Life Saving Drugs Program (LSDP): Review of Medicines for Hereditary Tyrosinaemia Type 1 (HT1)

Review summary and Expert Panel recommendations

Purpose of the HT1 review

Nitisinone (Orfadin®) was listed on the LSDP for treatment of HT1 on 1 June 2016. Nityr™ (generic nitisinone) was listed on LSDP for treatment of HT1 on 1 May 2019; however, only Orfadin® was within scope of the review. The Expert Panel considered this review at its October 2020 meeting and out of session.

This review of nitisinone sought to develop a better understanding of this LSDP medicine by comparing its current use against the recommendations and expectations at the time of listing.

The review further aimed to assess the clinical benefits achieved through the use of nitisinone; ensure the ongoing viability of the LSDP; and ensure testing and access requirements for nitisinone remain appropriate. It identified immediate and future changes that may be required to the funding criteria for nitisinone and to the LSDP more broadly.

The review of each of the LSDP medicines was supported by an approved disease specific Review Protocol, which was structured around seven terms of reference (ToRs). The ToRs were tailored specifically to each disease and the relevant medicine(s).

HT1 medicine review terms of reference

1. Review the prevalence of HT1 in Australia.
2. Review evidence for the management of HT1 and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of nitisinone on the program (including the validity of the tests).
3. Review clinical effectiveness and safety of nitisinone for the treatment of HT1, including analysis of LSDP patient data and international literature to provide evidence of life extension.
4. Review relevant patient based outcomes that are most important or clinically relevant to patients with HT1.
5. Assess the value for money of nitisinone under the current funding arrangements by evaluating the benefit of its treatment outcomes and cost.
6. Review the utilisation of nitisinone including storage, dispensing and evidence of patient compliance to treatment.
7. Investigate developing technologies that may impact future funded access.

Key findings and recommendations from the Expert Panel

ToR 1 – Review the prevalence of HT1 within Australia

The Expert Panel noted the prevalence of HT1 in Australia is best estimated as 1 per million, which is less than the 1 per 50,000 threshold for a rare disease on the LSDP. The prevalence does not appear to have changed significantly since nitisinone was first listed on the LSDP in 2016.

The Expert Panel noted the current approach to newborn bloodspot screening (NBS) in Australia is unlikely to detect all patients. The Expert Panel also noted the introduction of succinylacetone-based NBS could result in some patients being identified at a younger age, resulting in an earlier initiation of nitisinone treatment and increased use of nitisinone. Succinylacetone-based NBS was not available in Australia at the time of the review but appeared to be an effective tool to identify patients and lead to earlier treatment. The Expert Panel noted that NBS is outside its remit and that of the LSDP.

Recommendation 1:

The Expert Panel considered that HT1 meets the LSDP prevalence criterion of less than 1:50,000 and on that criterion currently remains suitable for inclusion on the LSDP.

ToR 2 – Review evidence for the management of HT1 and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of nitisinone on the program (including the validity of the tests)

The Expert Panel noted there were no major inconsistencies between LSDP treatment guidelines and best practice.

There was ambiguity around whether the LSDP criteria allowed use post-liver transplant. There was no indication that best practice involved use of nitisinone in the post-liver transplant population, although the Therapeutic Goods Administration indication for nitisinone did not exclude use in these patients. The Expert Panel noted there was a lack of safety and efficacy evidence concerning the use of nitisinone in patients with HT1 post-liver transplant. The sponsor stated it did not recommend the use of nitisinone in this patient group.

Recommendation 2:

The Expert Panel recommended amending the eligibility guidelines to exclude use in patients post-liver transplant.

ToR 3 – Review clinical effectiveness and safety of nitisinone for the treatment of HT1, including analysis of LSDP patient data and international literature to provide evidence of life extension

The Expert Panel noted that despite limitations of the evidence, nitisinone appeared to be an effective and safe treatment for HT1. Nitisinone also appeared to extend survival in patients, although the extent remained uncertain due to a lack of long-term data.

The Expert Panel noted various published studies have identified neurocognitive impairment in some patients with HT1, although it was unclear whether there was a causal relationship to nitisinone.

There was also a lack of evidence indicating whether nitisinone is safe and effective to use in patients with HT1 post-liver transplant.

Recommendation 3:

The Expert Panel noted that there was evidence that nitisinone extends survival for patients with HT1, although the extent is unclear. Based on the evidence identified through the Review, the Expert Panel advised that nitisinone remains suitable for listing on the LSDP.

ToR 4 – Review relevant patient based outcomes that are most important or clinically relevant to patients with HT1

The Expert Panel noted survival and quality of life outcomes are of most importance to patients with HT1 and their carers.

The Expert Panel discussed the option of providing two months' supply of nitisinone to patients. The Expert Panel noted alternative methods of supply had been utilised during the COVID pandemic and supply of increased quantities improved convenience for patients. The Expert Panel also noted the potential for wastage (discarded product after bottle opened) was substantially increased when increased quantities were supplied. The Expert Panel concluded there was no justification for more than one month's supply of medication for this condition.

The Report noted there was limited reporting of clinical data into the LSDP for patients with HT1. This resulted in gaps in LSDP data. Considering the rarity of HT1, the Expert Panel noted it may be of benefit to reassess which clinical data are requested.

The Expert Panel noted there was substantial variation in clinical practice around dosing. The Expert Panel also noted one treating physician's request for an easier and more rapid process to change the LSDP-approved dose.

Recommendation 4:

The Expert Panel noted that the approach to data collection and analysis required improvement. The availability of consistent and complete data extracted from initial and ongoing applications to the program is essential. The LSDP should implement a streamlined solution that enables treating physicians to enter patient data both for everyday administration of the program and for future reviews of new medicines. The Expert Panel recommended that this revised approach should improve treating physician and patient satisfaction and facilitate availability of complete and comprehensive data for any future review of nitisinone.

Recommendation 5:

The Expert Panel considered that treating physicians should be made aware of the process for dose adjustments outside of the annual reapplication process.

ToR 5 – Conduct an analysis of the value for money of nitisinone under the current funding arrangements by evaluating the benefit of its treatment outcomes and cost

The average total annual cost of treating an HT1 patient with LSDP nitisinone in 2019 was $[redacted].

The Expert Panel noted value for money was better than expected for nitisinone, per patient, driven by lower dosing (in mg/kg) than anticipated, and also by a price decrease in May 2019. A true value for money assessment remained uncertain, given that the modelled benefit was extrapolated beyond trial data.

The incremental cost per life-year gained, post price reduction, may be 35 to 40 percent lower than was expected at the time of LSDP listing. An incremental cost per quality-adjusted life-year of $[redacted] was estimated.

Recommendation 6:

The Expert Panel noted that there appeared to be a survival gain and improvement in quality of life from treatment with nitisinone, and that the cost of nitisinone remained very high. The Expert Panel therefore recommended that pricing and listing arrangements for nitisinone be reassessed with the goal of improving value for money when:

(i) current deed of agreement with sponsor expires; and/or

(ii) new medicines for HT1 are considered for entry onto the LSDP or other subsidy programs; and/or

(iii) changes in eligibility criteria are being considered.

ToR 6 – Review the utilisation of nitisinone, including the way it is stored and dispensed, and evidence of patient compliance to treatment

The number of patients, dose (mg/kg), and expenditure on nitisinone were all lower than expected at the time of listing. In 2018, total LSDP expenditure on nitisinone was $[redacted].

Patients appeared to be largely compliant with treatment, and there were no concerns around product wastage as only one month supply is provided to patients. There did not appear to be any use beyond the LSDP eligibility criteria.

ToR 7 – Investigate developing technologies that may impact future funded access

The Expert Panel noted from the Report there were gene therapies being researched for the treatment of HT1 but these were not likely to have an impact on the use of nitisinone and the LSDP in the near future.

Should succinylacetone-based NBS be introduced in Australia, earlier diagnosis of HT1 could benefit a small number of patients who may have otherwise been diagnosed later. This

may have flow on effects for the cost-effectiveness of nitisinone. Again, the Expert Panel noted there was no indication that succinylacetone-based NBS would be introduced in the immediate future. The Expert Panel also noted that NBS was outside its remit and that of the LSDP.

Next Steps

The then Minister for Health, the Hon Greg Hunt MP, agreed to these recommendations on 29 March 2022. The implementation of these recommendation is currently being considered and progressed by the Department of Health and Aged Care in consultation with sponsors, treating physicians and patient advocacy groups.