean: 97.7 versus 97.5 days). The median and mean treatment duration before surgery was just over 40 days in both study arms.

The median observation period for overall survival was slightly longer in the intervention arm than in the comparator arm (4.6 vs. 4.2 years). No data on observation periods are available

for the other outcomes. For the outcome of hearing loss (BROCK grade ≥ 1), the observation period was determined by the outcome definition (hearing loss after completion of the study treatment or at an age of at least 3.5 years [whichever was later], see Section I 4.1). With the median age at baseline being 13 months, it can be assumed that the median observation period was approximately 29 months. For the side effect outcomes, the observation period was linked to the end of treatment (see Table 8). Therefore, the observation periods for these outcomes were presumed to be shorter in comparison with the observation period of overall survival.

Subsequent antineoplastic therapies

In the given curative treatment situation, subsequent antineoplastic therapies only play a role in a few cases. All patients in the SIOPEL study underwent surgery or transplantation (partial hepatectomy: 93.0% vs. 92.3%, liver transplantation 7.0% vs. 7.7%). Following the operation, the patients received postoperative chemotherapy, which completed the treatment. Only 5 [8,8%] versus 2 [3,8%] of the patients had recurrence.

If the disease progressed after ≥ 2 cycles, the treatment in the SIOPEL 6 was discontinued, and treatment with 2 to 4 cycles of cisplatin + doxorubicin (without sodium thiosulfate) was recommended. If there was a sufficient response, surgery was performed followed by 2 cycles of cisplatin + doxorubicin. According to the information in the dossier (percentages based on patients who received at least 1 dose of the study medication, analysed according to the study medication actually received [N = 53 versus N = 56]), 4 (7.5%) versus 5 (8.9%) patients received doxorubicin, 3 (5.7%) versus 5 (8.9%) patients received carboplatin, and one patient in the intervention arm (1.9%) received irinotecan.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
SIOPEL 6	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the SIOPEL 6 study. Limitations resulting from the open-label study design are described in Section I 4.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

In its dossier, the company described that the results of the SIOPEL 6 study are assumed to be transferable to the German health care context, without justifying this in more detail.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the SIOPEL 6 study results, see also Section I 3.2.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Failure of the curative treatment approach
  - Hearing loss (BROCK grade ≥ 1), determined by pure-tone audiometry using the BROCK scale
- Health-related quality of life
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Vomiting (Preferred Term [PT], AEs)
  - Nausea (PT, AEs)
  - Other specific AEs, if any

The patient-relevant outcomes selected deviate from those selected by the company.

Table 12: Matrix of outcomes – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin

Study	Outcomes									
	Overall survival	Failure of the curative treatment approach	Hearing loss (BROCK grade ≥ 1)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Vomiting (PT, AEs)	Nausea (PT, AEs)	Other specific AEs[b]
SIOPEL 6	Yes	No[c]	Yes	No[d]	No[c]	Yes	No[c]	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are taken into account (coded according to MedDRA): hypokalaemia (PT, severe AEs), hypophosphataemia (PT, severe AEs).
c. No suitable data available; see body of text below for reasons.
d. Outcomes in this category were not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

Measurement of hearing loss using the BROCK scale

In the SIOPEL 6 study, hearing loss was determined using the BROCK scale. The BROCK scale is a scale designed in 1991 to measure cisplatin-induced hearing impairment in children [27]. Whereas other scales measure changes between 2 points in time, the BROCK scale was developed primarily for younger children, for whom baseline measurements often do not provide reliable hearing measurements due to their young age. The BROCK scale measures hearing loss using absolute values at a specific point in time when the children are old enough to have their hearing assessed by pure-tone audiometry [27].

As hearing loss under cisplatin affects higher frequencies first and lower frequencies as hearing loss progresses, the BROCK scale is used to assess hearing ability at different frequencies starting at 8000 Hz, and then at 4000, 2000 and 1000 Hz. A limit of 40 dB is set as the threshold for the respective hearing loss, from which the following severity levels of hearing loss on the BROCK scale are derived:

- Grade 0 (minimal): < 40 dB at all frequencies
- Grade 1 (mild): ≥ 40 dB at 8000 Hz only
- Grade 2 (moderate): ≥ 40 dB at 4000 Hz and above
- Grade 3 (marked): ≥ 40 dB at 2000 Hz and above
- Grade 4 (severe): ≥ 40 dB at 1000 Hz and above

The better of the 2 ears is used to determine the severity of hearing loss [27]. The severity measured on the BROCK scale is associated with the expected impairment in everyday life. It should be noted that even a BROCK grade 0 is not equivalent to normal hearing. Children with grade 1 hearing loss will require preferential classroom seating and monitoring [9]. Children with grade 2 hearing loss will likely have difficulty hearing high-frequency consonant speech sounds and understanding speech in noise or over distance, and may require assistive listening devices, particularly during the early language-learning years. Children with grades 3 and 4 hearing loss will require hearing aids for speech development and for communication [9,27].

In the SIOPEL 6 study, hearing loss was determined 6 to 12 weeks after completion of the study treatment or at the age of at least 3.5 years (whichever was later). This takes into account the fact that reliable measurements using pure-tone audiometry are only possible from about this age [27]. The definition of this outcome ensures that the majority of children have adequate follow-up to detect any hearing impairment. The children's median age at baseline was 13 months, so the majority of children were followed up for at least 2 years (until the age of 3.5 years).

Overall, the BROCK scale is a valid scale for measuring hearing loss in children undergoing cisplatin therapy. The definition of hearing loss from a BROCK grade of 1 (≥ 40 dB at 8000 Hz only) is considered patient relevant, as even minor hearing loss is relevant especially during the speech development phase. The normal hearing range for children is below 20 dB [28]. It should be critically noted that normal hearing was not an inclusion criterion in the SIOPEL 6 study and that no information on hearing ability at baseline was available in the study documents despite the planned survey. However, it can be assumed that the young children included in the SIOPEL 6 study had normal hearing at baseline, and that hearing loss could be adequately measured using the BROCK scale. According to the study documents, 2 further instruments for the assessment of hearing loss were additionally planned. However, results for these instruments are available neither in the company dossier (including Module 5) nor in the approval documents. According to the study protocol, the use of ASHA criteria was planned to assess hearing loss wherever baseline measurements were available, as this scale determines changes from baseline. Due to the further development of instruments to assess hearing impairment, the statistical analysis plan from 2017 additionally included the use of a newer scale, the International Society of Pediatric Oncology (SIOP) BOSTON scale [29], which can determine hearing loss from 20 dB and is thus a more sensitive instrument. Overall, however, the lack of data is not an argument against the usability of the primary analysis with the BROCK scale. For the benefit assessment, hearing loss is determined using grade ≥ 1 on the BROCK scale.

Dealing with missing values

According to the statistical analysis plan version 1.0 (dated 4 June 2017), the evaluation initially prespecified as the primary analysis for the outcome of hearing loss (BROCK grade ≥ 1) only included patients with evaluable audiometric measurements (modified intention to treat [mITT] population of the company, N = 55 versus N = 46 patients). In addition to the primary analysis, various sensitivity analyses were planned to investigate the effect of missing values. Following feedback from the Food and Drug Administration (FDA) during the marketing authorization process, the primary analysis in the statistical analysis plan version 1.1 (dated 12 July 2017) was prespecified in such a way that the analysis population also included patients for whom no evaluable audiometric measurements were available (intention to treat [ITT] population of the company, N = 57 versus N = 52 patients). The proportion of patients with missing values in relation to the ITT population of the company was n = 2 [3.5%] versus n = 6 [11.5%] patients. The imputation strategy to be used for the primary analysis was not prespecified. In its sensitivity analyses, the company prespecified 2 analyses for the ITT population: the imputation of missing values as hearing loss responders and the imputation as hearing loss non-responders. The company ultimately used the planned hearing loss responder imputation as the primary analysis. In the given data situation, it was assumed that the result for the outcome of hearing loss (BROCK grade ≥ 1) would have been between the 2 analyses (imputation as hearing loss responders and imputation as hearing loss non-responders) if evaluable audiometric measurements had been available for all patients. Both analyses are therefore presented below and used to derive the added benefit.

Failure of the curative treatment approach

For patients with newly diagnosed hepatoblastoma, like those included in the SIOPEL 6 study, complete tumour removal (resection) is generally possible and is the aim of the treatment. As described in Section I 3.1, although sodium thiosulfate prevents cisplatin-induced hearing impairment due to its interaction with cisplatin, it also harbours the risk of a possible reduction in the effectiveness of cisplatin and thus of a tumour-protective effect. In the present treatment situation, failure of the curative treatment approach is a patient-relevant event because, albeit still possible, cure at a later time point is far less likely to be achieved. Failure of the curative treatment approach was therefore considered a patient-relevant outcome in this assessment. In the SIOPEL 6 study, failure of the curative treatment approach was not directly recorded as an outcome. As an approximation, the events that were recorded as part of the secondary outcome of the SIOPEL 6 study, i.e. the composite outcome of event-free survival (EFS), were to be used as an operationalization for the outcome for this assessment.

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

- Progression

- Relapse
- Secondary malignancy
- Death

In this operationalization, the EFS subcomponent of progression does not necessarily reflect the failure of the curative treatment approach. There were 11 versus 11 EFS events in the study. Information regarding the events qualifying for the outcome, and a corresponding breakdown of the subcomponents, are not available. In each of the 2 study arms 5 patients showed progression during preoperative chemotherapy. These patients were recommended to be treated with a combination therapy of cisplatin and doxorubicin and, if the response was sufficient, surgery was followed by postoperative combination therapy. Thus, curative treatment by surgery was still possible after progression. This is also reflected in the fact that all patients received surgery with curative intent (partial hepatectomy: 93.0% versus 92.3%, liver transplantation 7.0% versus 7.7%). The proportion of preoperative progression events in relation to EFS events was 45.5% (5 of 11) in both study arms, although it is unclear whether all progression events were included as qualifying events in the EFS outcome. Overall, therefore, it is uncertain if the EFS outcome reflects failure of the curative treatment approach. Irrespective of this, the study showed no statistically significant differences between the study arms with regard to progression before surgery (5 [8.8%] versus 5 [9.6%] patients, p-value calculated by the Institute, unconditional exact test [convexity, symmetry, z-score (CSZ) method] = 0.921) or recurrences (5 [8.8%] versus 2 [3.8%] patients, p-value = 0.441). Despite the lack of a suitable operationalization for the outcome of failure of the curative approach, detrimental, tumour-protective effects of sodium thiosulfate in the SIOPEL 6 study were generally not expected in the present data situation (also in conjunction with the results for the overall survival outcome, see Table 14).

Outcomes on side effects

SAEs

In the SIOPEL 6 study, an SAE was defined as any AE that

- resulted in death,
- was life-threatening,
- required hospitalization or prolongation of existing inpatients' hospitalization,
- was progression of the disease,
- was an overdosage,
- was a second primary malignancy,
- resulted in persistent or significant disability or incapacity,

- was a congenital anomaly/birth defect, or
- was an unexpected grade 3 or 4 toxicity

Expected grade 3 or 4 toxicities (as a distinction from unexpected toxicities) were not regarded as SAEs. These included the following:

- Transient hypernatraemia in the sodium thiosulfate arm
- Haematological toxicity, nausea, vomiting, anorexia with tube feeding, alopecia, hypomagnesaemia and renal toxicity in both arms

Besides the international protocol, the SIOPEL 6 study had a separate protocol for patients in Great Britain (36% of the total study population [20]) with a slightly different definition of expected AEs that should not be regarded as SAEs.

In summary, no suitable data were available for SAEs due to under and over-reporting and differences in reporting between the study arms in the SIOPEL 6 study. On the one hand, AEs were recorded as SAEs that were potentially not SAEs at all according to the common definition of SAEs (unexpected grade 3 and 4 AEs). On the other hand, expected AEs were defined that should not be documented as SAEs per se, although they could potentially be SAEs according to the common definition of SAEs (e.g. expected toxicities associated with hospitalization, according to the British protocol). In addition, the AE of transient hypernatraemia (grade 3 or 4) was only recorded as an SAE in the comparator arm but not in the intervention arm.

Discontinuation due to AEs

In the SIOPEL 6 study, discontinuations due to AEs were only documented for SAEs. No suitable data were therefore available for the outcome of discontinuation due to AEs. In total, only one discontinuation (due to hypersensitivity [Preferred Term, PT]) was documented in the intervention arm of the SIOPEL 6 study. Furthermore, it is unclear whether discontinuations due to AEs only included discontinuations of sodium thiosulfate and were therefore only documented in the intervention arm.

I 4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin

Study	Study level	Outcomes									
		Overall survival	Failure of the curative treatment approach	Hearing loss (BROCK grade ≥ 1)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Vomiting (PT, AEs)	Nausea (PT, AEs)	Other specific AEs[b]
SIOPEL 6	L	L	–[c]	H[d]	–[e]	–[c]	L	–[c]	H[f]	H[f]	L

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are taken into account (coded according to MedDRA): hypokalaemia (PT, severe AEs), hypophosphataemia (PT, severe AEs).
c. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
d. Potentially relevant difference in the proportion of missing values between the treatment groups (3.5% in the intervention arm vs. 11.5% in the comparator arm).
e. Outcomes in this category were not recorded.
f. Lack of blinding in subjective recording of outcomes.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event

The risk of bias of the results for the outcome of overall survival was rated as low. The risk of bias for the outcome of hearing loss (Brock grade ≥ 1) was rated as high due to a potentially relevant difference in the proportion of missing values between the treatment groups. In the outcome category of side effects, the risk of bias of the results for the outcomes of severe AEs and other specific AEs (hypokalaemia [severe AEs] and hypophosphataemia [severe AEs] was rated as low in each case. The results for the outcomes of vomiting (AEs) and nausea (AEs) had a high risk of bias due to the lack of blinding in subjective outcome recording. No suitable data were available for the outcomes of failure of the curative treatment approach, SAEs and discontinuation due to AEs (see Section I 4.1). Outcomes on health-related quality of life were not recorded.

I 4.3 Results

Table 14 and Table 15 summarize the results of the comparison of sodium thiosulfate + cisplatin versus cisplatin in patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours with an indication for the prevention of ototoxicity induced by cisplatin chemotherapy.

Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier. Kaplan-Meier curves on the presented time-to-event analyses can be

found in I Appendix D of the full dossier assessment. Results on common AEs and severe AEs are presented in I Appendix E of the full dossier assessment.

Table 14: Results (morbidity, time to event) – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin

Study Outcome category Outcome	Sodium thiosulfate + cisplatin N	Sodium thiosulfate + cisplatin Median time to event in months [95% CI] Patients with event n (%)	Cisplatin N	Cisplatin Median time to event in months [95% CI] Patients with event n (%)	Sodium thiosulfate + cisplatin vs. cisplatin HR [95% CI]; p-value[a]
SIOPEL 6					
Mortality					
Overall survival	57	NA 2 (3.5)	52	NA 4 (7.7)	0.44 [0.08; 2.41]; 0.332[b]

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; unstratified.
b. Discrepant data between Module 4 A and the CSR; the p-value from the CSR is shown.

CI: confidence interval; CSR: clinical study report; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial

Table 15: Results (morbidity and side effects, dichotomous) – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin (multipage table)

Study Outcome category Outcome Time point	Sodium thiosulfate + cisplatin N[a]	 Patients with event n (%)	Cisplatin N[a]	 Patients with event n (%)	Sodium thiosulfate + cisplatin vs. cisplatin RR [95% CI]; p-value[b]
SIOPEL 6					
Morbidity					
Hearing loss (BROCK grade ≥ 1)					
Responder imputation[c]	57	20 (35.1)	52	35 (67.3)	0.52 [0.36; 0.76]; < 0.001[d]
Non-responder imputation[e]	57	18 (31.6)	52	29 (55.8)	0.60 [0.39; 0.93]; 0.020
Failure of the curative treatment approach	No suitable data[f]				
Health-related quality of life	Outcomes in this category were not recorded				
Side effects					
AEs (supplementary information)	53	51 (96.2)	56	49 (87.5)	–
SAEs	No suitable data[f]				
Severe AEs[g]	53	35 (66.0)	56	34 (60.7)	1.09 [0.82; 1.45]; 0.564
Discontinuation due to AEs	No suitable data[f]				
Vomiting (PTs, AEs)	53	45 (84.9)	56	30 (53.6)	1.58 [1.21; 2.07]; < 0.001
Nausea (PT, AEs)	53	21 (39.6)	56	17 (30.4)	1.31 [0.78; 2.19]; 0.310
Hypokalaemia (PT, severe AEs[g])	53	5 (9.4)	56	0 (0.0)	–[h]; 0.021[i]
Hypophosphataemia (PT, severe AEs[g])	53	5 (9.4)	56	0 (0.0)	–[h]; 0.021[i]

a. Outcome of hearing loss: number of randomized patients who received at least 1 dose of the study medication; outcomes in the side effects category: number of patients who received at least 1 dose of study medication. The patients were analysed according to the treatment they actually received.
b. Outcome of hearing loss: Cochran-Mantel-Haenszel method, stratified by country groups (categorization unclear), age (< 15 vs. > 15 months) and PRETEXT classification (I and II vs. III); outcomes in the side effects category: CI: Wald method; p-value: Pearson's chi-square test, unstratified.
c. Patients without any hearing data (n = 2 [3.5%] vs. n = 6 [11.5%]) were considered hearing loss responders.
d. Discrepant data between Module 4 A and the CSR; the data from the CSR are shown.
e. Patients without any hearing data (n = 2 [3.5%] vs. n = 6 [11.5%]) were considered hearing loss non-responders.
f. See Section I 4.1 for reasons.
g. Operationalized as CTCAE grade ≥ 3.
h. No presentation of RR and CI, as these are not informative.
i. Institute's calculation, unconditional exact test (CSZ method according to [30]).

Table 15: Results (morbidity and side effects, dichotomous) – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin (multipage table)

Study Outcome category Outcome Time point	Sodium thiosulfate + cisplatin		Cisplatin		Sodium thiosulfate + cisplatin vs. cisplatin
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PRETEXT: Pre-treatment Tumour Extension; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event					

As described in Section I 3.3, based on the results of the SIOPEL 6 study, at most hints, e.g. of an added benefit, can be derived for all outcomes.

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. There is neither a hint of an added benefit nor a hint of lesser benefit of sodium thiosulfate in comparison with watchful waiting; an added benefit or lesser benefit is therefore not proven.

Morbidity

Failure of the curative treatment approach

No suitable data were available for the outcome of failure of the curative treatment approach (see Section I 4.1). There is neither a hint of an added benefit nor a hint of lesser benefit of sodium thiosulfate in comparison with watchful waiting; an added benefit or lesser benefit is therefore not proven.

Hearing loss (BROCK grade ≥ 1)

For the outcome of hearing loss (BROCK grade ≥ 1), assessed using the BROCK scale, both analyses presented (imputation of missing values as hearing loss responders or non-responders) showed a statistically significant difference in favour of sodium thiosulfate + cisplatin compared with cisplatin. There is a hint of an added benefit of sodium thiosulfate in comparison with watchful waiting. Depending on the imputation strategy, the extent of the added benefit differs (imputation of missing values as hearing loss responders: extent considerable; imputation of missing values as hearing loss non-responders: extent minor).

Health-related quality of life

Outcomes on health-related quality of life were not recorded. There is no hint of an added benefit of sodium thiosulfate in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No suitable data were available for the outcomes of SAEs and discontinuation due to AEs (see Section I 4.1). In each case, there is no hint of greater or lesser harm from sodium thiosulfate in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs

No statistically significant difference between treatment groups was found for the outcome of severe AEs. There is no hint of greater or lesser harm from sodium thiosulfate in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Vomiting (AEs)

For the outcome of vomiting (AEs), a statistically significant difference was found to the disadvantage of sodium thiosulfate + cisplatin in comparison with cisplatin. There is a hint of greater harm from sodium thiosulfate in comparison with watchful waiting.

Nausea (AEs)

No statistically significant difference between treatment groups was found for the outcome of nausea (AEs). There is no hint of greater or lesser harm from sodium thiosulfate in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Other specific AEs

Hypokalaemia and hypophosphataemia (both severe AEs)

For each of the outcomes of hypokalaemia and hypophosphataemia (AEs), a statistically significant difference was found to the disadvantage of sodium thiosulfate + cisplatin in comparison with cisplatin. In each case, there is a hint of greater harm from sodium thiosulfate in comparison with watchful waiting.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account in the present benefit assessment:

- Age (< 15 months versus > 15 months)
- Sex (male versus female)

- PRETEXT classification (I and II versus III)

Subgroup analyses were not prespecified in the SIOPEL 6 study. The subgroup characteristics of age and PRETEXT classification were defined a priori as stratification factors, however.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Applying the methods described above, there were no effect modifications for the characteristics considered.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is assessed based on the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for the outcome of hearing loss (BROCK grade ≥ 1)

It cannot be inferred from the dossier whether the outcome of hearing loss (BROCK grade ≥ 1) was serious/severe or non-serious/non-severe. The classification of this outcome/these outcomes is justified below.

The company provided no information on the distribution of patients with hearing loss according to BROCK severity. Table 16 below shows the proportion of patients with the respective severity grades in relation to all patients with hearing loss in the SIOPEL 6 study, taken from the publication by Brock et al [19].

Table 16: Hearing loss by BROCK grade – RCT, direct comparison: sodium thiosulfate + cisplatin vs. cisplatin

BROCK grade	Sodium thiosulfate + cisplatin N[a] = 55	Cisplatin N[a] = 46
SIOPEL 6		
Grade 0 (minimal)	37	17
Grade 1 (mild)	10 (55.6[b])	12 (41.4[b])
Grade 2 (moderate)	6 (33.3[b])	11 (37.9[b])
Grade 3 (marked)	1 (5.6[b])	5 (17.2[b])
Grade 4 (severe)	1 (5.6[b])	1 (3.4[b])
Hearing loss responders (BROCK grade ≥ 1)	18	29

a. Number of randomized patients who received at least 1 dose of the study medication and for whom information on hearing loss is available.
b. Refers to the hearing loss responders (BROCK grade ≥ 1) per treatment group.
N: number of analysed patients; RCT: randomized controlled trial

The company also did not provide any information with regard to which BROCK grade of hearing impairment would signify a severe or serious event of hearing impairment. Children with grade 2 hearing loss (≥ 40 dB at 4000 Hz and above) will likely have difficulty hearing high-frequency consonant speech sounds and understanding speech in noise or over distance, and may require assistive listening devices, particularly during the early language-learning years. Children with grade 3 (≥ 40 dB at 2000 Hz and above) and grade 4 (≥ 40 dB at 1000 Hz and above) hearing loss will require hearing aids for speech development and for communication [9,27]. The proportion of patients with grades 2 to 4 in relation to all patients with hearing loss was calculated in order to estimate whether the outcome should be assigned to the outcome category serious/severe or non-serious/non-severe. This proportion was 44.4% (8 patients) in the intervention arm and 58.6% (17 patients) in the comparator arm.

In the given situation, the outcome of hearing loss was allocated to the outcome category of serious/severe. This is due to the fact that children in a potentially curative treatment situation in the therapeutic indication of hepatoblastoma are very young children who are in the process of speech development, and in whom even irreversible hearing loss of moderate extent is of particular importance for speech development and social participation [28].

Table 17: Extent of added benefit at outcome level: sodium thiosulfate vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Sodium thiosulfate + cisplatin vs. cisplatin** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA HR: 0.44 [0.08; 2.41]; p = 0.332	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Hearing loss (BROCK grade ≥ 1)	Responder imputation: 35.1% vs. 67.3% RR: 0.52 [0.36; 0.76]; p < 0.001 Non-responder imputation: 31.6% vs. 55.8% RR: 0.60 [0.39; 0.93]; p = 0.020 Probability: hint	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ or $0.90 \leq CI_u < 1.00$ Added benefit, extent: non-quantifiable, at most considerable[c]
Failure of the curative treatment approach	No suitable data[d]	Lesser/added benefit not proven
Health-related quality of life		
Outcomes in this category were not recorded		
Side effects		
SAEs	No suitable data[d]	Greater/lesser harm not proven
Severe AEs	66.0% vs. 60.7% RR: 1.09 [0.82; 1.45]; p =0.564	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data[d]	Greater/lesser harm not proven
Vomiting (AEs)	84.9% vs. 53.6% RR: 1.58 [1.21; 2.07]; RR: 0.63 [0.48; 0.83][e] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Greater harm, extent: minor
Nausea (AEs)	39.6% vs. 30.4% RR: 1.31 [0.78; 2.19]; p = 0.310	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: sodium thiosulfate vs. watchful waiting (multipage table)

Outcome category **Outcome**	**Sodium thiosulfate + cisplatin vs. cisplatin** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Hypokalaemia (severe AEs)	9.4% vs. 0% RR: –[f] p = 0.021 Probability: hint	Outcome category: serious/severe side effects Greater harm, extent: minor[g]
Hypophosphataemia (severe AEs)	9.4% vs. 0% RR: –[f] p = 0.021 Probability: hint	Outcome category: serious/severe side effects Greater harm, extent: minor[g]

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Depending on the imputation strategy for missing values, the extent differs: imputation of missing values as hearing loss responders: extent considerable; imputation of missing values as hearing loss non-responders: extent minor.
d. See Section I 4.1 for reasons.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. No presentation of RR and CI, as these are not informative.
g. The result of the statistical test is decisive for the derivation of the added benefit; the smallest possible extent is assumed, i.e. the extent is rated as minor.

AE: adverse event; CI: confidence interval; CI_u: upper confidence limit of the confidence interval; HR: hazard ratio; NA not achieved; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of sodium thiosulfate in comparison with watchful waiting

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
-	-
Outcomes with shortened observation period	
Serious/severe symptoms/late complications ▪ Hearing loss (BROCK grade ≥ 1): hint of an added benefit – extent: non-quantifiable, at most considerable	-
-	Serious/severe side effects ▪ Hypokalaemia (severe AEs), hypophosphataemia (severe AEs): hint of greater harm – extent: minor
-	Non-serious/non-severe side effects ▪ Vomiting (AEs): hint of greater harm – extent: minor
Outcomes in the outcome category of health-related quality of life were not recorded. No suitable data are available for the outcomes of SAEs and discontinuation due to AEs.	
AE: adverse event; SAE: serious adverse event	

Based on the SIOPEL 6 study, this benefit assessment can only draw conclusions on children with localized, non-metastatic hepatoblastoma with a therapeutic indication for the prevention of ototoxicity induced by cisplatin chemotherapy. Patients with localized, non-metastatic hepatoblastoma are characterized by a young patient population in a potentially curative treatment situation. Due in particular to the young age at disease onset and the single dose of cisplatin per cycle, which is not administered over several days, these are patients with a comparatively high risk of cisplatin-induced ototoxicity (see I 3.1 and I 3.3).

No suitable data were available for patients 1 month to < 18 years of age with other localized, non-metastatic, solid tumours with a therapeutic indication for the prevention of ototoxicity induced by cisplatin chemotherapy. The added benefit was therefore derived separately for these 2 patient groups.

Patients with hepatoblastoma

The overall assessment showed one positive and several negative effects of sodium thiosulfate in comparison with watchful waiting. In the outcome category of serious/severe symptoms/late complications, a hint of a non-quantifiable added benefit of at most considerable extent was shown the outcome of hearing loss. In contrast, there were hints of greater harm, in each case of minor extent, in severe and non-severe side effects such as vomiting and severe hypokalaemia and hypophosphataemia. No data were available for the outcome category of health-related quality of life. The negative effects of various specific side

effects, some of which were severe, do not completely call into question the positive effect regarding hearing loss.

In summary, here is a hint of a minor added benefit of sodium thiosulfate in comparison with watchful waiting for children with localized, non-metastatic hepatoblastoma with indication for the prevention of ototoxicity induced by cisplatin chemotherapy.

Patients with other solid tumours

No suitable data were available for patients 1 month to < 18 years of age with other localized, non-metastatic, solid tumours with a therapeutic indication for the prevention of ototoxicity induced by cisplatin chemotherapy. For these patients, there is no hint of an added benefit of sodium thiosulfate in comparison with watchful waiting; an added benefit is therefore not proven.

Table 19 summarizes the result of the assessment of the added benefit of sodium thiosulfate in comparison with the ACT.

Table 19: Sodium thiosulfate – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Patients 1 month to < 18 years of age with localized, non-metastatic, solid tumours with indication for the prevention of ototoxicity induced by cisplatin chemotherapy	Watchful waiting	Patients with hepatoblastoma: hint of minor added benefit
		Patients with other solid tumours: 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 by the company, which derived an indication of considerable added benefit for patients in the entire therapeutic indication based on the SIOPEL 6 and ACCL0431 studies.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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