Chair’s presentation
Cenegermin for treating neurotrophic keratitis (ID946)

2nd Appraisal Committee meeting, Committee C

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ERG: Liverpool reviews and implementation group (LRiG)

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Company: Dompé UK

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Slides for projector and public [redacted]

Key issues

- Company's new cost effectiveness results based on ACD committee-preferred assumptions and proposed PAS
  - Can these estimates be used for decision making?
  - Most plausible ICER?
- Company's response to ACD
  - Is the new model structure appropriate for decision-making?
  - Do the scenarios address the uncertainties that have been identified previously?
- Potential equalities issues?

Cenegermin (Dompé)

Marketing authorisation (granted July 2017)	Treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis (NK) in adults
Mechanism of action	Recombinant human nerve growth factor (rhNGF) that aims to improve nerve function and stimulate healing
Administration	Eye drops
Dosage	1 drop (20µg/ml) 6 times a day at 2-hourly intervals (starting from the morning and within 12 hours), for 8 weeks
List price	£14,500 for 8-week course of treatment (simple discount patient access scheme proposed after ACM1)

Key clinical trials

	REPARO (unilateral disease)	0214 (bilateral disease)
Design	Double-masked, randomised, multicentre, vehicle-controlled parallel group study	
Population	156 adults with 1 eye affected by stage 2 or 3 NK with corneal ulcer, and refractory to 1 or more previous conventional non-surgical treatments.	Adults with 1 or both eyes affected by stage 2 or 3 NK with corneal ulcer, and refractory to 1 or more previous conventional non-surgical treatments
Intervention	Cenegermin 10µg/ml* or 20µg/ml** 6 times daily	Cenegermin 20µg/ml (with methionine antioxidant), 6 times daily
Comparator	Vehicle (considered proxy for preservative-free artificial tears & includes ingredients widely used in artificial tears & other ocular lubricants)	
Follow up	8 weeks controlled 56 or 64 weeks uncontrolled	8 weeks controlled 32 or 40 weeks uncontrolled
*Results from 10µg/ml not reported here or in model because not licensed dose ** formulation without methionine antioxidant which is the licensed formulation		

ACD: preliminary recommendation

- Cenegermin is not recommended for treating moderate or severe neurotrophic keratitis in adults
  - clinical evidence suggests cenegermin may be effective treatment when used at 8 weeks but this is uncertain
  - cost effectiveness estimates are uncertain because of a number of errors in modelling
  - most plausible cost effectiveness estimate is higher than the range NICE normally considered acceptable use of NHS resources

ACD summary (1)

ACD section	Committee conclusion
Current management (3.2)	Underlying cause of neurotrophic keratitis varies, and clinicians are faced with a heterogeneous patient population that is difficult to treat. No standard care pathway and choice of treatment depends on the severity of the disease, clinician preference, patient need and availability. Cenegermin is a potential early option for treating NK.
Clinical evidence (3.3 to 3.5)	Trial evidence from REPARO and study 0214 is uncertain: • vehicle treatment could not be considered a placebo because it will have some therapeutic benefit • REPARO included people with unilateral stage 2 or 3 neurotrophic keratitis while study 0214 also included people with bilateral disease (although only the worse-affected eye was studied) • Low patient numbers, short follow up and only a small proportion having the licensed methionine-containing formulation of cenegermin Cenegermin may be more clinically effective than vehicle (corneal healing was significantly improved at 8 weeks in both studies)

ACD summary (2)

ACD section	Committee conclusion
Recurrence rate (3.6)	The recurrence rate and need for further treatment with cenegermin after 8 weeks is uncertain: • no robust evidence to suggest cenegermin could effectively ‘cure’ neurotrophic keratitis or prevent recurrence • 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 NK • lack of long-term data
Model (3.7)	The model is structurally flawed and its results cannot be considered reliable for decision-making: • people who do not achieve sustained healing with their first treatment are never able to achieve sustained healing • model assumes SOC treatment basket not effective • implausible costs and cost-effectiveness results, (contradict company’s own assumptions that patients experience healing, non-healing and recurrences multiple times throughout their lifetime) • During clarification, company were unable to provide updated model to address these issues. Because of the structural flaw, the ERG was unable to present alternative cost-effectiveness results.

ACD summary (3)

ACD section	Committee conclusion
Consequences of flawed model structure (3.8 to 3.11)	• Extrapolating the treatment effect of cenegermin over a lifetime is inappropriate (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’). • Modelling fixed resource use and costs over time is inappropriate (number of implausible costs including visits to specialist that were included in the model but could not be changed due to flaws in the model). • There is considerable uncertainty in the utility values used in the model (disutility for tarsorrhaphy applied every year, whereas the ERG considered that most people would only have the procedure once in lifetime). • Considerable differences between company’s deterministic and probabilistic analyses.

ACD consultation (1)

- Received comments from company, NHSE and 2 web comments

Theme	Comments
Botulinum toxin-induced ptosis	**Company**: Clinical experts at the meeting may prefer to use new approach (botulinum toxin-induced ptosis), however many centres in England continue to favour surgical tarsorrhaphy.
Disutility for temporary tarsorrhaphy applied every year	**Company**: Disutility based on TA467 and was applied as part of annual standard of care (SOC) basket for a proportion who would receive temporary tarsorrhaphy for the period of which a temporary tarsorrhaphy is expected to be applied to the eye. A *small proportion* of the cohort *may* have another temporary tarsorrhaphy in subsequent years.
Standard of care (SOC) treatments not effective	**Company**: Healing rates between 5% and 100% with recurrence rate between 15% and 54%. Small chance of having complete healing sustained over significant time period. Basket approach used to capture use of treatments in an average cohort (rather than multiple assumptions to model each treatment). Explored in new scenario analyses.

ACD consultation (2)

Theme	Comments
Clinical effectiveness	**Web**: Cenegermin's efficacy and safety is demonstrated in 2 RCTs and results showed cenegermin treatment was statistically significantly superior to control/vehicle treatment in generating complete corneal healing in adult patients with NK.
Challenges in treatment	**Web**: Agree with ACD that NK is challenging to treat. Treatment is often in inpatient setting and is prolonged and very complicated with multiple episodes lasting several years.
Other	**NHSE**: company need to provide better economic report (successful 'remission' induction, conventional vs. cenegermin) **Company**: highlight some wording issues and errors

Company's new evidence
Summary

Committee preferred assumption	Company
Model is structurally flawed and results not reliable: • No transition from sustained healing and non-healing, SOC not effective, assumes all treatments in non-healing health state stop deterioration	Revised model structure allows transitions between sustained healing to non-healing (exploratory scenario analysis)
Extrapolating lifetime treatment effect inappropriate • effectively 'cured' if completely healed at 5 years	No new evidence.
Fixed resource use & costs over time not appropriate: • Unrealistic number of specialist visits over lifetime • Other implausible costs (e.g. same treatment costs for permanent tarsorrhaphy and amniotic membrane transplantation regardless of outcome)	ERG changes & proposed PAS: • surgical treatments occur in 1st year only • fewer specialist visits
considerable uncertainty in the utility values: • disutility for temporary tarsorrhaphy applied every year, but most would only have once in lifetime	ERG changes & proposed PAS: • disutility of tarsorrhaphy applied in the 1st year only
Differences in deterministic and probabilistic results	No new evidence. Small sampling error in programming (not structural uncertainty)

Company's new evidence

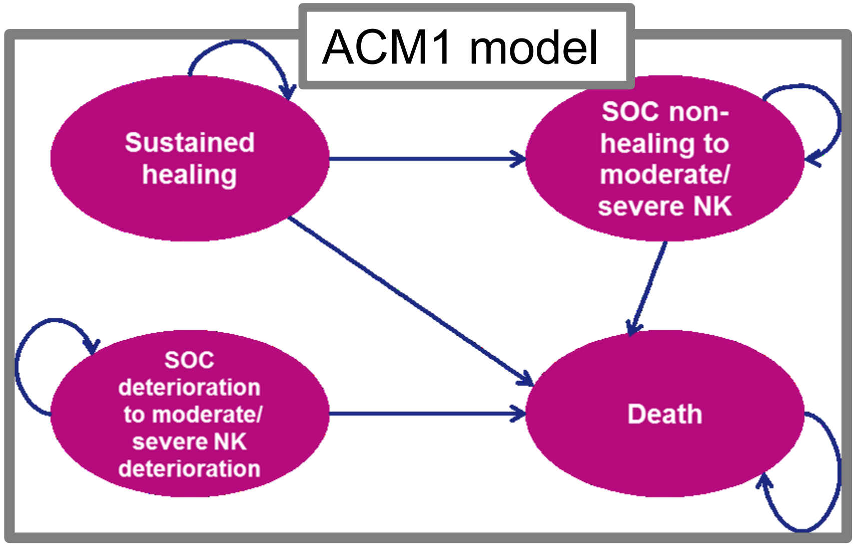
- Company have proposed a PAS
- Company report ICERs using ERG's exploratory changes from ACM1:
  - surgical treatments occur in the 1st year only
  - reduction in the number of specialist visits (2 specialist visits per month in non-healing health states) and
  - the disutility of tarsorrhaphy applied in the 1st year only

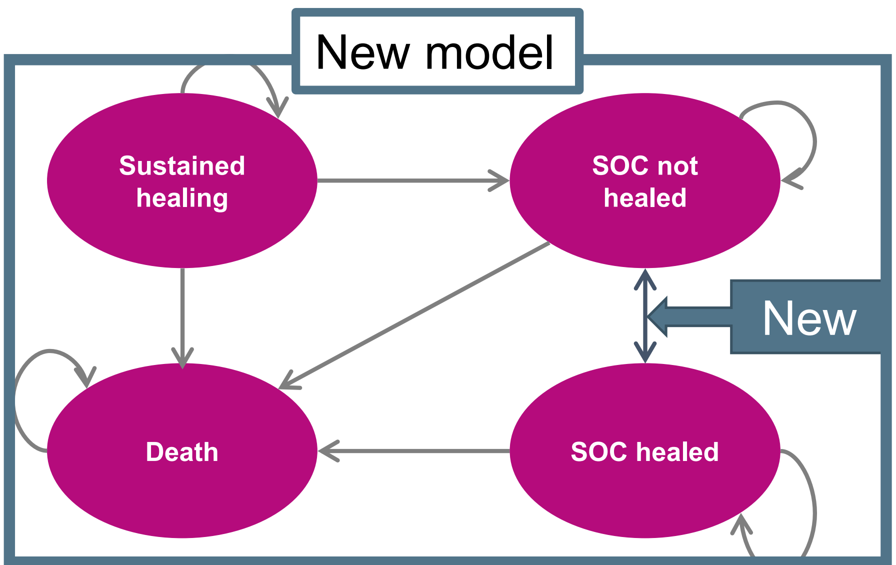
Technologies	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
ERG exploratory changes (without PAS)							
Artificial tears	£31,672	15.21	9.56	£5,602*	0	0.044	**£128,453**
Cenegermin	£37,274	15.21	9.61				
* Reported as -£5,602 in company's response appendix but corrected in this table							

Note: At ACM 1 the ERG could not present its preferred exploratory ICER due to model structure and noted ICER still likely to be <u>underestimated:</u>

- *Average number of specialist visits for people initially having artificial tears is still implausibly high (~450 over a lifetime)*
- *Utility decrements for tarsorrhaphy may be too high because all patients having tarsorrhaphy are assumed to have unilateral blindness*
- *Mortality has likely been underestimated*

Company scenario: new model structure (1)





Abbreviations: SOC standard of care

- Original model structurally flawed & results cannot be considered reliable.
  - If no sustained healing with 1st treatment, never able to achieve it
  - SOC has zero effectiveness
  - assumes all treatments in non-healing state effective at stopping deterioration

- Company's revised model allows transitions between the sustained healing to non-healing states & does not model proportion that deteriorate
- **SOC not healed:** not healed after initial treatment or after recurrence (weighted average costs and effectiveness)
- **SOC healed:** healing after treatment (weighted average of ongoing SOC costs and small disutility (-0.017) in 1st year for debilitating surgical treatments)

Company scenario: new model structure (2)
Estimating clinical effectiveness of SOC

- Model at ACM1 assumed SOC had zero effectiveness
- In new model structure, probability of healing or not healing and recurrence with SOC treatments based on clinical expert opinion in the absence of other data.
  - 12 clinical experts asked to provide estimates of complete healing and its estimated duration (company adjust to 4-week probability in line with cycle length)
  - Clinicians also asked to estimate recurrence rate with each treatment at 6 months, 1 year and 5 years (to avoid use of tunnel state, 5 year rate of recurrence used but adjusted to a 4-week probability).

Company scenario: new model structure (3)

Survey results from 12 clinical experts

	Complete healing			Recurrence	
SOC treatments	Proportion (mean, range)	Time (wks)	4-week probability (mean, range)	Proportion at 5 yrs	4 week probability
Artificial tears	77% (5%-100%)	9	48% (2%-100%)	N/A*	N/A*
Contact lenses	70% (30%-95%)	6	55% (21%-86%)	34%	0.64%
Tarsorrhaphy	78% (30%-100%)	6	64% (21%-100%)	43%	0.86%
Autologous serum eye drops	65% (50%-85%)	28	14% (9%-24%)	54%	1.19%
AMT	74% (50%-100%)	10	42% (24%-100%)	37%	0.71%
Conjunctival flap	73% (50%-100%)	8	48% (29%-100%)	18%	0.30%
Corneal transplant	72% (50%-95%)	18	25% (14%-49%)	15%	0.25%

*assumed to be same as cenegermin for consistency with sustained healing health state.
Abbreviations: AMT, amniotic membrane transplantation; SOC, standard of care; wks, weeks; yrs, years;

Company scenario: effectiveness of SOC

[redacted]

- The effectiveness of the SOC basket is highly uncertain. The probability of healing with the SOC basket was varied in the model (also includes ERG exploratory changes).
- Cenegermin is associated with a positive NMB regardless of efficacy but this decreases as the efficacy of the SOC basket increases.

Company scenario results
List price analyses

Scenario	ICER
Company base case ACM 1	Cenegermin dominant
ERG exploratory changes ACM 1 • surgical treatment in 1st year only • lower number specialist visits • tarsorrhaphy disutility in 1st year only	£128,453
ERG exploratory changes and multiple imputation approach used to account for missing data	£144,182
ERG exploratory changes and revised model structure	Cenegermin dominant
ERG exploratory changes, revised model structure and multiple imputation approach	Cenegermin dominant

ACD: The committee recalled that it had not been presented with any robust estimates of cost-effectiveness that were suitable for decision-making

Note: Analyses with proposed PAS will be discussed in part 2

ERG review of company's new evidence

Summary

Clinical effectiveness	• Questionable clinical effectiveness estimates of individual standard of care (SOC) treatments
SOC	• Method of calculating SOC effectiveness inappropriate
Cost	• Some long-term costs after healing are implausible
Errors	• 5 errors in company model for monthly health state costs calculation for both cenegermin & artificial tears.
Utilities	• Utility decrement for tarsorrhaphy not supported by evidence and may be inaccurate (QALY gain for cenegermin likely to be overestimated)
Other	• No account of cenegermin after recurrence • Although company have made changes, model too simple to produce accurate ICER for decisions makers • ERG corrections & scenarios substantially increases ICER.

ERG review of company's new evidence
Clinical effectiveness of SOC

- Effectiveness of individual SOC treatments (except autologous eyedrops) is equal or greater than cenegermin
  - Questionable effectiveness estimates in model from clinician survey
  - In clinician survey rate of 'complete healing' well above trial results
  - How could cenegermin ever be cost effective?
- Inappropriate method for incorporating clinical effectiveness estimates of SOC basket in model
  - Company use weighted average of individual treatments but can receive multiple treatments, therefore probability of healing with SOC could be greater than 1
  - Could be avoided by looking at treatments individually (not basket), or if basket modelled as chain of treatments that have incremental efficacy contingent on failure on a prior treatment.

ERG review of company’s new evidence
Implausibility in method of costing health states

1) Only difference in costs (healed vs. non-healed) is no surgical treatments in healed state (continue artificial tears, ASED and contact lenses for lifetime)

ERG scenario: stop ASED and contact lens costs after 12 months

2) Model assumes people healed with artificial tears or SOC use artificial tears for life, but this is not in line with trial protocol (stopped at 8 weeks)

ERG scenario: stop artificial tears after 1 year in sustained healing & healed states

3) Model assumed some achieve complete healing in 1st cycle but some people in healed state may need surgical treatment to achieve healing (surgical costs not included in healed state)

ERG scenario: costs in the healed state in 1st year are same as unhealed state.

Abbreviation: ASED, autologous serum eye drops

ERG review of company's new evidence

Errors

Errors identified by ERG	ERG comments
1. Cost of ASED (healed & non-healed states of both arms)	company used quarterly cost of maintenance treatment (£372.26) for each 4 week cycle rather than the actual 4-week cost (£114.59).
2. Cost of contact lenses (healed & non-healed states of both arms)	• one-off cost (£34.50) applied in each cycle • clinical expert survey: 1 contact lens per course of treatment, lasting 0.32 years on average • 4-week cycle cost should be £10.19
3. Cost of specialist visits (healed state of both arms)	• company ACD response: same number specialist visits in 'healed' & 'sustained healing' • In the model, healed: 2 visits per cycle, cost £174; sustained healing: 0.78 visits per cycle, cost £67.62
4. Weighting of costs by 12 months not 13 cycles (healed & non-healed states of both arms)	Inconsistent weighting of costs (Only sustained healing costs based on 13 cycles in a year, all other costs weighted by 12 months in a year)
5. Cost of surgical treatments (healed state of both arms)	Incorrectly implemented to healed state (assumed only occur in 1st year in non-healed state only)

Abbreviation: ASED, autologous serum eye drops

ERG exploratory cost effectiveness results
cenegermin vs. artificial tears (list price)

	Cycle costs 'Healed'		Cycle costs 'Non-healed'		Total costs		Incremental cost	ICER
	1-13	13+	1-13	13+	Cenegermin	Artificial tears		
Company base case*	£397	£326	£469	£397	£47,052	£49,379	-£2,327	Cenegermin dominant
ERG cost corrections								
ASED	£264	£193	£336	£264	£37,472	£32,024	£5,448	£127,007
contact lens	£389	£318	£460	£389	£46,433	£48,257	-£1,824	Cenegermin dominant
specialist visits	£291	£220	£469	£397	£39,625	£35,918	£3,707	£85,441
12 annual cycles	£396	£324	£462	£390	£46,934	£49,076	-£2,154	Cenegermin dominant
surgical treatment	£397	£397	£469	£397	£51,796	£57,895	-£6,099	Cenegermin dominant
ERG cost-corrected base case	£148	£148	£320	£248	£34,053	£25,654	£8,399	£195,819

*using revised model structure. Abbreviations: ASED, autologous serum eye drops

ERG exploratory scenarios
list price analyses

	Total costs		Incremental cost*	ICER**
	Cenegermin	Artificial tears		
Company base case using revised model structure	£47,052	£49,379	-£2,327	Cenegermin dominant
1. ERG cost-corrected base case	£34,053	£25,654	£8,399	£195,819
2. ASED and contact lens cost stopped after one year in healed state	£28,702	£17,986	£10,716	£249,841
3. Artificial tear use stops after one year in sustained healing and healed states	£32,884	£22,578	£10,306	£240,290
4. Costs in healed state equal to non-healed state in 1st year	£34,599	£26,848	£7,751	£180,740
ERG alternative scenario (all changes 1 to 4)	£29,250	£16,266	£12,983	£302,717

*For cenegermin vs artificial tears, negative values indicate cenegermin is cost saving
**Cenegermin vs artificial tears (incremental QALYs of 0.04 in company base case is unaffected by all ERG corrections). Abbreviations: ASED, autologous serum eye drops

Potential equality issues

- No equality issues raised by the company or in ACD
- ERG report
  - Company report (based on 1 2clinical experts) patients typically seen once a week for moderate NK and more frequently for severe NK
  - Given that many specialist centres are likely to have wide catchment areas, there may currently be issues in terms of access to treatment (feasibility of being able to travel and attend specialist centres) for patients living at the outer reaches of these catchment areas
  - Given that cenegermin would be given to patients weekly, this issue may remain even if cenegermin is made available

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