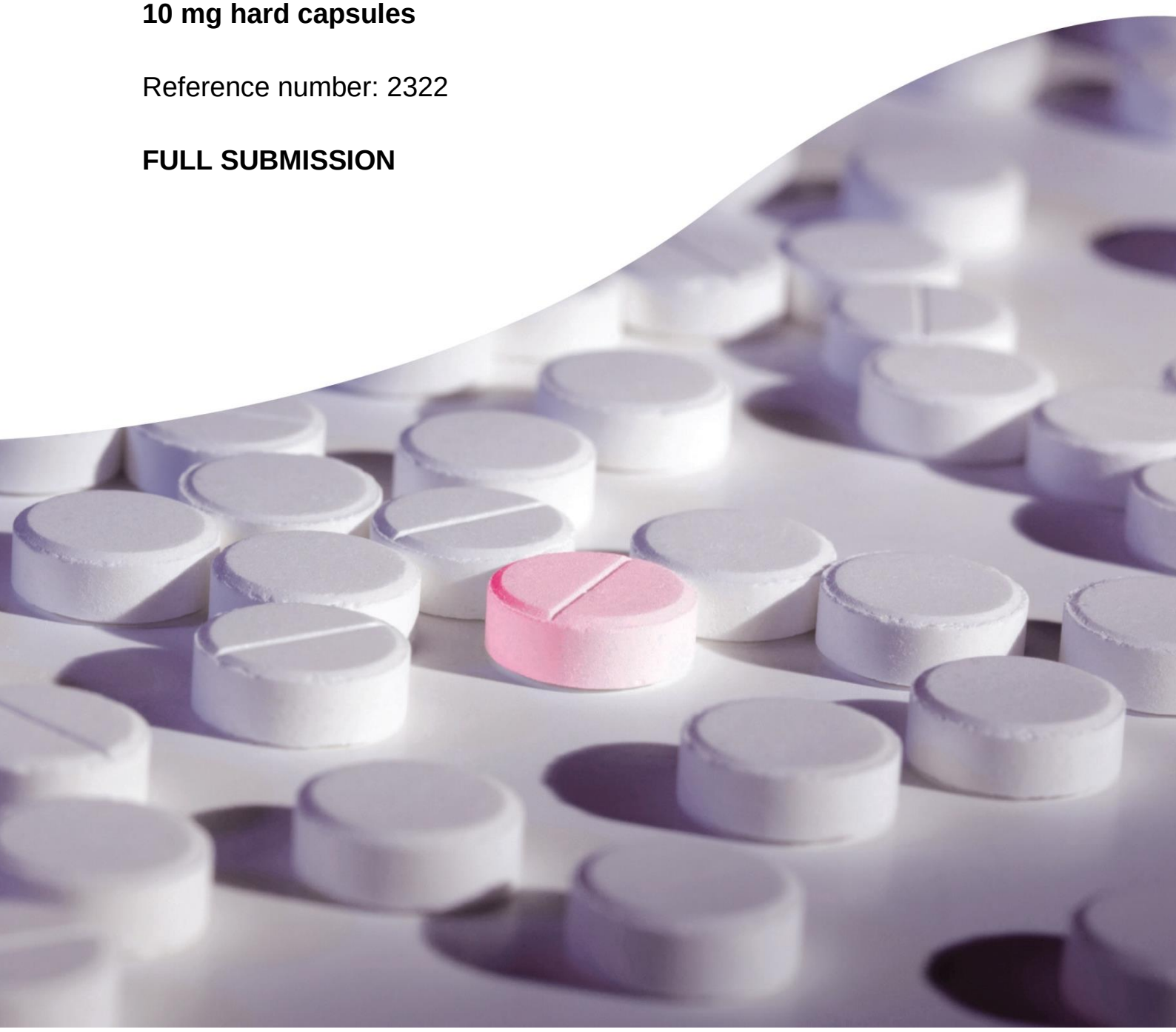
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Nitisinone (Orfadin®)
10 mg hard capsules

Reference number: 2322

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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AWMSG Secretariat Assessment Report
Nitisinone (Orfadin®) 10 mg hard capsules

1.0 KEY FACTS

Assessment details	Nitisinone (Orfadin®) for the treatment of adult patients with alkaptonuria.
Current clinical practice	There are currently no other licensed medicines available for the treatment of alkaptonuria and current clinical practice is limited to best supportive care. This includes regular outpatient appointments, physiotherapy, surgery and analgesia. Clinical experts indicate a significant unmet need in this population and an absence of any alternative active treatments that are able to prevent or stabilise clinical manifestations of this condition.
Clinical effectiveness	In the pivotal study SONIA 2, nitisinone treatment decreased 24 hour urinary homogentisic acid excretion and serum homogentisic acid concentrations. The benefit of nitisinone was also demonstrated by a trend across key secondary endpoints measuring changes including the All Alkaptonuria Severity Score Index and Quality of Life questionnaires. Additional supportive evidence from SONIA-1, demonstrated a clear dose-response relationship between nitisinone and the urinary excretion of homogentisic acid. An increase in tyrosine levels was seen at all doses but the dose-response relationship was less clear than the effect on homogentisic acid. Nitisinone is also licensed in adults and paediatric patients with hereditary tyrosinaemia type 1, at the daily dose of 1 mg/kg body weight, which is larger than the 10 mg fixed dose for the alkaptonuria indication in adults. Due to the mode of action, nitisinone increases tyrosine levels which has been associated with toxicity to eyes, skin, and the nervous system. However, when patients are prescribed nitisinone, they are also advised to follow a controlled protein diet. Overall, no safety concerns were identified at any of the tested doses of nitisinone in SONIA 1 and number of patients with adverse events was similar between treatment and no-treatment groups in SONIA 2.
Cost-effectiveness	No cost-effectiveness evidence is included in the submission.
Budget impact	It is estimated that 12 patients are eligible to receive treatment with nitisinone in Wales in Years 1 to 5. The base case suggests this will incur an additional cost of [commercial in confidence text removed] per annum. The base case also predicts additional NHS resource costs valued at £1,620 per year, resulting from increased monitoring requirements. The budget impact considerations are limited to medicine acquisition and monitoring costs only; other resource use

	associated with adverse events is not included. The omission of these costs is likely to underestimate the resource use associated with the administration of Orfadin®.
Additional factors to consider	Nitisinone (Orfadin®) is the first licensed medicine for the treatment of alkaptonuria and is already available for patients in England through national commissioning. AWTTC consider nitisinone eligible to be considered as an ultra-orphan equivalent medicine.

This assessment report is based on collaboration with Swedish Orphan Biovitrum Ltd (Sobi Ltd) and an evidence search conducted by AWTTC on 10 May 2021

2.0 BACKGROUND

2.1 Condition and clinical practice

Alkaptonuria (AKU) is a rare, autosomal recessive disorder that results from deficiency of homogentisate 1,2-dioxygenase (HGD), an enzyme of the phenylalanine and tyrosine catabolic pathway. The absence of this enzyme leads to accumulation of homogentisic acid (HGA) which oxidises to a melanin-like pigment polymer in urine, plasma, cartilage and connective tissues, a process termed ochronosis. Symptoms of AKU include dark colouration of urine, joint problems, cardiovascular complications, breathing difficulties as well as pigmentation of eyes (sclera) and ear cartilage[1,2].

AKU is caused by a single gene defect and more than 80 mutations in the HGD gene have been identified[2]. There is an estimated prevalence of between 1:250,000 and 1:1,000,000 worldwide[3]. In 2019/20 there were 12 Welsh patients registered at the National Alkaptonuria Centre (NAC) in the UK. While dark urine may be present from birth, it is often missed or ignored. Additional symptoms are generally slowly progressive and may not be noticeable until adulthood[4].

AKU is a lifelong condition and, while it does not seem to reduce life expectancy, the disease is characterised by multiple manifestations which may be life limiting[1]. These include renal failure, haemolysis, spondylo-arthropathy and cardiovascular issues such as aortic or mitral valve calcifications, regurgitation and aortic valve stenosis[4]. Surgery may be needed to replace blocked heart valves or vessels and 50% of patients require at least one joint replacement by age 55 years[3,4].

Currently, there is no pharmacological treatment approved for patients with AKU in Wales and treatment options are limited to best supportive care of symptoms, including physiotherapy, surgery and analgesia[1].

2.2 Medicine

Nitisinone is a competitive inhibitor of the enzyme, 4-Hydroxyphenylpyruvate dioxygenase (HPPD), which metabolizes 4-Hydroxyphenylpyruvate (HPP) to HGA. It prevents the accumulation of harmful metabolites downstream of 4-hydroxyphenylpyruvate dioxygenase by inhibiting the normal catabolism of tyrosine[5]. Due to the inhibition of HPPD, treatment with nitisinone leads to increased serum concentrations of tyrosine. High levels of tyrosine may lead to ocular signs and symptoms and adverse effects on the skin[1].

Nitisinone (Orfadin®) was granted marketing authorisation by the European Medicines Agency (EMA) in October 2020 for the treatment of for the treatment of adult patients

with AKU[1]. Nitisinone is the first licensed medicine for the indication under consideration.

The licenced dose in the adult AKU population is 10 mg once daily orally. Patients should also be encouraged to follow a controlled protein diet to keep the plasma tyrosine level below 500 micromol/l. It is recommended that plasma tyrosine levels should be monitored in patients who develop keratopathies. Nitisinone should be temporarily discontinued and may be reintroduced when the symptoms have been resolved[5].

2.3 Comparators

No comparators have been identified, the marketing authorisation holder and clinical expert suggest best supportive care as the comparator. Best supportive care may include physiotherapy, surgery and analgesia.

2.4 Guidance and related advice

- NHS England Manual For Prescribed Specialist Services 2018/2019 (2018)[6]
- NHS England Highly Specialised Services 2018[7]
- NHS England 2013/14 NHS Standard Contract for Alkaptonuria Service (Adults). Ref: E06/S(HSS)/a (2013)[8]
- NHS England 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). Ref: E06/S/a (2013)[9]

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, nitisinone (Orfadin®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that nitisinone (Orfadin®) may be supplied by a home healthcare provider.

3.0 CLINICAL EFFECTIVENESS

The evidence considered in this appraisal includes a dose-response study, SONIA 1 and main pivotal study, SONIA 2.

3.1 SONIA 1

SONIA 1 was an international, multicentre, randomised, open-label, no-treatment controlled, parallel-group, dose-response study[10]. The objective was to identify the nitisinone dose that lowers urinary excretion of HGA to as normal, or near normal, levels. The primary endpoint was 24 hour urinary HGA excretion (u-HGA_{24}) in patients with AKU after 4 weeks of treatment. Secondary endpoints to support the primary endpoint included urine HGA excretion adjusted per mol of urine creatinine ratio at weeks 2 and 4.Other secondary endpoints included pre-dose serum concentration of HGA (s-HGA) and serum concentration of Tyrosine (s-Tyr) at weeks 2 and 4. Patients ≥ 18 years old (n = 40) were randomised into five groups of eight patients each, with groups receiving no treatment (control), and oral daily doses of nitisinone of 1 mg, 2 mg, 4 mg and 8 mg[10].

At week 4, a clear dose-response relationship between nitisinone dose and u-HGA_{24} was observed[10]. The greatest reduction in u-HGA_{24} was seen with the 8 mg dose. The urine HGA excretion adjusted per mol of urine creatinine ratios confirm the results seen for the u-HGA_{24} values without creatinine correction, and indicate acceptably complete 24 hour urine collection[10].

Before treatment, s-HGA was quantifiable in all patients. After treatment, s-HGA values were below the lower limit of quantification (3.1 micromol/l) in 56% of all samples collected in treated patients. Mean s-Tyr increased with dose post nitisinone treatment. There was large inter-individual variability in the data, but most nitisinone-treated patients had levels above 500 micromol/l after 4 weeks, with the highest observation (1,117 micromol/l) seen for a patient in the 4 mg group[10].

3.2 SONIA 2

SONIA 2 was an international, multicentre, randomised, evaluator-blinded, no-treatment controlled, parallel-group study to assess the efficacy and safety of nitisinone in patients with AKU after 48 months of treatment[11].

The primary endpoint was u-HGA_{24} after 12 months[11]. The main secondary endpoint included an evaluation of treatment effect on the All Alkaptonuria Severity Score Index (AKUSSI score) at 48 months against baseline. The AKUSSI measures disease severity in clinical, joint and spine domains. Two types of AKUSSI score were used in this trial; cAKUSSI (with pigmentation) and mAKUSSI (without pigmentation)[11].

Other secondary endpoints included u-HGA_{24} after 3, 24, 36 and 48 months; occurrence of achieved target level (<300 µmol) of u-HGA_{24} at 3, 12, 24, 36 and 48 months; s-HGA at 3, 12, 24, 36 and 48 months; joint, spine and pre-defined rheumatology assessments at 12, 24, 36 and 48 months and change from baseline quality of life (QoL) measured by SF-36 at 12, 24, 36 and 48 months[1,11].

Patients aged ≥ 25 years with raised HGA and any clinical manifestation (n = 138) were randomly assigned (1:1) to receive either oral nitisinone 10 mg daily or no treatment. Fifty five patients in the nitisinone group and 53 in the control group completed the study[11].

Nitisinone treatment dramatically reduced the excretion of u-HGA_{24} reaching a nadir at month 3 and at 12 months was significantly decreased by 99·7% in the nitisinone group compared with the control group (adjusted geometric mean ratio of nitisinone/control 0·003 [95% Confidence Interval [CI] 0·003 to 0·004], $p < 0·0001$), see Table 1[11]. The proportion of subjects who had u-HGA levels below the pre-defined cut-off of 300 micromol was 88.4% at month 12, but decreased to 59.4% at month 48. This could be due to patient compliance to treatment, which was lower at month 48 compared to month 12 (85.5% and 100.0% respectively)[1].

At month 48, the increase in cAKUSSI score from baseline was significantly lower in the nitisinone group compared with the control group (adjusted mean difference –8·6 points [–16·0 to –1·2], $p = 0·023$). The difference between the two groups in change in mAKUSSI from baseline was not statistically significant (adjusted mean difference –3·6 [–9·6 to 2·4], $p = 0·23$; table 2). However, a continuous increase in mAKUSSI was seen in the control group from baseline to month 48, whereas a slower increase was seen in the nitisinone group (see Table 1)[11].

Table 1. Primary and main secondary endpoints from SONIA 2[11]

	Baseline		Month 12*		Month 48	
	Control	Nitsinone	Control	Nitsinone	Control	Nitsinone
HGA						
u-HGA$_{24}$, micromol						
Mean (SD)	35,394 (13,869)	35,019 (13,124)	26,444 (10,397)	179 (398)	33,207 (10,160)	1,569 (6,220)
Adjusted geometric mean, ratio nitisinone/ control (95% CI)	..	N/A	..	0·003 (0·003 to 0·004)	..	0·005 (0·003 to 0·008)
Serum HGA, millimol/L						
Mean (SD)	28·26 (8·66)	30·35 (10·98)	28·93 (13·04)	0·71 (1·63)	37·08 (21·03)	2·80 (7·33)
Adjusted geometric mean, ratio nitisinone/ control (95% CI)	..	N/A	..	0.01 (0·01 to 0·02)	..	0·02 (0·02 to 0·03)
AKUSSI						
cAKUSSI score						
Mean (SD)	80·5 (33·4)	87·0 (34·2)	80·1 (34·7)	84·5 (33·7)	95·6 (36·0)	93·7 (37·8)
Adjusted geometric mean, ratio nitisinone/ control (95% CI)	..	N/A	..	–2·5 (–5·7 to 0·7)	..	–8·6 (–16·0 to –1·2)
mAKUSSI score						
Mean (SD)	54·1 (24·9)	56·7 (26·7)	54·8 (25·7)	57·5 (26·8)	66·7 (29·7)	66·1 (31·1)
Adjusted geometric mean, ratio nitisinone/ control (95% CI)	..	N/A	..	–0·5 (–2·5 to 1·6)	..	–3·6 (–9·6 to 2·4)

* Primary end point
AKUSSI:Alkaptonuria Severity Score Index; cAKUSSI: clinical evaluation AKUSSI; mAKUSSI: modified AKUSSI; CI: confidence interval; HGA: homogentisic acid; u-HGA$_{24}$: daily urinary HGA excretion; N/A: not applicable; SD: standard deviation.

At month 12, the adjusted geometric mean s-HGA in the nitisinone group had statistically significantly decreased by 98·8% compared with the control group (adjusted geometric mean ratio of nitisinone/control 0·01 [95% CI 0·01–0·02]; p < 0·0001). At each visit after baseline, s-HGA was statistically significantly lower in the nitisinone group compared with the control group (p < 0·0001)[11].

3.3 Safety

Nitisinone is also licensed in adults and paediatric patients with hereditary tyrosinaemia type 1 (HT-1), at the daily dose of 1 mg/kg body weight, which is larger than the 10 mg fixed dose for the AKU indication in adults[1]. Due to the mode of action, nitisinone increases tyrosine levels and may cause eye-related adverse reactions, such as conjunctivitis, corneal opacity, keratitis, photophobia and eye pain[5].

In the SONIA 1 study, all adverse events (AEs) were mild, except for one event of moderate back pain in the 4 mg dose group there were no serious adverse events (SAEs) reported[10]. An increase in tyrosine levels was seen at all doses but the dose-response relationship was less clear than the effect on HGA, no patient experienced any corneal effects. Overall, no safety concerns were identified at any of the tested doses of nitisinone over 4 weeks[10].

In SONIA 2 the number of patients with AEs was similar between treatment (n = 59) and no-treatment groups (n = 57)[11]. The number of patients with SAEs was also similar between the two groups. The most common treatment emergent AEs reported with higher frequency with nitisinone compared to untreated group were within the musculoskeletal and connective tissue[1]. There was a slightly higher frequency of SAEs in the nitisinone group compared to control, the most common were musculoskeletal and cardiac disorders[1]. Eye disorders were the third most commonly reported AEs, markedly more frequent in the nitisinone group (36.2%) compared to control (11.6%). Eye disorders were the most common cause for discontinuation in the nitisinone group (8.7% versus 0 in the control group)[1]. Nitisinone was withdrawn in patients who developed signs of ocular tyrosine-related AEs. If possible, treatment was reintroduced once the symptoms had resolved at a lower dose (2 mg daily). If ocular tyrosine-related symptoms reappeared on the lower dose, nitisinone was permanently withdrawn and the patient was monitored until the symptoms resolved[11].

3.4 AWTTC critique

- Nitisinone (Orfadin®) is currently the only licensed treatment for AKU in the UK. Clinical experts indicate there is a significant unmet medical need for therapies that are able to prevent or stabilise ochronosis and the associated systemic manifestations.
- The National AKU Centre (NAC), based at the Royal Liverpool University Hospital, was established by the Department of Health (National Specialised Services Commissioning Group) in 2012. It delivers expert monitoring of disease and treatment by an experienced multidisciplinary team. Nitisinone is available to patients in England through NHS England Commissioning and is prescribed by specialists at NAC[6,12]. Although patients in Wales have accessed NAC through funding by the Welsh Health Specialised Service Committee (WHSSC), they do not receive nitisinone through this package of care. Nitisinone for treating AKU was proposed on the NICE work programme, however, it was concluded that an appraisal would not add value to the NHS. NICE highlight this decision should have no impact on existing commissioning arrangements for nitisinone[13]. There is therefore inequity of access to and a lack of advice for nitisinone for Welsh patients.
- Nitisinone meets the criteria for appraisal by AWMSG. Clinical experts and patient representatives have consistently raised the issue of a lack of advice for

Welsh patients. The marketing authorisation holder, Sobi Ltd, highlight they have worked with clinicians, patients and their representatives in progressing the licensed indication for AKU for which there are no alternative treatment options. However, they are not in a position to facilitate a full cost-effectiveness analysis due to a lack of resource and the imminent introduction of generics for this indication. The company have engaged with AWTTC and submitted a Wales Patient Access Scheme (WPAS).

- From the clinical development program of nitisinone in HT-1 and its effects on HGA, it was hypothesised that if HGA levels were reduced to, and maintained at, normal, or near normal levels in AKU patients before the onset of overt ochronosis (i.e. blue-black pigmentation), this might prevent the development of the debilitating clinical features of the disease[1]. Additionally, for those who have already developed some degree of ochronosis, nitisinone could slow down further progression and reduce incidence of related consequences. Through SONIA 1 the Committee for Medicinal Products for Human Use (CHMP) accepted the validity of u-HGA as a surrogate endpoint to test treatment effect and also requested correlation between this endpoint and long term clinical outcomes[1]. The pivotal study, SONIA 2, met its primary and secondary endpoint (cAKUSSI score) with demonstrated correlation between nitisinone treatment and clinical benefit. Despite the lack of statistical significance in the total population for the mAKUSSI score, overall two thirds of the point estimates of the individual mAKUSSI items favoured the nitisinone group[1,11]. In addition, the marketing authorisation holder completed different responder analyses further supporting the consistency between treatment effect across disease manifestations and u-HGA levels[1].
- There were differences noted across treatment arms in SONIA-2, CHMP considered the imbalances in baseline characteristics and differences in clinical guidelines used across the several recruiting countries. In addition, cAKUSSI were clearly driven by effect on eye pigmentation likely indicating a reduced rate of HGA precipitation in the eye but it is not known if similar effect on other tissue is observed[1].
- Nitisinone is already licensed in adults and paediatric patients with HT-1, at the daily dose of 1 mg/kg body weight, that is significantly larger than the 10 mg fixed dose proposal for the AKU indication in adults[1,5]. The safety profile is mainly characterised by the risks posed by treatment-induced elevated tyrosine levels that may be associated with toxicity to eyes, skin, and the nervous system; however, experience suggests nitisinone treatment is commonly associated to eye-related adverse reactions, and less commonly with skin disorders. Clinical experts contacted by AWTTC highlight these are monitored and well managed and understood.
- The literature acknowledges the significant burden AKU has on patients' health and health-related quality of life, and on the NHS in terms of the resource use associated with the clinical manifestations of the disease[14-19]. Aortic valve stenosis is often fatal with and without surgery in this patient group[15]. Patients also experience almost constant pain from age 30 onwards, due to spondylo-arthropathy. Over time, almost all of the joints in the body are affected. Patients can expect to have several joint replacements throughout their lifetime as a consequence[18]. Although the longer-term effects of nitisinone treatment on clinically-meaningful outcomes have yet to be fully determined, clinical experts report having observed positive results with nitisinone treatment.

4.0 COST-EFFECTIVENESS

4.1 Context

A cost effectiveness analysis has not been submitted.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC identified one relevant study published as a conference abstract in 2016[20]. This study assessed the cost-effectiveness of once daily treatment with nitisinone 10 mg compared with no treatment, for patients with alkaptonuria (AKU) in the UK[20,21]. The cost-utility analysis adopted a lifetime time horizon and an NHS perspective. The deterministic incremental cost-effectiveness ratio (ICER) produced was £82,297 per QALY gained. Sensitivity and scenario analyses revealed that the ICER was most sensitive to: discount rates, the annual cost of managing patients with severe AKU, the annual medicine acquisition cost of Orfadin®, the utility of the mild AKU health state, and the assumed effectiveness of nitisinone at slowing AKU disease progression. Notably, there is now a WPAS discount available for this medicine. The current medicine acquisition cost for Orfadin® is lower than it was when these analyses were conducted. New trial data are also available following the completion of SONIA 2[11]. Consequently, the results of these analyses cannot be considered transferable to this current assessment.

The AKU society facilitated a study in 2011 to estimate the average cost of AKU to the NHS[22]. This involved interviews with AKU patients, experts and NHS staff. Typical AKU symptoms were matched with the testing techniques and likely treatments to estimate cost per patient per annum. A number of diagnostic procedures, surgeries and therapies were identified and costed. It was recognised that costs can vary significantly, depending on the staging of the disease. However, the report concluded that there was an average direct cost to the NHS of £100,000 per patient per annum[22]. It is proposed that if patients are treated early enough in their disease progression, the cost of treatment will be somewhat offset by future cost savings, as a consequence of a reduction in clinical manifestations and related required diagnostics, surgeries and therapies[18]. However, evidence to support the long-term benefits is yet to be determined. Furthermore, the benefit of nitisinone to patients with established pigmentation and advanced ochronosis is likely limited; patients achieve greater benefit in terms of prevented morbidity when treatment is started early[19].

With regards to evidence relating to health-related quality of life, the SOFIA study (a cross sectional study of 30 patients with AKU) identified marked deterioration in health-related quality of life after the second decade of life in patients with AKU[23]. The SONIA 2 study also collected SF-36 data[11]. Analysis of the full analysis set identified higher reported health-related quality of life in the nitisinone treatment arm for both the single item measure of self-reported health and the main SF-36 results over the 48 month study period. Forest plots of yearly changes from baseline reveal that improvements were particularly evident in the mental health and social functioning components. The improvements for the single item measure were statistically significant at the each of the four yearly data collection points[11].

5.0 BUDGET IMPACT

5.1 Context and methods

An AWTTC generated budget impact analysis predicts that there will be 12 adults (aged 18 and over) with AKU in years 1 to 5. This estimate is based on prevalence data provided by NAC in the UK, which manages the care of all patients aged 16 and over diagnosed with AKU in Wales. Based on clinical expert opinion, it is assumed that incidence and mortality will in effect cancel each other out in the population estimates. All diagnosed patients are eligible for treatment with nitisinone, receiving a 10 mg once-daily dose. In line with current prescribing patterns elsewhere in the UK, again captured by NAC data, all patients are modelled to receive nitisinone in capsule form. The medicine acquisition cost for Orfadin® is based on a WPAS discounted price. All patients attend the NAC annually as part of standard care, comprising a three-day stay to undergo routine tests and monitoring. Patients receiving nitisinone are also seen in outpatients once yearly for additional monitoring, in keeping with SPC requirements[5]. NAC and additional monitoring costs are sourced from NHS Reference Costs[24] and Personal Social Services Research Unit (PSSRU)[25] respectively. Sensitivity analyses explore the potential impact of improvements in diagnosis as a result of ongoing campaigns to raise awareness of the condition, whereby the population is increased to 13 patients in year 3; and additional monitoring as a consequence of experiencing adverse events.

5.2 Results

The projected budget impact is presented in Table 2, based on the WPAS discounted price. It is estimated that introducing Orfadin® would lead to an overall cost of [commercial in confidence text removed] in each consecutive year, with a cumulative five-year cost of [commercial in confidence text removed]. This estimate incorporates cost differences resulting from medicine acquisition of Orfadin®. Sensitivity analysis exploring an increase in population to 13 patients in year 3, increases the medicine acquisition cost to [commercial in confidence text removed] in years 3 to 5, and the projected five-year cumulative budget impact to [commercial in confidence text removed].

Table 2. Company-reported costs associated with use of Orfadin® for the treatment of AKU

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (all licensed indications*) - see note below	42	42	42	42	42
Sub-population of eligible patients (indication under consideration)	12	12	12	12	12
Uptake of new medicine (%)	100%	100%	100%	100%	100%
Number of patients receiving new medicine allowing for discontinuations	12	12	12	12	12
Medicine acquisition costs in a market without new medicine	£0	£0	£0	£0	£0
Medicine acquisition costs in a market with new medicine	[commercial in confidence text removed]	[commercial in confidence text removed]	[commercial in confidence text removed]	[commercial in confidence text removed]	[commercial in confidence text removed]
Net medicine acquisition costs	[commercial in confidence text removed]	[commercial in confidence text removed]	[commercial in confidence text removed]	[commercial in confidence text removed]	[commercial in confidence text removed]

* Only required if a case is being made for an orphan/ultra-orphan treatment or a medicine developed specifically for rare diseases

The model estimates that net resource implications arising from the introduction of Orfadin® will lead to a cost of £1,620 each consecutive year. This is a consequence of increased monitoring, in keeping with the six monthly requirements detailed in the SPC[5]. Changing the monitoring requirements to an assumed three per annum for patients receiving Orfadin® increases these projected costs to £3,240 in years 1 to 5 consecutively. An increase in population to 13 patients in year 3 increases the projected resource use to £1,755 in years 3 to 5 consecutively. These resource costs are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The eligible patient estimates are based on prevalence data only. Incidence, mortality and discontinuation are not explicitly included in the model. However, the prevalence data are based on real-world data, and are therefore as certain as they can be in terms of identifying the current diagnosed population for this patient group in Wales. Given the rarity of this condition and the associated low incidence, it is assumed that mortality and incidence are effectively balanced. AWTTC-sought clinical expert opinion supported the assumption that the number of patients eligible for treatment is likely to remain constant over the next five years.

- The budget impact considerations are limited to medicine acquisition costs and monitoring costs only; other resource use associated with adverse events is not included. Nitisinone increases tyrosine levels in patients. Consequently, eye-related adverse events, such as eye pain, corneal opacity, keratitis, conjunctivitis, and photophobia, are common in patients treated with nitisinone for AKU[5]. In the pivotal study the incidence of eye-related adverse events was 1 in 10 patients[5]. The omission of these costs is likely to underestimate the resource use associated with nitisinone treatment.
- The analysis includes Orfadin® in capsule form only, which is less costly than the suspension. Exclusion of suspension in the calculations could underestimate the medicine acquisition costs associated with Orfadin®. However, the NAC verified that all adult patients in the UK currently receiving Orfadin® are prescribed capsules.
- Sensitivity analysis explores an increase in the eligible patient population to 13 patients in years 3 to 5. If prevalence is further adjusted to explore the budget impact associated with 26 eligible patients, to reflect the high end of worldwide prevalence estimates[3], this increases the projected net medicine acquisition cost and resource implication to [commercial in confidence text removed] and £3,510 per annum respectively.

6.0 ADDITIONAL FACTORS TO CONSIDER

6.1 Medicines developed to treat rare diseases

Consideration is required as to whether nitisinone should be considered as an ultra-orphan equivalent medicine.

In addition to being indicated for the treatment of adult patients with AKU, nitisinone is licenced for the treatment of adult and paediatric (in any age range) patients with confirmed diagnosis of HT-1 in combination with dietary restriction of tyrosine and phenylalanine.

The literature identifies the prevalence of AKU as being between 1 in 100,000 and 1 in 250,000 in most ethnic groups[26]. This equates to between 11 and 26 patients in Wales, when prevalence estimates are adjusted to reflect the adult population only to align with the licensed indication. NAC data reveals that the prevalence is likely to be at the lower end of this range in Wales. For HT-1, prevalence estimates are between 1 in 100,000 and 1 in 120,000 worldwide[27,28] which equates to between 27 and 32 patients in Wales.

AWTTC consider nitisinone eligible to be appraised as an ultra-orphan equivalent medicine. The full population of the licensed indication is unlikely to exceed the threshold of ≤ 1 in 50,000 people in Wales (or the UK).

New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 3 if they consider nitisinone is a medicine developed to treat a rare disease.

Table 3. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
Severity of the disease	AKU is a rare genetic complex inflammatory multisystem disease which affects multiple organs[29]. AKU results in an accumulation of HGA in the body, which is progressively deposited in connective tissues. As a result, tissues become more rigid, brittle and prone to degradation – a process termed ochronosis[11]. Ochronosis is a chronic process, which leads to clinical manifestations typically observed from 30 years of age, including: spondylo-arthropathy, ruptures of ligaments, tendons and muscles, osteopenia, fractures, valvular heart disease and renal, prostatic, gallbladder and salivary stones[14,19]. There is no cure for AKU. The effects of AKU in the body can have a significant impact on patients' health and health-related quality of life[11,23]. Deposits in the musculoskeletal system result in the need for joint replacements and spinal decompression surgery to manage spinal cord compression. Aortic valve stenosis is often fatal with and without surgery in this patient group[15]. Patients are in near-constant pain from aged 30 onwards, as a result of spondylo-arthropathy[18]. Depression and feelings of isolation are also experienced by this patient group[16].
Unmet need	There is currently no alternative treatment available for this patient group. Care provided tends to be palliative[18]. Analgesia is used to control pain. Physiotherapy helps to manage the musculoskeletal effects of the disease and maintain mobility. Joint replacements are common in the advanced stages of the disease[30].
Innovative nature of the medicine	Nitisinone blocks the enzymes that convert tyrosine into harmful substances, thereby reducing levels of HGA and resultant ochronosis. Nitisinone use does increase tyrosine levels, which can have a harmful effect on the body. It is therefore necessary to carefully monitor and managed tyrosine levels when treating patients with nitisinone, and for patients to be seen by an ophthalmologist without delay if they experience visual disorders during treatment[5].
Societal impact on non-health benefits that may not adequately be captured in the QALY	Nitisinone has the potential to help delay disease progression and the onset of clinical manifestations, such as debilitating arthritis[17]. If realised, these benefits would lessen the burden on patients and carers, in addition to society through reductions in productivity losses.
Does the medicine cure or reverse rather than stabilise the condition?	The SONIA 2 study results suggest that nitisinone significantly decreases u-HGA_{24} levels. Also, nitisinone can reverse the ochronotic process in the ear, and reduce it in the eye. The study data also reveal a statistically significant improvement in the cAKUSSI score. However, no statistically significant differences were found for many of the other measures used in the study, including the mAKUSSI score[11]. The longer-term effects of nitisinone treatment on clinically-meaningful outcomes have also yet to be determined.
Does the medicine bridge a gap to a definitive therapy?	Gene and enzyme replacement therapies are currently unavailable for this condition[18]. Until these therapies can be offered, nitisinone provides a means of slowing the progression of AKU and arresting ochronosis[31].
AKU: Alkaptonuria; AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; HGA: homogentisic acid; NMG: New Medicines Group	

REFERENCES

1. European Medicines Agency. Assessment Report: Orfadin®. Procedure No.: EMEA/H/C000555/II/0071. September 2020. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/orfadin. Accessed May 2021.
2. The AKU Society. Information and Support/AKU Symptoms. Jan 2020. Available at: https://akusociety.org/. Accessed May 2021.
3. Phornphutkul C, Introne W, Perry MB et al. Natural history of alkaptonuria. *New England Journal of Medicine.* 2002;347(26):2111-2121. Available at: https://www.nejm.org/doi/full/10.1056/nejmoa021736. Accessed May 2021.
4. National Organization for Rare Disorders. Alkaptonuria. Available at: https://rarediseases.org/rare-diseases/alkaptonuria/. Accessed May 2021.
5. Swedish Orphan Biovitrum Ltd. Orfadin®. Summary of Product Characteristics. November 2020. Available at: https://www.medicines.org.uk/emc/product/10052/smpc. Accessed May 2021.
6. NHS England. Manual for Prescribed Specialised Services 2018/19. Sept 2018. Available at: https://www.england.nhs.uk/publication/manual-for-prescribed-specialised-services/ Accessed May 2021.
7. NHS England. Highly Specialised Services 2018. Feb 2018. Available at: https://www.england.nhs.uk/commissioning/publication/highly-specialised-services-2018/. Accessed May 2021.
8. NHS England. 2013/14 NHS Standard Contract for Alkaptonuria Service (Adults) Sept 2018. Available at: https://www.england.nhs.uk/publication/201314-nhs-standard-contract-for-alkaptonuria-service-adults-november-2016/. Accessed May 2021.
9. NHS England. NHS Standard Contract for Metabolic Disorders (Adult). Ref: E06/S/A June 2016. Available at: https://www.england.nhs.uk/wp-content/uploads/2016/11/e06-alkapt-children.pdf. Accessed May 2021.
10. Ranganath LR, Milan AM, Hughes AT et al. Suitability Of Nitisinone In Alkaptonuria 1 (SONIA 1): an international, multicentre, randomised, open-label, no-treatment controlled, parallel-group, dose-response study to investigate the effect of once daily nitisinone on 24-h urinary homogentisic acid excretion in patients with alkaptonuria after 4 weeks of treatment. *Annals of the Rheumatic Diseases.* 2016;75(2):362-367. Available at: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01254836/full. Accessed May 2021.
11. Ranganath LR, Psarelli EE, Arnoux JB et al. Efficacy and safety of once-daily nitisinone for patients with alkaptonuria (SONIA 2): an international, multicentre, open-label, randomised controlled trial. *The Lancet. Diabetes & Endocrinology.* 2020;8(9):762-772. Available at: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02158906/full. Accessed May 2021.
12. NHS England. Medicines not reimbursed through national prices and directly commissioned by NHS Engand. Version 16. April 2021. Available at: https://www.england.nhs.uk/publication/nhs-england-drugs-list/. Accessed May 2021.
13. National Institute for Health and Care Excellence. Technology Appraisal Nitisinone for treating alkaptonuria [GID-TA10659 ID2691]. Nov 2020. Available at: https://www.nice.org.uk/guidance/proposed/gid-ta10659. Accessed May 2021.
14. Aktuglu-Zeybek AC, and Zubarioglu T. Nitisinone: A review. *Orphan Drugs: Research and Reviews.* 2017;7:25-35. Available at: https://www.dovepress.com/nitisinone-a-review-peer-reviewed-fulltext-article-ODRR. Accessed May 2021.

15. Davison AS, Hughes AT, Milan AM et al. Alkaptonuria - Many questions answered, further challenges beckon. *Annals of Clinical Biochemistry.* 2020;57(2):106-120. Available at: https://journals.sagepub.com/doi/full/10.1177/0004563219879957. Accessed May 2021.
16. Rana AQ, Saeed U, and Abdullah I. Alkaptonuria, more than just a mere disease. *Journal of Neurosciences in Rural Practice.* 2015;6(2):257-260. Available at: https://pubmed.ncbi.nlm.nih.gov/25883496/. Accessed May 2021.
17. Introne WJ, Perry MB, Troendle J et al. A 3-year randomized therapeutic trial of nitisinone in alkaptonuria. *Molecular Genetics and Metabolism.* 2011;103(4):307-314. Available at: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00811567/full. Accessed May 2021.
18. Lock E, Ranganath LR, and Timmis O. The Role of Nitisinone in Tyrosine Pathway Disorders. *Current Rheumatology Reports.* 2014;16 (457). Available at: https://pubmed.ncbi.nlm.nih.gov/25266991/. Accessed May 2021.
19. Zatkova A, Ranganath L, and Kadasi L. Alkaptonuria: Current Perspectives. *Application of Clinical Genetics.* 2020;13:37-47. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6986890/. Accessed May 2021.
20. McCarron C. Development of an economic model to assess the cost-effectiveness of nitisinone as a treatment for alkaptonuria in the UK. *Value in Health.* 2016;19:A589. Available at: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1098301516327632?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1098301516327632%3Fshowall%3Dtrue&referrer=. Accessed May 2021.
21. McCarron C. Development of an economic model to assess the cost-effectiveness of nitisinone as a treatment for alkaptonuria in the UK. Project submitted in partial fulfilment of the MSc in Economic Evaluation in Healthcare, Department of Economics, City University, London. 2016 Accessed May 2021.
22. AKU Society. AKU Society: Compilation of sample patient costs. 10 May, 2011. . Available at: https://www.rareconnect.org/uploads/documents/aku-study-compilation-of-sample-patient-costs.pdf. Accessed May 2021.
23. Cox T, Psarelli EE, Taylor S et al. Subclinical ochronosis features in alkaptonuria: A cross-sectional study. *BMJ Innovations.* 2018. Available at: https://innovations.bmj.com/content/5/2-3/82. Accessed May 2021.
24. NHS England. NHS Reference Costs (2020) National Schedule of NHS Reference Costs 2018/19. Available at: https://www.england.nhs.uk/national-cost-collection/#ncc1819. Accessed May 2021.
25. Curtis L, and Burns A. Unit Costs of Health and Social Care 2020. Personal Social Services Research Unit, University of Kent, Canterbury. 2020. Available at: https://kar.kent.ac.uk/84818/. Accessed May 2021
26. Zatkova A. An update on molecular genetics of Alkaptonuria (AKU). *Journal of inherited metabolic disease.* 2011;34(6):1127-1136. Available at: https://onlinelibrary.wiley.com/doi/10.1007/s10545-011-9363-z. Accessed May 2021.
27. Simoncelli M, Samson J, Bussieres JF et al. Cost-consequence analysis of nitisinone for treatment of tyrosinemia type I. *Canadian Journal of Hospital Pharmacy.* 2015;68(3):210-217. Available at: http://www.cjhp-online.ca/index.php/cjhp/article/view/1454/2135. Accessed May 2021.
28. Gallagher JA, Ranganath LR, and Zatkova A. *Alkaptonuria.* 2 ed. Brenner's Encyclopedia of Genetics,2013. Accessed May 2021.
29. Helliwell TR, Gallagher JA, and Ranganath L. Alkaptonuria – a review of surgical and autopsy pathology. *Histopathology.* 2008;53(5):503-512. Available at: https://pubmed.ncbi.nlm.nih.gov/18336562/. Accessed May 2021.

30. Ranganath LR, Jarvis JC, and Gallagher JA. Recent advances in management of alkaptonuria (invited review; Best practice article). *Journal of Clinical Pathology.* 2013;66(5):367-373. Available at: http://jcp.bmj.com/content/66/5/367.full.pdf. Accessed May 2021.
31. Ranganath LR, Khedr M, Milan AM et al. Nitisinone arrests ochronosis and decreases rate of progression of Alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre. *Molecular Genetics and Metabolism.* 2018;125(1-2):127-134. Available at: https://pubmed.ncbi.nlm.nih.gov/30055994/. Accessed May 2021.