Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours

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Technology appraisal committee B [11 September 2024]

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Company: Norgine

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Cost effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on hearing loss caused by cisplatin

Currently no preventative treatments for hearing loss caused by cisplatin

Cisplatin-induced ototoxicity in children and young people

Cause: cisplatin is widely used to treat a variety of cancers in children and young people. However, after it enters the cochlea (inner ear) it can cause inflammation and damage, known as ototoxicity or 'ear poisoning' (subsequently referred to as **hearing loss**)

Risk factors for more severe hearing loss include younger age and high cisplatin dosage

Incidence/prevalence: about 60% of children having cisplatin-based treatment develop irreversible hearing loss; 283 new cases of ototoxic hearing loss were diagnosed in people under 18 in England (2022/23)

Diagnosis and assessment of hearing loss

- Often delays in diagnosis as early signs of hearing loss may be missed
- A range of grading scales may be used to assess and define severity of hearing loss

Prognosis: Initially presents as bilateral, high-frequency (4,000 to 8,000 Hz) hearing loss and may worsen with subsequent doses of cisplatin – onset may be immediate or progressive (years after cisplatin treatment)

Treatment options: currently no treatment to prevent hearing loss in children and young people with localised, solid cancer tumours having cisplatin chemotherapy

Patient perspectives

Hearing loss may significantly impact health related quality of life in children

Joint submission from the National Deaf Children's Society (NDCS) and the Royal National Institute for Deaf People (RNID)

- Increasing numbers of people needing cancer treatment has increased the frequency and impact of ototoxic hearing loss in children
- Hearing loss in children may affect speech and language development, school performance and psychosocial functioning – particularly in younger children
- Hearing aids and cochlear implants have numerous limitations and people may choose not to use them – additional NHS and educational support is also needed
- Hearing loss may impact on ability to work in later life
- Long waiting times to access support services and/or not receiving adequate support may affect quality of life and increase health inequalities compared to people without hearing loss

Clinical perspectives

Severe unmet need to prevent hearing loss caused by cisplatin chemotherapy

Clinical expert submission

- Main aim of treatment to fully or partially prevent hearing loss
- Currently no preventative treatment options and no pharmacological way to reverse hearing loss
- Severe unmet need for preventative treatment options
- Some guidelines recommend switching cisplatin to carboplatin (less ototoxic) but cisplatin better drug in certain malignancies such as hepatoblastoma and germ cell tumours
- Treatment will be given as an inpatient after chemotherapy, so no extra admission or resources
- Preventing hearing loss would lead to significant improvement in quality of life and educational potential and significantly reduce socioeconomic burden
- All children on cisplatin chemotherapy should have a baseline hearing assessment before treatment starts and be monitored regularly afterwards
- Personal experience: significant reduction in hearing loss in people who have anhydrous sodium thiosulfate

Equality considerations

Potential equality issues raised in company and patient organisation submissions

Company

- Families with lower household income may struggle to afford advanced hearing aid equipment and educational resources beyond what is offered by the NHS, increasing care burden of HL
- Anhydrous STS may reduce the extent of this inequity

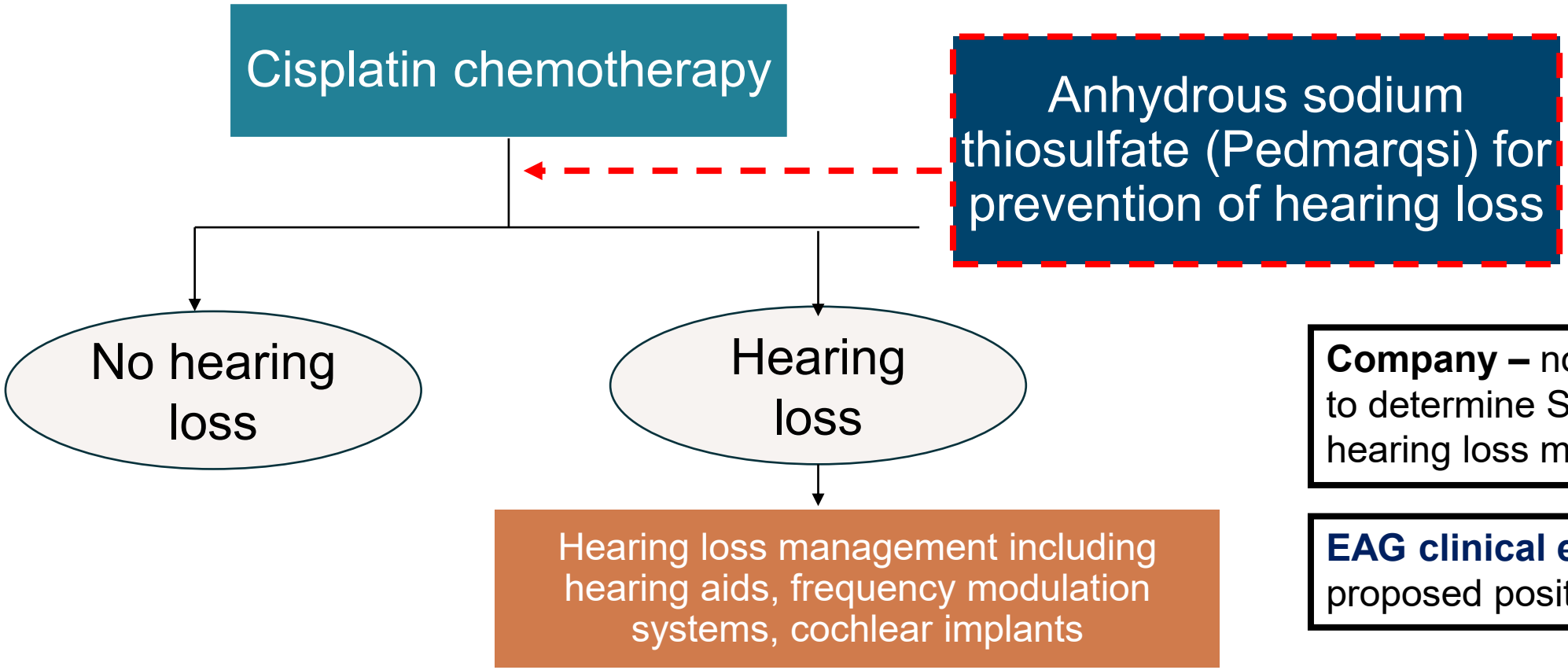
Patient organisation

- Deaf children from ethnic minorities have poorer educational outcomes compared with children with no hearing loss
- Black and Asian deaf children have lower attainment scores compared to other ethnic groups or to white deaf children, respectively

Are there other relevant equality or health inequality issues for decision making?

Treatment pathway

Company's proposed positioning: as an add on to established clinical management for people aged 1 month to <18 years with localised, non-metastatic solid tumours having cisplatin (around 222 per year)



Company – no extra testing needed to determine STS eligibility (standard hearing loss monitoring only)

EAG clinical experts – agree with proposed positioning

Does the company's description of the treatment pathway reflect NHS practice?
Is the proposed positioning for anhydrous STS appropriate?

Anhydrous sodium thiosulfate (Pedmarqsi, Norgine)

Marketing authorisation	Indicated for prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to <18 years of age with **localised, non-metastatic, solid tumours** • UK MA granted October 2023
Mechanism of action	Mechanism of protection against hearing loss 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
Administration	Intravenous infusion (80 mg/mL solution) 15-minute infusion - 6 hours after completion of each cisplatin infusion *Timing of sodium thiosulfate administration relative to cisplatin is critical (see below)
Price	• List price: [redacted] per 8g vial (excluding VAT) • Patient access scheme applies

*If sodium thiosulfate is administered:
- <6 hours after end of cisplatin infusion it may reduce cisplatin efficacy against the tumour
- >6 hours after end of cisplatin infusion it may not be effective in preventing hearing loss

Only use sodium thiosulfate following cisplatin infusion duration of ≤6 hours. Do not use if:
- cisplatin infusion exceeds 6 hours, or
- a subsequent cisplatin infusion is planned within 6 hours

Decision problem

	Final scope	Company	EAG comments
Population	People aged 1 month to less than 18 years of age with localised, non-metastatic, solid tumours having cisplatin chemotherapy	Pedmarqsi is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years with localised, non-metastatic, solid tumours	Population consists of patients receiving any cisplatin-containing regimens (**monotherapy or multi-drug regimens**)
Intervention	Anhydrous sodium thiosulfate (Pedmarqsi)	Pedmarqsi	In line with NICE scope
Comparators	ECM without anhydrous sodium thiosulfate (Pedmarqsi)	ECM without anhydrous sodium thiosulfate (Pedmarqsi)	In line with NICE scope. CS excludes cost of cisplatin-containing regimens (assumed equal across groups). EAG – reasonable given evidence presented
Outcomes	Frequency and severity of hearing loss, audiological outcomes, language and communication outcomes, psychosocial development/ adjustment, adverse effects of treatment, HRQoL	Percentage of patients experiencing hearing loss, hearing loss severity, audiological outcomes, overall survival, adverse effects of treatment, HRQoL	• CS does not explicitly include language, communication and psychosocial development/ adjustment – but covers NICE scope outcomes where data available • HRQoL data not available in clinical trials, based on literature.

CS, company submission; HRQoL, health-related quality of life; ECM, established clinical management; EAG, external assessment group

Key issues

Number	Issue	Resolved?	ICER impact
1	Uncertainty in accurate timing and administration of STS and potential effect on anti-tumour efficacy	No – for discussion	Unknown 
2	Small sample sizes in SIOPEL 6 and COG ACCL0431 trials (linked to issue 4)	No – for discussion	Unknown 
3	Use of multiple hearing loss grading scales (linked to issue 4)	No – for discussion	Unknown 
4	Uncertainty in efficacy data used in the model (linked to issues 2 and 3)	No – for discussion	Large 
5	Modelling of mortality risks after 5 years	No – for discussion	Large 

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Key clinical trials – SIOPEL 6 and COG ACCL0431

	SIOPEL 6 (NCT00652132)	COG ACCL0431 (NCT00716976)
Design	Open label phase 3 RCT	Open label phase 3 RCT
Population	Children aged >1 month to ≤18 years (n=109) receiving **single-agent cisplatin** chemotherapy for a newly diagnosed, histologically confirmed, **standard risk hepatoblastoma**	Children aged ≥1 to ≤18 years (n=125) newly diagnosed with **any histologically confirmed germ cell tumour**, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other solid malignancy (**localised and metastatic**) having various **chemotherapy containing cisplatin and other regimens**
Intervention	Anhydrous sodium thiosulfate (STS)	Anhydrous sodium thiosulfate (STS)
Comparator	Cisplatin without STS	Cisplatin without STS
Median follow up	4.27 years (per protocol)	5.33 years (ITT)
Primary outcome	Hearing loss, assessed by Brock scale (graded 0-4 where 0=no hearing loss and 4=most severe hearing loss)	Hearing loss, defined by ASHA criteria (binary measure based on change in hearing from baseline)*
Key secondary outcomes	Overall survival, adverse events	Overall survival, adverse events
Locations	12 countries including UK	USA and Canada
Used in model?	Yes (in scenario)	Yes (both company and EAG base case)*

ASHA, American Speech-Language-Hearing Association; RCT, randomised controlled trial; ITT, intention to treat; EAG, external assessment group; SIOP, International Society of Paediatric Oncology Boston ototoxicity scale

*Post-hoc analysis re-evaluating COG ACCL0431 using SIOP scale used to inform model HL severity

Trial baseline characteristics – SIOPEL 6

Differences in age, weight and tumour type between SIOPEL 6 and COG ACCL0431 populations

Characteristic	Cisplatin alone (n=52)	Cisplatin with STS (n=57)	Total (n=109)
Mean age (months) ± SD	18.2 ± 15.0	18.8 ± 16.7	18.5 ± 15.8
Female	23 (44.2)	27 (47.4)	50 (45.9)
Ethnicity - White	32 (61.5)	32 (56.1)	64 (58.7)
Weight (kg), mean (SD)	10.25 (3.26)	10.23 (3.76)	10.24 (3.51)
AFP at diagnosis (ng/mL), mean (SD)	374,405 (565,679)	496,085 (888,294)	438,036 (750,987)
Caudate lobe involvement, n (%)			
Yes	5 (9.6)	4 (7.0)	9 (8.3)
No	40 (76.9)	49 (86.0)	89 (81.7)
Uncertain	7 (13.5)	4 (7.0)	11 (10.1)
Distant metastases, n (%)			
No	52 (100.0)	55 (96.5)	107 (98.2)
Uncertain	0	2 (3.5)	2 (1.8)

*AFP = alpha fetoprotein (raised levels = tumour marker)

Company - Efficacy in both trials despite differences in baseline characteristics suggests that anhydrous STS is effective across a heterogenous paediatric patient population

NICE SD, standard deviation; STS, sodium thiosulfate

Trial baseline characteristics – COG ACCL0431

Company – COG ACCL0431 population most generalisable to UK setting

Characteristic	Cisplatin alone (n=64)	Cisplatin with STS (n=61)	Total (n=125)
Age (years), mean (SD)	8.9 (5.9)	9.4 (6.0)	9.2 (5.9)
Female	23 (35.9)	26 (42.6)	49 (39.2)
Ethnicity - White	39 (60.9)	42 (68.9)	81 (64.8)
Diagnosis			
Germ cell tumour	16 (25.0)	16 (26.2)	32 (25.6)
Osteosarcoma	15 (23.4)	14 (23.0)	29 (23.2)
Medulloblastoma	14 (21.9)	12 (19.7)	26 (20.8)
Medulloblastoma	14 (21.9)	10 (16.4)	24 (19.2)
Supratentorial PNET	0	2 (3.3)	2 (1.6)
Neuroblastoma	12 (18.8)	14 (23.0)	26 (20.8)
Hepatoblastoma	5 (7.8)	2 (3.3)	7 (5.6)
Other	2 (3.1)	3 (4.9)	5 (4.0)
Extent of disease, n (%)			
No metastases detected at diagnosis	38 (59.4)	39 (63.9)	77 (61.6)
Metastases present at diagnosis*	26 (40.6)	21 (34.4)	47 (37.6)
Unknown	0 (0)	1 (1.6)	1 (0.8)
Prior cranial irradiation	5 (7.8)	4 (6.6)	9 (7.2)

SD, standard deviation;
PNET, primitive neuroectodermal tumour

* Metastatic disease not included in marketing authorisation

Generalisability of the trials

Company: wide variability in use of hearing loss grading scales, ASHA scale common in the USA; Brock grades and SIOP in the UK

EAG: generalisability of trial results to clinical practice unclear

- **Population:** SIOPEL 6 conducted in patients with standard risk hepatoblastoma (localised disease), COG ACCL0431 in patients with various tumour types (localised and disseminated disease)
- **Grading scales**: caution needed when interpreting incidence of hearing loss assessed using different hearing assessment and hearing loss grading scales;
- **Severity assessment**:
  - Brock grades used in SIOPEL 6 has a cut-off of 40 dB hearing loss, less sensitive to early ototoxicity, does not detect mild hearing loss; ASHA criteria used in COG ACCL0431 trial do not assess severity

- What is the committee's view on the generalisability of:
  - the trial populations to children and young people with localised solid tumours in the NHS?
  - the hearing loss and severity assessment tools used in NHS practice?
  - STS's efficacy on hearing loss prevention and mortality to children and young people with solid localised tumours in the NHS?

ASHA, American Speech-Language-Hearing Association; SIOP: International Society of Paediatric Oncology Boston ototoxicity scale; BSA, British Society of Audiology

Clinical trial results, primary outcome: hearing loss

SIOPEL 6, COG ACCL0431 (efficacy population) and pooled analyses show statistically significant reduction in hearing loss incidence with STS

	SIOPEL 6*, mITT		COG ACCL0431**, efficacy, mITT		COG ACCL0431**, localised only		Pooled trial analysis (*localised and metastatic, mITT*)		Pooled analysis, localised only	
	Cisplatin alone (n=46)	Cisplatin with STS (n=55)	Cisplatin alone (n=55)	Cisplatin with STS (n=49)	Cisplatin alone (n=33)	Cisplatin with STS (n=31)	Cisplatin alone (n=[redacted])	Cisplatin with STS (n=[redacted])	Cisplatin alone (n=79)	Cisplatin with STS (n=86)
Hearing loss, n (%)	29 (63.0)	18 (32.7)	31 (56.4)	14 (28.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR (95% CI)	-		0.27 (0.11 to 0.66) p=0.0039		[redacted]		[redacted]		[redacted]	
RR (95% CI)	0.52 (0.34 to 0.79) p=0.002		0.52 (0.32 to 0.84) p=0.004		[redacted]		[redacted]		[redacted]	

*hearing loss defined by Brock grade ≥1, **hearing loss defined by ASHA criteria

- COG ACCL0431 localised disease subgroup does not show statistically significant reduction in hearing loss
- **Company**: ACCL0431 trial is not statistically powered for localised only subgroup
- **EAG:** pooling of trials may not be appropriate because of differences in population and study design

mITT, modified intention to treat; STS, sodium thiosulfate; ASHA, American Speech-Language-Hearing Association; OR, odds ratio; RR, relative risk; CI, confidence interval

Hearing loss grading scales as used in model

Link to model

Model health states	Classification systems		
	ASHA (COG ACCL0431) [used in trial as a binary criterion – yes/no – to detect hearing loss]	**SIOP** (Post hoc analysis of COG ACCL0431 – Orgel et al)	**Brock** (SIOPEL 6 and literature source for hearing loss severity [Knight et al])
Minimal/no hearing loss	Normal: -10-15 dB	Grade 0: ≤20 dB at all frequencies	Grade 0: <40 dB at all frequencies
Mild hearing loss	Slight: 16-25 dB	Grade 1: >20 dB at >4,000 Hz	Grade 1: ≥40 dB at 8,000 Hz
	Mild: 26-40 dB		
Moderate hearing loss	Moderate: 41-55 dB	Grade 2: >20 dB at ≥4,000 Hz	Grade 2: ≥40 dB at ≥4,000 Hz
	Moderately severe: 56-70 dB		
Marked hearing loss	Severe: 71-90 dB	Grade 3: >20 dB at 2,000 Hz or 3,000 Hz / Indication for hearing aids	Grade 3: ≥40 dB at ≥2,000 Hz
Severe hearing loss	Profound: 91+ dB	Grade 4: >40 dB at ≥2,000 Hz	Grade 4: ≥40 dB at ≥1,000 Hz

*Hearing loss defined as a one of (1) 10 dB change from baseline at 2 consecutive frequencies (2) 20 dB change at 1 frequency (3) loss of measurable hearing for 3 consecutive frequencies when hearing previously measurable

ASHA, American Speech-Language-Hearing Association; SIOP: International Society of Paediatric Oncology Boston ototoxicity scale; BSA, British Society of Audiology

Link to key issue 4

Link to key issue 2

Link to sound examples (speech banana)

Clinical trial results – severity of hearing loss by Brock grades

SIOPEL 6 shows reduction in proportion of children with more severe HL

SIOPEL 6 HL trial, severity:

HL severity, Brock grade (hearing threshold)	%, mITT		% ≥Brock grade 1	
	Cisplatin alone (n=46)	Cisplatin with STS (n=55)	Cisplatin alone (n=29)	Cisplatin with STS (n=18)
0* (<40 dB, all frequencies)	37%	67%	-	-
1 (≥40 dB, 8,000 Hz)	26%	18%	41%	55%
2 (≥40 dB, 4,000 Hz)	24%	11%	38%	33%
3 (≥40 dB, 2,000 Hz)	11%	2%	18%	6%
4 (≥40 dB, 1,000 Hz)	2%	2%	3%	6%

- Company – degree of HL was less severe in the cisplatin with STS group in addition to reduced incidence of HL
- Pooled analysis including HL severity unavailable – not assessed in COG ACCL0431 primary analysis

* = Brock grade 0 equals no HL for primary study endpoint but does not necessarily equate to normal hearing

ITT; intention to treat; mITT, modified intention to treat; HL, hearing loss; STS, sodium thiosulfate

Post hoc analysis of COG ACCL0431 trial results: hearing loss

Post hoc analysis using SIOP scale shows statistically significant reduction in hearing loss in COG ACCL10431

- The ASHA criteria used in COG ACCL0431 trial to define hearing loss does not assess severity; Orgel 2023 re-evaluated the audiology data from the trial using SIOP scale
  - Used in model by company and EAG
- SIOP grade 1 (HL of >20 dB at 6000 or 8000 Hz), and grade 2 (HL of >20 dB at 4000 Hz and above) used to define HL
- Does not discriminate between all HL levels

	Hearing loss by SIOP, Grade ≥1		Hearing loss by SIOP, Grade ≥2	
	Cisplatin alone (n=59)	Cisplatin with STS (n=50)	Cisplatin alone (n=59)	Cisplatin with STS (n=50)
Hearing loss, (%)	45.8	18.0	27.1	4.0
OR (95% CI)	0.25 (0.10 to 0.64), p=0.004		0.10 (0.02 to 0.50), p=0.005	

NICE

SIOP: Society of Paediatric Oncology (SIOP) Ototoxicity Scale; mITT, modified intention to treat; HL, hearing loss; STS, sodium thiosulfate; ASHA, American Speech-Language and Hearing Association

Secondary outcome: overall survival – pooled results

No statistically significant difference in pooled OS for cisplatin with STS vs cisplatin alone

KM curve for pooled ITT OS, localised disease only

Pooled ITT OS (localised and metastatic):

Pooled ITT	Cisplatin alone (n=116)	Cisplatin with STS (n=118)
Events, n (%)	16 (13.8)	20 (16.9)
HR (95% CI); P	1.29 (0.67 to 2.53), p=0.4464	

Pooled ITT OS, localised disease only:

	Cisplatin alone (n=90)	Cisplatin with STS (n=96)
Events, n (%)	10 (11.1)	9 (9.4)
HR (95% CI); P	0.86 (0.34 to 2.13), p=0.7364	

Are there any concerns about the impact of STS on overall survival in localised disease?

ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival; CI, confidence interval; STS, sodium thiosulfate

Key issue: Timing and administration of STS

Uncertainty in how inaccuracies in timing of STS administration may affect STS or cisplatin efficacy

Background – STS SmPC

- A 15-minute intravenous STS infusion should be administered exactly 6 hours following completion of each cisplatin infusion:
  - Administration before 6 hours post cisplatin infusion or within 6 hours of a subsequent infusion may impact efficacy of cisplatin chemotherapy against tumours
  - Administration >6 hours after cisplatin infusion = may not prevent hearing loss

Company

- SmPC provides clear instructions for use to ensure gap of >6 hours between cisplatin and STS infusions
- Minimum 6-hour gap adhered to in clinical trials
- Delayed administration occurred in [redacted] of SIOPEL 6 recorded administrations - mostly because of delays in receiving STS from pharmacy, ward staff changeovers, and blocked/unusable infusion lines

EAG comments

- Further studies needed to evaluate potential effect of delaying STS administration on anti-tumour efficacy and prevention of HL
- EMA assessment report – exact mechanism of interaction between STS and cisplatin still unknown

What is the maximum time after cisplatin infusion that STS should still be given? What is the likelihood of loss in efficacy if there is a delay in STS administration?
Is there likely a wastage issue if STS can no longer be administered due to delays?

STS, sodium thiosulfate; SmPC, summary of product characteristics

Key issue: Small sample sizes in SIOPEL 6 and COG ACCL0431

Population from trials relatively small and COG ACCL0431 population broader than licensed indication

Background

- SIOPEL 6 (n=114) and COG ACCL0431 (n=125) trials have relatively small sample sizes
- COG ACCL0431 included patients with localised or metastatic disease and various tumour types
  - Marketing authorisation = localised, non-metastatic solid tumours only

Company:

- Analyses of localised only patients not appropriate since COG ACCL0431 is underpowered for subgroup analysis in localised disease – small sample size may lead to uncertainty in estimated treatment effect
- Cisplatin use in children is rare, which limits ability to conduct larger trials
- Efficacy of STS not dependent on tumour type

EAG:

- Not enough statistical power to detect difference between treatment groups in licensed population – but subgroup analyses should be considered with full population for completeness
- Uncertain impact on treatment effects – further studies needed to address this uncertainty

Is the COG ACCL0431 full trial population (i.e. localised and metastatic disease) or the localised disease only population (including those from COG and SIOPEL 6) more appropriate for decision making and for informing the model?

STS, sodium thiosulfate

Key issue: Use of different hearing loss grading scales across trials

Background

- Different grading scales for ototoxicity are used in the clinical trials to define HL – ASHA criteria in COG ACCL0431 and Brock scale in SIOPEL 6

EAG comments

- ASHA criteria for HL used in COG ACCL0431 is used as a binary measure – severity of HL not measured
- Brock scale used in SIOPEL 6 has absolute HL cut-off of 40dB for HL – less sensitive to early hearing loss and does not detect mild HL or baseline hearing abnormalities
- Interpretation of HL incidence between studies needs consideration and generalisability to UK unclear

Company

- Audiologist feedback (2018, n=5 US and n=5 UK) – variability in ototoxicity scales for cisplatin-induced HL
  - ASHA commonly used in the USA and Brock scale used in UK practice
- Leading clinical centre for paediatric ototoxicity (GOSH) uses Brock and SIOP grading scales
- Good concordance between ototoxicity grading scales according to literature despite differences in how HL severity is defined

What measurements of hearing loss are currently used in current clinical practice? Are the results from the clinical trial generalisable to NHS practice based on grading scales used?
Do the results of the clinical trials sufficiently capture incidence and severity of hearing loss?

ASHA, American Speech-Language and Hearing Association; SIOP: International Society of Paediatric Oncology Boston ototoxicity scale; HL, hearing loss; GOSH, Great Ormond Street Hospital

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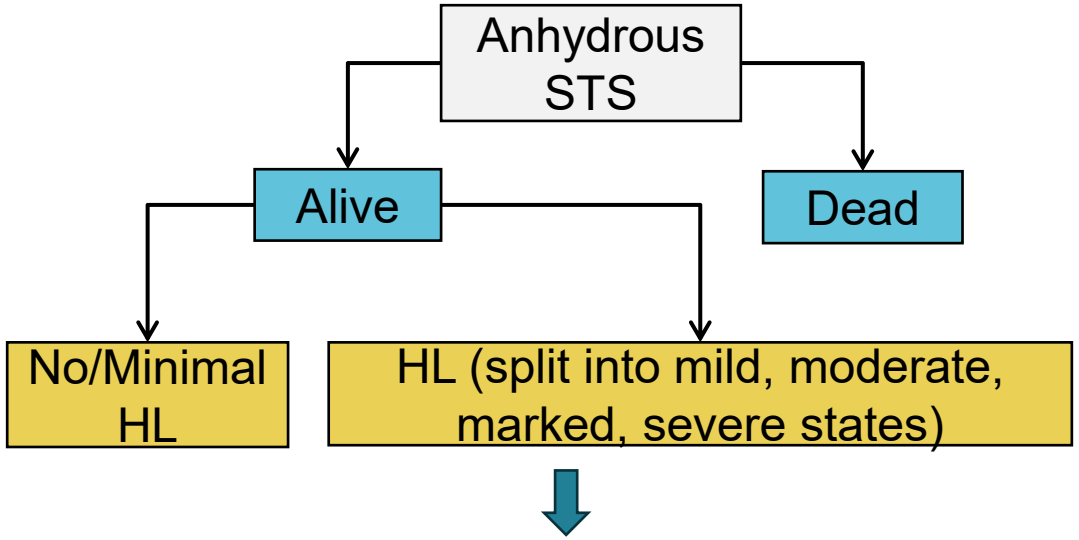
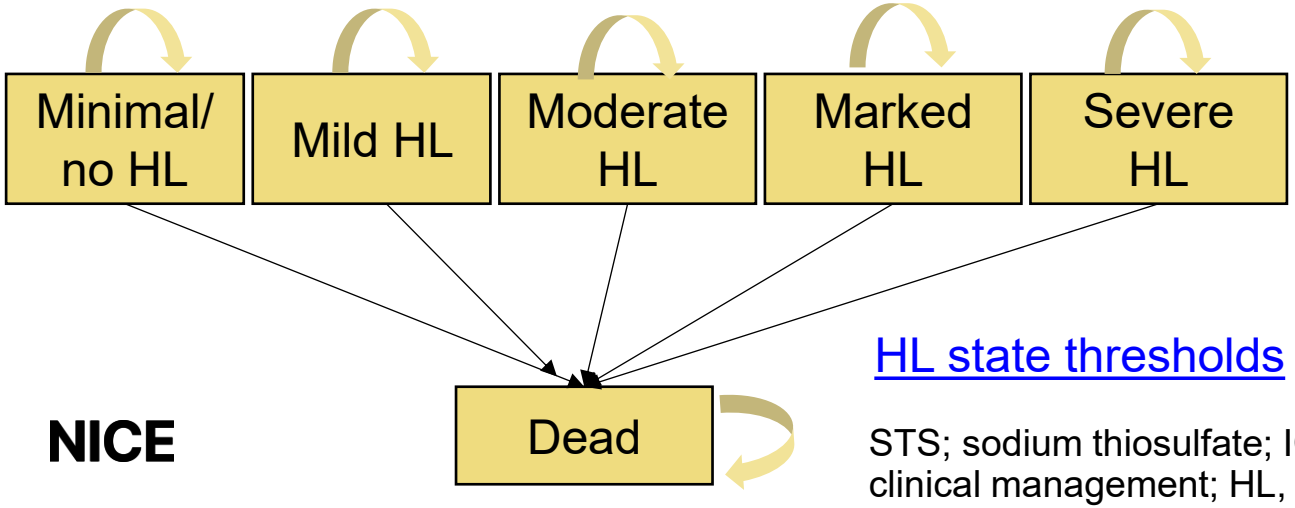
Company's model overview

Decision tree structure for first year followed by state-transition (Markov) model

Decision tree (STS arm shown; same structure for ECM):



Markov model with health states (long term modelling):



Anhydrous STS affects **costs** by:

- Introducing acquisition costs of STS
- Reducing costs of depression linked to HL and HL management costs (hearing assessments, speech and language therapy, CIs/hearing aids) vs ECM
  - Due to increased proportion of people with no/minimal or mild HL vs severe HL

Anhydrous STS affects **QALYs** by:

- Increasing the proportion of people with minimal/no HL
- Increasing the proportion of people in lower severity HL health states compared with ECM

Assumptions with greatest ICER effect:

- Source of data for HL incidence
- Inclusion of cure assumption at 10 years

HL state thresholds

Is the model structure appropriate for decision making?

STS; sodium thiosulfate; ICER; incremental cost effectiveness ratio, ECM, established clinical management; HL, hearing loss; CI, cochlear implant; QALY, quality adjusted life year

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	COG ACCL0431 localised disease subgroup (starting age [redacted] years, [redacted] male)
Time horizon; cycle length	Lifetime up to age 100 ([redacted] years); cycle length 1 year (with half cycle correction)
Discount rate	3.5% (1.5% explored in scenario analyses)
Treatment efficacy	**HL incidence** (ASHA scale): COG ACCL0431, overall efficacy population **HL severity** (SIOP scale): literature, including post hoc analysis of COG ACCL0431 (Orgel et al 2023) **Treatment effects in first year only; no change in hearing loss after (that is, no movement between Markov model states)**
Mortality	Years 1-5: Kaplan–Meier overall survival from COG ACCL0431 localised disease subgroup Years 6-10: SMR of 9.1 from literature (Fidler et al) applied to general population life tables After 10 years: general population mortality (assumption of cure)
Adverse events	Serious adverse events in ≥2% of patients in either arm of COG ACCL0431
Utilities	Treatment-independent utilities for alive health states derived from HUI3 based on literature* (see Utility values for health states)
Costs	Costs sourced from NHS National Cost Collection, literature, PSSRU
Resource use	Hearing assessments, speech and language therapy, cochlear implants, hearing aids and FM systems. Costs for managing depression and anxiety included
Treatment waning	None

*Company: HUI3 appropriate for measuring hearing loss, used in TA566 (appraisal of cochlear implants for children and adults with severe to profound deafness)

ASHA, American Speech-Language-Hearing Association; HUI: health utility index; SMR, standardised mortality ratio; PSSRU, Personal Social Services Research Unit; SIOP; Society of Paediatric Oncology Ototoxicity Scale

Key issue: Uncertainty in efficacy data used in the model

Background

Company base case uses **3 sources** with different HL grading scales for treatment efficacy:

- COG ACCL0431 (whole efficacy population-localised and metastatic) for HL incidence,
- Post-hoc analysis of COG ACCL0431 using SIOP (grades 1 and 2+) (Orgel et al) combined with literature using Brock (grade 2 and above) (Knight et al.) for severity

EAG comments

- Company HL incidence not specific to population of interest. EAG prefers localised disease subgroup of COG ACCL0431 for modelling HL incidence - consistent with other model parameters
- Analysis combines multiple grading systems without consideration of differences between grading scales (see issue 3) or how they match model health states
  - EAG scenario with 2 sources of data (Orgel et al. for HL incidence, Orgel et al and Knight et al for severity) reduces uncertainty in difference between grading scales and still uses COG ACCL0431 population for incidence, but analysis not possible in localised disease only

Company

- Not enough data available to adjust for difference in grading scales between studies
- Explored multiple scenarios using different sources for both HL incidence and severity

Which source of data is preferred by the committee for modelling efficacy/risk of HL?
Which source of data is preferred by the committee for modelling HL severity?

SIOP: International Society of Paediatric Oncology Boston ototoxicity scale; HL, hearing loss

HL grading scales

Key issue: Modelling of mortality risks after 5 years

Company – single SMR at years 6-10 followed by cure assumption, EAG prefers multiple SMRs + no cure

Background

- Company models mortality risk in base case by applying a single SMR of 9.1 from literature (Fidler et al., all causes of death except mental disorders) to general population life tables at years 6-10
- Company base case assumes cure after 10 years – risk of death becomes identical to general population

Company

- Cure assumption at 10 years preferred by committee in previous paediatric oncology appraisal (Dinutuximab beta for treating neuroblastoma, TA538)

EAG comments

- EAG clinical expert – increased mortality of paediatric patients with solid tumours vs general population persists even after 40 years
  - May not be appropriate to assume risk of death decreases to match general population – EAG preferred analysis removes cure assumption
- SMRs from specific groups in Fidler et al available, including by cause of death and length of follow up – EAG prefers to apply multiple SMRs from same literature source according to time of follow up
  - Changing SMR values without removing cure assumption has minimal impact on cost effectiveness

Is it reasonable to assume that the risk of death drops to that of the general population? If so, at what point should this be applied?
Is applying a single SMR across years 6-10 or specific SMR estimates by follow up period preferred?

EAG, external assessment group; SMR; standardised mortality ratio; TA, technology appraisal

Summary of company and EAG differences in base case

Assumption	Company base case	EAG base case
Efficacy data for HL incidence	COG ACCL0431 overall efficacy population (localised and metastatic disease)	COG ACCL0431 localised disease subgroup (in line with MA population)
Long-term background mortality	Mortality assumed same as general population from 10 years	Increased mortality over whole time horizon
Approach to SMR after 5 years	Years 6-10: single SMR of 9.1 After 10 years: General population mortality	Multiple SMR estimates from 5 years onwards by follow-up period
Frequency of hearing assessments + SALT sessions	• Hearing assessments: from literature, based on HL health state and current age in model • SALT sessions: from literature	• Hearing assessments: from literature, based on HL health state and initial age in model • SALT sessions: from company audiologist report
Disease management costs	FM systems for all patients	FM systems only for patients with cochlear implants or hearing aids
Depression costs	Included	Excluded
Inclusion of AEs	Treatment-related SAEs in ≥2% of patients in each arm from COG ACCL0431	Grade 3+ AEs in ≥10% of patients from COG ACCL0431

 = large impact on cost effectiveness

 = small impact on cost effectiveness

HL, hearing loss; EAG, external assessment group; AE, adverse event; SALT, speech and language therapy; SAE, serious adverse event; SMR, standardised mortality rate; MA, marketing authorisation; FM = frequency modulation

Correction of errors in company base case post clarification

- Company base case uses life tables for England and Wales – EAG amended model to include general population life tables for England only (2020-2022).
- Company base case uses incorrect proportion of males – EAG amended model to include the mean proportion of males using the count data from both treatment arms in the COG ACCL0431 trial, thus replacing [redacted] with [redacted].
- EAG corrected error on the costs of the internal component of cochlear implants linked to issue with modelling the probability of internal component cochlear implants requiring replacement in each cycle of the model.
- **Combined corrections have minimal impact on cost effectiveness**

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EAG, external assessment group

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Cost effectiveness results**
- ❑ Other considerations
- ❑ Summary

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Summary of cost effectiveness results

Company ICERs

Company base case – results below 30k per QALY gained

EAG ICERs

- EAG base case – results above 30k per QALY gained
- EAG assumptions with the biggest impact on the ICER = exclusion of cure assumption and the source of efficacy data for hearing loss
- EAG scenario analyses of company base case led to an increase in the ICER in all cases except for correction of model errors (minimal decrease in ICER) and applying FM system costs to people with hearing aids or cochlear implants only (no change in ICER)
- EAG scenarios have small impact on incremental costs – changes to the ICER are driven by a decrease in incremental QALYs

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; FM, frequency modulation

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Company base case results (before EAG corrections)

Company base case ICER below 30k per QALY gained

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Anhydrous sodium thiosulfate	[redacted]	18.43	[redacted]	1.54	[redacted]
Established clinical management	£10,187	16.89	-	-	-

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Anhydrous sodium thiosulfate	[redacted]	18.42	[redacted]	1.54	[redacted]
Established clinical management	£10,256	16.88	-	-	-

EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

EAG base case results

EAG base case ICER above 30k per QALY gained

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Anhydrous sodium thiosulfate	[redacted]	15.95	[redacted]	1.20	[redacted]
Established clinical management	£14,332	14.75	-	-	-

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Anhydrous sodium thiosulfate	[redacted]	15.92	[redacted]	1.19	[redacted]
Established clinical management	£17,754	14.73	-	-	-

EAG, external assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Cost effectiveness results
- ✓ **Other considerations**
- ❑ Summary

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Other considerations

Managed access – company has not put forward a managed access proposal for this appraisal

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Cost effectiveness results
- ❑ Other considerations
- ✓ **Summary**

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Summary of key issues for discussion

Key questions

- What is the maximum time after cisplatin infusion that STS should still be given? What is the likelihood of loss in efficacy if there is a delay in STS administration?
- Is there likely a wastage issue if STS can no longer be administered because of delays?
- Is the COG ACCL0431 full trial population (localised and metastatic disease) or the localised disease only population (including those from COG ACCL0431 and SIOPEL 6) more appropriate for decision making and for informing the model?
- What measurements of hearing loss are currently used in current clinical practice? Are the results from the clinical trial generalisable to NHS practice based on grading scales used?
- Do the results of the clinical trials sufficiently capture incidence and severity of hearing loss?
- Which source of data is preferred by the committee for modelling efficacy/risk of hearing loss? And for hearing loss severity?
- What is the committee's view on the source of utilities used in the model?
- Which assumption on adverse events does the committee prefer?
- Should costs for depression treatment be included or excluded?
- Is it reasonable to assume that the risk of death drops to that of the general population? If so, at what point should this be applied?
- Is applying a single SMR across years 6-10 or specific SMR estimates by follow up period preferred?

NICE SMR, standardised mortality ratio; STS, sodium thiosulfate

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Thank you