NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Cenegermin for treating neurotrophic keratitis

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

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

The appraisal 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 13 April 2018

Second appraisal committee meeting: 26 April 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Cenegermin is not recommended for treating moderate or severe neurotrophic keratitis in adults.

1.2 This recommendation is not intended to affect treatment with cenegermin 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 clinician consider it appropriate to stop.

Why the committee made these recommendations

There is no standard care pathway for neurotrophic keratitis in the NHS. Treatment options include artificial tears and serum-derived eye drops, as well as surgery such as eyelid closure.

Evidence suggests that cenegermin may be an effective treatment than vehicle in terms of corneal healing (<0.5 mm epithelial defect) when used at 8 weeks, but this is uncertain.

The cost-effectiveness estimates are also uncertain because of a number of problems in the modelling. Although no robust cost-effectiveness analyses had been presented the most likely cost-effectiveness estimate is higher than the range NICE normally considers to be an acceptable use of NHS resources. Because of this, cenegermin cannot be recommended.

2 Information about cenegermin

Marketing authorisation indication	Cenegermin is indicated for the 'treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults'.
Dosage in the marketing authorisation	The recommended dose of cenegermin is 1 drop (20µg/ml) 6 times a day at 2-hourly intervals (starting from the morning and within 12 hours), for 8 weeks.
Price	£14,500 for 8-week course of treatment (company submission). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Dompé and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Unmet need

People with neurotrophic keratitis would welcome a new treatment option

3.1 Neurotrophic keratitis is a rare degenerative condition which is classed as an orphan disease. The clinical experts noted that it is a difficult condition to treat: there is no standard care pathway and many treatments are ineffective in healing the cornea. They noted that when the disease progresses, there is high risk of permanent vision loss as a result of fibrotic scars. The experts explained that disfigurement caused by corneal scarring and surgical procedures such as tarsorrhaphy (medical or surgical eyelid closure) can significantly impair quality of life. The committee agreed that people with neurotrophic keratitis have an unmet clinical need and would welcome any new treatment that improves outcome and reduces the need for surgery.

Current management

Cenegermin is a potential early option for treating neurotrophic keratitis

3.2 The underlying cause of neurotrophic keratitis varies, and clinicians are faced with a heterogeneous patient population that is difficult to treat. The

clinical experts highlighted that there is no standard care pathway and choice of treatment depends on the severity of the disease, clinician preference, patient need and availability. Current treatments are palliative in nature, such as preservative-free artificial tears and prophylactic antibiotics routinely used along with other treatments. Because there is no standard treatment that works for all patients, more than 1 treatment is normally prescribed in clinical practice. The committee noted that autologous serum-derived eye drops may take 6 to 8 weeks to prepare, and they are not available in many centres in England. The clinical experts stated that although tarsorrhaphy is not a popular treatment option with patients (because it can cause disfigurement), it is an effective and inexpensive procedure that is often used when all other options have failed. The clinical experts also highlighted that surgical tarsorrhaphy has been replaced by botulinum toxin-induced ptosis. The committee understood that cenegermin would be used early in the treatment pathway but that topical treatments may still be used concomitantly in clinical practice. It concluded that there is no standard care for neurotrophic keratitis but that cenegermin would be used as a potential early option.

Clinical evidence

Trial evidence from REPARO and study 0214 is uncertain

3.3 The company's clinical evidence came from 2 trials, REPARO and study 0124, which were unpublished at the time of the company's submission. Both trials are double-blinded, randomised, multicentre, vehicle-controlled, parallel group studies comparing cenegermin with vehicle. Vehicle acts a proxy for artificial tears, which is the only comparator identified by the company (owing to lack of clinical evidence for other comparators listed in the final NICE scope). The treatment duration was 8 weeks, in line the marketing authorisation (see section 2). The clinical experts highlighted that the vehicle treatment could not be considered a placebo because it will have some therapeutic benefit. The committee heard that REPARO was done in Europe and included people with unilateral stage 2 or 3

neurotrophic keratitis, refractory to 1 or more previous conventional non-surgical treatments (n=156). Study 0214 was done in the US; it included a similar population to REPARO, but also included people with bilateral disease (although only the worse-affected eye was studied; n=48). The committee noted that the trials had low patient numbers but this was to be expected considering the rarity of the disease. However, in both trials the controlled follow-up period was short (8 weeks), there was little long-term follow-up and withdrawal rates were high (up to 37.5%). Further uncertainty came from only a small proportion of patients having the licensed methionine-containing formulation of cenegermin (24 across both studies). The committee concluded that the results of both trials were associated with significant uncertainty.

Cenegermin may be more clinically effective than vehicle

3.4 Corneal healing (defined as having less than 0.5 mm epithelial defect) at week 8 was a co-primary end point of study 0214 and a secondary end point of REPARO. The difference in the percentage of patients achieving corneal healing between the cenegermin and vehicle arms at 8 weeks was 30.9% (97.06% confidence interval [CI] 10.60 to 51.13; p=0.002) in REPARO and 40.4% (95% CI 14.2 to 66.6; p=0.006) in study 0214. The primary analysis approach of both studies at 8 weeks was determined by a central reading centre and last observation carried forward (LOCF) methodology was used to account for missing data. The ERG raised concerns about the use of the LOCF method because of the associated biases; it stated that the multiple imputation approach would have been a more appropriate method to account for missing data in the trials. However, the committee noted that the different approaches did not lead to different conclusions about the comparative effectiveness of cenegermin and vehicle. The committee also noted that, in both studies, there was no statistically significant difference between the treatment arms at week 8 in secondary outcomes (specifically, percentage of patients achieving complete corneal clearing, time to onset of disease deterioration, and change from baseline in mean best corrected distance

visual acuity score). The committee concluded that cenegermin may be more clinically effective than vehicle in terms of corneal healing at 8 weeks.

The REPARO and study 0124 trial populations are generalisable to clinical practice in England

3.5 The committee noted that tarsorrhaphy was an exclusion criteria for both REPARO and study 0214, but heard from the clinical experts that it is frequently used in current management of neurotrophic keratitis. The experts noted that tarsorrhaphy is unpopular with patients and ideally cenegermin would be given earlier in the treatment pathway. The ERG also noted that although differences in the baseline characteristics exist between the populations in the 2 trials, the patient populations are generalisable to NHS clinical practice. The committee concluded that the REPARO and study 0124 trial populations are generalisable to clinical practice in England.

The recurrence rate and need for further treatment with cenegermin after 8 weeks is uncertain

3.6 The clinical experts explained that there is no robust clinical evidence to suggest that cenegermin could effectively 'cure' neurotrophic keratitis or prevent recurrence. The committee recalled that people who were healed at week 8 but no longer healed at 32 or 56 weeks of the extended follow-ups of REPARO and study 0214 were considered to have had a recurrence of neurotrophic keratitis. Recurrence rates at 32 weeks in the 2 trials varied from 0% to 3% in REPARO and 0% to 14% in study 0214, depending on the arm to which people were originally randomised. At 56 weeks, recurrence rates were 3% to 5% in REPARO. It was noted that these analyses were exploratory and based on a small number of patients for whom response data were available, so no conclusions could be drawn. The committee concluded that the recurrence rate and need for further treatment with cenegermin after 8 weeks is uncertain because of a lack of long-term data.

The company's economic model

The model is structurally flawed and its results cannot be considered reliable

3.7 The ERG highlighted several errors in the company's model which would invalidate any derived results. It stated that the model had a structural flaw in that it only allowed transitions from the sustained healing to non-healing states, and from any state to death. People who do not achieve sustained healing with their first treatment are never able to achieve sustained healing, and the model implicitly assumes that treatments in the standard of care basket have zero effectiveness. The model also assumes that all treatments in the non-healing health state are effective at stopping deterioration, whereas in the deteriorating health state no treatment stops deterioration and disease continues to progress until death. The ERG noted that these anomalies result in implausible costs and cost-effectiveness results, and they contradict the company's own assumptions that patients experience healing, non-healing and recurrences multiple times throughout their lifetime. The ERG further noted that clinical experts consulted by the company suggested that healing rates with autologous serum-derived eye drops are between 50% and 85%, so assuming zero effectiveness for serum drops is incorrect. During clarification NICE asked the company to provide an updated model to address these issues but the company were unable to fulfil this request. Because of the structural flaw, the ERG was unable to present alternative cost-effectiveness results. The committee acknowledged the challenges of modelling a complex disease area with no established treatment pathway and minimal clinical evidence. Nevertheless, it clarified that it could not make recommendations without being presented with robust cost-effectiveness estimates. The committee concluded that the company's model was structurally flawed and its results could not be considered reliable.

Consequences of the model structure

Extrapolating the treatment effect of cenegermin over a lifetime is inappropriate

3.8 The committee recalled that, as a result of the structure of the company's model, people in the sustained healing state do not experience a recurrence of disease after 5 years and will remain healed until death. Clinical advice received by the company suggested that the recurrence rate reduces with time and tends to plateau after 5 years. There is no clinical evidence to support the assumption that people who are completely healed at 5 years will remain healed for the rest of their lifetime and are effectively 'cured'. The committee concluded that it is inappropriate to extrapolate the treatment effect of cenegermin over a lifetime.

Modelling fixed resource use and costs over time is inappropriate

3.9 The committee heard that resource use and costs in each health state do not change over time, which generates implausible average estimates. The committee discussed whether it was feasible that people having artificial tears would visit a specialist 1,224 times over their lifetime. The clinical experts explained that some people may need frequent visits to a specialist in the acute phase of the disease but once the condition is stabilised and a maintenance treatment period is reached, visits to a specialist would fall to 2 to 3 a year. The ERG explained that in response to its clarification questions, the company had re-estimated an average of 2 visits a month in the standard of care non-healing and standard of care deteriorated health states. However, the committee still considered this estimate to be too high because it equates to 450 specialist visits over a lifetime; the committee heard from the clinical experts that this seemed very unlikely. The committee noted a number of other implausible costs were included in the model such as the same treatment costs were applied to permanent tarsorrhaphy and amniotic membrane transplantation regardless of the outcome. It reiterated that because of the

flaws in the model, amendments to resource use and costs were not possible and would not yield robust cost-effectiveness estimates. The committee concluded that it was inappropriate to model fixed resource use and costs and that this resulted in cost-effectiveness estimates that were very uncertain.

There is considerable uncertainty in the utility values used in the model

3.10 The committee noted that the only difference between the healed and non-healed health states in the company's model is a disutility applied for tarsorrhaphy. The ERG queried the accuracy of this disutility value, because there was little supportive evidence and it was also applied inappropriately. The disutility for temporary tarsorrhaphy was applied every year, whereas the ERG considered that most people would only have the procedure once in their lifetime. The combined errors in the utility values lead to overestimating the lifetime quality-adjusted life year (QALY) loss from tarsorrhaphy. The committee concluded that there was significant uncertainty associated with the utility values used in the company model.

The company's base-case economic analysis

There are considerable differences between the deterministic and probabilistic analyses

3.11 The ERG noted that the differences between the deterministic and probabilistic analyses may be because of the structural uncertainties in the model, and that they highlighted the model's lack of face validity. The committee concluded that the discrepancies between the deterministic and probabilistic analyses indicate that the company's model is inherently The most likely incremental cost-effectiveness ratio (ICER) is above £30,000 per quality-adjusted life year gained.

3.12 The committee recalled the uncertainty in the evidence provided and the structural flaws in the company's model that prevented the ERG from doing any exploratory analyses. It also noted that the assumptions in the

company's cost effectiveness analyses were implausible (see sections 3.8- 3.10). Although the committee was not presented with a robust incremental cost-effectiveness ratio (ICER) that reflects clinical practice in England, it considered that the most likely ICER for cenegermin compared with artificial tears would be more than £30,000 per QALY gained.

Innovation

Cenegermin is potentially innovative and there is no evidence of additional health benefits not captured

3.13 The company considered cenegermin to be innovative because it is the only treatment represents a major change in treating a rare condition. The mechanism of action of cenegermin is to induce nerve regrowth to the cornea, although the committee heard from the clinical experts that this was not always evident in biological studies. The committee noted that cenegermin was developed over 20 years ago and so could not be considered a new treatment. However, it acknowledged that there is a large unmet need for people with neurotrophic keratitis. The committee concluded that cenegermin would be beneficial for patients, but it had not been presented with evidence of any additional benefits that were not captured in the QALY calculations.

Conclusion

Cenegermin is not recommended for use in the NHS

3.14 The committee recalled that it had not been presented with any robust estimates of cost-effectiveness that were suitable for decision-making and that the most likely ICER for cenegermin compared with artificial tears is likely to be over £30,000 per QALY gained, which is higher than the range usually considered a cost-effective use of NHS resources. It therefore concluded that it could not recommend cenegermin to treat neurotrophic keratitis in adults.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
March 2018

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

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

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

NICE project team

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

Sana Khan
Technical Lead

Sally Doss

Technical Adviser

Stephanie Yates

Project Manager

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