SMC2730

sodium thiosulfate solution for infusion (Pedmarqsi®)

Norgine

04 April 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan equivalent medicine process

sodium thiosulfate (Pedmarqsi®) is accepted for use within NHSScotland.

Indication under review: for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to <18 years of age with localised, non-metastatic, solid tumours.

In two randomised, open-label, phase III studies, sodium thiosulfate treatment resulted in statistically significant reductions in hearing loss induced by cisplatin chemotherapy in patients with localised, non-metastatic, solid tumours compared with best supportive care.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Sodium thiosulfate is a water-soluble thiol compound with reducing agent properties, the mechanism of action for the prevention of ototoxicity induced by cisplatin chemotherapy is not completely understood. Sodium thiosulfate may act in several ways to prevent ototoxicity, this includes increasing levels of endogenous antioxidants to prevent damage to cochlear cells caused by oxygen free radicals and blocking the effects of free cisplatin molecules.[1]

The licensed formulation of sodium thiosulfate (Pedmarqsi®) is as an anhydrous salt. The recommended dose of sodium thiosulfate is 6.4 g/m^2 for patients with a body weight <5 kg, 9.6 g/m^2 for patients 5 to 10 kg and 12.8 g/m^2 for patients >10 kg via intravenous infusion. Due to the hypertonic formulation, administration through a central vein is recommended. Sodium thiosulfate is administered 6 hours after the end of cisplatin infusions following disease-specific treatment protocols. The timing of sodium thiosulfate administration relative to cisplatin chemotherapy is critical. Further details are included in the summary of product characteristics (SPC).[1, 2]

1.2. Disease background

Ototoxicity, comprising of hearing loss, tinnitus and vertigo, is a common adverse effect of cisplatin chemotherapy in paediatric patients. The prevalence of any degree of ototoxicity in paediatric patients receiving cisplatin is approximately 60% (range 26% to 90%).[3, 4]

The mechanism of cisplatin induced ototoxicity is unknown; however, it is thought to be linked to the damage of outer hair cells and spiral ganglion cells in the cochlea. Furthermore, cisplatin is thought to be retained in these cells for months to years, thereby increasing the risk of ototoxicity with cumulative doses. Ototoxicity can occur following the first dose of cisplatin, initially affecting high and very high hearing frequencies and progressively worsening, affecting lower hearing frequencies with repeated doses. The severity of hearing loss induced by cisplatin chemotherapy can be measured using grading scales, with differing hearing frequency ranges and criteria for measuring hearing loss severity between scales. There appears to be no single ototoxicity grading scale used in practice.[3, 5, 6]

Risk factors for cisplatin induced ototoxicity include young age (particularly children <5 years due to immaturity of the auditory system), cumulative cisplatin dose (≥400 mg/m^2), impaired renal function, pre-existing hearing loss and possible genetic disposition.[7]

Ototoxicity can have a significant impact on quality of life, particularly in young children during a time in which they are developing speech and language. Socialisation, education, and cognitive development may also be impacted. Additionally, patients who develop ototoxicity are at increased risk of mental health issues, dementia and are twice as likely to be unemployed.[3, 8, 9]

1.3. Treatment pathway and relevant comparators

There are no pharmacological treatments available to prevent ototoxicity induced by cisplatin chemotherapy. If patients develop ototoxicity, cisplatin dose reductions or alternative chemotherapy medicines would be used. These treatment modifications have the potential to

adversely affect disease prognosis. Non-pharmacological treatment options include communication strategies, speech and language therapy and hearing aids.[3]

Sodium thiosulfate is the first medicine to be licensed for the prevention of ototoxicity induced by cisplatin chemotherapy therefore best supportive care is the relevant comparator.

1.4. Category for decision-making process

Eligibility for a PACE meeting

Sodium thiosulfate meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of sodium thiosulfate for the prevention of ototoxicity induced by cisplatin chemotherapy comes from the SIOPEL 6 and the Children's Oncology Group (COG) ACCL0431 studies.[2, 10] Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	SIOPEL 6 [2, 11]	COG ACCL0431 [10, 11]
Study design	A randomised, open-label, multicentre, parallel-group, phase III study.	A randomised, open-label, multicentre, parallel-group, phase III study.

Eligible patients	• Aged >1 month and ≤18 years.
	• Histologically confirmed newly diagnosed hepatoblastoma.
	• Standard-risk hepatoblastoma defined as:
	  • Pre-treatment tumour extension (PRETEXT) I, II or III.
	  • Serum alpha-fetoprotein >100 micrograms/L.
	  • No additional PRETEXT criteria.
		• Aged ≥1 year and ≤18 years
		• Histologically confirmed newly diagnosed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy.
		• Planned cumulative cisplatin dose of ≥200 mg/m^2 with an infusion duration of 6 hours or less.
		• Performance status score ≥50 using Karnofsky scale (>16 years) or Lansky scale (≤16 years).
		• No previous cisplatin or carboplatin treatment.
		• Normal hearing.

Treatments	Cisplatin with sodium thiosulfate or cisplatin without sodium thiosulfate for four pre-operative cycles and two post-operative cycles. All treatment was administered IV. Sodium thiosulfate dosing was: 6.4 g/m^2 <5kg, 9.6 g/m^2 if ≥5 kg and ≤10 kg and 12.8 g/m^2 if >10kg. Sodium thiosulfate was administered 6 hours after the end of each cisplatin infusion. Concomitant supportive medicines such as	Cisplatin with sodium thiosulfate or cisplatin without sodium thiosulfate for up to six cycles. All treatment was administered IV. Sodium thiosulfate dosing was: 10.2 g/m^2 or 341 mg/kg if the disease-specific protocol prescribed cisplatin on a mg per kg basis. Sodium thiosulfate was administered 6 hours after the end of each cisplatin infusion. Concomitant medicines such

	antiemetics, hydration infusions and oral magnesium supplements were allowed. Cisplatin dosing was: 1.8 mg/kg if <5 kg, 2.7 mg/kg if ≥5 kg and ≤10 kg and 80 mg/m^2 if >10 kg.	as antibiotics, antiemetics, fluids and electrolytes were allowed. Cisplatin dosing was in accordance with disease-specific treatment protocols.
Randomisation	Patients were randomised equally to cisplatin with sodium thiosulfate or cisplatin without sodium thiosulfate with stratification according to median age at randomisation (≤15 months versus >15 months), tumour extent (PRETEXT I and II versus III) and country.	Patients were randomised equally to cisplatin with sodium thiosulfate or cisplatin without sodium thiosulfate with stratification according to prior cranial irradiation (yes versus no). For patients with no prior cranial irradiation, randomisation was further stratified according to age (<5 years versus ≥5 years) and duration of cisplatin infusion (<2 hours versus ≥2 hours).
Primary outcome	Proportion of patients with Brock Grade ≥1 hearing loss as measured by pure-tone audiometry (using the better ear), after the end of study treatment or at a minimum age of 3.5 years (whichever was later). The Brock Grade ranges from 0 to 4, with higher grades indicating more severe hearing loss. Centrally reviewed by blinded reviewers.	The proportional incidence of hearing loss according to ASHA criteria between the cisplatin with sodium thiosulfate group compared with cisplatin without sodium thiosulfate at 4 weeks post final cisplatin dose relative to baseline measurements. Hearing loss was defined by ASHA criteria as ≥20 dB decrease from baseline pure tone audiometry threshold at one frequency, ≥10 dB decrease at two adjacent test frequencies or loss of response at three consecutive test frequencies where results were previously obtained.
Key secondary outcomes	• Overall survival	• Overall survival • Mean change in hearing thresholds for key hearing frequencies
Statistical analysis	Efficacy analyses were performed in the ITT population, which included all patients who underwent randomisation excluding those in which informed consent was withdrawn prior to the start of the study and patients who were subsequently diagnosed with high-risk hepatoblastoma, regardless of whether they had received sodium thiosulfate or not. Safety analyses were performed in all patients who underwent randomisation and received at least one dose of study treatment. A hierarchical statistical testing strategy was not applied in the study with no formal testing of outcomes other than the primary outcome. Therefore, the results reported for these outcomes are descriptive only and not inferential (no p-values reported).	Efficacy analyses were performed in the efficacy population, which included all patients who underwent randomisation, excluding patients who did not receive hearing assessments at baseline and/or 4-weeks post-final cisplatin dose. Safety analyses were performed in all patients who underwent randomisation and received at least one dose of study treatment. A hierarchical statistical testing strategy was not applied in the study with no formal testing of outcomes other than the primary outcome. Therefore, the results reported for these outcomes are descriptive only and not inferential (no p-values reported).

ASHA = American Speech-Language-Hearing Association; dB = decibel; ITT = intention to treat; IV = intravenously; mITT = modified intention to treat; PRETEXT = pre-treatment tumour extension

In the ITT population of the SIOPEL 6 study, there was a statistically significant reduction in hearing loss using the Brock Grade in the cisplatin with sodium thiosulfate compared with cisplatin without sodium thiosulfate.[2, 11] Details of results of the SIOPEL 6 study are presented in Table 2.2.

Table 2.2: Results for the primary and secondary outcomes in the SIOPEL 6 study [2, 11]

	Cisplatin with sodium thiosulfate	Cisplatin without sodium thiosulfate
Primary outcome: proportion of patients with Brock Grade ≥ 1 hearing loss after the end of study treatment or at a minimum age of 3.5 years (whichever was later)		
ITT population, n	57	52
Yes, n (%)	20 (35)	35 (67)
No, n (%)	37 (65)	17 (33)
Relative risk (95% CI) [a]	0.52 (0.35 to 0.78), p<0.001	
Secondary outcome: Overall survival (median 4.3-year follow-up) [b]		
PP population, n	53	52
Number of patients who died, n (%)	2 (3.8)	4 (7.7)
Hazard ratio (95% CI)	0.48 (0.09 to 2.61) [c]	

CI = confidence interval; ITT = intention to treat; PP = per protocol
[a] P-value and relative risk from Chi-square test.
[b] Overall survival (OS) was calculated from the time of randomisation to death. OS of alive patients was censored at the time of last known follow-up visit. Median estimate could not be calculated as fewer than 50% of patients in either group died. Kaplan Meier estimates not reported.
[c] Descriptive results only, therefore no p-value reported.

In a post-hoc analysis of patients who experienced hearing loss in the SIOPEL 6 study, the severity of hearing loss was lower in the cisplatin with sodium thiosulfate group compared with cisplatin without sodium thiosulfate group.[2]

In the efficacy population of COG ACCL0431, the incidence of hearing loss according to ASHA criteria was significantly reduced in the cisplatin with sodium thiosulfate group compared with the cisplatin without sodium thiosulfate group.[10, 11] Primary and secondary outcome results have been summarised in Table 2.3.

Table 2.3: Results for the primary and secondary outcomes in the COG ACCL0431 study [10, 11]

	Cisplatin with sodium thiosulfate	Cisplatin without sodium thiosulfate
Primary outcome: proportional incidence of hearing loss according to ASHA criteria at 4-weeks post-final cisplatin dose relative to baseline measurements		
Efficacy population, n	49	55
Yes, n (%)	14 (29)	31 (56)
No, n (%)	35 (71)	24 (44)
Odds ratio (95% CI) [a]	0.27 (0.11 to 0.66), p=0.004	
Secondary outcome: Overall survival (median 5.3-year follow-up) [b]		
ITT population, n	61	64
Number of patients who died, n (%)	18 (30)	12 (19)
Hazard ratio (95% CI)	1.79 (0.86 to 3.72) [c]	

ASHA = American Speech-Language-Hearing Association; CI = confidence interval; ITT = intention to treat
[a] Based on logistic regression including treatment and stratification variables as covariates in the model.

[b] Overall survival (OS) was calculated from the time of randomisation to death. OS of alive patients was censored at the time of the last known follow-up visit. Median estimate could not be calculated as fewer than 50% of patients in either group died. Kaplan Meier estimates not reported.
[c] Descriptive results only, therefore no p-value reported.

Results of the secondary outcome, mean change in hearing thresholds for key frequencies from baseline to 4 weeks post final cisplatin dose, indicated that there were similar changes in hearing thresholds between the cisplatin with sodium thiosulfate group and the cisplatin without sodium thiosulfate group at frequencies ≤2000 Hz. There was a difference at higher frequencies ≥4000 Hz, with less hearing loss in the cisplatin with sodium thiosulfate group compared with the cisplatin without sodium thiosulfate group.[10]

A pre-planned analysis of the primary outcome was performed in subgroups of patients aged <5 years (n=29) and ≥5 years (n=75) subgroups. This analysis is relevant due to the higher risk of ototoxicity in younger patients. The descriptive results of this analysis indicated that the magnitude of benefit of sodium thiosulfate in the prevention of ototoxicity was greater in the <5 years old group compared with the ≥5 years group, hearing loss was reported in 21% and 31% of patients that received cisplatin with sodium thiosulphate in each subgroup respectively.[10, 11]

Due to the higher incidence of deaths in the COG ACCL0431 cisplatin with sodium thiosulfate group, the regulator requested a post-hoc analysis to explore the effect of sodium thiosulfate on the extent of disease. In the post-hoc analysis of patients with localised disease (relevant to the licensed indication) at a median of 5.6 years follow-up, the descriptive results indicated similar overall survival between the cisplatin with sodium thiosulfate group and the cisplatin without sodium thiosulfate group (hazard ratio 1.23 [95% CI: 0.41 to 3.66]).[11]

2.2. Supportive studies

A secondary analysis of the results of COG ACCL0431 was performed using the more recent International Society of Paediatric Oncology (SIOP) Ototoxicity Scale. This scale was developed by a consensus group of clinical experts to provide standardisation in the assessment of ototoxicity between studies and supersedes the Brock Grade and ASHA criteria. To align with the primary outcome of COG ACCL0431, the primary outcome of the secondary analysis was hearing loss at the end of cisplatin treatment and prior to autologous bone marrow transplantation. At the end of cisplatin treatment, there was a lower incidence of SIOP grade ≥2 cisplatin induced hearing loss in the cisplatin with sodium thiosulfate arm (4% [2/58]) compared with the cisplatin without sodium thiosulfate arm (27% [17/63]), the odds ratio was 0.10 (95% CI 0.02 to 0.50). The results from the secondary analysis were consistent with the primary analysis of data from COG ACCL0431 and favoured cisplatin with sodium thiosulfate compared with cisplatin without sodium thiosulfate.[12]

A pooled analysis of the SIOPEL 6 and COG ACCL0431 data was also performed as requested by the regulator due to the small sample sizes of both studies. In the target population including patients with localised disease only, there were no differences between treatment groups for overall survival (hazard ratio 0.86, 95% CI 0.34 to 2.13). The regulator considered there to be no detrimental effect of sodium thiosulfate on overall survival.[11]

3. Summary of Safety Evidence

The safety profile of sodium thiosulfate was similar in the SIOPEL 6 and COG ACCL0431 studies. Regulators concluded that the safety profile of sodium thiosulfate and cisplatin appears acceptable in the intended population.

At the end of the treatment period of the SIOPEL 6 study, the median number of treatment cycles in both groups of the safety population (n=109) was six cycles. Patients reporting a grade 3 or higher adverse event (AE) were 66% versus 61%, patients with a reported serious AE were 40% versus 34%, and patients discontinuing therapy due to an AE was 1.9% versus zero patients in the cisplatin with sodium thiosulfate and cisplatin without sodium thiosulfate groups respectively.[11]

The most frequently reported grade ≥3 AEs were similar across both groups and included infection (26% versus 27%), neutrophil count decreased (23% versus 16%), haemoglobin decreased (19% versus 16%) and febrile neutropenia (15% versus 16%).[11]

At the end of the COG ACCL0431 study at data cut-off 28 February 2018, the mean number of treatment cycles was 3.1 in the cisplatin with sodium thiosulfate group and 3.8 in the cisplatin without sodium thiosulfate group, in the safety population (n=123). .[11]

The most frequently reported grade ≥3 AEs were similar across both groups and included neutrophil count decreased (83% versus 80%), white blood cell count decreased (64% versus 66%), platelet count decreased (64% versus 61%) and anaemia (51% versus 56%). More grade ≥3 AEs related to electrolyte disturbances were observed in the cisplatin with sodium thiosulfate group. These were: hypokalaemia (27% versus 20%), hypophosphataemia (20% versus 11%) and hyponatraemia (12% versus 6.2%).[11]

In both studies SIOPEL 6 and COG ACCL0431 electrolyte imbalances were more commonly observed in the cisplatin with sodium thiosulphate group. See the SPC for further safety information including advice on the management of other specific adverse events including hypersensitivity reactions, nausea and vomiting and renal impairment.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the SIOPEL 6 and COG ACCL0431 studies, the addition of sodium thiosulfate treatment following cisplatin chemotherapy resulted in a statistically significant and clinically meaningful reduction in the proportion of patients with cisplatin induced hearing loss. Additionally, secondary and pooled analyses of the SIOPEL 6 and COG ACCL0431 studies provided further reassurance of the clinical effectiveness of sodium thiosulfate.[2, 10, 11]
- In a post-hoc analysis in patients who experienced hearing loss, the severity of hearing loss was lower in the cisplatin with sodium thiosulfate group compared with the cisplatin without sodium thiosulfate group.[2]

4.2. Key uncertainties

- There were some differences in the COG ACCL0431 study compared with the licensed indication: patients with metastatic disease were included (38% of the study population), children <1 year old were excluded, and a different dose (10.2 g/m^2) was given. SIOPEL 6 included children with newly diagnosed hepatoblastoma only. These limitations may affect the generalisability of the study results. [2, 10]
- Due to the small sample size for both studies and immature survival data some uncertainty remains around whether sodium thiosulfate could decrease cisplatin efficacy. Due to the requirement of accurate timing of sodium thiosulfate administration, there is a risk of loss of efficacy of cisplatin or sodium thiosulfate in the event of medication errors. This will be monitored post-marketing authorisation.
- Both studies were open-label in design therefore there was a risk of bias in the assessment of subjective efficacy and safety outcomes, this risk was partly reduced by independent assessment of hearing tests. There was no adjustment for multiplicity, therefore secondary outcomes are descriptive only. Post-hoc and pooled analyses were performed as requested by the regulator, therefore these were not pre-planned and results are also considered descriptive.
- COG ACCL0431 was not powered to detect differences between subgroups and some groups contained limited patients, therefore results of subgroup analyses should be interpreted with caution. There is a lack of long-term data on safety outcomes including long-term effects on hearing. This will be collected post-marketing authorisation.[11]
- Health-related quality of life outcomes were not assessed as part of the SIOPEL 6 and COG ACCL0431 studies.

4.3. Clinical expert input

Clinical experts consulted by SMC consider sodium thiosulfate to be a therapeutic advancement and that it fulfils an unmet need for this indication, as it represents the only licensed treatment option for the prevention of ototoxicity induced by cisplatin chemotherapy.

4.4. Service implications

No significant service implications are expected.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of sodium thiosulfate (Pedmarqsi), as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Ototoxicity, comprising of hearing loss, tinnitus and vertigo, is a common adverse effect of cisplatin chemotherapy. Approximately 50% of children who receive cisplatin develop permanent hearing loss and this can have a lifelong negative impact on quality of life. Babies

and young children are at a particular risk of hearing loss and this can significantly impact cognitive development and reaching developmental milestones. Hearing loss can have a significant impact on children's speech and language development, educational achievements and socialisation. Furthermore, as children with hearing loss get older they are more likely to experience poor mental health, low self-esteem, social isolation, unemployment and may lack independence. PACE participants note that without support, people with hearing loss are more likely to experience health inequalities, have multiple health conditions and have overall worse health than those without hearing loss. Families and carers of children with hearing loss can have a high burden of care with poor emotional, mental and social wellbeing. Hearing loss can develop suddenly while families and carers are also coping with the challenges of a cancer diagnosis, this can place additional emotional and mental strain on families and carers.

- PACE participants considered that there is a high unmet need for a preventative treatment for hearing loss induced by cisplatin chemotherapy as there are no treatments currently available in Scotland for this indication. PACE participants note that if hearing loss occurs, current guidelines recommend switching to an alternative chemotherapy, carboplatin. However, carboplatin is less effective for certain cancer types. Once hearing loss has occurred, there are no treatments to reverse hearing loss and the pathway of care includes management of the symptoms of hearing loss. These treatments include hearing aids with or without cochlear implants, with some children also using alternative communication methods such as British Sign Language and assistive hearing technologies. These treatments are beneficial however, they do not restore hearing function and have limitations including the associated stigma of wearing a hearing aid, discomfort, lack of perceived benefit, need for ongoing maintenance and limited efficacy in environments with high levels of background sound. Children with hearing loss also require support and access to additional services such as audiologists, speech and language therapists and specialist teachers. This places a financial burden on families, healthcare and educational services.

- PACE participants considered that sodium thiosulfate is beneficial at reducing the incidence of hearing loss caused by cisplatin chemotherapy. Participants noted that sodium thiosulfate will be given as part of cisplatin treatment protocols and sodium thiosulfate has not been shown to negatively impact cancer progression or survival for patients. Sodium thiosulfate has the potential to significantly improve patients' quality of life by reducing the incidence of hearing loss and protecting against the detrimental effects of hearing loss.

- PACE participants noted that the correct timing of sodium thiosulfate administration is critical to minimise the risk of loss of efficacy of cisplatin or sodium thiosulfate and development of local protocols should be prepared to ensure the safe administration of sodium thiosulfate. Children should have a hearing assessment prior to commencing cisplatin treatment, regularly throughout treatment and after treatment is completed. PACE participants agreed that the medicine should be used in line with the licensed indication.

Additional Patient and Carer Involvement

We received a joint patient group submission from the Royal National Institute for Deaf People (RNID) and the National Deaf Children's Society (NDCS), both organisations are registered charities. RNID has not received any pharmaceutical company funding in the past two years. NDCS has also not received any pharmaceutical company funding in the past two years. A representative from the RNID participated in the PACE meeting. The key points of the joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary of the economic analysis provided by the submitting company is outlined in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime time horizon.
Population	Sodium thiosulfate is indicated for the prevention of ototoxicity caused by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.
Comparators	Cisplatin without sodium thiosulfate.
Model description	The submitting company presented a de novo decision tree and Markov model with six health states: Minimal/no hearing loss (HL), Mild HL, Moderate HL, Marked HL, Severe HL and Death. In the first year a cohort-based decision tree applied where patients entered in the Minimal/no HL health state and moved into a hearing loss state or remained in the Minimal/no HL health state by the end of year one. From year two onwards, patients entered the Markov model in whatever health state they were assigned to in the decision tree model. In the Markov model, patients could not transition between hearing loss health states and were only at risk of moving to the Dead state. The model had a cycle length of one year with a half-cycle correction applied.
Clinical data	Clinical efficacy data in the model were from COG ACCL0431.[10] The ratios of patients assigned to different hearing loss severities were taken from Orgel et al. (2023) and Knight et al. (2005).[4, 12]
Extrapolation	In the first five years the overall survival data from COG ACCL0431 were used to calculate the mortality risk in the model. Beyond that, an age-dependent post-cancer standardised mortality ratio (SMR) was applied based on data from Fidler et al. (2016).[13]
Quality of life	Utility values for hearing loss states were taken from Pogany et al. (2006) and Barton et al. (2006).[14-16] In the base case, health state utility values ranged from 0.92 for Minimal/no HL to 0.49 for Severe HL. Cancer-related disutilities were applied based on Chen et al. (2022).[17] A utility gain for cochlear implants was applied to the percentage of patients receiving cochlear implants in each health state of the model.
Costs and resource use	Medicine costs included were acquisition costs, administration costs and adverse event costs. Other NHS costs included were hearing assessments, hearing loss management, speech and language therapy and depression and anxiety costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. SMC would wish to present the with-PAS cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

6.2. Results

Use of sodium thiosulfate was estimated as leading to an average gain of 1.37 quality adjusted life years (QALYs). This heath improvement was generated through a greater number of patients remaining in the minimal/no HL health state in the sodium thiosulfate treatment arm. Sodium thiosulfate was also associated with a higher incremental cost, although the submitting company considered that value as commercial in confidence (CiC) and so it cannot be presented. Similarly, the incremental cost effectiveness ratio (ICER) is also considered CiC.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Table 6.3 below.

Table 6.3 Scenario Analysis Results (PAS prices)

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			CiC	1.37	CiC
1	Perspective	NHS and social services (SMC guidance)	Societal	CiC	1.37	CiC
2			SMC guidance with education costs (including FM system costs) included	CiC	1.37	CiC
3	Clinical efficacy source	COG ACCL0431 mITT	SIOPEL 6 mITT	CiC	1.89	CiC
4			Orgel et al. (2023) re-analysis of COG ACCL0431	CiC	1.26	CiC
5	Source for HL severity	Orgel et al. (2023) combined with Knight et al. (2005)	Orgel et al. (2023) combined with SIOPEL 6	CiC	1.37	CiC
6			SIOPEL 6	CiC	1.18	CiC
7	Source for utilities	Barton et al. (2006)	Gumbie et al. (2022)[18]	CiC	1.11	CiC
8	Adjustment of utility values at adulthood	None	+5% to all utility values except 'Minimal/no HL'	CiC	1.26	CiC
9	Antiemetics	Cost of additional antiemetics included	Cost of additional antiemetics not included	CiC	1.37	CiC
10	Exacerbated hearing loss for a proportion of patients with hearing loss	Exacerbated hearing loss not modelled	Exacerbated hearing loss modelled	CiC	1.39	CiC
11	Cure assumption	No cure assumption applied	Cure assumption applied at year 20 of the model. At which point, mortality probabilities for both treatment arms	CiC	1.45	CiC

			revert to that of the general population.			

AE = adverse event; CiC = commercial in confidence; FM = frequency modulation; HL = hearing loss; ICER = incremental cost-effectiveness ratio; mITT = modified intent-to-treat; QALY = quality-adjusted life year

6.4. Key strengths

- Based on results from the scenario analyses, applying the SIOPEL 6 study as the clinical efficacy source in the model would significantly reduce the ICER (see Scenario 3, Table 6.3). The submitting company therefore applied the most conservative efficacy source in their base case.
- The submitting company applied an age-dependent post-cancer standardised mortality ratio to the general population mortality to account for the increased mortality risk of patients experiencing cancer in childhood. This was appropriate.
- Both COG ACCL0431 and SIOPEL 6 reached their primary objectives where sodium thiosulfate treatment resulted in a significant reduction in the proportion of patients with hearing loss induced by cisplatin chemotherapy.
- The model type was appropriate and used the appropriate comparator.

6.5. Key uncertainties

- There is uncertainty as to the most appropriate source for quality-of-life inputs in the model. The submitting company selected Barton et al. (2006). Gumbie et al. (2022) was also a possible source and may be preferred due to the age range of the population included and time horizon. Applying the Gumbie et al. utility values increased the ICER by 24% (Scenario 7).
- The submitting company applied paediatric utility values over a lifetime time horizon, including after patients entered adulthood. The submitting company explained that hearing loss acquired during childhood would be severely detrimental to the speech and language development, literacy ability, and a person's educational attainment. However, the age range for the licensed indication span many different stages of childhood and may have varying implications with regard to these detriments depending on when the hearing loss occurs. To explore this further the company provided an additional scenario where the utility values in all states apart from Minimal/no HL were increased by 5% when the patient reaches the age of 18 (Scenario 8). While this had a modest upward impact on the ICER, the values of utilities across the time horizon of the model were still seen as an area of uncertainty.
- There is uncertainty in how well COG ACCL0431 or SIOPEL 6 align with the Scottish setting as neither study population is fully generalisable to the Scottish one.

7. Conclusion

The Committee considered the benefits of sodium thiosulfate in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as

sodium thiosulfate is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted sodium thiosulfate for use in NHSScotland.

8. Guidelines and Protocols

The American Academy of Audiology guideline 'American Academy of Audiology Position Statement and Clinical Practice Guidelines: Ototoxicity Monitoring' was published in October 2009.[19]

The consensus statement 'Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline' was published in December 2019. The guideline was developed by an international, multidisciplinary panel of clinical and patient experts and included clinical experts from three UK paediatric oncology hospital sites (no Scottish sites).[20]

The International Society of Paediatric Oncology Supportive Care consensus report 'Recommendations for age-appropriate testing, timing and frequency of audiologic monitoring during childhood cancer treatment' was published in August 2021.[21]

9. Additional Information

9.1. Product availability date

25 January 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per dose (£)
sodium thiosulfate	**Weight** / **Dose** **<5 kg** / **6.4 g/m²** **5 to 10 kg** / **9.6 g/m²** **> 10kg** / **12.8 g/m²** **by intravenous infusion 6 hours after cisplatin following the disease-specific treatment protocol**	**8,278 to 24,834**

Costs from Dictionary of Medicines and Devices Browser on 25 March 2025. Costs calculated based on a body weight ranging from 4 kg to 70 kg and body surface area ranging from 0.26 m^2 to 1.8 m^2. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 24 patients eligible for treatment with sodium thiosulfate each year. The number of eligible patients has been estimated largely based on the Children, Teenagers, and Young Adults (CTYA) data and focused on solid tumour cancers most commonly treated with cisplatin.

Experts consulted by SMC suggested that the number of eligible patients in Scotland may be higher than estimated by the submitting company.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 February 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.