Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Sodium thiosulphate (prevention of ototoxicity induced by cisplatin chemotherapy, solid tumours, 1 month to < 18 years)

of 17 July 2025

At their session on 17 July 2025, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Sodium thiosulphate as follows:

Sodium thiosulphate

Resolution of: 17 July 2025
Entry into force on: 17 July 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 26 May 2023):

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

Therapeutic indication of the resolution (resolution of 17 July 2025):

See therapeutic indication according to marketing authorisation.

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

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

Appropriate comparator therapy:

- Monitoring wait-and-see approach

Extent and probability of the additional benefit of sodium thiosulphate compared to monitoring wait-and-see approach:

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

Indication of non-quantifiable additional benefit.

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

An additional benefit is not proven.

Study results according to endpoints:[1]

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

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantage in the endpoint of hearing loss (BROCK grade ≥ 1)
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant difference for the benefit assessment for severe AEs. There are no assessable data for SAEs and therapy discontinuation due to AEs. In detail, disadvantages in specific AEs.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

[1] Data from IQWiG's dossier assessment (A25-15)

SIOPEL 6 study:

- Multicentre, randomised, controlled, unblinded phase III study
- Patients with newly diagnosed, histologically confirmed, standard-risk hepatoblastoma
- Sodium thiosulphate + cisplatin **vs** cisplatin[2]

Mortality

Endpoint	**Sodium thiosulphate**		**No administration of sodium thiosulphate[a]**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[b] Absolute difference (AD)[c]
Overall survival					
	57	n.r. 2 (3.5)	52	n.r. 4 (7.7)	0.44 [0.08; 2.41] 0.332[d]

Morbidity

Endpoint	**Sodium thiosulphate**		**No administration of sodium thiosulphate[a]**		Intervention vs control
	N[e]	Patients with event n (%)	N[e]	Patients with event n (%)	Relative risk [95% CI] p value[f]
Hearing loss (BROCK grade ≥ 1)					
Responder imputation[g]	57	20 (35.1)	52	35 (67.3)	0.52 [0.36; 0.76] < 0.001[h]
Non-responder imputation[i]	57	18 (31.6)	52	29 (55.8)	0.60 [0.39; 0.93] 0.020
Failure of the curative therapeutic approach					
	No suitable data				

Health-related quality of life

Endpoints in this category were not collected

[2] In the SIOPEL 6 study, cisplatin is described as part of the study medication. However, with regard to the research question of the benefit assessment, cisplatin is not part of the intervention or control

Side effects

Adverse events in total					
	53	51 (96.2)	56	49 (87.5)	–
Serious adverse events (SAE)					
	No suitable data				
Severe adverse events (CTCAE grade ≥ 3)					
	53	35 (66.0)	56	34 (60.7)	1.09 [0.82; 1.45] 0.564
Therapy discontinuation due to adverse events					
	No suitable data				
Specific adverse events					
Vomiting (PT, AE)	53	45 (84.9)	56	30 (53.6)	1.58 [1.21; 2.07] < 0.001
Nausea (PT, AE)	53	21 (39.6)	56	17 (30.4)	1.31 [0.78; 2.19] 0.310
Hypocalcaemia (PT, severe AE[k])	53	5 (9.4)	56	0 (0.0)	–[L] 0.021
Hypophosphataemia (PT, severe AE[k])	53	5 (9.4)	56	0 (0.0)	–[L] 0.021

[a.] The investigations conducted in the control arm of the SIOPEL 6 study are considered sufficient implementation of the appropriate comparator therapy of the wait-and-see approach.
[b.] HR and CI: Cox proportional hazards model; p value: Log-rank test; unstratified
[c.] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
[d.] Discrepant data between Module 4 A and the study report; the p value from the study report is shown
[e.] Endpoint of hearing loss: Number of randomised patients who received at least 1 dose of the study medication; endpoints in the side effects category: Number of patients who received at least 1 dose of the study medication. The patients were evaluated according to the treatment they actually received.
[f.] Endpoint of hearing loss: Cochran-Mantel-Haenszel method, stratified by country group (categorisation unclear), age (< 15 vs > 15 months) and PRETEXT classification (I and II vs III); endpoints in the side effects category: CI: Method according to Wald; p value: Pearson's Chi² test, unstratified
[g.] Patients without hearing data (n = 2 [3.5%] vs n = 6 [11.5%]) were considered hearing loss responders
[h.] Discrepant data between Module 4 A and the study report; the data from the study report is shown
[i.] Patients without hearing data (n = 2 [3.5%] vs n = 6 [11.5%]) were considered hearing loss non-responders
[k.] Operationalised as CTCAE grade ≥ 3
[L.] No presentation of RR and CI, as not informative

HR: hazard ratio; CI: confidence interval; n: number of patients with event; N: number of patients evaluated; n.r. = not reached; RCT: randomised controlled trial

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; CI = confidence interval; N = number of patients evaluated; n = number of patients with event; n.c. = not calculable; n.r. = not reached; vs = versus; PT = preferred term; RCT = randomised controlled trial; SAE = serious adverse event; AE= adverse event

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

There are no assessable data.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: No data available.
n.a.: not assessable

2. Number of patients or demarcation of patient groups eligible for treatment

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

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

   Approx. 18 to 23 patients

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

   Approx. 20 to 205 patients

3. Requirements for a quality-assured application

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

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

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

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

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

4. Treatment costs

Treatment costs:

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

The costs represented relate to a single cycle of cisplatin chemotherapy.

Designation of the therapy	Treatment costs per chemotherapy cycle/ patient
Medicinal product to be assessed:	
Sodium thiosulphate	€ 12,534.27 - € 37,602.81
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Not calculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 June 2025)

Costs for additionally required SHI services: not applicable

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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

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

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

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

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

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

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

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 17 July 2025.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 17 July 2025

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

Prof. Hecken