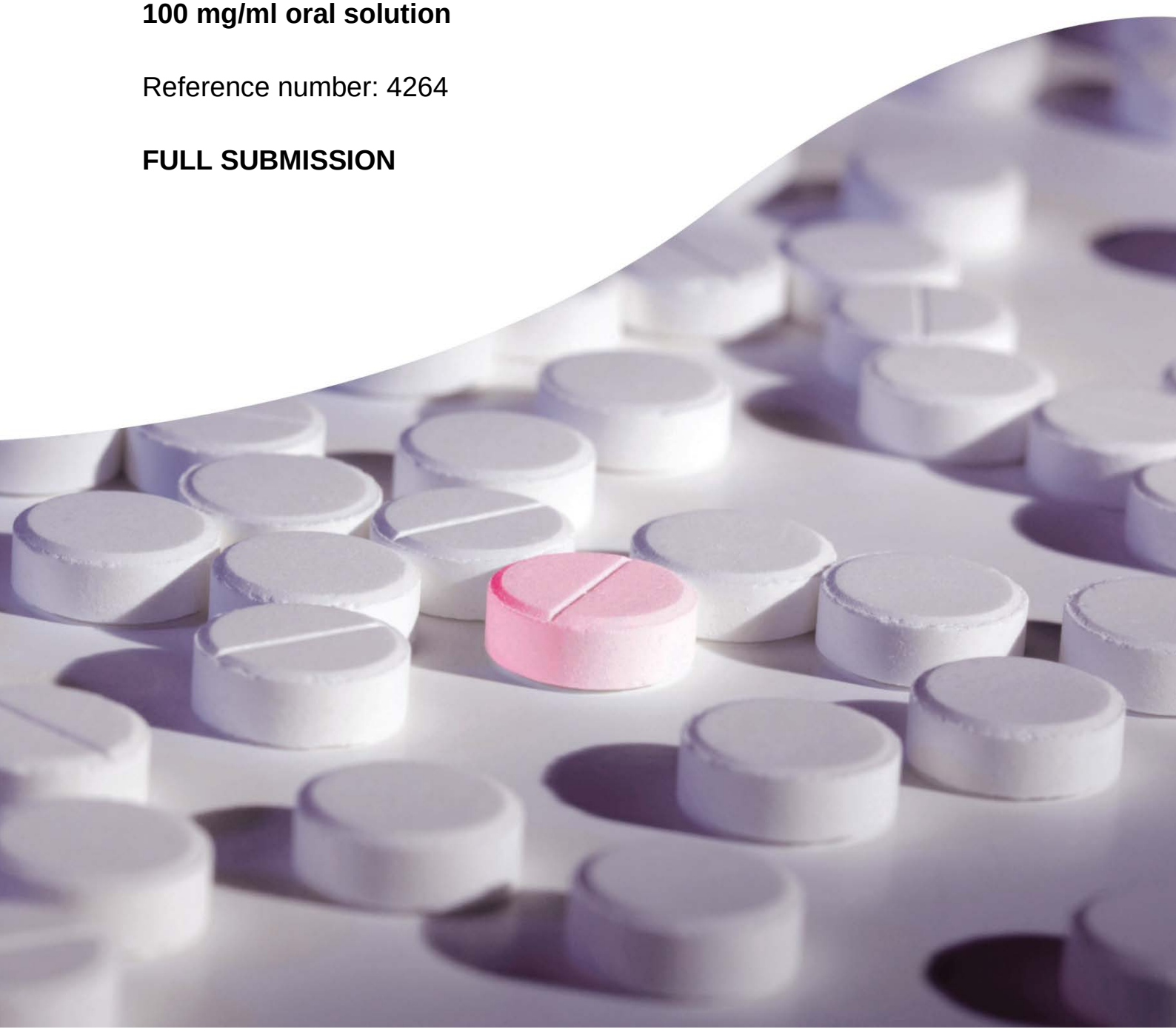
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Hydroxycarbamide (Xromi®)
100 mg/ml oral solution

Reference number: 4264

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Hydroxycarbamide (Xromi®) 100 mg/ml oral solution

1.0 KEY FACTS

Assessment details	Hydroxycarbamide (Xromi®) for the prevention of vaso-occlusive complications of sickle cell disease in patients over 2 years of age. The applicant company has submitted evidence for a subpopulation of the licensed indication and requests that AWMSG considers hydroxycarbamide oral solution for patients over two years of age who are unable to swallow capsules. Xromi® is the first licensed oral liquid formulation of hydroxycarbamide.
Current clinical practice	For the indication under consideration, off-label hydroxycarbamide 500 mg hard capsule formulation (Hydrea®) and unlicensed oral liquid formulations of hydroxycarbamide are established practice in Wales.
Clinical effectiveness	There are no efficacy studies for hydroxycarbamide oral solution. One study showed that Xromi® oral solution was bioequivalent to oral hydroxycarbamide capsules (Hydrea®) in healthy adults. Therefore hydroxycarbamide capsules are used as a proxy for hydroxycarbamide oral solution. Three phase III studies in children and adults showed that treatment with hydroxycarbamide capsules resulted in a reduced number of painful crises and fewer hospitalisations compared to placebo.
Cost-effectiveness	Further to the demonstrated bioequivalence of Xromi® oral solution to Hydrea® capsules, the company's submission includes a cost-minimisation analysis comparing Xromi® 100 mg/ml oral solution with the cost of unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution for the prevention of vaso-occlusive complications of sickle cell disease. The analysis focuses on children aged 2–9 years. It is assumed that when patients reach nine years of age they will switch to capsules. The company base case suggests cost savings of £22 per patient per annum. However, AWTTC considers an additional cost of £312 per patient per annum to be more plausible (if company base case assumptions relating to weight and dosage are maintained). Although cost savings are generated in patients of ≤ 14 kg (due to shelf-life related wastage for the comparator), patients weighing > 14 kg do not incur wastage costs. The AWTTC-preferred scenario excludes wastage costs, given the base case patient weight of 20 kg.

Budget impact	The company estimates that 8 patients are eligible to receive treatment with Xromi® in Wales in Year 1, increasing to 9 patients in Year 5. The base case suggests additional costs to NHS Wales of £2,496 in Year 1, increasing to £2,808 in Year 5. However, the cost applied to the comparator reflects the NHS Drug Tariff price for the unlicensed oral suspension; there is uncertainty around the unit cost for the special oral solution used in the analysis. Hospital pharmacies may procure the unlicensed solution at lower cost than that provided in the NHS Drug Tariff.
Additional factors to consider	The company and AWTTC consider Xromi® eligible to be considered as an orphan-equivalent medicine.

This assessment report is based on evidence submitted by Nova Laboratories Limited[1] and an evidence search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) on 9 December 2019.

2.0 BACKGROUND

2.1 Condition and clinical practice

Sickle cell disease is a group of inherited health conditions that affect red blood cells[2]. The most serious type is called sickle cell anaemia[2]. The main symptoms are chronic anaemia, an increased risk of serious infection and recurrent acute pain episodes due to vaso-occlusion[2-4]. Sickle cell disease is a serious and lifelong condition but treatment can help manage many of the symptoms[2].

Hydroxycarbamide is available in Wales as a 500 mg hard capsule formulation (Hydrea®) which is only currently licensed for oncology indications[5] and is used off-label for the prevention of vaso-occlusive complications of sickle cell disease. Hydroxycarbamide is also available as unlicensed oral solution and suspension formulations.

2.2 Medicine

Xromi® 100 mg/ml is the first licensed oral liquid solution of hydroxycarbamide for the prevention of vaso-occlusive complications of sickle cell disease in patients over two years of age[6]. The usual starting dose of Xromi® is 15 mg/kg/day, the usual maintenance dose is between 20–25 mg/kg, and the maximum dose is 35 mg/kg/day[6].

The applicant company has submitted evidence for a subpopulation of the licensed indication and requests that the All Wales Medicines Strategy Group (AWMSG) considers Xromi® for patients over two years of age who are unable to swallow capsules[1].

2.3 Comparators

The comparator included in the company's submission is unlicensed hydroxycarbamide oral solution. AWTTC-sought clinical expert opinion suggests that off-label hydroxycarbamide capsules are used for patients who are able to swallow the capsules and that unlicensed oral liquid formulations are available from specials manufacturers for patients over two years of age who are unable to swallow capsules.

2.4 Guidance and related advice

- Sickle Cell Society (2019). Sickle cell disease in childhood: standards and recommendations for clinical care[3].
- Sickle Cell Society (2018). Standards for the clinical care of adults with sickle cell disease in the UK[4].
- British Society for Haematology (2018). Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease[7].
- National Institute for Health and Care Excellence (NICE) quality standard 58 (2014). Sickle cell disease[8].
- NICE clinical guideline 143 (CG143) (2012). Sickle cell disease: managing acute painful episodes in hospital[9].

In the absence of a submission from the marketing authorisation holder, hydroxycarbamide film-coated tablets (Siklos®) for the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents and children older than two years suffering from symptomatic sickle cell syndrome is not endorsed for use within NHS Wales[10,11].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, hydroxycarbamide (Xromi®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

3.0 CLINICAL EFFECTIVENESS

There are no efficacy studies for hydroxycarbamide oral solution. Bioequivalence to Hydrea® capsules has been demonstrated and therefore hydroxycarbamide capsules are used as a proxy for hydroxycarbamide oral solution.

The company's submission includes one bioequivalence study comparing oral hydroxycarbamide solution to two formulations of oral hydroxycarbamide capsules in healthy adults. The company also submitted three phase III studies comparing the efficacy of hydroxycarbamide capsules to placebo in children and adults with sickle cell disease.

3.1 Bioequivalence study

This was a single centre, open-label, three-way crossover study comparing oral hydroxycarbamide (Xromi®) 100 mg/ml solution to two formulations of oral hydroxycarbamide 500 mg capsules (Hydrea®: one formulated in the UK and one in the USA) in healthy adults under fasting conditions[12].

Thirty adults aged between 18 and 50 years were enrolled in the study; 28 completed the study per protocol, receiving in random order a single dose of Xromi® oral solution, Hydrea® capsules UK and Hydrea® capsules USA, with at least a three-day washout period between each administration[12]. The results showed that Xromi® oral solution is bioequivalent to the two formulations of Hydrea® capsules.

3.2 Efficacy studies

Three studies in adults and/or children with severe sickle cell anaemia compared treatment effects with hydroxycarbamide capsules to placebo[13-15].

A randomised, double-blind, multicentre study by Charache et al (1995) compared the reduction in frequency of painful crises in 152 adults who received hydroxycarbamide capsules with 147 who received placebo[12,13]. To be eligible, patients had to have reported at least three crises in the previous year. Participants received 15 mg/kg per

day of hydroxycarbamide, increasing by 5 mg/kg per day every 12 weeks, unless marrow depression was present. The trial was stopped after a mean follow-up of 21 months, earlier than the planned 24 months because beneficial effects were observed. The median number of painful crises was significantly lower in the hydroxycarbamide group (2.5 crises per year) compared with the placebo group (4.5 crises per year; 44% difference, $p < 0.001$). The median time to first crisis was longer in the hydroxycarbamide group (3.0 months) compared with the placebo group (1.5 months; $p = 0{\cdot}01$), as was the time to second crisis (8.8 versus 4.6 months; $p < 0{\cdot}001$). Fewer patients receiving hydroxycarbamide developed chest syndrome compared with patients who received placebo (25 versus 51, $p < 0.001$) and fewer patients in the hydroxycarbamide group received transfusions (48 patients versus 73 patients, $p = 0.001$)[12,13].

The Ferster et al study (1996) was a randomised, single-centre, cross-over study that compared the number of hospitalisations and number of days in hospital, in 22 children and young adults who received hydroxycarbamide capsules for a period of six months followed by placebo for six months, or placebo first followed by hydroxycarbamide[7,12,14]. To be eligible, patients had to have had at least three vaso-occlusive crises in the previous year and/or previous history of stroke, acute chest pain, recurrent crises without a free interval or splenic sequestration[12,14]. Patients received 20 mg/kg per day of hydroxycarbamide, which was increased to 25 mg/kg per day if no change in fetal haemoglobin had occurred after two months, unless bone marrow toxicity developed[7]. Ages ranged from 2 to 22 years[12,14]. A total of 16/22 patients (73%) did not require any hospitalisation for painful episodes during the hydroxycarbamide treatment period compared with 3/22 (14%) during placebo treatment ($p = 0.0016$)[7,12,14]. The number of days in hospital was also significantly lower ($p = 0.0027$) when patients received hydroxycarbamide (range 0 to 19 days) than when they were on placebo (range 0 to 104 days)[7,12,14].

Jain et al (2012) conducted a randomised, single-centre, double-blind placebo-controlled study comparing the reduction in the number of painful crises, blood transfusion requirements and hospitalisations, in 60 children who received 10 mg/kg per day hydroxycarbamide capsules or placebo for 18 months[12,15]. To be eligible, patients had to have had more than three vaso-occlusive crises or blood transfusions per year. Ages ranged from 5 to 18 years. When compared with the placebo group, patients who received hydroxycarbamide had 94.0%, 93.4% and 89.5% lesser vaso-occlusive crises, blood transfusions and hospitalisations, respectively[12,15].

3.3 Comparative safety

There are no safety data directly comparing Xromi® oral solution with off-label preparations and unlicensed hydroxycarbamide oral liquid formulations. The safety profile for Xromi® in people with sickle cell disease is based on data from a comparative safety study, randomised controlled trials and observational studies that altogether included over 3,500 patients[12].

The safety profile of Xromi® oral solution in adults and children appears to be similar[12]. The most frequent adverse events reported were cytopenias, skin disorders, gastrointestinal disorders and neurological disorders. Cytopenias that are caused by bone marrow depression are mild, transient and reversible[12]. Bone marrow suppression is the major toxic effect of hydroxycarbamide and is dose related[6]. Other common side effects include neutropenia, reticulocytopenia, macrocytosis, thrombocytopenia, anaemia, headache, dizziness, nausea, constipation, skin ulcer, oral, nail and skin hyperpigmentation, dry skin and alopecia[12].

3.4 AWTTC critique

- Xromi® is the first licensed oral liquid formulation of hydroxycarbamide. There are currently no other licensed hydroxycarbamide formulations recommended by AWMSG or NICE for use in Wales for the indication under consideration.
- AWTTC-sought clinical expert opinion indicates that, currently, Hydrea® capsules are used off-label for this indication for patients who are able to swallow capsules. If an oral liquid formulation is required then unlicensed oral solutions and suspensions are available from specials manufacturers.
- Unlicensed oral liquid formulations of hydroxycarbamide have been used for several years in the UK to treat sickle cell disease in children and for those who have swallowing difficulties. There may be increased risks associated with using unlicensed medicines for patients, prescribers, people involved in the preparation of unlicensed cytotoxic specials and for health boards/trusts[16].
- There is an unmet need for a licensed oral liquid formulation for children and for those who have swallowing difficulties. The company suggests that the availability of a licensed oral liquid formulation will improve safety, and offer greater flexibility and accuracy for dosing with improved ease of administration, and therefore improved adherence. It will also allow titration and person individualisation of dosing, especially in the youngest children[1]. Furthermore some patients with sickle cell disease suffer dysphagia as a complication of stroke and hence cannot swallow a solid oral dosage form[1,12].
- Xromi® oral solution was licensed via a hybrid application and has been shown to be bioequivalent to Hydrea® capsules in healthy adults[12]. In support of these findings, an AWTTC literature search identified a bioequivalence study of oral solution versus capsule formulation which showed the two are bioequivalent in children with sickle cell anaemia[17].
- The company comparators are hydroxycarbamide oral solutions which, at the time of writing, includes hydroxycarbamide oral solution produced by the applicant company. However AWTTC-sought prescribing data shows that there may be some use of oral suspensions.

4.0 COST-EFFECTIVENESS

4.1 Context

Further to the demonstrated bioequivalence of Xromi® oral solution to Hydrea® capsules, the company's submission includes a cost-minimisation analysis (CMA) comparing Xromi® 100 mg/ml oral solution with the cost of unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution for the prevention of vaso-occlusive complications of sickle cell disease. The analysis focuses on children aged 2–9 years. It is assumed that when patients reach nine years of age they will switch to capsules. However, oral solution may also be used in some adolescents and adults as an alternative to capsules where swallowing is an issue.

A simple Excel-based cost comparison model estimates the difference in treatment costs between Xromi® 100 mg/ml oral solution and unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution. The model adopts a one-year time horizon and an NHS Wales perspective. The model includes medicine acquisition costs, dispensing costs, equipment costs, and transportation costs. No discounting is applied given the short time horizon of the model.

The acquisition cost for Xromi® 100 mg/ml oral solution is available via the British National Formulary[18]. The unit cost used in the model for the unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution is provided by the company; it reflects the cost of hydroxycarbamide 100 mg/ml oral suspension, as detailed in the NHS Drug

Tariff[19]. The base case assumes a patient weight of 20 kg and a regimen of 22.5 mg/kg/day. This weight is based on the 50th percentile recorded for a six year old boy in the World Health Organization growth data tables[20]. The regimen dose represents the midpoint in the usual maintenance range (20 mg/kg to 25 mg/kg), as detailed in the Summary of Product Characteristics[6]. It is thereby assumed that patients receive 450 mg per day.

The dispensing of 'special' hydroxycarbamide 100 mg/ml oral solution is associated with a £20 fee each time a prescription is dispensed[19]. This is a standard fee associated with costs incurred in obtaining unlicensed specials[21]. The model assumes that two bottles are prescribed at a time. Equipment costs include oral syringes and bottle adaptor for the comparator (these items are included in the pack for Xromi® 100 mg/ml oral solution).

The model assumes one delivery of the unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution per month and one delivery every three months for Xromi® 100 mg/ml oral solution, which has a three months in-use shelf life and a two year storage shelf life[6]. In contrast, the company identifies that the in-use shelf life of the comparator is one month and storage shelf life is three months. Transportation costs have been estimated by the company based on its experience of shipping products. A wastage cost, calculated as 15% of the acquisition cost, is also applied to the comparator to factor in wastage of pharmacy and patient-held expired stock resulting from the limited shelf life.

The company conducted sensitivity analyses to test the influence of varying unit prices for both medicines and alternative dosing regimens.

4.2 Results

The results of the company base case analysis and sensitivity analyses are detailed in Table 1. When compared with unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution, the company analyses suggest that Xromi® 100 mg/ml oral solution is less costly in the base case and in most sensitivity analyses conducted. The acquisition cost of Xromi® 100 mg/ml oral solution is relatively higher than the comparator. The overall projected cost savings are predominantly attributed to avoidance of additional dispensing fees for the unlicensed medicine and wastage.

Table 1. Results of the base case analysis and scenario/sensitivity analyses

Scenario	Costs	Xromi®	Unlicensed 'special' solution	Difference	Plausibility
Company base case: assuming patient aged 6 years, weight of 20 kg and dose of 22.5 mg/kg/day					
Hydroxycarbamide (Xromi®) 100 mg/ml oral solution versus unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution	Medicine acquisition costs	£2,765	£2,226	£539	
	Dispensing costs	£0	£166	−£166	
	Equipment costs	£0	£14	−£14	
	Transportation costs	£61	£108	−£47	
	Wastage costs	£0	£334	−£334	
	Total costs	**£2,826**	**£2,848**	**−£22**	
AWTTC generated: base case (aged 6, 20 kg weight and 22.5 mg/kg/day) excluding wastage cost					
a) Removal of wastage costs from base case hydroxycarbamide (Xromi®) 100 mg/ml oral solution versus unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution	Medicine acquisition costs	£2,765	£2,226	£539	This scenario offers a plausible alternative to the base case for this patient age, weight and dose. There would be no wastage of the comparator, despite its limited shelf life.
	Dispensing costs	£0	£166	−£166	
	Equipment costs	£0	£14	−£14	
	Transportation costs	£61	£108	−£47	
	Total costs	**£2,826**	**£2,514**	**£312**	
AWTTC requested scenarios: alternative age/weight					
b) Weight 12.2 kg (50th percentile for 2 year old) and dose of 22.5 mg/kg/day – assuming one bottle per month dispensing of 'special', due to limited shelf life hydroxycarbamide (Xromi®) 100 mg/ml oral solution versus unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution	Medicine acquisition costs	£1,750	£1,609	£141	This scenario offers a plausible scenario for children aged 2 years; and factors in the wastage attributed to the limited shelf-life of the comparator. It represents a subpopulation for whom the introduction of Xromi® is most cost-effective.
	Dispensing costs	£0	£120	−£120	
	Equipment costs	£0	£9	−£9	
	Transportation costs	£61	£108	−£47	
	Total costs	**£1,811**	**£1,846**	**−£35**	
c) 9 year old, weight of 28 kg and dose of 22.5 mg/kg/day – no wastage hydroxycarbamide (Xromi®) 100 mg/ml oral solution versus unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution	Medicine acquisition costs	£3,967	£3,262	£705	This scenario offers a plausible scenario for children aged 9 years. AWTTC sought clinical expert opinion supports the general assumption of patients switching to oral capsules around this age.
	Dispensing costs	£0	£120	−£120	
	Equipment costs	£0	£21	−£21	
	Transportation costs	£61	£108	−£47	
	Total costs	**£4,028**	**£3,511**	**£517**	

4.3 AWTTC critique

The company justified using a CMA, as opposed to a cost-utility analysis, on the basis that bioequivalence between Xromi® 100 mg/ml oral solution and Hydrea® 500 mg

capsules has been demonstrated. Notably, the cost comparison is based on a comparator that is currently used in practice, i.e. unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution, not the capsule. Although the use of two different comparators to inform efficacy and costs is not the conventional approach taken in CMAs, it is acceptable in this instance given that the known comparators for the targeted patient population are unlicensed special oral liquid formulations (i.e. no efficacy data are available).

The submission is characterised by both strengths and limitations:

- The submission is based on a simple cost-comparison and provides a transparent account of the methods and assumptions used in the analysis.
- The inclusion of an additional 15% medicine acquisition cost for the comparator to capture wastage is not justified in the base case scenario. At the assumed weight of 20 kg, a patient would require more than one bottle per month and pharmacy expired stock costs should not be included in cost calculations. The inclusion of the wastage cost biases the analysis in favour of Xromi® 100 mg/ml oral solution. That said, a two year old patient weighing 12.2 kg would accrue wastage costs. Table 1 reveals that for these patients there would be a cost saving of £35 per patient per year associated with the use of Xromi® 100 mg/ml oral solution.
- The unit cost for the comparator is taken from the NHS Drug Tariff for oral suspension. Unit costs for the unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution are not included in the NHS Drug Tariff and are known to be subject to variations over time. Hospital pharmacies may procure the unlicensed solution at lower cost than that provided in the NHS Drug Tariff. There is therefore uncertainty around the acquisition costs applied for the comparator in the model. The company has aimed to address this via sensitivity analyses.
- The base case analysis is potentially limited in scope, as it focuses on children aged 6 years, rather than exploring age and dose distributions. However, the company have conducted additional analyses to explore alternative ages and weights. In addition to exploring comparative costs for patients aged two years, for children aged nine years the use of Xromi® 100 mg/ml oral solution is associated with additional costs of approximately £517 per patient per year (Table 1).
- The time horizon of the analysis is limited given that sickle cell disease is a chronic condition.
- There are inconsistencies in the rounding approach applied to the costing of medicine acquisition. While these inconsistencies have the potential to bias the analysis, they do not influence the overall outcome of the cost comparisons undertaken.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of Xromi® 100 mg/ml oral solution versus unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution for the prevention of vaso-occlusive complications of sickle cell disease in patients over two years of age who are unable to swallow capsules.

5.0 BUDGET IMPACT

5.1 Context and methods

The company has estimated that there will be 86 patients with sickle cell disease in Year 1, increasing to 94 in Year 5. These estimates have been produced by combining

population data[22-24], prevalence and incidence data for sickle cell disease from a UK analysis of national databases and local data from the Cardiff Sickle Cell and Thalassaemia Centre[25]. To calculate the number of people who require treatment in Wales, the company has combined incidence and prevalence estimates with a mortality rate of 1.5%. Both incidence and mortality rates are assumed to remain constant over the five year period. Guided by population data[26] it is assumed that 11.8% of the total sickle cell disease population are ≤ 9 years of age. The model further assumes that 80% of this population are eligible to be treated with Xromi® 100 mg/ml oral solution. It additionally assumes a patient weight of 20 kg, a maintenance dose of 22.5 mg/kg/day, and that all patients receiving unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution will switch to Xromi® 100 mg/ml oral solution in Years 1 to 5. Sensitivity analyses explore the impact of varying the assumption for the percentage of 2–9 year olds eligible to receive treatment.

5.2 Results

The budget impact is presented in Table 2. The company estimates that introducing Xromi® 100 mg/ml oral solution would lead to an increased cost to NHS Wales of £2,496 in Year 1, increasing to £2,808 in Year 5. This estimate incorporates cost differences resulting from the displacement of unlicensed 'special' hydroxycarbamide 100 mg/ml oral solution. The company sensitivity analyses further report additional costs ranging between £1,872 and £2,184 in Years 1 to 5 when 60% of patients are assumed eligible for treatment and additional costs between £3,120 and £3,432 when 100% are assumed eligible.

Table 2. Company-reported costs associated with use of hydroxycarbamide (Xromi®) 100 mg/ml oral solution for the prevention of vaso-occlusive complications in the target population

	Year 1	Year 2	Year 3	Year 4	Year 5
Sub-population of eligible patients (indication under consideration)	10	10	10	11	11
Uptake of new medicine (%)	80%	80%	80%	80%	80%
Number of patients receiving new medicine	8	8	8	9	9
Medicine acquisition costs in a market without new medicine	£20,112	£20,112	£20,112	£22,626	£22,626
Medicine acquisition costs in a market with new medicine	£22,608	£22,608	£22,608	£25,434	£25,434
Net medicine acquisition costs	£2,496	£2,496	£2,496	£2,808	£2,808

5.3 AWTTC critique

- The submission gives a transparent account of the methods and data sources used to estimate budget impact.
- The budget impact analyses takes a different costing approach than the primary CMA analysis. The budget impact base case does not include wastage of 15% for the comparator. This is a more appropriate approach for the weight/dose used in the analyses.
- The dosing/weight assumption applied in the budget impact model does not facilitate exploration of the budget impact over a wider distribution of patient weights. In patients weighing more than 20 kg, the estimates provided will underestimate additional costs. The base case also does not take into account the cost savings associated with patients weighting ≤ 14 kg. The analyses is

therefore limited in scope. However, cost comparisons per patient have been conducted in the primary CMA analysis (excluding wastage).

- The cost applied to the comparator reflects the NHS Drug Tariff price for the unlicensed oral suspension; there is uncertainty around the unit cost for the special oral solution used in the analysis (as detailed in section 4.3).
- The company acknowledges that there is some uncertainty around the prevalence and incidence of patients with sickle cell disease in Wales. Only patients already known to Welsh services are used to estimate prevalence (i.e. those unknown to the service are not accounted for). Also, incidence estimates are based on proportionality assumptions linking new-born positive screening for sickle cell disease to the distribution of the black population in Wales. The assumed proportion of children under the age of 9 years may also be an underestimation.

6.0 ADDITIONAL FACTORS TO CONSIDER

6.1 Medicines developed to treat rare diseases

The applicant company suggests Xromi® oral solution should be considered as an orphan-equivalent medicine.

AWTTC considers Xromi® oral solution eligible to be appraised as an orphan-equivalent medicine. The full population of the licensed indication does not exceed the threshold of ≤ 1 in 2,000 people in Wales (or the UK). Eligible patient population figures have been verified against the references provided in section 5.1.

The New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 3) if they consider Xromi® oral solution 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	SCD is a multisystem disease associated with episodes of acute illness and progressive organ damage. The most common symptom of SCD is vaso-occlusive crises that are painful, cause complications and may even lead to death[27]. Vaso-occlusive painful episodes disrupt patients' everyday life and are the primary cause for their hospitalisation. A complication of vaso-occlusive crises is priapism in children and adolescents[28]. The second-most common symptom of SCD is ACS that accounts for about 25% of deaths in patients with SCD and is the second most common cause of hospital admission. The most frequent problems seen in paediatric SCD are pain, infection, acute splenic sequestration, ACS, and stroke. The most common causes of death in childhood from SCD are infection, ACS and stroke[29]. There are data to suggest that children, adolescents and adults with SCD suffer from pain on a daily basis that is intense enough to disrupt day to day functioning[30].
Unmet need	The company has requested that Xromi® oral solution be considered for the prevention of vaso-occlusive complications in patients with SCD over two years of age. The company identify patients who are unable to swallow capsules as the sub-population of the licensed indication to be the most likely to receive an oral liquid formulation. There are no other licensed oral liquid preparations available for this patient group; unlicensed special liquids are currently produced for patients with swallowing difficulties. Provision of a licensed medicine is desirable as it offers enhanced safety, quality and effectiveness over special preparations. It also offers greater flexibility and accuracy for dosing with improved ease of administration, and therefore improved adherence. Xromi® oral solution has better stability (two year storage shelf life).
Innovative nature of the medicine	N/A
Societal impact on non-health benefits that may not adequately be captured in the QALY	This criterion is not applicable as the company has submitted a cost-minimisation analysis, not a cost-utility analysis.
ACS: acute chest syndrome; AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; NMG: New Medicines Group; QALY: quality-adjusted life year; SCD: sickle cell disease.	

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