NICE National Institute for Health and Care Excellence

NICE guidance

Holoclar for treating limbal stem cell deficiency after eye burns

Technology appraisal guidance
Published: 16 August 2017

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells) is recommended as an option in people with moderate to severe limbal stem cell deficiency after eye burns, only if:

- it is only used to treat 1 eye and
- people have already had a conjunctival limbal autograft or
- there is not enough tissue for a conjunctival limbal autograft or it is contraindicated and
- the company provides it with the discount agreed in the patient access scheme.

Moderate to severe limbal stem cell deficiency is defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity.

1.2 Holoclar is recommended in people with moderate to severe limbal stem cell deficiency after eye burns for treating both eyes only:

- in the context of research and
- when there is not enough tissue for a conjunctival limbal autograft.

Such research should be designed to generate robust evidence of the clinical- and cost-effectiveness of Holoclar in treating 2 eyes in people who do not have enough tissue for a conjunctival limbal autograft.

1.3 These recommendations are not intended to affect treatment with Holoclar that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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.

2 The technology

Description of the technology

2.1 The technology is ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar, Holostem Terapie Avanzate). It is a treatment used in the eye to replace damaged cells on the corneal surface.

Marketing authorisation

2.2 It has a conditional marketing authorisation for 'the treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns'. At least 1 mm^2 to 2 mm^2 of undamaged limbus is needed for biopsy before it can be used.

Adverse reactions

2.3 For full details of adverse reactions and contraindications, see the summary of product characteristics.

Recommended dose and schedule

2.4 The exact dosage depends on the size of the corneal surface: the recommended dose is 79,000 to 316,000 cells/cm^2. A biopsy is first taken of the eye, which needs at least 1 mm^2 to 2 mm^2 of undamaged tissue. The treatment is then implanted in the eye.

Price

2.5 According to the company's submission, a single treatment for 1 eye costs £80,000 excluding VAT. The company has a commercial arrangement. This makes Holoclar available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Evidence

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

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells), having considered evidence on the nature of moderate to severe limbal stem cell deficiency after eye burns and the value placed on the benefits of the treatment by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Treatment pathway and unmet need

4.1 The committee was aware that limbal stem cell deficiency (LSCD) is caused by an injury (such as a chemical or physical burn) to the source of limbal stem cells, which interrupts the renewal and replacement of the surface of the cornea. LSCD can either be unilateral (in 1 eye) or bilateral (in both eyes). The committee heard from the clinical experts that LSCD can be life-changing: in addition to visual impairment, the condition is associated with high levels of pain and photophobia. LSCD also represents a major psychological burden, both from the trauma of the original incident and the ongoing management of eye disfigurement. The highly visible nature of the injury can also impair a person's confidence and cause social isolation. Some people with LSCD are unable to continue working because of the physical or psychological effects. The committee agreed that LSCD can be a life-changing and severely debilitating condition.

4.2 The committee heard from the clinical experts that the aim of treatment for LSCD is to restore the surface of the eye, achieve corneal clarity and improve visual acuity. Current practice usually starts with supportive care treatments such as lubrication, autologous serum eye drops, and therapeutic soft and scleral contact lenses. Conservative surgery such as corneal scraping may also be offered before attempting limbal stem cell transplantation. Limbal stem cell transplantation includes a number of invasive surgical options to transplant stem cells to the affected eye which differ in terms of where the cells come from and how they are transferred, specifically:

- conjunctival limbal autograft, in which stem cells are taken from the patient's

healthy eye

- conjunctival limbal allograft, in which stem cells are taken from a living, related donor or dead donor
- keratolimbal allograft, in which the entire limbus may be transplanted from a dead donor, using the cornea as carrier tissue.

4.3 The committee heard from the clinical experts that successfully treating LSCD could be life-changing. However, current treatments are associated with many disadvantages. Conjunctival limbal autograft needs a relatively large amount of donor tissue from the healthy eye (equivalent to around 40% of the available reserves of the donor tissue). This increases the risk of damage to the donor eye: the clinical experts stated that 3% to 5% of patients having an autograft would have permanent serious damage. The clinical experts also estimated a transplant success rate with conjunctival limbal autograft of only 50%. Therefore, patients often choose to not have the treatment because their perceived risk of damage to the donor eye was not worth the chance of the procedure being a success in the affected eye. The committee assumed that people would have a conjunctival limbal autograft before approaching a living, related donor. One clinical expert stated they no longer did conjunctival limbal autografts because of the risks, although they acknowledged that the procedure is still used in clinical practice. Because both conjunctival limbal and keratolimbal allografts rely on external donors, they need immunosuppression which is in itself associated with several side effects. Even when treatment is successful, most allografts fail within 5 years. The clinical experts explained that finding a source of donor tissue can also be problematic.

4.4 The committee asked the clinical experts if patients with bilateral LSCD would have treatment in 1 or both eyes. It heard that ideally both eyes would be treated, but in practice it is likely for 1 eye to be worse than the other and that only the worst eye would be treated. The committee also asked if any of the procedures could be done more than once in the same eye. The clinical experts stated this would be unlikely for existing procedures, but that Holoclar represents a more viable option for retreatment because it needs a smaller amount of tissue. The smaller biopsy also means a much lower risk of damage to the donor eye; 1 clinical expert stated that in data for around 1,000 Holoclar procedures, they were unaware of any instances of damage to the patient's donor eye. The clinical

experts stated that there is a subgroup of patients who have had conjunctival limbal autograft previously whose only option for further treatment was Holoclar. The committee concluded that the company had used the most appropriate comparators in its submission (that is: conjunctival limbal autograft, conjunctival limbal allograft, keratolimbal allograft and best supportive care), and Holoclar offered several advantages over these treatments.

Clinical effectiveness

4.5 The committee noted that the evidence for Holoclar comprised 3 studies with follow-up of 12 months or less (HLSTM01, HLSTM02 and HLSTM04) and 5 studies with follow-up of 12 months up to 14.5 years (Rama 2001 and 2010, Pellegrini 1997 and 2013, Marchini 2012). The comparator evidence consisted of 23 smaller studies with high levels of heterogeneity, which the company, ERG and committee agreed made them unsuitable for data pooling. The 8 main studies were mostly case series, which offer poor quality evidence because they do not contain a comparison group, but the committee noted that data for Holoclar were available for a reasonably high number of patients given the rarity of the condition (n=219 across all studies). However, the company had run statistical analyses on the available data despite case series not being designed for this purpose (they are intended to be descriptive only). The committee also noted that the clinical evidence for Holoclar was limited to treating 1 eye only (of the 13 patients with bilateral disease, only 1 had treatment in both eyes). In the absence of stronger evidence in this disease area, the committee accepted this clinical evidence for its decision-making. However, it agreed that when making its recommendations it would need to take into account that no clinical evidence had been presented for using Holoclar in 2 eyes when both eyes are affected.

Clinical evidence results

4.6 The primary outcome of the pivotal HLSTM01 study was treatment success, defined as stable corneal epithelium without significant recurrence of neovascularisation 12 months after treatment. The main secondary outcomes included symptom resolution (pain, burning and photophobia), inflammation, neovascularisation, visual acuity, number of successful keratoplasties and safety.

4.7 The results from HLSTM01 showed that 72.1% of patients had a successful Holoclar transplant. For the comparators, transplant success varied between 60.0% and 100.0%. Given its concerns with the quality of evidence, the committee asked the clinical experts if these success rates were likely to be reflective of those in clinical practice. The experts stated that the results for Holoclar were plausible, but that the results for the comparators should be interpreted with more caution. They considered the studies of conjunctival limbal autograft to be poorly conducted and biased, and the rates to be overestimated (in their experience, success rates were closer to 50%). The committee concluded that the evidence showed Holoclar to be an effective treatment in terms of the outcomes described in section 4.6. However, there was uncertainty about the comparator success rates and the effectiveness of Holoclar compared with them.

Cost effectiveness

Model structure

4.8 The company presented 2 separate models: a 'unilateral' and a 'bilateral' model. The models were similar, with both consisting of a decision tree followed by a Markov model, but the bilateral model assumed that patients had treatment in both eyes (and so included an additional year without treatment before treating the second eye). The evidence review group (ERG) considered the model to be reasonably well constructed. However, the committee noted that the company had not actually presented separate results for unilateral and bilateral populations. The 2 models did not, in fact, distinguish between unilateral and bilateral disease; both models included exactly the same population (that is, both included patients with unilateral and bilateral disease). Instead, the main difference was that only 1 eye was treated in the unilateral model, whereas both eyes were treated in the bilateral model. The committee agreed that it would be more informative to consider the company's unilateral model as the '1-eye treatment' model and the bilateral model as the '2-eye treatment' model. The committee concluded that the model structures were acceptable for its decision-making. It would take into account treatment between 1 eye and 2 eyes but it would be difficult to distinguish between unilateral and bilateral populations in the

cost-effectiveness modelling when making its final recommendations.

Discount rate

4.9 The company had deviated from the reference case by using a discount rate for future costs and benefits of 1.5%, rather than 3.5% as outlined in NICE's guide to the methods of technology appraisal. The company justified this by explaining that it believed Holoclar to have a prolonged effect (over 30 years), and that it could return patients to a high utility state. The committee was aware that the NICE methods guide states that when appraising treatments that 'restore people who would otherwise die or have severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)', non-reference case rates may be considered. However, the committee noted that it is rarely considered appropriate to change the discount rate and that LSCD was very different from the fatal and near-fatal conditions implied by the methods guide. The committee therefore concluded that the company should have used a 3.5% discount rate.

Modelled long-term success rates

4.10 The committee noted that if treatment with Holoclar were successful at 1 year, it remained successful for the lifetime of the model. When questioned about the plausibility of this assumption, the clinical experts stated that there currently was not enough evidence to support strong assumptions about the long-term effectiveness of Holoclar. However, the transplant being successful at 1 year would demonstrate that the patient's body has regenerated the cornea 3 to 4 times, suggesting there may be some scientific merit to this model assumption. The committee accepted the company assumption about long-term success in the model, but agreed that this was subject to a high level of uncertainty that could increase the incremental cost-effectiveness ratio (ICER).

Model parameters

4.11 The committee noted that the clinical-effectiveness assumptions in the model

were taken from HLSTM01 for Holoclar, and from the literature for the comparators. For Holoclar, the committee had previously heard that the estimated transplant success rates were plausible. However, for the comparators, the committee noted that the company had pooled the data, despite the company and ERG agreeing that pooling these data would not be appropriate. The company had presented a limited exploration of different success rates for the comparators, but these scenarios included changes in other assumptions and so did not explore the effect of this rate change alone. Furthermore, only 1 alternative rate for each comparator had been explored. The committee agreed that it would have been more useful to explore a range of different success rates (between 50% and 80%) because there was no comparative evidence for Holoclar and the clinical experts considered the comparator success rates to be overestimated. The committee concluded that there was a substantial level of uncertainty in the clinical-effectiveness assumptions in the company's model.

4.12 In response to consultation, the company provided additional sensitivity analyses which included the committee's preferred assumptions (a discount rate of 3.5%, a utility value of 0.84 and a utility decrement for disfigurement of 0.140). The company varied the probability of initial transplant success and long-term probability of transplant failure for each comparator separately. The sensitivity analyses showed that the ICERs for Holoclar were sensitive to the annual failure probability and initial success rates for the comparator treatments; a higher probability of transplant success increased the ICERs. The committee recalled that the company's model may overestimate comparator success rates (section 4.7). It concluded that lower transplant success rates would decrease the ICER, but agreed that this was subject to a high level of uncertainty.

Utility values

4.13 The committee was aware that conjunctival limbal autograft needs a substantial amount of tissue from the donor eye. It queried whether the potentially negative effect on the donor eye had been captured, and heard from the company, ERG and clinical experts that it had not. The committee noted further that the effect on the donor in the event of a transplant from a living, relative donor had also not been captured. It assumed that if donor disutility had been taken into account, the ICER would likely decrease. The committee agreed that it would have

preferred to have seen analyses including the effect on the donor eye when comparing with conjunctival limbal autograft and the effect on the donor when comparing with conjunctival limbal allograft from a living, relative donor. The committee noted that the utility values used in the model were extraordinarily low: the values were far lower than any used in previous appraisals for eye treatments, with some lower than those for people in the last 3 months of life having palliative treatment for various cancers. The committee noted that the main reason for these low values appeared to be the utility decrement of 0.318 applied to patients experiencing disfigurement. This was over 100-times higher than the utility decrement applied to people experiencing any pain, burning or photophobia (the highest decrement was 0.019). The committee highlighted that company's 0.318 decrement was derived from non-reference case methods, which were likely to generate exaggerated results. The committee asked the clinical experts about the plausibility of these values. The clinical experts found the low overall utility difficult to quantify, but stated that LSCD has a long-term substantial negative effect on quality of life. For the high utility decrement for disfigurement, the committee heard varied reports about the relative importance of disfigurement. The clinical experts stated that for people with unilateral disease, contrary to conventional wisdom, visual acuity was not the most important outcome: because of its lasting and significant effect on their day-to-day lives, these people often prioritise disfigurement. For people with bilateral disease, disfigurement would be less of a priority than visual acuity because of the risk of complete loss of sight. The committee agreed that it was difficult to resolve this inconsistency in the relative importance of disfigurement. Furthermore, this was not the approach taken in the model, with utility values applying equally irrespective of whether disease was unilateral or bilateral. The committee agreed that the utility values used were implausibly low, noting that the ERG had used alternative values. For visual acuity, the ERG used a range with a more plausible maximum value of 0.861 (rather than the company's assumption of 0.706). For disfigurement, it used a decrement of 0.140 (rather than the company's assumption of 0.318), using cataracts as a proxy. The ERG noted that the decrement associated with cataracts also includes a loss of utility from both disfigurement and vision loss. The committee recognised that cataract disutilities were used as a proxy for disfigurement although uncertainty remained in the utility values, the ERG's values were a more realistic reflection of the impact on quality of life.

Resource use and costs

4.14 The committee noted that the cost of autologous serum eye drops were a substantial driver of cost-effectiveness results in the model. The company had assumed in the model that patients having the comparators needed these drops after treatment and for flare-ups, but patients having Holoclar did not. The committee heard from the clinical experts that autologous serum eye drops are essential after treatment with the comparators, but less so with Holoclar because the stem cells are cultivated in a laboratory and not on the patient's eye. However, some clinicians may still choose to use them with Holoclar. The clinical experts also stated that drops would rarely be used for flare-ups because they take up to 6 weeks to prepare. Although alternative eye drops are available that would be ready for immediate use (allogenic serum eye drops), the committee heard from the ERG that using these drops would not make much difference to the model results because they were similarly priced. The committee agreed that the costs of eye drops for Holoclar had been underestimated in the model, but that the effect of this was difficult to quantify. It also agreed that eye drops after treatment were more necessary for the comparators than for Holoclar. It therefore concluded that it could cautiously accept the company's assumptions about eye drops, but remained aware that any increase in the use of eye drops would make Holoclar less cost effective.

Cost-effectiveness results and conclusions

4.15 The committee considered the estimates of cost effectiveness calculated by the company. The base-case results were:

- Conjunctival limbal autograft dominated (that is, was both less costly and more effective than) all treatments including Holoclar in both models.
- The ICERs for Holoclar compared with conjunctival limbal allograft from a living, related donor were £7,185 per quality-adjusted life year (QALY) gained in the 1-eye treatment model, and £12,438 per QALY gained in the 2-eye treatment model.
- The ICERs for Holoclar compared with keratolimbal allograft were £2,255 per QALY gained in the 1-eye treatment model and £6,533 per QALY gained in

the 2-eye treatment model.

- Holoclar dominated best supportive care in both models.

None of these ICERs took into account the committee's preferred assumptions about utility values (section 4.13) and discount rate (section 4.9). However, the ERG had presented scenarios using both of these assumptions. In these scenarios, the ICERs became less favourable:

- Conjunctival limbal autograft remained dominant in the 1-eye treatment model (the ERG did not compare Holoclar with conjunctival limbal autograft in the 2-eye treatment model).
- The ICERs for Holoclar compared with conjunctival limbal allograft from a living, related donor were £42,139 per QALY gained in the 1-eye treatment model, and £63,047 per QALY gained in the 2-eye treatment model.
- The ICERs for Holoclar compared with keratolimbal allograft were £30,415 per QALY gained in the 1-eye treatment model and £69,455 per QALY gained in the 2-eye treatment model.
- The ICERs for Holoclar compared with best supportive care were £6,948 per QALY gained in the 1-eye treatment model and £12,669 per QALY gained in the 2-eye treatment model.

Using the committee's preferred assumptions, Holoclar was not cost effective except compared with best supportive care.

4.16 The committee was aware that there were uncertainties in the assumptions about the comparators' long-term success rates and the use of eye drops. It noted that the success rates for conjunctival limbal allograft from a living, related donor and keratolimbal allograft in particular were likely to have been overestimated. Furthermore, if the effect on the donor were taken into account, the ICERs for Holoclar would likely decrease and fall within the range of £20,000 to £30,000 per QALY gained. Given the patient need (section 4.1) and innovative nature of the treatment (section 4.17), the committee agreed that it would pragmatically accept this as a demonstration of cost effectiveness. The committee noted that Holoclar was only cost effective for treating 1 eye. It recalled that there was almost no evidence concerning Holoclar's clinical effectiveness for treating both

eyes, and agreed that it could not recommend Holoclar for routine use in the NHS to treat both eyes. However, it agreed that its recommendations for treating a single eye should apply equally to unilateral and bilateral disease. The committee therefore concluded that it could recommend Holoclar as a cost-effective use of NHS resources in people with moderate to severe LSCD after eye burns, only if it is used to treat 1 eye and they have already had a conjunctival limbal autograft or there is not enough tissue for a conjunctival limbal autograft, or it is contraindicated, and the company provides it with the discount agreed in the patient access scheme.

4.17 The committee took several factors into account when considering if Holoclar could be recommended to treat both eyes. Firstly, the clinical experts explained that usually only the worst eye would be treated in practice. Secondly, the committee discussed the very limited clinical evidence for this group; only 1 patient with bilateral disease had treatment in both eyes, which the committee considered to be uninformative. Thirdly, the ERG's clinical experts stated that there are plausible reasons why Holoclar would not be as effective when used in both eyes. Specifically, the biopsy must be taken from a damaged eye where it may be more difficult to locate and extract healthy limbal cells, and it may not be possible to take the same number of biopsies from a damaged eye in the case of transplant failure. Fourthly, the company's economic model analysis showed that treating both eyes gave ICERs for Holoclar that were too high for it to be considered a cost-effective use of NHS resources. The 2-eye economic model also included several limitations such as not accounting for differential effectiveness of a second Holoclar treatment and using a population of both unilateral and bilateral patients. Finally, the committee considered that for a patient with bilateral disease, there are treatment options available in current clinical practice to treat the second eye (conjunctival limbal allograft and keratolimbal allograft). Taking all of this into account, the committee recommended Holoclar for treating both eyes only in the context of clinical research.

4.18 The committee recommended that further research should be designed to generate robust evidence of the clinical- and cost-effectiveness of Holoclar in treating both eyes in people who do not have enough tissue for a conjunctival limbal autograft. The study should recruit people with bilateral disease and evaluate the effectiveness of treatment in both eyes. Outcomes should include

transplant success and assessments of health-related quality of life using a generic preference-based measure.

Innovation

4.19 The committee considered the innovative nature of the technology. It noted that the company had won the UK Prix Galien Orphan Product award for innovation and research. In addition, the European Medicines Agency had recognised Holoclar as the first approved stem cell medicine in Europe. The committee also agreed that the company had presented evidence to show that it offered several advantages over existing treatments. Taking all of this into account, the committee concluded that Holoclar could be considered innovative. It also agreed that most of the benefits of treatment with Holoclar were likely to have been captured in the QALY calculation.

4.20 Because Holoclar is a regenerative technology for an ultra-orphan condition, the company argued that the modelling was more challenging and suggested that the standard NICE reference case may be inappropriate. However, the committee was aware that NICE had worked with the Centre for Reviews and Dissemination and Centre for Health Economics, University of York, which produced an extensive independent report. This report looked at the appraisals methods and whether they are fit for purpose for regenerative medicines and cell therapies, and it found that the appraisal methods and decision framework was applicable to these treatments. The committee concluded that the standard NICE reference case was appropriate for appraising Holoclar.

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has limbal stem cell deficiency after eye burns and the doctor responsible for their care thinks that Holoclar is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 The committee agreed that further research was needed because there is currently no clinical- or cost-effectiveness evidence evaluating the use of Holoclar in both eyes in bilateral patients. The committee was aware of the ongoing HOLOCORE trial which is recruiting both unilateral and bilateral patients, but only evaluates the success of a second transplant in 1 eye rather than transplant success in both eyes.

6.2 The committee recommended that further research should be designed to generate robust evidence of the clinical- and cost-effectiveness of Holoclar for treating both eyes in people with bilateral limbal stem cell deficiency after eye burns if they do not have enough tissue for a conjunctival limbal autograft. The study should recruit people with bilateral disease and evaluate the effectiveness of treatment in both eyes. Outcomes should include transplant success and assessments of health-related quality of life using a generic preference-based measure.

7 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.

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.

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.

Irina Voicechovskaja
Technical lead

Carl Prescott and Alexandra Filby
Technical advisers

Stephanie Yates
Project manager

Update information

September 2020: Section 2 of the guidance updated because the marketing authorisation holder changed from Chiesi Farmaceutici to Holostem Terapie Avanzate. The company contact details were removed from section 5 and updated details put on the overview page for the guidance.

Information in tables was presented in a different way, to meet accessibility requirements.

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