National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns

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	Chiesi Farmaceutici	The NHS England Manual for service specification for adult specialist ophthalmology services states that NHS England commissions the following services[1]: • Ocular surface reconstruction - keratolimbal allografts, ex vivo stem cell allografts, cultured oral mucosal epithelial transplant, conjunctival limbal autograft (living related also). The commissioning of Holoclar is expected to be included by NHS England as a specialised/highly specialised service. **NICE Highly Specialised Treatments** In light of the small patient pool likely to be eligible for and receive treatment with Holoclar, we would ask whether the NICE Highly Specialised Treatments route would be more appropriate. The decision making framework to be used by the Highly Specialised Technologies Evaluation Committee builds on the work by AGNSS, and incorporates NICE's exploratory work on appraising medicines and technologies, including the 2004	Comment noted. Topics are referred to NICE by the Department of Health, taking into account comments received. This topic will be accordingly scheduled into the appropriate work programme.

Section	Consultee/ Commentator	Comments [sic]	Action
		exploratory work on 'ultra-orphan drugs'.[2] Given the very small numbers of patients living with this very rare condition a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of this very rare condition. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for a manufacturer in making a reasonable return on the research and development investment because of the very small populations treated.[2] **Patient numbers for Holoclar** Corneal lesions with associated limbal stem cell deficiency, due to ocular burns, affect approximately 0.3 in 10,000 people in the European Union.[3] The estimated number of people with LSCD is around 1,938 in the UK overall, with 1629 in England and 93 in Wales, based on population estimated from 2014 of 64.6 million, 54.3 million and 3.1 million respectively.[4] Not all patients will be suitable for Holoclar, and the licence defines use only in adult patients with 'moderate to severe' limbal stem cell deficiency (LCSD) (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1 - 2 mm^2 of undamaged limbus is required for biopsy'.[5] Following advice from 9 UK specialists at a recent advisory board, 51 patients in 6 specialist centres had been identified as eligible to receive treatment with Holoclar. This included the majority of UK specialist centres, but not all.[6] Market research conducted on behalf of Chiesi has indicated a patient pool of up to 107 patients eligible for Holoclar treatment in the UK.[7] The incident population was expressed as variable by specialists, and patients who received recent chemical or physical burns would still need to wait for ~18months until stabilisation had occurred before starting on the pathway of care, of which Holoclar is a part.[6]	

Section	Consultee/ Commentator	Comments [sic]	Action
		It is anticipated that there will be only 2 UK treatment centres that will be approved and trained by Chiesi to deliver this intervention, and designated by NHS England as specialist centres.	
Wording	Chiesi Farmaceutici	Yes	Comment noted.
Timing Issues	Chiesi Farmaceutici	There is currently no other EMA approved *medical* treatment available for corneal lesions with associated LSCD, caused by ocular burns.[3] Holoclar was recommended for approval by the EMA in December 2014, as the first medicinal product for LSCD and the first advanced therapy medicinal product (ATMP) containing stem cells.[8,9] There has already been a significant delay between granting of the marketing authorisation and the potential for the first patient to receive treatment funded by the NHS (subject to NICE approval). Current treatment options are limited to surgical treatments, mainly[10]: • Conjunctival limbal autograft • Cadaveric conjunctival limbal allograft • Living-related/non-related conjunctival limbal allograft • Keratolimbal autograft • Cadaveric keratolimbal allograft • Combined conjunctival and keratolimbal limbal allograft[11] These surgical interventions carry their own risks and potential for benefit. There are a number of patients who have exhausted all current treatment options, or for whom these are not suitable, and currently have no treatment option available to them which will improve long term visual acuity.[6]	Comment noted. The topic will be scheduled into the work programme once referral from the Department of Health is received.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Chiesi Farmaceutici	Background information refers to '*Ocular burns because of chemicals or heat'*. Holoclar is indicated for moderate and severe burns both of chemical and physical origin.[8] Background information state that *'In 2014/15, there were approximately 3600 corneal transplants for a variety of indications in the UK[2]. The number of corneal transplants for ocular surface burns is thought to be very small.'* The reference to corneal transplantation –which is dramatically different from Holoclar, maybe misleading in terms of patient pool and the overlap between these two different procedures. Background information states that *'The estimated incidence of severe chemical corneal injury in the UK is 0.02 in 100,000 people.'* Holoclar is indicated for moderate and severe burns both of chemical and physical origin.[8] The EMA state that corneal lesions with associated limbal stem cell deficiency (LSCD), due to ocular burns, affect approximately 0.3 in 10,000 people in the European Union.3 However not all patients will be suitable for Holoclar. Holoclar is NOT indicated in patients with[5]: • mild disease (defined by the presence of superficial corneal neovascularisation in less than two corneal quadrants) • no central corneal involvement • visual acuity which is not severely impaired There are several risk factors for transplanted stem cell survival. Liang *et al*. identified preoperative clinical characteristics and risk factors that lead to ocular surface deficits, which included: Infrequent blinking, blink-related microtrauma, conjunctival inflammation, increased intraocular pressure, aqueous deficient dry eye, and previous failed corneal or stem cell graft which can impact on the survival of keratolimbal allografts.[12] As such patients with	Comment noted. The epidemiology data in the background section in the scope has been amended to remove reference to corneal transplant. Ex vivo expanded autologous human corneal epithelial cells containing stem cells will be considered within the boundaries of its marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
		these characteristics (where not corrected) may be less suitable for treatment with Holoclar. The main objective before transplanting limbal stem cells is to prepare their new “home” and to provide the best opportunity for graft survival. Several issues need to be addressed before stem cell transplantation, including optimising lids and the tear film, controlling inflammation, and the management of glaucoma. Optimisation of lids may require oculoplastic reconstruction for example.[6] The eye also needs to be quiet for at least 3 months before surgery to enhance the chances of survival for transplanting stem cells.[13] As such, patients may not be suitable for these many interventions which may be required prior to transplantation.	
The technology/ intervention	Chiesi Farmaceutici	Holoclar is part of a package of care to provide both symptom relief and improvement of visual acuity in this patient pool. It is not a single standalone intervention. Many patients may require numerous surgical oculoplastic interventions before treatment with Holoclar could be considered.[6] **HLSTM01**, a retrospective case-series evaluating the efficacy and safety of autologous cultivated limbal stem cell transplantation in 104 patients with limbal stem cell deficiency due to ocular burns.[14] The primary objective was to evaluate the success of transplantation based on a stable corneal epithelium without significant recurrence of neovascularisation at 12 months post-intervention. In this study, 13 out of 26 patients (50%) who had at least one previous failed keratoplasty had subsequent successful keratoplasty after Holoclar treatment which improved their visual acuity.[14] Keratoplasty surgery is successful when there is a viable corneal cell population to augment the procedure and the Holoclar transplant helps in providing a favourable environment for this to occur. Holoclar in this way may offer a bridge to subsequent successful keratoplasty, which in turn can improve visual acuity. It is therefore important that the impact of Holoclar on visual acuity is measured within the context of subsequent keratolplasty, and	Comment noted. The intervention section in the scope has been updated to ex vivo expanded autologous human corneal epithelial cells containing stem cells in combination with best supportive care. The company submission should include full details about the treatment pathway and impact of Holoclar, including the potential impact on keratoplasty.

Section	Consultee/ Commentator	Comments [sic]	Action
		that this is included in the technologies that depend on a successful graft with Holoclar before they themselves can be successful in turn.	
Population	Chiesi Farmaceutici	Patients with bilateral damage, which may be partial in both eyes, or total in one and partial in the second, have a disproportionate burden of disease. They are not suitable for autolimbal grafts, due to the risk of inducing LSCD in the donor eye, and most cadaver donor cases fail within 5 years.[15] As such treatment options can often be best supportive care.	Comment noted. The comparators section in the scope includes different interventions considered to be established clinical practice in the NHS for people with unilateral limbal stem cell deficiency (conjunctival limbal autograft and best supportive care) and for people with bilateral limbal stem cell deficiency (conjunctival limbal autograft, limbal epithelial stem cells allografts and best supportive care).
Comparators	Chiesi Farmaceutici	There is currently no other EMA approved *medical* treatment available for corneal lesions with associated LSCD, caused by ocular burns.[3] The two comparators put forward in the draft scope include two surgical techniques, which although accepted treatments, have not been defined as the standard of care.[6] There are a range of surgical treatments, and the use of these is not standardised.[6]	Comment noted. The comparators section in the scope includes different interventions considered to be established clinical practice in the NHS for

Section	Consultee/ Commentator	Comments [sic]	Action
		Depending on the surgeon's experience, access to clinical trials and preference, a different range of treatments are available in different centres, with no agreed single standard of care.6 There have been no published prospective head to head studies of these techniques to establish whether any offer advantages in efficacy or safety over one another, either in unilateral or bilateral disease. Current techniques include: **Autolimbal grafts** • Risk of iatrogenic LSCD and consequences in donor eye[16] • Not repeatable in case of failure[16] • Only unilateral LSCD[16] **Living related donor** • Requires long-term immunosuppression[15] • Not an option for all patients[15] **Cadaver donor** • Most cadaver donor cases fail within 5 years[15] • Requires long-term immunosuppression[17] In addition, some centres offer simple limbal epithelial transplantation (SLET): a novel surgical technique for the treatment of unilateral limbal stem cell deficiency. This is offered in certain UK centres only.[6,18] Current or previous use of experimental advanced therapy (ex vivo expanded stem cell) treatments which have not received approval from the EMA should not be considered as these are not an established comparator, although have been available through research routes in the UK.[6] Holoclar is not expected to significantly displace other interventions, but act as an additional treatment option. Holoclar is a regenerative medicine allowing successful treatment of moderate-severe LSCD due to physical or chemical ocular burns in adult patients for which best supportive care is the current standard of care. As	people with unilateral limbal stem cell deficiency (conjunctival limbal autograft and best supportive care) and for people with bilateral limbal stem cell deficiency (conjunctival limbal autograft, limbal epithelial stem cells allografts and best supportive care).

Section	Consultee/ Commentator	Comments [sic]	Action
		such, best supportive care should be the comparator arm. This was recognised by the EMA who in the EPAR report for Holoclar stated '*At the time of this report, no medicinal products had been approved in the European Union/European Economic Area (EU/EEA) for this indication and there was no gold-standard in treatment.'14* The draft scope itself also states that *'There are no specific treatments available for treating LSCD due to physical or chemical ocular burns.'* As such it appears inconsistent to then include an active comparator, which is not standard UK clinical practice.	
Outcomes	Chiesi Farmaceutici	The element of psychological distress and social withdrawal as a result of being disfigured is not included in the current outcomes. In addition, the outcomes do not capture the psychological distress of the reaction from other people to patients with full conjunctivalisation of the entire corneal surface. This is where the eye is completely covered in conjunctival tissue and the patient is in effect blind.[19]	Comment noted. Psychological distress and social withdrawal are covered by health-related quality of life, which is listed as a relevant outcome measure in the scope. The company submission should describe whether change in health-related quality of life has been inadequately captured and whether there are demonstrable and distinctive benefits of a substantial nature which

Section	Consultee/ Commentator	Comments [sic]	Action
			may not have been adequately captured in the quality-adjusted life years calculation.
Economic analysis	Chiesi Farmaceutici	The economic modelling is likely to be substantially challenging for a number of reasons: The ultra-orphan nature of the technology raises the obvious and known issue of evidence generation. It also creates the well-known issues of a need to spread high technology development fixed costs across a small population, whilst at the same ensuring equality of access to effective treatments for patients unfortunate enough to be in orphan conditions. The innovative nature of the technology may also lead to high early-developer development costs. The learning curve for the delivery of regenerative technologies may be steep though future development lessons may be learned through the process. It is well known that the current NICE reference case model focuses on the current cost-effectiveness (albeit with future costs and benefits discounted to Net Present Value) but does not incorporate the future benefits that may only be made possible by setting the correct incentives for truly innovative technologies such as this. NICE themselves recognise the huge challenges in capturing all the relevant components for assessing regenerative medicine and are assessing whether the current reference case model is fit for purpose.[20] These two issues, regenerative technology for an ultra-orphan condition, make the economic modelling extremely challenging and may not adequately assessed by the standard reference case model. In addition, the appropriate time horizon is a life time horizon, yet the evidence based may only cover the first few years. It is the intention to maintain a registry which can help generate evidence over time.[14] Furthermore there are little start-up fixed costs for adoption to be borne by the	Comment noted. Consultees are encouraged to describe in their evidence submissions the innovative nature of the technology, whether the assessment of the change in health-related quality of life has been inadequately captured and whether there are demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the quality-adjusted life years calculation.

Section	Consultee/ Commentator	Comments [sic]	Action
		NHS. Therefore it will be possible to reverse a decision on adoption when further evidence becomes available without generating large sunk costs. The preferred instrument of measuring HRQoL, the EQ-5D, is known to not capture all the elements associated with vision loss. The EQ-5D vision bolt-on may be required.	
Equality and Diversity	Chiesi Farmaceutici	NICE recognise that 'Evidence from patients and users of health and social care services and their carers, equality and other organisations, and the public is essential in identifying areas of potential discrimination or opportunities for advancing equality.'[21] Any recommendation on the use of Holoclar could lead to and have an adverse impact on people with a particular disability such as blindness (total or partial) following their chemical or physical burn injury. Any recommendation on the use of Holoclar could disproportionately affect these sub-populations: Military personnel injured in action (e.g. due to explosive devices) – a group covered by The Armed Forces Covenant • Women of black/minority ethnic origin injured in malicious chemical acid attacks – a group with protected characteristics • Workers injured in industrial accidents – a group potentially affected by health inequalities and access to treatments The Armed Forces Covenant states that *'Those who serve in the Armed Forces, whether Regular or Reserve, those who have served in the past, and their families, should face no disadvantage compared to other citizens in the provision of public and commercial services. Special consideration is appropriate in some cases, especially for those who have given most such as the injured and the bereaved.'*[22]	Comments noted. These potential equality issues have been noted in the Equality Impact Assessment form.

Section	Consultee/ Commentator	Comments [sic]	Action
Innovation	Chiesi Farmaceutici	Holoclar is a breakthrough in LSCD[9] • The first tissue engineered advanced medicinal therapeutic product using stem cells approved in Europe[9] • First approved product for the treatment of LSCD[9] • Substantial numbers of patients (n = 148) in studies for a rare disease[14] Holoclar offers a bridge to subsequent successful keratoplasty for some patients, with deep stromal scarring, which in turn can improve visual acuity.[14] Patients who receive Holoclar do not need lifelong immunosuppression, which can be needed with some allograft transplantation procedures. Lifelong immunosuppression is itself associated with a range of adverse events, risks, and costs.[6] There is a substantial burden of illness for patients who receive an eye injury early in their life and for whom there is currently no curative treatment. This is substantiated by evidence from experts which indicate a number of patients they would consider suitable for Holoclar whom received the injury several years ago[6]; the health related quality of life of patients with vision issues is known to be low even though instruments such as the EQ-5D are known not to be particularly sensitive to visual impairments [23]; and in addition the wider societal costs in terms of absence from the active labour force (due to age and loss of sight) may be substantial.	Comment noted. Consultees are encouraged to describe in their evidence submissions the innovative nature of the technology.
Questions for consultation	Chiesi Farmaceutici	Do you consider that the use of Holoclar can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? In patients who have bilateral disease, with almost or total blindness, which may have been the result of injury many years, or even decades ago, the incredible impact of having sight returned through the use of Holoclar as part of a package of care cannot be adequately captured in the current outcome measurement tools.[6] For patients who were attacked maliciously, the fear associated with significant visual loss, and the fear of subsequent attack but being unable to	Comment noted. Consultees are encouraged to describe in their evidence submissions the innovative nature of the technology, whether the assessment of the change in health-related

Section	Consultee/ Commentator	Comments [sic]	Action
		see who may be approaching them in any situation is not currently captured in the outcome assessments.[6] For patients with bilateral disease, the current outcome measures do not capture the benefits for patients where they are unable to drive due to central visual involvement, especially where driving is required for employment. The impact of this can be devastating for patients, and the potential that Hololcar offers can be significant in helping patients return to a normal working life again.[6]	quality of life has been inadequately captured and whether there are demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the quality-adjusted life years calculation.
Additional comments on the draft scope		Chiesi has implemented a training program which is mandatory for surgeons interested in treating patients with Holoclar, including training for collection of a biopsy sample including guidance on location and size of sample to collect. As starting material, a limbus biopsy of 1-2 mm^2 in size from a patient's unaffected limbal eye area is procured at the hospital and transported to the manufacturing site in Modena, Italy. Once a viable graft is produced, this is transported back to the centre.[14] The transport costs and logistics are included in the cost of Holoclar, and are organised by Chiesi.	Comment noted. If introduction of the technology requires changes in infrastructure or service delivery, costs should be included in the analysis.

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

British and Eire Association of Vitreoretinal Surgeons
Royal College of Nursing
Royal College of Pathologists
Royal College of Surgeons