National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cenegermin for treating neurotrophic keratitis [ID946]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Dompé	Yes	Comment noted. No action required.
	The Royal College of Ophthalmologists	Yes	Comment noted. No action required.
Wording	Dompé	No Amendments should be made to reflect the following: 1. Page 2, comparators: Preservative free artificial tears should be re-inserted into the comparators, as they are used in all stages of disease	Comment noted. Preservative free artificial tears have been added to the list of comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
		2. Page 3, other considerations: The sentence ”If evidence allows, separate consideration will be given to people with neurotrophic keratitis (NK) associated with progressive or non-progressive underlying causes.” should be deleted, as there are no data to support these sub groups in terms of differential approach to sequencing off label, unlicensed or surgical treatment options. In consultation with clinical experts, they do not ever classify NK as progressive or non-progressive. All clinical trials have classified by grade.	Comments noted. The scope grades neurotrophic keratitis using the Mackie classification. The purpose of the subgroup analysis is to consider whether there is a differential response depending on the underlying cause of neurotrophic keratitis. Feedback from clinicians indicate that understanding of the underlying causes of neurotrophic keratitis is important in management. No action required.
	The Royal College of Ophthalmologists	Yes	Comment noted. No action required.
Timing Issues	Dompé	NK represents one of the most difficult and challenging corneal diseases to be managed. There is no standard medical treatment to address the corneal innervation impairment in NK patients. Current non-licensed therapies promote corneal healing and aim to halt disease progression but do not address the neurotrophic deficit which is believed to play a pivotal role in the development of NK.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		There is no current licensed therapeutic alternative for NK patients. There is, therefore, a high, unmet medical need for new treatments and any innovative pharmacological attempt should merit high priority. This is in the context of some alternative approaches including surgical procedures, which carry additional risk of infection and/or complications.	Comment noted. No action required.
		Cenegermin received marketing authorisation from the European Medicines Agency in July 2017 (EC Decision (2017) 4940 of 06/07/2017). A small number of patients will receive treatment via the Early Access to Medicines Scheme but the recruitment window was short so there is a significant number of patients with no licensed treatment options available.	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10131. No action required.
	The Royal College of Ophthalmologists	Not urgent	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. See the NICE website: https://www.nice.org.uk/

Section	Consultee/ Commentator	Comments [sic]	Action
			guidance/indevelopment/gid-ta10131. No action required.
Additional comments on the draft remit	-	-	-

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Dompé	The disease background information is comprehensive however Dompé has some concerns. The following text in the second scoping document is not supported by evidence and should be removed: “Treatment options may depend on the underlying cause of the neurotrophic keratitis, in particular whether it is related to an ongoing progressive condition (such as diabetes or multiple sclerosis) or an acute or non-progressive cause (such as surgery or an injury)”. Dompé has discussed this statement with clinicians and UK experts have confirmed that this statement is incorrect.	Comment noted. Feedback from clinicians highlight the importance of taking into consideration the underlying cause of neurotrophic keratitis. The wording has been amended to “Management should consider the underlying cause …” Comment noted. The text has been amended

Section	Consultee/ Commentator	Comments [sic]	Action
		Preservative free artificial tears are referenced in the background section as a treatment for early-stage disease but this treatment option is used routinely at all stages of disease and should be referenced as such (Sacchetti, 2014).	to reflect that preservative free artificial tears may be used at all stages of neurotrophic keratitis.
		Estimates of the prevalence of NK in the first and second scoping document have been updated to include a range from 1.6 up to 4.2 per 10,000 people. The upper number of 4.2 per 10,000 should be treated with caution as, based on feedback from clinicians on patient numbers, it is likely to be an overestimate.	Comment noted. The estimate of 4.2 per 10,000 people is based on EMA's document on orphan designation for recombinant human nerve growth factor for the treatment of neurotrophic keratitis. The scope emphasises that "the precise number is unknown." No action required.
		It should be noted that it is widely accepted that corneal sensory nerves play a key role in maintaining the anatomical integrity and function of the cornea and particularly of the epithelium. The corneal epithelium is the first target of neurotrophic keratitis showing dystrophic changes and defects with poor tendency to spontaneous healing. The disease is characterised by decreased or absent corneal sensitivity (hypo/anaesthesia), spontaneous epithelial breakdown and reduced corneal healing. The absence/reduction of corneal sensitivity increases the likelihood of at-risk patients developing an indolent corneal lesion and triggering a detrimental loop of events. These events include reduced tearing caused by reduced reflex tear production, reduced blinking reflex and reduced trophic support of the corneal nerves to the corneal stroma and epithelium. With a lack of trophic support and	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		protection by tears, the corneal epithelium breaks down and the disease progresses to stromal involvement, corneal melting and perforation if not recognised and properly treated.	
	The Royal College of Ophthalmologists	The amount of background information presented is limited	Comment noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal. No action required.
The technology/ intervention	Dompé	Yes	Comment noted. No action required.
	The Royal College of Ophthalmologists	Yes, but the amount of information provided is not sufficiently detailed.	Comment noted. This section of the scope aims to provide a brief overview of the technology for the appraisal; additional details may be considered by the committee, if appropriate, at the time

Section	Consultee/ Commentator	Comments [sic]	Action
			of the appraisal. No action required.
Population	Dompé	The population is defined appropriately. We do not consider that there are groups within the population that should be considered separately.	Comment noted. No action required.
	The Royal College of Ophthalmologists	Yes 1. If evidence allows separate consideration should be given to people with neurotrophic keratitis associated with progressive non-progressive underlying causes but also to the group of people whose neurotrophic keratitis may reduce or resolve once the inciting cause is removed or does not recur. The proposed treatment may affect (accelerate) the recovery. 2. Consideration should be given to subgroups based on the stage or severity of neurotrophic keratitis and the underlying cause of the disease	Comments noted. The population in the scope is consistent with the wording in the marketing authorisation for the technology. The proposed subgroups are included in the 'Other considerations' section of the scope. No action required.
Comparators	Dompé	None of the listed comparators can be described as "best alternative care". Medical or surgical eyelid closure, serum eye drops, therapeutic contact lenses and surgery are used as methods to avoid further damage to the eye, but are symptomatic in nature and do not address the underlying pathology. Furthermore, they are not standardised and surgery in particular can have a significant unpleasant aesthetic impact, reducing patients' quality of life. In engagement with clinicians, collagenase inhibitors were not identified as a comparator, as collagenase inhibitors are only used at later more severe stages, so should not be listed as such in the scoping document. Although it has similar shortcomings, the omission of preservative free artificial tears as a comparator in the second scoping document is a notable	Comment noted. The scope includes stage 3 neurotrophic keratitis which may be complicated by stromal melting for which collagenase inhibitors may be considered (Sacchetti 2014). Comment noted. Preservative free

Section	Consultee/ Commentator	Comments [sic]	Action
		anomaly. Preservative free artificial tears are used for patients with NK at all stages of disease. Currently there is no standard, licensed medical treatment to address corneal nerve impairment in NK patients. Current therapies are palliative and do not address the neurotrophic deficit, which is believed to play a pivotal role in the development of NK. Cenegermin has been recognised by the Early Access to Medicines Scheme (EAMS) as a treatment that meets unmet need in a seriously debilitating condition. Additionally, there is uncertainty in the efficacy and safety of current therapies, as a consequence of limited clinical evidence. The designs of clinical studies have not been robust, they include only a small number of patients and are subject to a significant risk of bias. They can also vary to a great extent in terms of production process or surgical technique.	artificial tears have been added to the list of comparators. Comments noted. No action required. Comments noted. No action required.
	The Royal College of Ophthalmologists	Yes. Not possible to restrict to one comparator as several are needed and they may also be peculiar to the disease causing the neurotrophic keratopathy	Comment noted. No action required.
Outcomes	Dompé	The single reason to treat the eye is to heal the lesion and save the eye, anatomically and functionally. Therefore, the outcomes to be used in the model and specifically the exclusion of visual acuity and corneal sensitivity from the model must be understood in this context. In the model, healing, adverse events and quality of life are included (corneal sensitivity informs the data on healing). Separate effect measures such as corneal sensitivity can be considered in the clinical results section but will not be used in the model.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	The Royal College of Ophthalmologists	Yes but in addition, one of the particular adverse reactions may be that of reactivation and recurrence of herpetic disease particularly in patients with neurotrophic keratopathy due to the neurotrophic Human herpesviruses (HHV). There is a potential risk of reactivation of latent HHV with nerve growth factors and I think patients receiving nerve growth factors should be specifically monitored for this.	Comment noted. The impact of reactivation and recurrence of herpetic disease will be captured in 'adverse effects'. No action required.
Economic analysis	Dompé	The lifetime time horizon of the model ensures it is long enough to capture all expected consequences in cost and health effect (e.g. QALYs) between the interventions being compared. Cenegermin would benefit NK patients all the way through their lifetime avoiding progressively more severe health consequences over time which affect the quality of life of patients and potentially also the chance of recurrence. It is expected that patients will receive a single 8-week course of treatment. In responding patients, it will be assumed that the treatment effect will persist for the time horizon of the model. Considering that NK is mainly a unilateral disease, it is not appropriate to include consideration of the benefit in the best seeing eye in the cost effectiveness model. NK creates a very unstable situation that may quickly deteriorate; the epithelial lesion most likely gets worse, leading to perforation, infection and even loss of the eye. As a consequence, there is a need to treat the affected eye in order to promote anatomical healing of the cornea and prevent disease progression, which in the long run could support better visual acuity outcomes.	Comment noted. No action required. Comment noted. No action required. Comment noted. Trials on cenegermin have included people with bilateral disease. Consideration of both eyes has been retained to ensure the scope is adequately broad to reflect potential marketing authorisation

Section	Consultee/ Commentator	Comments [sic]	Action
		As is often the case in a rare condition, there is likely to be significant uncertainty in the economic analysis of cenegermin due to the lack of clinical evidence precluding a robust mixed treatment comparison. The usual measures of variability will be included to assess the impact of this uncertainty on results via deterministic and probabilistic sensitivity analyses, and scenario analysis.	inclusion and address relevant issues in the economic analysis. Comment noted. The NICE Guide to the methods of technology appraisal 2013 states that 'the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases' (section 6.2.16). No action required.
	The Royal College of Ophthalmologists	The stated analysis is appropriate, that is, *'The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.* *The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.* *Costs will be considered from an NHS and Personal Social Services perspective.*	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.'	
Equality and Diversity	Dompé	N/A	Comment noted. No action required.
	The Royal College of Ophthalmologists	I don't think there are equity issues	Comment noted. No action required.
Innovation	Dompé	The innovative nature of cenegermin in an area of high unmet need has been confirmed by the Promising Innovative Medicine designation, awarded by the MHRA, allowing a positive Scientific Opinion to be received under the Early Access to Medicines Scheme. Cenegermin eye drops, a recombinant human nerve growth factor, is a "step-change" in the management of moderate and severe NK and a disease modifier with the potential to heal the cornea. The nerve growth factor (NGF) is an endogenous protein involved in the differentiation and maintenance of neurons, which acts through specific high affinity (i.e., Trk A) and low affinity (i.e. p75NTR) NGF receptors. NGF receptors are expressed in the anterior segment of the eye (cornea, conjunctiva, iris, ciliary body and lens) and by the lacrimal gland as well as by posterior segment intraocular tissues. The treatment with cenegermin, administered as eye drops, is the first intended to address corneal nerve impairment in NK patients and to restore corneal integrity. Because NK is very often unilateral, and visual acuity (i.e. unilateral and bilateral) is not always affected, it is very difficult to capture the QALY impact accurately.	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	The Royal College of Ophthalmologists	Yes, the technology is innovative and may make have a significant and substantial benefit. I would regard it as a step change. I think the outcomes will be included in QALY. The data which is accessible, is that contained in publications on nerve growth factor for neurotrophic keratitis.	Comments noted. The Appraisal Committee will discuss the potentially innovative nature of this technology. No action required.
Other considerations	Dompé	Despite the rarity of the disease, the Marketing Authorisation Application included two independent, well controlled Phase II studies to support efficacy and safety in patients affected by stage 2 and 3 NK. Pooled safety data from these two studies comprise all randomised patients who received at least one dose of study medication. The safety database will include additional subjects exposed to the drug, including healthy volunteers and patients affected by other ocular pathologies.	Comments noted. No action required.
Questions for consultation	Dompé	N/A	Comment noted. No action required.
	The Royal College of Ophthalmologists	There are many different causes of neurotrophic keratitis, which fall into the progressive and non-progressive but also into partially or potentially fully recoverable depending on the cause. In addition, each of the groups of causes will follow a different course. The beneficial evidence for each will therefore vary accordingly and the outcomes will need to be tailored appropriately to the causative group.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Dompé	No further comments	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health