National Institute for Health and Care Excellence

Health Technology Evaluation

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours (ID1001)

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Company (Fennec Pharmaceuticals Inc)	**Please note:** throughout the draft scope document provided by NICE, the product is referred to as "sodium thiosulfate". Whilst sodium thiosulfate-anhydrous is the active ingredient, Pedmarqsi is a novel formulation of sodium thiosulfate-anhydrous specifically manufactured for the prevention of hearing loss in patients 1 month to < 18 years of age. In addition, Pedmarqsi also contains the following excipients: boric acid (0.25 mg/mL), water for injections, and hydrochloric acid and sodium hydroxide for pH adjustment.[3] The above distinctions are important to recognise as other formulations of sodium thiosulfate are available in some European countries outside the UK for the treatment of cyanide poisoning. However, these formulations do not have marketing authorisations in the UK for the prevention of ototoxicity in cisplatin treated patients and therefore should not be used in this indication. Given the specific and novel formulation of Pedmarqsi, the Company response will use "Pedmarqsi" throughout this document as opposed to sodium thiosulfate.	Thanks for your comments. The title and scope of appraisals normally refers to the active ingredient, rather than the branded name. Excipients are also not normally referred to. Also, it will be clear in the guidance what formulation the guidance applies to. However, given the safety concerns raised by the company during

Section	Stakeholder	Comments [sic]	Action
		Please note: the population prevalence and incidence figures quoted in this document reflect the combined population of both England and Wales given that the NICE scoping documentation requests data for this population. The Company's HST application, which has been submitted to NICE separately, presents data for England only as the form criteria dictates that only England's prevalence and incidence are assessed. However, in order to present figures with a consistent methodology, for *this document only* values referring to HST criteria are updated to be reflective of the population for both England and Wales. These figures are presented in detail in the Appendix. Fennec Pharmaceuticals agree that it is appropriate to refer this topic to NICE for appraisal. However, the proposed evaluation through the Single Technology Appraisal (STA) is not suitable for Pedmarqsi and it should instead be referred to NICE's Highly Specialised Technology (HST) programme as this is a treatment for an ultra-rare condition. Below is an overview of eligibility based on the four eligibility criteria for the HST programme. • The prevalence of deafness in paediatric patients treated with cisplatin is estimated to be very rare – **1 case per 264,000 people** in England and Wales per year (rounded to the nearest whole thousand). • Fennec Pharmaceuticals estimate the number of children eligible to receive Pedmarqsi to be **227 children per year** in England and Wales.[1] • Cisplatin-induced ototoxicity is a bilateral, progressive, irreversible, sensorineural hearing loss. It occurs in around 60% of children treated with cisplatin and begins when the first dose of cisplatin is administered, progressing after each subsequent dose.[2] • There are currently no other treatments to prevent cisplatin-induced	the decision problem meeting relating to high levels of potassium in other formulations of sodium thiosulfate, the title has been changed to incorporate the brand name. This topic will be routed as a single technology appraisal. Criterion 1 for eligibility of HST 'The condition is very rare defined by 1:50,000 in England and criterion 3 'The very rare condition significantly shortens life or severely impairs its quality' were not met. Therefore, it is not appropriate for this topic to be routed as an HST.

Section	Stakeholder	Comments [sic]	Action
		ototoxicity other than Pedmarqsi. Further information (including the calculations to derive the above figures) as to how Pedmarqsi meets the HST programme eligibility criteria is provided in the Appendix. In addition, it is clear Pedmarqsi meets HST criteria when applying the broader England and Wales population (as per this scoping form) or for England only, as presented in the separate HST application.	
Wording	Company (Fennec Pharmaceuticals Inc)	While the population defined in the remit is appropriate, it should be noted that the wording used throughout the scope to describe the population is inconsistent. The marketing authorisation for Pedmarqsi is described in the section "Draft remit/evaluation objective" as "preventing ototoxicity in people aged 1 month to 17 years old with localised cancer having cisplatin chemotherapy". However, in the section "The technology", it is stated that Pedmarqsi has a marketing authorisation "in patients 1 month to less than 18 years of age with localised, non-metastatic, solid tumours". While these statements are not incorrect, it would be the Company's preference for the avoidance of any uncertainty to use a consistent description of the marketing authorisation. Thus, Fennec Pharmaceuticals suggest that throughout the scope, the population should be defined using the wording used in the marketing authorisation for Pedmarqsi: **"Pedmarqsi is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours."**[3]	Thanks for your comments. The remit and wording of the population have been made more in line with the summary of product characteristics, but the title has been retained as it reflects NICE-style. "Non-metastatic" is removed from the title as it is superfluous to localised.
Timing issues	Company (Fennec Pharmaceuticals Inc)	There is an urgency of this evaluation to the NHS given that there are currently no other licensed treatments recommended to prevent cisplatin-induced ototoxicity in England and Wales and no new treatments are currently expected to be recommended. A timely evaluation will ensure that eligible patients with high unmet need will have access to Pedmarqsi at the	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
		earliest opportunity. There are currently no specific guidelines available for the prevention of cisplatin-induced ototoxicity and there is a need for effective preventative treatment strategies. Once hearing loss has occurred (which is irreversible) support is typically offered via management strategies such as hearing aids. However, the quality of life provided by such medical devices remains substantially lower than that of a person who has not experienced ototoxic hearing loss. There is, therefore, a high unmet need to prevent cisplatin-induced ototoxicity in England and Wales and to have timely access to an effective therapeutic agent which aims to prevent cisplatin-induced hearing loss in children altogether.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Company (Fennec Pharmaceuticals Inc)	Fennec Pharmaceuticals would like to note that the incidence figures of cancer in young people provided in the draft scope refer to those aged under 15. As Pedmarqsi is indicated in the population of people aged 1 month to under 18 years, the Company suggest the use of an incidence figure of **2,357** new cases of cancer in people aged under 18 years, inflated to a 2023 population (for the calculations to derive this figure, please see the Appendix: Table 1: Cancer diagnosis in England and Wales). Furthermore, Fennec Pharmaceuticals note that the statement *"Ototoxicity can impair the function of the inner ear related to balance (causing dizziness or vertigo). It can also affect hearing, such as hearing sounds in the absence of external noises (tinnitus) and hearing loss. While these impairments can sometimes be temporary, it can also cause irreversible damage resulting in,*	Thank you for your comment. A reported estimate by a reputed resource is preferred for the scope. The incidence estimates referenced in the scope are for people under age 15 and this is clearly reported in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		for example, permanent hearing loss" should be rephrased. Firstly, it is important to note that the mechanism of cisplatin-induced hearing loss means it is irreversible because the accumulation of platinum within the inner ear produces toxic levels of reactive oxygen species, which cause irreversible damage to the sensory outer hair cells on the cochlea. Subsequent doses of cisplatin result in further hearing loss as the cumulative dose of platinum in the inner ear accumulates.[4] Therefore, it is not accurate to describe cisplatin-induced hearing loss as "sometimes temporary". Fennec Pharmaceuticals suggest that the phrase "hearing loss associated with cisplatin-induced ototoxicity is irreversible" should be included in the draft scope. Secondly, the main focus of the scope should be on the hearing loss associated with cisplatin-induced ototoxicity. While dizziness and vertigo may be experienced by some patients with cisplatin-induced ototoxicity, the relative burdens of these symptoms are lower when compared to that of hearing loss in paediatric patients, which has substantial lifelong effects on quality of life through impaired psychosocial development. As such, the focus of this background information should be on the hearing loss. Although the SIOPEL 6 and ACCL0431 trials did not record data on the non-hearing effects of cisplatin-induced ototoxicity such as dizziness and vertigo, they may be considered qualitatively outside the quality adjusted life year (QALY) calculation.	The scope has been amended to be clear that some impairments can be temporary but other symptoms like hearing loss is irreversible. While it is appreciated that hearing loss will likely have the greatest burden, the scope is intended to capture the whole population covered by the marketing authorisation. The introduction reflects this but does focus on the impact of hearing loss on a person.
Population	Company (Fennec Pharmaceuticals Inc)	As previously stated, Fennec Pharmaceuticals disagree that the population proposed in the scope is defined appropriately. Pedmarqsi has received European Medicines Agency (EMA) marketing authorisation for use in "children aged 1 month to less than 18 years old"[3] and Fennec Pharmaceuticals request that the population in the draft scope be updated to align with the following wording:	Thanks for your comments. The remit and wording of the population have been made more in line with the summary of product

Section	Consultee/ Commentator	Comments [sic]	Action
		"Pedmarqsi is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours."	characteristics but the title has been retained as it reflects NICE-style, "non-metastatic" is removed from the title as it is superfluous to localised.
Subgroups	Company (Fennec Pharmaceuticals Inc)	Fennec Pharmaceuticals agree that there are no relevant subgroups to be considered in the draft scope.	Thanks for your comments.
Comparators	Company (Fennec Pharmaceuticals Inc)	Fennec Pharmaceuticals agree with the proposed comparator of "established clinical management without sodium thiosulfate" as there are currently no other licensed treatments for the prevention of cisplatin -induced ototoxicity.	Thanks for your comments.
Outcomes	Company (Fennec Pharmaceuticals Inc)	Fennec Pharmaceuticals appreciate that the proposed outcomes capture important health related benefits for patients with cisplatin-induced hearing loss. The Company agrees that frequency of hearing loss and sound perception are relevant outcomes to include in the scope. The Company also notes that it is important to consider not only outcomes related to the frequency of hearing loss in cisplatin-treated patients, but also the severity of hearing loss which is an important outcome for patients and captured in the SIOPEL 6 trial. Therefore, Fennec Pharmaceuticals would suggest that the severity of hearing loss should be considered as an additional outcome within the scope of this appraisal.	Thanks for your comments. While the severity of hearing loss is likely to be incorporated in audiological outcomes, it has been added as an outcome. As outlined in NICE's health technology

Section	Consultee/ Commentator	Comments [sic]	Action
		Furthermore, the Company has concerns that the proposed outcome measures of speech recognition, sound localisation, language and communication outcomes and psychosocial development/adjustment do not align with the data that is available from the SIOPEL 6 and ACCL0431 trials. Sound perception, speech recognition, sound localisation, language and communication outcomes and psychosocial development/adjustment were not endpoints collected in the SIOPEL 6 or ACCL0431 trials, therefore there is no data available to inform these outcomes in the economic modelling. Therefore, Fennec Pharmaceuticals would suggest that NICE reconsiders the inclusion of these measures and remove them from the scope of this appraisal.	evaluation manual (section 2.2.18 – 2.2.21), outcomes listed in the scope are selected on the basis of their importance to patients and carers rather than on their availability in the clinical studies.
Equality	Company (Fennec Pharmaceuticals Inc)	No equality issues have been identified in the scope. However, it should be noted that there are equality considerations to be made during the appraisal of Pedmarqsi. Firstly, preventing hearing loss is vital to enable children to reach their full potential. Once hearing loss has occurred, management strategies are available, however these have limitations in compensating for the irreversible damage to the inner ear caused by cisplatin and are not as effective in restoring patients' quality of life when compared to the prevention of hearing loss altogether. Therefore, the introduction of Pedmarqsi will greatly improve the opportunities and prospects for children receiving cisplatin chemotherapy. Secondly, management strategies such as hearing aids and speech and language therapy are offered through the NHS, however, it should be noted that patients from wealthier backgrounds are likely to seek higher quality management services through private providers, which are likely to provide higher quality equipment or specialist services. This introduces inequality, because patients from lower income backgrounds do not have access to	Thanks for your comments and for outlining potential equalities issue. Equalities issues are not normally listed in the scope. All issues raised are captured in the Equalities Impact Assessment (EIA) form, which will be published alongside the final scope. Where appropriate and relevant, they may be considered by the committee during the

Section	Consultee/ Commentator	Comments [sic]	Action
		these services. Pedmarqsi can have a positive impact on this inequity by offering a safe and effective treatment to *prevent* ototoxicity and therefore avoid hearing loss (and the subsequent inequity) in children receiving cisplatin chemotherapy.	appraisal.
Other considerations	Company (Fennec Pharmaceuticals Inc)	No additional considerations that are not covered by the draft scope have been identified.	Thank you for your comments.
Questions for consultation	Company (Fennec Pharmaceuticals Inc)	**Q1. How many people aged between 1 month and 17 years are newly diagnosed with cancer in England and Wales each year?** The Company estimates that **2,357** people aged between 1 month and < 18 years are newly diagnosed with cancer in England in Wales per year – [See Appendix: Table 1: Cancer diagnosis in England and Wales] **Q2. Among people aged between 1 month and 17 years living with cancer in England and Wales, how many of them have localised, non-metastatic cancer?** Not all patients with localised non-metastatic cancer will be eligible for Pedmarqsi, only those receiving cisplatin-based chemotherapy. That said, the Company estimates that **325** people aged between 1 month and < 18 years live with localised, non-metastatic cancer in England and Wales per year – [See Appendix: Table 2: Eligible population]. **Q3. What proportion of people aged 1 month to 17 years with localised, non-metastatic cancer are having cisplatin in England and Wales? Among those having cisplatin, how many of them experience ototoxicity? And how many experience hearing loss? What are the other potential factors that may be associated with ototoxicity and/or hearing**	Thank you for your comments. 1) – 4) These points have been taken into consideration for application of the HST criteria. Please see more details in the HST checklist. 5) – 10) Comments noted. No change to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		loss in children and young people (aged 1 month to 17 years) with localised, non-metastatic cancer and having cisplatin? It is estimated that, of those with localised, non-metastatic cancer, 70% will be treated with cisplatin chemotherapy. This results in an estimate of **227** people per year.[1] Approximately 60% (and up to 90%) of patients receiving cisplatin chemotherapy will develop irreversible ototoxicity.[5,6] In the SIOPEL 6 trial, 63% of participants who received cisplatin chemotherapy alone developed hearing loss.[7] Similarly, in the ACCL0431 trial, 56% of participants who received cisplatin chemotherapy alone developed hearing loss.[8] Ototoxicity initially presents as bilateral high-frequency sensorineural hearing loss, progressing in severity with increasing cumulative doses, to impact the lower frequencies of hearing and thus having an impact on frequency ranges related to speech.[9] Risk factors for more severe hearing loss include younger age at exposure (under 5 years) and a high cumulative dose of cisplatin ($\geq$ 400mg/m^2).[9] **Q4. For people aged 1 month to 17 years with localised, non-metastatic cancer having cisplatin, what proportion would be eligible for treatment with sodium thiosulfate to prevent ototoxicity? How would eligibility for sodium thiosulfate be determined in clinical practice?** There are currently no preventative treatments for cisplatin-induced hearing loss and as such there is a high unmet need in patients aged 1 month to < 18 years with localised cancer having cisplatin chemotherapy. No additional testing would be required to determine eligibility, therefore the majority of patients who meet the eligibility criteria defined in the marketing authorisation for Pedmarqsi, i.e. patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours who are receiving cisplatin chemotherapy would be	

Section	Consultee/ Commentator	Comments [sic]	Action
		eligible for treatment with Pedmarqsi. **Q5. Where do you consider sodium thiosulfate will fit into the existing care pathway for preventing ototoxicity in people aged 1 month to 17 years with localised, non-metastatic cancer having cisplatin chemotherapy?** As noted above, Sodium thiosulfate will be the first licensed treatment to prevent ototoxic hearing loss in patients undergoing cisplatin chemotherapy, given that no other pharmacological treatment options are available which prevent ototoxicity in patients 1 month to < 18 years of age with localised, non-metastatic cancer having cisplatin chemotherapy.[10] Current non-pharmacological best supportive care, such as hearing aids and other assistive devices are only used for the management of hearing loss once it has already occurred, instead of the prevention of hearing loss.[4] **Q6. Is sodium thiosulfate currently used in the NHS for treating other conditions? If so, which conditions?** Pedmarqsi's marketing authorisation does not include any additional therapeutic indications, and Pedmarqsi is not recommended by NICE in any other indications.[3] **Q7. Are there any other treatments or services currently used in clinical practice to prevent ototoxicity or support people with hearing loss in people aged 1 month to 17 years with localised, non-metastatic cancer and having cisplatin chemotherapy? if so, what are the treatments or services in place? Are cisplatin dose reductions used if symptoms of toxicity become evident?** As described above, there are no other pharmacological interventions for the prevention of cisplatin-induced ototoxicity. Therefore, current management is	

Section	Consultee/ Commentator	Comments [sic]	Action
		focused exclusively on supportive services which occur once ototoxic hearing loss has occurred and are neither preventative nor can reverse hearing loss. The most common of these post-ototoxicity management strategies involves the use of hearing aids throughout the patient's life.[4] Although hearing aids amplify sound, they cannot restore normal hearing and can reduce the patient's ability to discriminate speech in noisy environments.[4,11] In children with severe to profound sensorineural hearing loss who are unable to benefit from hearing aids, cochlear implants may be used.[14,22] These provide a modified sense of sound but require commitment to an audiology and speech therapy rehabilitation programme.[4] Therefore, although management strategies are available once hearing loss has occurred, these have limitations in compensating for the irreversible damage to the inner ear caused by cisplatin, and are not effective in restoring patients' quality of life when compared to the prevention of hearing loss altogether. **Q8. Do you consider that the use of sodium thiosulfate can result in any potential substantial health related benefits that are unlikely to be included in the QALY calculation? If so, what these would be?** Due to the severe impact of hearing loss on patients' quality of life, especially in young patients undergoing chemotherapy for cancer, it is expected that the introduction of Pedmarqsi is likely to result in substantial benefits outside of the QALY calculation. Notably, Pedmarqsi will reduce the emotional burden on parents and caregivers of children with cancer of choosing between an appropriate chemotherapy regimen which includes cisplatin and risks irreversible hearing loss, or a less preferable chemotherapy regimen which may be less efficacious in treating the cancer but reduces the risk of ototoxic hearing loss. Therefore, by preventing cisplatin-induced hearing loss, Pedmarqsi removes one of the major challenges associated with cisplatin	

Section	Consultee/ Commentator	Comments [sic]	Action
		chemotherapy as a treatment option for children with cancer. The benefits of this cannot be quantified in the QALY calculation. In addition, the SIOPEL 6 and ACCL0431 trials did not record data on the non-hearing effects of cisplatin-induced ototoxicity such as dizziness and vertigo. As such, these factors, which are also likely to affect patients' quality of life, may be considered qualitatively outside the QALY calculation. **Q9. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** There are no data available to inform the point discussed above regarding the emotional burden of caregivers. However, it is the Company's understanding of the disease area that this is an issue faced by parents and caregivers of children with cancer. **Q10. Would sodium thiosulfate be a candidate for managed access?** No. The clinical benefits of Pedmarqsi in preventing cisplatin-induced hearing loss have been previously established in the SIOPEL 6 and ACCL0431 trials. Therefore, a managed access scheme is unlikely to collect additional evidence to address uncertainties in the clinical evidence. Additionally, there are no planned or ongoing trials which would report data within a managed access timeframe.	

References provided by the company:

1. ONS. *Ethnic group by age and sex, England and Wales: Census 2021*. (2023). at <https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicgroupbyageandsexenglandandwales/census2021#ethnic-group-by-age>

2. Brock P, Rajput K, Edwards L, *et al.* in *Hearing Loss - From Multidisciplinary Teamwork to Public Health* (IntechOpen, 2021). doi:10.5772/intechopen.96744

3. EMA. Pedmarqsi. *European Medicines Agency* 2023. at <https://www.ema.europa.eu/en/medicines/human/EPAR/pedmarqsi>
4. Landier W. Ototoxicity and cancer therapy. *Cancer* 2016. 122: 1647–1658.
5. Knight KRG, Kraemer DF & Neuwelt EA. Ototoxicity in Children Receiving Platinum Chemotherapy: Underestimating a Commonly Occurring Toxicity That May Influence Academic and Social Development. *JCO* 2005. 23: 8588–8596.
6. Brock PR, Knight KR, Freyer DR, *et al.* Platinum-Induced Ototoxicity in Children: A Consensus Review on Mechanisms, Predisposition, and Protection, Including a New International Society of Pediatric Oncology Boston Ototoxicity Scale. *J Clin Oncol* 2012. 30: 2408–2417.
7. Brock PR, Maibach R, Childs M, *et al.* Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. *New England Journal of Medicine* 2018. 378: 2376–2385.
8. Freyer DR, Chen L, Krailo MD, *et al.* Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. *The Lancet Oncology* 2017. 18: 63–74.
9. Gurney JG & Bass JK. New International Society of Pediatric Oncology Boston Ototoxicity Grading Scale for pediatric oncology: still room for improvement. *J Clin Oncol* 2012. 30: 2303–2306.
10. Foster AC, Jacques BE & Piu F. Hearing loss: The final frontier of pharmacology. *Pharmacol Res Perspect* 2022. 10: e00970.
11. Paken J, Govender CD, Pillay M, *et al.* Cisplatin-Associated Ototoxicity: A Review for the Health Professional. *Journal of Toxicology* 2016. 2016: e1809394.
12. Youlden DR, Frazier AL, Gupta S, *et al.* Stage at diagnosis for childhood solid cancers in Australia: A population-based study. *Cancer Epidemiology* 2019. 59: 208–214.
13. Meel R, Radhakrishnan V & Bakhshi S. Current therapy and recent advances in the management of retinoblastoma. *Indian J Med Paediatr Oncol* 2012. 33: 80–88.
14. Fligor BJ. Pediatric Ototoxicity: Current Trends and Management. *Semin Hear* 2019. 40: 154–161.
15. Bess FH, Dodd-Murphy J & Parker RA. Children with Minimal Sensorineural Hearing Loss: Prevalence, Educational Performance, and Functional Status: *Ear and Hearing* 1998. 19: 339–354.
16. Bass JK, Knight KR, Yock TI, *et al.* Evaluation and Management of Hearing Loss in Survivors of Childhood and Adolescent Cancers: a Report from the Children's Oncology Group. *Pediatr Blood Cancer* 2016. 63: 1152–1162.
17. Grewal S, Merchant T, Reymond R, *et al.* Auditory Late Effects of Childhood Cancer Therapy: A Report From the Children's Oncology Group. *Pediatrics* 2010. 125: e938–e950.
18. NDCS. *Deaf children and Working Together*. (2015).
19. Brinkman TM, Bass JK, Li Z, *et al.* Treatment-induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: Results from the St. Jude Lifetime Cohort Study. *Cancer* 2015. 121: 4053–4061.
20. Cancer Research UK. *Children's cancers incidence statistics*. at <https://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/incidence#heading-Zero>
21. Cancer Research UK. *Young people's cancers incidence statistics*. at <https://www.cancerresearchuk.org/health-professional/cancer-statistics/young-people-cancers/incidence>

22. Cancer incidence. *NDRS* at <https://digital.nhs.uk/ndrs/data/data-outputs/ctya-uk-cancer-statistics-report-2021/cancer-incidence>

Appendix to company's response

HST eligibility

As mentioned in Comment 1, Fennec Pharmaceuticals have considerable concerns regarding the statement in the draft scope that NICE intends to evaluate Pedmarqsi through the STA programme and urge NICE to consider evaluation through the HST programme instead. To aid this decision, the Company have provided details of how Pedmarqsi meets HST programme criteria below. **Please note:** As the HST checklist requires data from England only, and this scoping form requires data from England and Wales, the data used previously to populate the HST checklist has been updated in this form to include data for the consideration of England **and** Wales.

1. The disease is very rare defined by 1:50,000 in England and Wales

The prevalence of deafness in paediatric patients treated with cisplatin is estimated to be very rare – **1 case per 264,000 people in England and Wales per year** (rounded to the nearest whole thousand):

- While NICE would traditionally use a prevalence statistic to define how rare a disease is during the health technology assessment (HTA) eligibility assessment, Fennec Pharmaceuticals feel that this is not a reflective measurement for this population as prevalence statistics are traditionally a summary of the whole population across all time. However, the lifetime prevalence is not relevant for Pedmarqsi as it is administered only alongside cisplatin, and the time on treatment with cisplatin for initial management of localised tumours is less than 1 year. As such, when defining the eligible population for Pedmarqsi, it is more reflective to identify the annual incident population size for the key paediatric solid tumours treated with cisplatin:
  - Intracranial and intraspinous tumours
  - Ependymomas
  - Neuroblastomas
  - Retinoblastomas
  - Hepatoblastomas
  - Osteosarcomas
  - Malignant extracranial germ cell tumours
  - Malignant gonadal germ cell tumours
- The incidence rates for the above cancers are reported within the CTYA UK cancer incidence 1997-2016 statistics, these can be used to infer the rarity of the disease in any given year since the frequency of each tumour is not changing over time – within this cohort the most recent data cut is 2012-2016, which is used within Fennec Pharmaceutical's subsequent calculations.

Summary of calculations

1. Firstly, the calculations are based on the list of cancers above, which are those solid tumours most common in the paediatric population which are treated with cisplatin.
2. Following this identification, only a proportion of patients will have localised disease (the remainder having metastatic disease). The following proportions for localised disease per cancer sub-group are applied to remove those not aligned to Pedmarqsi's label. Where a range has been used, a median value has been used for calculations:
   - 69-83% of intracranial and intraspinous tumours,[8,12] median 75.8%
   - 90% of ependymomas,[12]
   - 26-32% of neuroblastomas,[8,12] median 28.8%
   - 90-97% of retinoblastomas,[12,13] median 93.7%
   - 66-86% of hepatoblastomas,[8,12] median 76.2%
   - 69-74% of osteosarcomas,[8,12] median 71.4%
   - 56% of malignant extracranial germ cell tumours,[8]
   - 56-65% of malignant gonadal germ cell tumours,[8,12] median 60.5%
3. Further, it is assumed that only a proportion of paediatric patients with localised cancers will receive a chemotherapy regimen containing cisplatin and therefore be eligible for Pedmarqsi. For subsequent calculations, a flat-rate estimate across all cancer subgroups of 70% of patients being treated with cisplatin is applied.
4. The CTYA UK cancer incidence statistics are for the UK, and grouped by age categories of 0-24 years, meaning calculations are applied to reduce the population size to be reflective of only the population aged under 18 years in England and Wales.
5. Finally, as the above will only present the average size of the population from 2012 to 2016, the value must be inflated to a 2023 value. To do this, it is calculated that a population growth rate of 0.80% (the average growth rate of the population of England and Wales from 2012 to 2016) is applied, compound, from the median point in the data read out.

Based on the above, Fennec Pharmaceuticals are confident in their assessment that the condition requiring treatment is classed as "very rare" in England and Wales with **1 case per 264,000** people in England and Wales per year (rounded to the nearest whole thousand).

2. The population eligible for treatment in England and Wales is very small

- As indicated above, identifying a prevalent population for Pedmarqsi eligibility in England and Wales is not possible due to the duration of initial treatment with cisplatin being less than 1 year, and Pedmarqsi only being administered concurrently after cisplatin. This means calculations used in the above section to show Pedmarqsi's status as "very rare" can also be leveraged here to identify the annual incidence.
- In England and Wales, accounting for whether patients are likely to be treated with a cisplatin chemotherapy, and the proportion of localised disease at diagnosis, Fennec Pharmaceuticals estimate the number of children eligible to receive Pedmarqsi, is **227 children per year,**[1] (see Table 2: Eligible population).
- It is not considered that any patients other than those identified above will be eligible to receive Pedmarqsi. The provision of Pedmarqsi to children at risk of ototoxicity as a HST is provided for under Schedule 4 (Services for rare and very rare conditions), article 107: "Specialist Cancer Services for children and young people", since Pedmarqsi will only be given to children with localised solid tumour diagnoses and receiving cisplatin chemotherapy.

- Fennec Pharmaceuticals are not researching nor intending to pursue any other licensed indication within oncology or outside oncology.

Summary of calculations:

- As presented above, Stages 1 to 5 are also used to calculate the value of **227 children per year** (Table 2: Eligible population).

3. The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life

- Cisplatin-induced ototoxicity is a bilateral, progressive, irreversible, sensorineural hearing loss. It occurs in around 60% of children treated with cisplatin and begins when the first dose of cisplatin administered, progressing after each subsequent dose.[2]
- The extent of hearing loss depends on age and cumulative cisplatin dose; younger age and higher cumulative cisplatin dose increase the risk of hearing loss.
- The effects of cisplatin-induced hearing loss are lifelong. In very young (pre-lingual) children hearing loss leads to poor development of verbal skills, difficulty with communication and understanding, academic delay, and delayed social development. In school-aged children, hearing loss impacts school performance, psychosocial behaviour, emotional development and leads to social isolation, behaviour issues, problems with self-esteem and increased stress. For adolescents the effects damage academic performance, cause social isolation, under-employment and in some cases the inability to live independently.[14–17]
- The National Deaf Children's Society reports that deaf children with poor communication skills are more likely to suffer neglect and emotional abuse.[18]
- The St. Jude Lifetime Cohort Study examined adult social outcomes in survivors of childhood CNS (central nervous system) and non-CNS tumours.[19] The study examined the proportion of childhood cancer survivors with severe hearing loss and found this in 39% of non-CNS and 36% of CNS tumour survivors. In non-CNS tumour survivors this was associated with an increased risk, compared to those without hearing loss, of not living independently (Odd ratio 2.19; 95% CI 1.19-4.04), never having married (OR, 1.61; 95% CI, 0.81-3.20) and not graduating or being unemployed (OR, 1.85; 95% CI, 1.02-3.35) and 20% of non-CNS tumour survivors used hearing aids or had cochlear implants. In CNS tumour survivors, 69% (95% CI 62-76%) were not living independently, 79% (95% CI 72-85%) never married and 61% (95% CI 54-68%) had not graduated or were unemployed. 48% CNS tumour survivors used hearing aids or cochlear implants.
- While cisplatin use in paediatric solid tumours leads to very high survival chances, it is clear that the long term effects of hearing loss seriously impact a child's potential and severely interfere with their quality of life.
- For those with normal hearing to experience hearing loss there are simulators available at https://www.ndcs.org.uk/information-and-support/childhood-deafness/what-is-deafness/what-does-hearing-loss-sound-like/

4. There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.

- There are currently no other treatments to prevent cisplatin-induced ototoxicity other than Pedmarqsi.
- Currently, there are anecdotal attempts to reduce the development of ototoxicity by reducing the dose of cisplatin or removing cisplatin from the treatment regimen. But this is usually only done after a child has already experienced ototoxicity from cisplatin doses already administered. Since the toxicity is irreversible it will simply slow hearing loss deterioration or prevent further hearing loss. The Company are

not aware of any specific studies where a randomised trial of lower doses of cisplatin has been used to evaluate the effects of this strategy on hearing loss and survival.

- There are no treatments for the reversal of hearing loss once it has occurred. Management of the effects of ototoxicity is focused on alleviation of the problems children experience including speech therapy, classroom aids such as FM (frequency modulation) devices, sign language, lip reading or interventions such as hearing aids and cochlear implants. While these interventions work towards reducing the impact of hearing loss, none restore normal hearing. Additionally, children may be resistant to such interventions, such as declining to wear their hearing aids, or to use devices because of fear of social stigma. Children require devices to be checked and replaced regularly to ensure they are the right size and finely tuned to their hearing needs; this creates a carer burden with parents who often find intervention management challenging to keep up with.
- Preventing hearing loss caused by cisplatin is therefore an important step in ensuring childhood cancer survivors can survive without a permanent hearing disability.

Fennec Pharmaceuticals believe that Pedmarqsi therefore fulfils all the HST programme criteria and should be considered for HST routing.

Table 1: Cancer diagnosis in England and Wales

Number of patients diagnosed with all cancer	Number diagnosed in 2016 to 2018 in England	Number diagnosed in 2016 to 2018 in Wales	Number diagnosed in 2016 to 2018 in England and Wales	Estimated number diagnosed in England and Wales (inflated to a 2023 population)
Aged 0-14 years[a]	1,562	75	1,637	
Aged 15-24 years[b]	2,007	104	2,111	
Aged 0 to <18 years			2,270	**2,357**

[a]Taken from Cancer Research UK, children's cancers incidence statistics.[20]

[b]Taken from Cancer Research UK, young people's cancers incidence statistics.[21]

Table 2: Eligible population

Newly diagnosed tumours potentially treated with cisplatin chemotherapy	Number of patients diagnosed 2012 to 2016 in the UK. *(Aged 0 to 19 years)*	Estimated number of patients diagnosed 2012 to 2016 in the UK. *(Aged 0 to <18 years)*	Estimated number of patients diagnosed 2012 to 2016 in England and Wales. *(Aged 0 to <18 years)*	Mean number of patients diagnosed per year	Estimated number of patients diagnosed with localised disease[a]	Estimated number of patients treated with cisplatin chemotherapy[b]
Intracranial and intraspinous tumours	463	417	371	93	70	49
Ependymomas	314	283	252	63	57	40
Neuroblastomas	533	480	427	107	31	22
Retinoblastomas	221	199	177	44	41	29

Hepatoblastomas	110	99	88	22	17	12
Osteosarcomas	364	328	292	73	52	36
Malignant extracranial germ cell tumours	158	142	127	32	18	12
Malignant gonadal germ cell tumours	136	123	109	27	16	12
Total	2,299	2,071	1,843	461	302	212
Total – inflated to a 2023 population					**325**	**227**

[a]Taken from ACCL0431 study and literature for those tumours not represented in the study.
[b]Based on Appendix B CTYA cancer incidence, birth to 19 years from 2012-2016.[22]