NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Polihexanide 0.8 mg/ml eye drops for treating acanthamoeba keratitis in people 12 years and over

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using polihexanide eye drops in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: February 2026

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using polihexanide eye drops in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 06 March 2026
- Second evaluation committee meeting: To be confirmed
- Details of membership of the evaluation committee are given in section 4.

1 Recommendations

1.1 Polihexanide 0.8 mg/ml eye drops should not be used to treat acanthamoeba keratitis in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with polihexanide 0.8 mg/ml eye drops that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For young people, this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.

What this means in practice

Polihexanide 0.8 mg/ml eye drops are not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to determine if polihexanide 0.8 mg/ml eye drops are value for money.

Why the committee made these recommendations

Usual treatment for acanthamoeba keratitis is unlicensed and off-label anti-amoebic therapies (AATs) alone or in combination. These include chlorhexidine, polihexanide (0.2 mg/ml and 0.6 mg/ml), propamidine and hexamidine.

Clinical trial evidence suggests that polihexanide 0.8 mg/ml eye drops with placebo have similar effectiveness to polihexanide 0.2 mg/ml with propamidine. But there is some uncertainty around the results.

Polihexanide 0.8 mg/ml eye drops have not been directly compared in a clinical trial with other AATs and the results of indirect comparisons are uncertain.

Because of the uncertainties in the clinical evidence, it is not possible to determine the most likely cost-effectiveness estimate for polihexanide 0.8 mg/ml eye drops.

So, polihexanide 0.8 mg/ml eye drops should not be used.

2 Information about polihexanide eye drops

Marketing authorisation indication

2.1 Polihexanide 0.8 mg/ml eye drops (Akantior, SIFI) is indicated for 'the treatment of Acanthamoeba keratitis in adults and children from 12 years of age'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for polihexanide eye drops (PDF only).

Price

2.3 The list price for the polihexanide 0.8 mg/ml is £5,960.00 for 30 vials (excluding VAT; company submission). The company has a commercial arrangement, which would have applied if polihexanide 0.8 mg/ml eye drops had been recommended.

Sustainability

2.4 Information on the Carbon Reduction Plan for UK carbon emissions for SIFI will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by SIFI, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Acanthamoeba keratitis (AK) is a rare but serious parasitic infection of the cornea caused by Acanthamoeba species. The condition is strongly associated with poor contact lens hygiene, with around 90% of cases linked to wearing lenses while swimming or wearing them overnight. It can also occur following corneal trauma or exposure to contaminated water. In the UK, the estimated incidence is approximately 0.12 cases per 50,000 people per year. Acanthamoeba exists in 2 life-cycle stages: an active trophozoite form that invades corneal tissue and a dormant cyst form that is highly resistant to treatment. AK typically only affects 1 eye, but infection of both eyes occurs in up to 11% of cases. Symptoms typically last for several months and include:

- severe eye pain
- excessive tearing
- light sensitivity
- redness or irritation
- blurred or cloudy vision and
- ring-shaped corneal infiltrates.

In more advanced cases, the cornea becomes cloudy and the shape of the eye may become distorted. Prognosis varies but most cases are curable with early, intensive, and sustained treatment. Delay in diagnosis or initiation of treatment is associated with poorer outcomes. Severe and permanent vision loss in the affected eye occurs in up to 25% of people, although estimates vary. The patient expert submissions highlighted that AK is associated with a substantial physical and psychological burden, particularly for people experiencing prolonged pain or reduced vision. The committee concluded that AK is a painful, sight-threatening condition that can significantly impact the lives of people affected.

Clinical management

Treatment options

3.2 The clinical experts explained that the main aim of treatment is to irradicate AK and prevent vision and eye loss. There are no licensed treatments for AK that are routinely available and there is no clearly defined standard care or national clinical guidelines. The current treatment is an intensive regimen of off-label and unlicensed anti-amoebic therapies (AATs). Initial treatment usually consists of a biguanide such as lower dose polihexanide eye drops (0.2 mg/ml or 0.6 mg/ml). This is generally used in combination with a diamidine such as propamidine or hexamidine. Treatment typically lasts for several months. The clinical experts explained that because some of these treatments (including polihexanide and hexamidine) are unlicensed, they must be made up on request as 'specials' for each person with AK. This may cause a delay in starting treatment after diagnosis. The clinical experts also said that there have been recent supply issues for 0.2 mg/ml and 0.6 mg/ml polihexanide. Treatment for AK is time-critical so treatment choice may depend on what is available at the time. They also said breaks in treatment due to supply issues are common. These factors contribute to substantial variation across the NHS in the treatment regimens used. The clinical experts explained that if polihexanide is unavailable, they would typically use chlorhexidine with or without a diamidine. The company noted that 0.8 mg/ml polihexanide is available to some people via an Early Access Programme, and that this has displaced some use of the lower polihexanide doses. The clinical experts explained that people whose condition does not respond to initial treatment would normally try another combination of AATs. If AK is still unresolved, therapeutic surgery is an option to replace or remove the damaged eye tissue. This includes corneal transplant (keratoplasty, including deep lamellar keratoplasty to replace diseased stroma) and removal of the entire eyeball (enucleation) or eye contents only (evisceration). Optical surgery, consisting of keratoplasty or cataract surgery, is sometimes used for visual

rehabilitation after assumed eradication of AK. All treatments are used alongside symptomatic relief such as pain medication and topical corticosteroids or antibiotics. The committee concluded that there is an unmet need for AK treatments that are available as an off-the-shelf, licensed treatment with standardised protocols.

Treatment administration

3.3 The patient expert submissions highlighted that treatment for AK can negatively impact the quality of life of people with the condition. Existing treatments typically require 2 sets of eye drops to be administered hourly during the initial intensive phase (around 3 days). The clinical experts said that if the person can manage it, this may include overnight dosing. People with AK are sometimes admitted to hospital to support this, based on their preference, local practice and the availability of beds. The marketing authorisation for polihexanide 0.8 mg/ml states that it can be used as monotherapy and during the daytime only. The clinical experts also noted that diamidines can cause temporary a stinging sensation, making AAT treatment painful. They agreed that using polihexanide 0.8 mg/ml as monotherapy would avoid the side effects associated with diamidines and may reduce the administrative burden of overnight treatment. The clinical experts explained that providing support through treatment, especially during the intensive-treatment phase, can be burdensome for carers. The committee concluded that current treatment, which may include dual therapies administered hourly overnight, can be painful and is burdensome for people with AK and their carers.

Clinical effectiveness

ODAK trial

3.4 Clinical-effectiveness data for polihexanide 0.8 mg/ml came from the ODAK trial, a multicentre, randomised, active-controlled trial that included 3 sites in the UK. It enrolled people with untreated AK confirmed by

clinical and in vivo confocal microscopy findings. For people with bilateral AK, only 1 eye was treated. In the trial:

- 69 people had polihexanide 0.8 mg/ml with placebo (hereafter referred to as polihexanide 0.8 mg/ml) and
- 65 people had polihexanide 0.2 mg/ml with propamidine 1 mg/ml (hereafter referred to as polihexanide 0.2 mg/ml with propamidine).

Treatment in both arms was administered according to the regimen in the summary of product characteristics for polihexanide 0.8 mg/ml (PDF only). This included an intensive phase with up to 16 daytime administrations, which were gradually reduced over a period of 19 days. From day 20 onward, the schedule decreased to 4 daytime administrations per day, until cure or for a maximum duration of 1 year. The primary outcome was medical-cure rate within 12 months of starting treatment. The company defined cure as clinical evidence of the elimination of AK, indicated by an intact (healed) corneal epithelium and the absence of any clinical signs or symptoms of ocular inflammation. This was confirmed 30 days after stopping all AATs and anti-inflammatory treatment, with no recurrence by 90 days of stopping treatment and within 11 months of randomisation. The clinical experts confirmed this broadly aligned with the criteria for cure used in clinical practice. The key secondary outcomes were corneal scarring and ulceration, anterior chamber inflammation, best corrected visual acuity and health-related quality of life. Time to cure was an exploratory endpoint. The company presented data from the completed ODAK trial from the November 2021 data cut. The committee recalled that AATs are traditionally administered hourly for the first few days throughout the day and night if the person can manage this (see section 3.3). It noted that this differed from the ODAK trial regimen, in which both treatment arms used daytime-only dosing. The committee concluded that the relevant evidence for polihexanide 0.8 mg/ml came from the ODAK trial.

Results

3.5 At the November 2021 data cut off, 56 people (85%) having polihexanide 0.8 mg/ml and 54 people (89%) having polihexanide 0.2 mg/ml with propamidine had met the company's criteria for a medical cure. The difference in cure rate between the 2 arms was not statistically significant (odds ratio 0.73, 95% confidence interval [CI] 0.26 to 2.04, p value 0.544). Polihexanide 0.8 mg/ml met the company's predefined non-inferiority margin, demonstrating that it was at least 80% as effective as the active comparator. There was a longer median time to cure in the polyhexanide 0.8 mg/ml arm (140 days) than the comparator arm (114 days, hazard ratio 0.68; 95% CI 0.49 to 0.94). Both treatments positively impacted health-related quality of life, but slightly higher changes were seen in people who had polihexanide 0.2 mg/ml with propamidine than polihexanide 0.8 mg/ml. Differences between the intervention and comparator arm in other secondary outcomes were generally not statistically significant.

The EAG was concerned that the ODAK trial results did not show evidence of clinical benefit over the comparator. It was also concerned that some outcomes with long-term implications on vision after cure (for example health-related quality of life, visual function and structural sequelae such as corneal scarring) had been excluded from the company's definition of cure. It noted the European Medicines Agency's initial assessment report, which concluded that non-inferiority with the comparator arm could not be inferred because the margin was inadequately justified. The committee noted the uncertainty regarding the non-inferiority margin. But they concluded that polihexanide 0.8 mg/ml has similar efficacy to polihexanide 0.2 mg/ml and propamidine in untreated AK for the purposes of decision making.

Indirect treatment comparison

Inclusion of ODAK comparator data

3.6 The company said that the comparator arm in the ODAK trial was not generalisable to the NHS. This was because:

- Polihexanide 0.2 mg/ml with propamidine needs compounding before use in clinical practice. The company explained that the quality of compounded treatments varies considerably, because they are not regulated in the same way as licensed products. So, the polihexanide 0.2 mg/ml with propamidine regimen used in clinical practice was likely to have a different efficacy to that used in the trial, which was a Good Manufacturing Practice trial-grade standard. The company stated that this was supported by analyses from other countries, which suggested the dose of compounded products may be incorrect by several orders of magnitude.
- Compounding can cause delays in accessing treatment that were not present in the ODAK trial, where people had immediate access.
- The comparator treatment in ODAK followed a rigid protocol, unlike clinical practice where there is considerable variation in treatment regimen by centre (for example, in timing of doses or duration of intensive-treatment phase).

So, the company considered that that the ODAK trial overestimated the treatment effect of polihexanide 0.2 mg/ml with propamidine compared with clinical practice. Because of this, it did an indirect treatment comparison comparing the data from the ODAK polyhexanide 0.8 mg/ml arm with real-world data for the comparator arm from Papa et al. (2020). Papa et al. was a retrospective, multinational, observational study in 227 people with AK treated between 1991 and 2012. The treatment regimens included combinations of polihexanide 0.2 mg/ml and 0.6 mg/ml, chlorhexidine, propamidine and hexamidine. Because Papa et al. was real-world evidence, the company said that it

better reflected the variation in treatment efficacy for compounded products in the NHS. But, the EAG was concerned that the company had excluded direct comparator data from the ODAK study for polihexanide 0.2 mg/ml with propamidine. This was supported by the EAG's clinical experts. They said that the ODAK comparator was reflective of UK clinical practice and felt that the delay in starting treatment reported by the company (17.7 days from diagnosis) was likely an overestimate. The EAG highlighted that polihexanide 0.2 mg/ml with propamidine was the most commonly used regimen in both Papa et al. and a Delphi panel of 10 UK clinical experts done by the company in 2023. The committee also noted that the company had not submitted any scenarios comparing polihexanide 0.8 mg/ml against best supportive care. It felt that NICE's technology appraisal and highly specialised technologies guidance manual considers high-quality randomised controlled trials to be the preferred source of comparative evidence. Also, the committee noted that the company had not completed analyses on compounded products in the UK. Because of this, it felt that the claim that there is a difference in efficacy between the products used in the trial and NHS clinical practice was unsubstantiated. So, the committee agreed that the comparator data from the ODAK trial was likely generalisable to the NHS and is a suitable data source to inform the relative treatment effect of the intervention.

Indirect treatment comparison methodology

3.7 Because the company had access to individualised data from ODAK and Papa et al. (2020), it used a propensity scoring analysis to derive relative effectiveness. It used an overlap weighting approach to adjust baseline characteristics from both studies to balance covariates between arms. Adjusted covariates included age, gender, AK disease stage, prior use of corticosteroids and antivirals and any delay in starting treatment at baseline. Medical-cure rate at 12 months was the only outcome evaluated. The results of the company's indirect treatment comparison

(ITC) favoured polihexanide 0.8 mg/ml with a relative risk for 12-month medical-cure rate of 1.75 (95% CI 1.46 to 2.11).

The EAG felt that the company's approach to the ITC was methodologically weak. This was because:

- Papa et al. was a retrospective cohort study, whereas ODAK was a randomised controlled trial. The EAG was concerned that combining evidence from different study designs could introduce bias. It also highlighted that Papa et al. used older data (see section 3.6) and had methodological limitations, including heterogeneous treatment regimens and incomplete data.
- Key covariates were not adjusted for, such as contact lens use, which could introduce confounding.
- There was a higher level of treatment switching in Papa et al. compared with the ODAK study, which may have diluted the treatment effect of single-agent AAT.
- There was an inconsistent approach to handling missing data: participants with missing data were excluded from the analyses, except for treatment delay (median-imputed) and age (mean-imputed).

The EAG was also concerned that using Papa et al. for the comparator underestimated the treatment effect for pooled AATs, given the lack of benefit for polihexanide 0.8 mg/ml seen in ODAK (see section 3.5). So, the EAG base case assumed that everyone in the comparator arm had polihexanide 0.2 mg/ml with propamidine and used the comparator treatment effect from ODAK in its model (a relative risk of 0.96). But the committee considered that around 20% of people in Papa et al. and the company's Delphi panel did not have the ODAK trial regimen (or what they would consider equivalent). These other regimens were likely to be less effective than the gold standard treatment used in the ODAK study comparator arm. The committee concluded there were significant uncertainties about the methodology and results of the company's ITC.

But, it agreed that the relative treatment effect between polihexanide 0.8 mg/ml and AATs in the NHS lay between that reported in the ODAK study and the company's ITC.

Alternative ITC approaches

3.8 The committee considered alternative approaches to deriving the treatment effect for pooled AATs. It noted that the EAG had explored alternative approaches, including:

- using the data from the ODAK comparator arm as a bridge to the polihexanide with diamidine subgroup from Papa et al. (2020)
- naive comparisons of the Papa et al. subgroups with polihexanide 0.8 mg/ml to find a plausible range for AAT treatment effect.

These analyses resulted in relative risks that fell between those used in the company and EAG approach. Based on this, the EAG provided scenarios varying the relative risk for medical-cure rate between 0.96 and 1.65, which it considered the upper and lower bound of the plausible range. The committee recalled that the available evidence suggested that polihexanide 0.8 mg/ml had a similar MCR to polihexanide 0.2 mg/ml with propamidine (see section 3.5). So it agreed that assuming equal efficacy between regimens containing polihexanide 0.8 mg/ml and 0.2 mg/ml, and consequently with polihexanide 0.6 mg/ml, was appropriate. So, it preferred to apply a relative risk of 1 for all polihexanide-containing regimens regardless of the dose. The committee noted that at least 70% of people in Papa et al. and the 2023 Delphi panel had a polihexanide-containing regimen (either 0.2 mg/ml or 0.6 mg/ml). It considered the available approaches for deriving relative treatment effects for people having chlorhexidine or diamidine monotherapy. It noted that the company discounted the ODAK comparator arm as not reflecting clinical practice. So because of this, it did not explore including polihexanide 0.2 mg/ml with propamidine separately in a network meta-analysis. So, studies

comparing this combination with other AAT regimens may exist and could form a complete network. But, it noted that the limited availability of data would likely require the assumption of a class effect for diamidines when using this approach. The committee agreed that its preferred approach for estimating the relative effectiveness was a network meta-analysis using the ODAK comparator arm regimen as an anchor between polihexanide and other AATs. It added that this should be supported by a new search for relevant evidence to inform the network. But, it agreed that, if such a network meta-analysis was explored and were not possible, an ITC using the ODAK comparator arm as a bridge to the polihexanide and diamidine subgroup in Papa et al. would also be acceptable. For people who have a combination of these treatments, the company should explore the most appropriate approach. It concluded that the company should assume equal efficacy between polihexanide doses, between diamidine monotherapies, and between chlorhexidine regimens (assuming a class effect for each group). The relative treatment effects for polihexanide compared with diamidine monotherapy and with chlorhexidine regimens should be presented separately.

Economic model

Company's modelling approach

3.9 The company developed a hybrid model to estimate the cost effectiveness of polihexanide 0.8 mg/ml, consisting of 2 phases. In the first phase, people entered a decision-tree structure to model outcomes in the first year of AK infection. People whose AK did not resolve with initial treatment could change to an alternative AAT or have therapeutic surgery. Upon AK resolution (with initial or subsequent AATs or after therapeutic surgery), people entered health states based on their visual acuity (good vision, poor vision, severe vision loss or post therapeutic surgery only, loss of eye function). A proportion of people were assumed to be waiting for therapeutic surgery at the end of year 1. After year 1, people

transitioned into a semi-Markov model based on the health state they were in at the end of year 1. People with resolved AK remined in the health state according to their visual acuity until optical surgery, graft failure, AK infection recurrence or death. People re-entered the decision tree for 1 year upon AK recurrence after medical or surgical resolution of AK infection. People could transition to death from any health state in the semi-Markov model. The ODAK study informed cure rates for polihexanide 0.8 mg/ml, visual acuity outcomes, and health-related quality of life. The company's ITC with Papa et al. (2020) informed 12-month cure rates for pooled AATs. The UK Delphi panel and published literature informed treatment switching, surgical pathways, and long-term outcomes. The EAG considered the company's model to appropriately capture all important health states associated with AK infection. The committee agreed that the company's economic model was appropriate for decision making.

Comparator

3.10 The company used a pooled comparator of available AATs in its model. The distribution of treatments was informed by a Delphi panel of 10 UK clinical experts. The committee noted the distribution of treatments in the Delphi panel was similar to that in Papa et al. (2020) (see section 3.6). The committee also noted a company scenario using the distribution of treatments in Papa et al. had little impact on the cost-effectiveness results. The clinical experts confirmed that the treatment combinations and their proportions used were representative of those in the NHS. The committee recalled that all current treatments for AATs were off-label or unlicensed. It noted that NICE's technology appraisal and highly specialised technologies guidance manual states that comparators can include technologies that do not have regulatory approval for the population under appraisal if they are considered to be established clinical practice for that population in the NHS. So, the committee agreed that the Delphi panel captured all appropriate comparators and regimens for polihexanide 0.8 mg/ml in clinical practice. But, it recalled that its preferred

approach to ITC was to assume equal efficacy for polihexanide-containing regimens and compare them with diamidines and chlorhexidine separately (see section 3.8). The committee concluded that the company's pooled comparator was not appropriate and that diamidines and chlorhexidine should be modelled as separate comparators.

Time-on-treatment data in the model

3.11 The company's drug acquisition costs incorporated treatment-specific dosing frequencies for polihexanide 0.8 mg/ml and pooled AATs, adjusted for the duration of therapy. The median time to cure from Papa et al. (2020) of 152 days informed the treatment duration for pooled AATs. For polihexanide 0.8 mg/ml, the mean treatment duration reported in Franch et al. (2024) of 101 days was applied. This was because the company thought that it best reflected treatment exposure to polihexanide in real-world clinical practice. It felt that this approach was conservative because people in Franch et al. generally had more severe AK than people in ODAK. This was demonstrated by higher rates of stage 3 disease and prior corticosteroid use. It also highlighted data from 40 people in Italy showing a similar duration of treatment with polihexanide 0.8 mg/ml. But, the EAG was concerned that the company's use of the data from Franch et al. was unsuitable because:

- it only included 11 people so was too small to be generalisable to clinical practice, and
- there were differences in baseline characteristics between Franch et al. and ODAK, such as the mean age on study entry and previous corticosteroid use.

The EAG preferred to use the median time to cure from ODAK for the polihexanide 0.8 mg/ml (140 days) in its base case. It also provided scenarios that used the median time to cure from the polihexanide 0.2 mg/ml with propamidine arm from ODAK (114 days) for the comparator arm in the model. At the committee meeting, the company

explained that it did not think the ODAK trial was an appropriate source of time on treatment. This was because in ODAK people who had polihexanide 0.8 mg/ml also used placebo eye drops, which can increase ocular surface inflammation, potentially delaying cure. The clinical experts at the meeting explained that time on treatment is variable but depends on the initial severity of the condition and time to diagnosis. But, they expected a shorter time on treatment with polihexanide 0.8 mg/ml compared with pooled AATs in clinical practice. This was because it used a standardised treatment protocol without the variation seen in other treatment regimens. The committee also noted that the EAG's and company's preferred evidence sources reported a mix of median and mean time on treatment. It agreed that the mean generally more accurately reflects the average treatment duration. The committee considered the large variation in time on treatment between sources. It agreed that the same source should be used for each arm but thought that time on treatment with both polihexanide 0.8 mg/ml and other AATs was uncertain. So, it concluded that the company should consider alternative sources for time on treatment by including this outcome in the network meta-analyses for all comparators (see section 3.8).

Recurrence after AK cure

3.12 The company assumed that people whose AK was cured following treatment with polihexanide 0.8 mg/ml would experience no recurrence over the modelled lifetime horizon. This was based on the absence of reported recurrence in the available data for polihexanide 0.8 mg/ml, which included 526 people across Europe who had treatment for AK. In contrast, for the polihexanide 0.2 mg/ml plus propamidine arm, AK recurrence was modelled to occur in 12% of people in year 1 and 3% annually from year 2 to year 15. This was informed by estimates from the company's Delphi panel and 2 published case studies. Recurrence was also assumed to occur in a proportion of people following therapeutic surgery or after switching to a new AAT in both treatment arms. The EAG

considered that the company's assumption favoured polihexanide 0.8 mg/ml and was uncertain given the lack of long-term follow up. So, it applied the comparator arm's AK recurrence rates to polihexanide 0.8 mg/ml in its base case. The clinical experts explained that recurrence in AK is rare and is only usually seen in people with severe corneal infiltration at diagnosis, which can be harder to reach with treatment. They noted that the recurrence rates in ODAK were lower than expected in clinical practice, likely because the trial applied a strict definition of cure. They explained that, in clinical practice, the dormant cyst form of the amoeba can lead less-experienced healthcare professionals to incorrectly declare AK cured. AK can then recur after treatment is stopped. They also considered that stronger doses of polihexanide might lower the risk of recurrence by penetrating more deeply into the corneal tissue. But, the committee felt this was uncertain. It agreed that recurrence should be included as and additional endpoint in the network meta-analysis done at consultation (see section 3.8). If no alternative data sources are found, it agreed that, to be conservative, the same risk of recurrence should be modelled for all treatment arms.

Utility values

Disutilities for long-term complications following AK resolution

3.13 The company derived health-state utility values for the modelled health states from EQ-5D-5L data collected in the ODAK trial. It mapped the EQ-5D-5L data to the EQ-5D-3L value set. Because the ODAK trial only had a 12-month follow up, the company included disutilities for long-term complications of the condition. This included a disutility of −0.0647 for persistent tearing, light sensitivity and pain, and −0.1910 for depression and anxiety. This was based on clinical expert advice that symptoms of AK can continue for years after being cured. For people with multiple complications, the company combined disutilities using prevalence estimates from the published literature. It then applied the disutilities in the model according to the health-state-specific complication rates reported in

the UK Delphi panel. The EAG was concerned that the company's method double-counted the impact of long-term AK complications, because these effects were already reflected in the EQ-5D data collected in the trial. It also questioned the face validity of applying these disutilities to people with good vision, because people in this health state were assumed to have a quality of life comparable to the general population. So, the EAG excluded disutilities for long-term complications in its base case. The committee noted that the company's model included a disutility for the people who had an AK infection or were cured with poor vision, vision loss and loss of eye function based on the trial EQ-5D. It felt that the long-term complications highlighted by the company would likely have presented in the trial, so were somewhat captured in the disutilities applied to people without good vision. The committee concluded that a separate disutility for long-term complications of AK should not be included in the model.

Disutilities for the intensive-treatment phase

3.14 The company included disutilities during the intensive-treatment phase in the comparator arm only. They were applied for people with AK and for their carers. They said this was to reflect the higher burden of care for current AATs, which require overnight treatment with multiple therapies compared with polihexanide 0.8 mg/ml, a monotherapy with daytime administration only. The EAG's clinical advisers stated that polihexanide 0.8 mg/ml would be given during the day and night during the intensive-treatment phase. So, it included these disutilities for both treatment arms. The clinical experts at the meeting stated that they would follow the ODAK treatment regimen, which administered polihexanide 0.8 mg/ml during the daytime only. But they would use other AATs overnight for the first few days if possible (see section 3.3). The committee recalled that the ODAK trial used daytime-only dosing for both treatments (see section 3.4). It felt that, given the lack of established guidance for using AATs, healthcare professionals were likely to align use with the trial protocol for all treatments moving forwards. It acknowledged that, given the variation in treatment regimens throughout the NHS, some people would be still

hospitalised for overnight dosing but thought this would be the same for all treatments. So, it concluded that disutilities associated with overnight use during the intensive-treatment phase should not apply to either arm in the model.

Carer quality of life

3.15 The company included carer quality-of-life decrements in its model. It applied disutilities during the intensive-treatment phase (comparator only), surgery, graft failure, and severe vision loss or loss of eye function. The company could not find any AK-specific disutility values for carers. So, it based the disutilities on NICE's highly specialised technology appraisal on voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations (from here referred to as HST11). It felt these values were acceptable as a proxy for AK because both conditions involve similar care burdens related to chronic visual impairment. The EAG regarded the inclusion of carer disutilities as reasonable but presented scenarios in which they were excluded. The committee noted that retinal dystrophies affect both eyes, typically from childhood and ultimately lead to near total blindness. It also noted that, in HST11, the committee only accepted carer disutilities for children and the disutility values were based on limitation in school, play or social activities. The clinical experts explained that retinal dystrophies are generally more severe than AK because people are very likely to be visually impaired, unlike in AK which typically only affects 1 eye in otherwise healthy adults. The company explained that a carer disutility was applied only at specific timepoints when quality of life was expected to be most affected. It noted that severe AK symptoms, including light sensitivity and emotional distress, can require up to 5 hours of care per day in people with severe vision loss or loss of eye function. Clinical experts confirmed a substantial care burden following surgery. But they noted that care needs during the intensive-treatment phase vary depending on the person's ability to self-administer eye drops, their vision in the unaffected eye, and whether hospitalisation is required. The committee agreed that there was a carer burden

associated with specific timepoints in the treatment pathway for AK that should be included in the model. But, it felt that this was unlikely to be comparable to a condition that causes progressive and irreversible sight loss in both eyes, particularly in children. It concluded that lower carer-disutility values should be explored during consultation.

Costs

Costs for the intensive-treatment phase

3.16 The company included hospitalisation costs for 26.6% of the pooled AAT arm, representing people hospitalised during the intensive-treatment phase to support adherence to overnight dosing. The proportion admitted was informed by the company's UK Delphi panel. The company assumed that people having polihexanide 0.8 mg/ml would not incur hospitalisation costs because the daytime-only regimen meant they could self-administer the drops at home. But, based on the EAG clinical expert's opinion that polihexanide would be given in the day and night during the intensive phase, the EAG included hospitalisation costs for 26.6% of people in both arms. The committee noted that the EAG's assumption did not align with the drug costs included in the model, which were based on the dosing schedule outlined in the marketing authorisation for polihexanide 0.8 mg/ml (that is, a maximum of 16 drops per day). The clinical experts at the meeting explained that some people are currently hospitalised for overnight treatment, but this depends on personal preference and local resources, including the availability of beds in a dedicated eye ward. But, the committee recalled its earlier conclusion that most healthcare professionals were likely only to use AATs during the day to align with the ODAK protocol (see section 3.14). So, to be consistent, it concluded that hospitalisation costs for the intensive phase should not apply to either arm in the model and a maximum of 16 doses per day should be assumed.

Severity

3.17 NICE's methods on conditions with a high degree of severity did not apply.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.18 Because of confidential commercial arrangements for polihexanide 0.8 mg/ml, the exact cost-effectiveness estimates are confidential and cannot be reported here. The company's base-case incremental cost-effectiveness ratio (ICER) for polihexanide 0.8 mg/ml compared with pooled AATs was towards the top of the range normally considered a cost-effective use of NHS resources. This was using the results of the company's ITC for the comparator arm. The committee recalled that the EAG's preferred source of comparator treatment effect came from the ODAK trial. It noted that, using the ODAK treatment effect for both arms, polihexanide 0.8 mg/ml was dominated by (that is, it was more costly and less effective than) polyhexanide 0.2 mg/ml with propamidine. Excluding disutilities for ongoing long-term complications and including the median time to cure from ODAK and AK recurrence for the polihexanide 0.8 mg/ml arm also increased the ICER.

Acceptable ICER

3.19 NICE technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £20,000 per quality-adjusted life year gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty. This was mainly about the relative treatment effect between polihexanide 0.8 mg/ml and other AAT regimens (see section 3.8). But

there was also uncertainty around the time on treatment, rates of recurrence after cure and impact on carer quality of life (see section 3.11, section 3.12 and section 3.15). The committee felt that, given this uncertainty, it could not establish a preferred ICER threshold at this stage. It said an ICER threshold would be established once the additional analyses it requested had been provided.

Committee preferred ICER

3.20 For the model assumptions, the committee preferred to:

- Include all comparators currently being used in the NHS, according to the company's Delphi panel, but model polihexanide, diamidines and chlorohexidine as separate comparators in a fully incremental analysis (see section 3.10).
- Assume equal effectiveness for all regimens containing polihexanide (that is, a relative risk of 1), including 0.2 mg/ml, 0.6 mg/ml and 0.8 mg/ml doses as dual or monotherapies. Also, to explore alternative approaches to derive relative effectiveness between polyhexanide-containing regimens and other AATs (see section 3.8).
- Explore alternative sources for modelling time on treatment (see section 3.11).
- Explore alternative sources for recurrence rates in each arm or assume an equivalent risk of recurrence for polihexanide 0.8 mg/ml and other AATs if no further evidence is identified (see section 3.12).
- Assume daytime-only administration for polihexanide and other AATs, that is, no hospitalisation costs or disutilities for people with AK and carers during the intensive phase in either arm and a maximum of 16 doses per day in each arm (see section 3.14 and section 3.16).
- Exclude disutilities associated with long-term complications of AK (see section 3.13).
- Include carer disutilities for time-dependant events, but explore alternatives to those used in HST11 (see section 3.15).

The committee could not establish a plausible ICER because of the uncertainty in the modelling of relative effectiveness. It concluded that further analyses that addressed these uncertainties is needed to establish the cost effectiveness of polihexanide 0.8 mg/ml.

Uncertainties to explore further in the modelling

3.21 The committee noted that there was considerable uncertainty surrounding the cost effectiveness of polihexanide 0.8 mg/ml for AK. It agreed that the company's model after consultation should:

- Explore alternative approaches to deriving relative effectiveness for polihexanide-containing regimens compared with chlorhexidine and diamidines, assuming a class effect for diamidines (see section 3.8):
  - ideally using a network meta-analysis supported by a new systematic search to identify additional relevant evidence to inform the network, or
  - if a network meta-analysis cannot be established, consider an ITC using the ODAK comparator arm as a bridge to relevant real-world evidence from Papa et al. (2020).
- Include time on treatment and rates of AK recurrence following cure as additional outcomes in the network meta-analysis (see section 3.11 and section 3.12).
- Explore alternative carer-disutility values that are comparable to the severity and time-limited care burden associated with AK (see section 3.15).

Managed access

3.22 Having concluded that polihexanide 0.8 mg/ml eye drops could not be recommended for routine use in the NHS, the committee then considered if it could be recommended for use during a managed access period for treating AK. It noted that the company had not submitted a managed access proposal in its initial submission. The committee considered

whether a recommendation with managed access could be made, given the following:

- It could not establish a preferred ICER threshold given the uncertainty in the clinical-effectiveness data, so plausible potential for cost effectiveness was currently unclear.
- The key uncertainty was the relative treatment effect of polihexanide 0.8 mg/ml compared with diamidines and chlorhexidine. The committee noted that the ODAK trial had completed and had not provided comparative effectiveness data against non-polihexanide AATs.

The committee judged that a managed access agreement was unlikely to resolve the key issues and uncertainties. So, it concluded that, based on the evidence presented, polihexanide 0.8 mg/ml eye drops did not meet the criteria to be considered for managed access.

Other factors

Equality

3.23 The company highlighted that AK is currently treated at specialist centres so there might be variable access to treatment centres, particularly because rapid treatment is crucial to improve outcomes. The committee recalled the variation in care by location (see section 3.2). But it but did not consider this as an equalities issue that it could address through its recommendations. The committee concluded there were no equality issues identified for this evaluation.

Uncaptured benefits

3.24 The committee noted that some potential benefits of polihexanide 0.8 mg/ml eye drops may not have been included in company's model:

- It considered that polihexanide was a monotherapy, unlike most other regimens, which are used in combination (see section 3.3). The clinical experts explained that dual therapies can be burdensome to administer

for both carers and people with AK. This is particularly the case during the intensive-treatment phase, when multiple eye drops must be administered hourly and spaced 5 minutes apart. The committee noted that people having polihexanide 0.8 mg/ml in ODAK also had to administer placebo drops. So, any quality-of-life benefit associated with the ease of use of a monotherapy may not have been captured in the modelling.

- The committee recalled that current treatments for AK usually included a diamidine, which would not usually be used with polihexanide 0.8 mg/ml eye drops (see section 3.3). The clinical experts noted that diamidine-associated side effects may lead some people to switch treatments or stop therapy altogether. The committee considered this an uncaptured benefit for polihexanide 0.8 mg/ml in the modelling.
- The committee noted that the model assumed 23.4% of people in both arms whose condition was not cured by initial treatment switched to an alternative AAT. This was informed by the Delphi panel. The committee recalled that both the ODAK trial and Papa et al. collected data on treatment switching that could have been included in the model. It also recalled that there was considerably more switching reported in Papa et al. than in ODAK (see section 3.7). So, the committee agreed that the full effects of treatment switching may not be captured in the company's model.

The committee considered these uncaptured benefits in its decision making.

Conclusion

Recommendation

3.25 The committee noted the important uncertainties in the clinical-effectiveness evidence. This meant it was not possible to reliably estimate the cost effectiveness of polihexanide 0.8 mg/ml. So, it should not be used. The committee concluded that the company should provide

additional information for consideration at the next evaluation committee meeting.

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

Emma Douch

Technical lead

Alexandra Sampson

Technical adviser

Thomas Feist

Project manager

Richard Diaz

Associate director

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