NCPE Assessment

Technical Summary

Sodium thiosulfate (anhydrous);

(Pedmarqsi®)

HTA ID 25002

05 January 2026

Applicant: Norgine Pharmaceuticals Ltd

Sodium thiosulfate (anhydrous) for the prevention of ototoxicity caused by cisplatin chemotherapy in patients 1 month to less than 18 years of age with localised, non-metastatic, solid tumours

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of anhydrous sodium thiosulfate (Pedmarqsi®; herein referred to as sodium thiosulfate).

Following assessment of the Applicant's submission, the NCPE recommends that sodium thiosulfate (Pedmarqsi®) not be considered for reimbursement unless cost-effectiveness can be improved.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Norgine Pharmaceuticals Ltd) Health Technology Assessment of sodium thiosulfate (Pedmarqsi®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In June 2025, Norgine Pharmaceuticals Ltd submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of sodium thiosulfate anhydrous (Pedmarqsi®) for the prevention of ototoxicity caused by cisplatin chemotherapy in patients aged 1 month to less than 18 years with localised, non-metastatic, solid tumours. Of note, the sodium thiosulfate anhydrous formulation relevant to this assessment is a novel formulation of sodium thiosulfate, licensed for the preventive treatment of cisplatin-induced ototoxicity. While sodium thiosulfate is not a new drug, this formulation differs from other available sodium thiosulfate preparations. Norgine Pharmaceuticals Ltd is seeking hospital pricing approval for sodium thiosulfate anhydrous.

The recommended dose of sodium thiosulfate anhydrous, herein referred to sodium thiosulfate, for the prevention of cisplatin-induced ototoxicity is weight based and normalised to body surface area. Sodium thiosulfate should be administered as a 15-minute intravenous infusion, six hours after the completion of each cisplatin administration. The duration of sodium thiosulfate treatment course is dependent on the duration of the administered cisplatin regimen. The mechanism by which sodium thiosulfate reduces ototoxicity is not fully understood, but may include increasing levels of endogenous antioxidants, inhibition of intracellular oxidative stress, and direct interaction between cisplatin and the thiol group in sodium thiosulfate to produce inactive platinum species.

The current management involves audiologic, non-pharmacological interventions. These include the use of frequency modulation systems, hearing aids, and cochlear implants. However, these interventions are not considered as preventive treatments but rather applicable to patients once hearing loss has occurred. Thus, no active comparator (herein referred to as no sodium thiosulfate) was considered for sodium thiosulfate.

1. Comparative effectiveness of sodium thiosulfate

The clinical trial programme supporting the regulatory approval of sodium thiosulfate for the indication under assessment was composed of the COG ACCL0431 and SIOPEL 6 studies. Both were phase III, multi-centre, open label randomised controlled trials. These trials evaluated the efficacy of sodium thiosulfate when administered following cisplatin

treatment versus no administration of sodium thiosulfate following cisplatin treatment.

The COG ACCL0431 trial investigated the efficacy and safety of sodium thiosulfate in participants aged 1 year to less than 18 years with a germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, and other solid malignancies. The primary endpoint was the proportional incidence of hearing loss between the sodium thiosulfate arm (n=61) and the no sodium thiosulfate arm (n=64). Hearing loss was defined by comparing hearing sensitivity at the follow-up period (four weeks following the last dose of cisplatin) relative to baseline measurements using American Speech-Language-Hearing Association (ASHA) criteria. Event-free survival (EFS) and overall survival (OS) were evaluated as secondary endpoints. The Review Group noted that the COG ACCL0431 trial included a heterogeneous population with localised and metastatic, solid tumours, which is broader than the licensed population of patients with localised, non-metastatic, solid tumours. Within the licensed population in this trial, there were 39 participants in the sodium thiosulfate arm and 38 participants in the no sodium thiosulfate arm.

The SIOPEL 6 trial investigated the efficacy and safety of sodium thiosulfate in reducing ototoxicity in participants, aged 1 month to less than 18 years, receiving cisplatin chemotherapy for standard-risk hepatoblastoma (n=57 in the sodium thiosulfate arm and n=52 in the no sodium thiosulfate arm). The primary endpoint was the proportion of patients with Brock Grade ≥ 1 hearing loss, measured by pure tone audiometry, after end of study treatment or at an age of at least 3.5 years, whichever was later. EFS and OS were secondary endpoints. The Review Group noted that the SIOPEL 6 trial included a homogenous population with standard-risk hepatoblastoma, which is not representative of the patient population with localised, non-metastatic, solid tumours in Ireland.

At final analysis, the results of the COG ACCL0431 trial showed that the risk of hearing loss development was statistically significantly lower in the sodium thiosulfate arm versus the no sodium thiosulfate arm (28.6% versus 56.4%; relative risk 0.52; 95% CI 0.32 to 0.84, p =0.004). The SIOPEL 6 trial demonstrated that the risk of hearing loss (Brock Grade ≥ 1) was statistically significantly lower in participants receiving sodium thiosulfate compared with those who did not receive sodium thiosulfate (35.1% versus 67.3%; relative risk 0.52, 95% CI 0.35 to 0.78, p<0.001). In both the COG ACCL0431 and SIOPEL 6 trials, at median follow-up of

5.33 and 4.27 years, respectively, there were no statistically significant differences in EFS and OS between the two treatment arms.

The Review Group considered the small size, open-label study design, and variation in patient populations included in the COG ACCL0431 and SIOPEL 6 trials to be a major limitation. The COG ACCL0431 trial included a small patient population with both localised and metastatic tumours and was underpowered to assess the efficacy of sodium thiosulfate in patients with localised, non-metastatic, solid tumours (i.e., the licensed population). Additionally, the Review Group had concerns regarding the use of the ASHA criteria to assess the primary endpoint, as they are not widely used in Irish clinical practice and have been reported to be unreliable in young children. The Review Group considered these factors to be a major limitation in interpreting the clinical efficacy of sodium thiosulfate. Furthermore, both the COG ACCL0431 and SIOPEL 6 trials differed considerably in study designs, patient populations, and primary outcomes. Thus, a pooled analysis of patients with localised, non-metastatic, solid tumours across the two trials would introduce considerable uncertainty and bias into the efficacy estimates.

2. Safety of sodium thiosulfate

Safety analyses of the COG ACCL0431 trial showed that 91.1% of participants in this trial experienced at least one grade ≥ 3 adverse event (AE), with 93.2% participants in the sodium thiosulfate arm and 89.1% participants in the no sodium thiosulfate arm. Serious AEs (SAEs) were only reported for the sodium thiosulfate arm, where 35.6% of participants experienced at least one SAE. The most common SAEs were febrile neutropenia (20.3%), decreased neutrophil count (16.9%), decreased platelet count (13.6%), decreased white blood cell count (13.6%), and anaemia (11.9%).

The clinical safety results of the SIOPEL 6 trial showed that 91.7% of participants experienced at least one AE, with 96.2% participants in the sodium thiosulfate arm and 87.5% participants in the no sodium thiosulfate arm. In the sodium thiosulfate arm, 66% of participants reported grade ≥ 3 AEs compared to 60.7% in the no sodium thiosulfate arm. The proportion of participants that experienced a SAE was 39.6% and 33.9% in the sodium thiosulfate and no sodium thiosulfate arms, respectively.

Overall, according to the SmPC, the most commonly reported AEs with a frequency of at least one case per 10 patients are vomiting (44%), nausea (23%), hypokalaemia (21%), hypernatremia (19%), hypophosphatemia (18%), and hypersensitivity (11%). As per the EPAR, the submitted clinical data did not identify any new safety issues associated with the use of sodium thiosulfate in the claimed indication.

3. Cost effectiveness of sodium thiosulfate

Methods

The cost-effectiveness model (CEM) submitted by the Applicant was a combination of a decision tree model in year one and a health state-transition (Markov) model from year two onwards. In year one, patients could transition to one of five health states; minimal/no, mild, moderate, marked, and severe hearing loss. The decision tree model assumed that ototoxic effects from cisplatin chemotherapy occur and are diagnosed within the first year of initiating treatment. In year two, patients entered the Markov model from the health state that they were in at the end of year one. Here, patients could not transition between the hearing loss health states and could only transition to the death state.

Treatment effects were captured in the CEM by two separate factors: the probability of acquiring hearing loss and, for patients with acquired hearing loss, the probability of progressing to one of the four hearing loss severity levels (mild, moderate, marked, severe hearing loss). These probabilities were informed by the primary outcome in the efficacy population of the COG ACCL0431 trial combined with external data from Orgel et al. and Knight et al. The Review Group noted that the efficacy population of the COG ACCL0431 trial included patients with localised and metastatic, solid tumours, which is broader than the licensed population of patients with localised, non-metastatic, solid tumours. As the COG ACCL0431 trial was underpowered for subgroup analyses, efficacy data derived from the subgroup of patients with localised, non-metastatic, solid tumours are associated with uncertainty. Additionally, the Review Group had concerns regarding the combination of studies which used different hearing loss scales in different populations. Scenario analyses, using efficacy data derived from alternative sources, were not considered robust by the Review Group. The lack of robust efficacy data specific to the population under assessment is considered a major limitation.

Health-related quality of life data were not collected in the COG ACCL0431 or SIOPEL 6 trials. Published literature by Barton et al., Pogany et al., and Chen et al. were identified from a systematic literature review and considered, by the Applicant, to be the most appropriate sources to inform utility values of hearing loss health states. However, these studies did not report utility data specific to the patient population with localised, non-metastatic, solid tumours who developed hearing loss due to cisplatin-induced ototoxicity. The Review Group considered the lack of utility data specifically pertaining to the patient population, and hearing loss health states, under assessment to be a limitation. Due to the lack of data, the Applicant made several assumptions, which the Review Group considered to be highly uncertain. Thus, the Review Group had concerns regarding the generalisability of the data used to the patient population under assessment.

The CEM also included costs related to drug acquisition, antiemetic premedication, and intravenous administration. Other healthcare resources were aggregated as health state-specific costs and included costs of hearing assessment, hearing aids, cochlear implants, speech and language therapy, and depression treatment. The Review Group highlight that almost all of the inputs and assumptions used to estimate these costs were derived from sources outside of Ireland.

Results

The result of the Applicant base case deterministic cost-effectiveness analysis is presented in Table 1.

Table 1: Applicant base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Sodium thiosulfate	11,692	13.56	-	-	-
No sodium thiosulfate	117,734	14.89	106,042	1.33	79,924

ICER: incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year.
[a] Corresponding probabilistic ICER using 10,000 iterations = €80,135/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.
[b] A PAS is offered for sodium thiosulfate, not included in this table.

The Review Group had a number of concerns regarding the reliability of results presented in the Applicant base case. The Review Group considered that the limitations of the evidence base underpinning the cost-effectiveness estimates could not be overcome by making adjustments to develop an NCPE adjusted base case. As such, the Review Group did not

consider it appropriate to present an adjusted NCPE base case.

Sensitivity analysis

The Review Group did not consider that the probabilistic sensitivity analysis captured the uncertainty in estimates of cost effectiveness. The results are thus not presented here.

4. Budget impact of sodium thiosulfate

The price-to-wholesaler (PtW) of one 100mL vial of sodium thiosulfate 8g (80mg/mL) is €9,748.00. Treatment with sodium thiosulfate was assumed to be one year, with an average of 6.79 doses and 12.69 packs of sodium thiosulfate 8g received per patient per year. The estimated total cost, per patient, per treatment course of sodium thiosulfate is €140,971 (including VAT).

Eligible population estimates were informed by the UK Children, Teenagers, and Young Adults (CTYA) database and clinical opinion. The Review Group considered these estimates to be highly uncertain and likely to be underestimated due to limitations in the methodology employed by the Applicant.

Based on the Applicant assumptions, two patients were estimated to receive treatment with sodium thiosulfate in year one, increasing to five patients by year five. The resultant five-year cumulative gross drug-budget impact was €2.7 million (including VAT). The net drug-budget impact is equivalent to the gross. Due to the high degree of uncertainty associated with the Applicant estimates, the Review Group conducted additional scenarios. In the first scenario, it was assumed that five patients would receive treatment in year one, increasing to 13 patients by year five. The five-year cumulative gross/net drug budget impact, under this scenario, was €7.4 million (including VAT). In the second scenario, it was assumed that seven patients would receive treatment in year one, increasing to 19 by year five. The five-year cumulative gross/net drug budget impact, under this scenario, was €10.6 million (including VAT).

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that sodium thiosulfate (Pedmarqsi®) not be considered for reimbursement, for this indication, unless cost-effectiveness can be improved*.

** This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*