



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Summary of the risk management plan (RMP) for Holoclar (*ex vivo* expanded autologous human corneal epithelial cells containing stem cells)

This is a summary of the risk management plan (RMP) for Holoclar, which details the measures to be taken in order to ensure that Holoclar is used as safely as possible. For more information on RMP summaries, see [here](#).

This RMP summary should be read in conjunction with the EPAR summary and the product information for Holoclar, which can be found on [Holoclar's EPAR page](#).

Overview of disease epidemiology

Holoclar is an eye implant for replenishing corneal cells in adults with moderate to severe limbal stem-cell deficiency caused by chemical or physical burns to the eyes. Patients with this condition do not have enough limbal stem cells (found at the edge of the cornea), which normally act as a repair system, replenishing the corneal cells when they get damaged.

The prevalence of corneal lesions, with associated corneal (limbal) stem-cell deficiency, due to chemical or physical burns, is estimated to be approximately 0.3 in 10,000 people in the European Union (EU). Limbal stem-cell deficiency can lead to persistent pain, photophobia, increased susceptibility to corneal infections, corneal perforation and blindness. There are many causes of limbal stem-cell deficiency, such as burns to the eye, inflammatory diseases and hereditary diseases. Chemical burns mainly occur at the workplace in people aged between 16 and 65 years.

Summary of treatment benefits

Holoclar is an individualised medicine prepared from the patient's own cells. Two retrospective studies of the medical records of patients who had received Holoclar showed that the product was effective in restoring the cornea in patients with moderate or severe limbal stem-cell deficiency caused by chemical or physical burns. One year after Holoclar implantation, 75 out of 104 patients studied (72%) were judged to have had successful treatment based on the presence of stable cornea with little or no defects or blood vessels present in the cornea (a common feature of limbal stem-cell deficiency). There were also reductions in patients' symptoms, such as pain and inflammation, and improvements in vision.



Unknowns relating to treatment benefits

There is no or limited information in patients under 18 years old, the elderly, and pregnant or breastfeeding women. Holoclar is only indicated for adult patients, and as a precautionary measure, it is preferable to avoid the use of the product during pregnancy and breastfeeding. Holoclar is for use in patients with moderate to severe limbal stem-cell deficiency. Use in patients with less severe deficiency or with a deficiency due to causes other than eye burns is not indicated because the safety and effectiveness of Holoclar in these patients have not been studied.

There was no apparent difference in the way the product worked in people of different ages or in men and women. There are no data on the way Holoclar works in people of different races (as only people living in Italy were studied).

Summary of safety concerns

Important identified risks

| Risk | What is known | Preventability |
|----------------|---|---|
| Glaucoma | Glaucoma, a condition caused by increased pressure in the eye, was reported in 23 out of 142 patients who received an implant. For five implantations it was reported that glaucoma was potentially related to anti-inflammatory corticosteroids medicines given within 3 months of implantation, since this is a well-known side effect of corticosteroids. | Patients should be closely monitored for glaucoma and should be warned of all possible side effects of Holoclar and of anti-inflammatory eye drugs during the consent process. |
| Lack of effect | Lack of effect, manifesting as corneal defects, were reported for 8 implantations out of 142. Patients with other eye problems may be at increased risk of their implant failing to work, including patients with: <ul style="list-style-type: none">• uneven eyelids• scarring of the conjunctiva with fornix (the folds) shortening• corneal anaesthesia or hypoesthesia, where the patient cannot feel pain• growth of the conjunctiva over the cornea (pterygium)• severe dry eye. | Other eye problems should be corrected prior to implantation of Holoclar, and patients and doctors are advised that corneal epithelium defects are common side effects. Patients should be informed about all possible side effects, including implant rejection, before giving consent to undergo the procedure and to have the cells implanted. Holoclar must be administered by an appropriately qualified eye surgeon and is restricted to hospital use only. Surgeons are only allowed to administer Holoclar after appropriate training. |

Important potential risks

| Risk | What is known |
|---|---|
| Inflamed eyelids (blepharitis) | Inflamed eyelids are common after administration of Holoclar. However, this condition is also a common recurrent long-term problem in the general population. It is not clear whether implanting Holoclar triggers this condition. |
| Use of eye drops containing the preservative benzalkonium chloride | Benzalkonium chloride can damage the newly regenerated cells in the eye. Therefore, patients should not use eye drops containing benzalkonium chloride. |
| Post-implant infection | As with all surgical procedures there is a risk of bacterial infection post-implantation. The experience from clinical studies with Holoclar indicates that infection of the eye post-implant is uncommon. Treatment with antibiotics is recommended for 2 weeks following implantation to reduce the risk of eye infection. |
| Errors administering Holoclar (e.g. patient does not meet correct medical criteria for Holoclar treatment, patient receives Holoclar intended for a different patient, or incorrect surgical technique) | <p>Errors in the way that Holoclar is administered may affect the chances of the treatment being successful. Holoclar is intended for patients with eye injury due to chemical or physical burns. The product may not work for patients with similar eye conditions due to other causes.</p> <p>Other eye conditions should be treated prior to Holoclar administration, because these could also affect the success of the treatment (see section above on 'lack of effect').</p> <p>It is important to check that patients are not allergic to any of the ingredients in Holoclar before administration.</p> <p>As Holoclar is an individualised medicine prepared from the patient's own cells, the patient's name should be carefully checked with the patient/donor identification before implantation to ensure that the patient receives the correct product containing their own limbal stem cells.</p> <p>Holoclar must be administered by an appropriately qualified surgeon and is restricted to hospital use only.</p> <p>Surgeons and other healthcare professionals are provided with information concerning the correct surgical technique to be used, as well as post-operative administration of anti-inflammatory and antibiotic drugs.</p> |
| Development of tumours | Holoclar is applied locally to the surface of the eye, and information from experiments suggests that it is unlikely to cause tumours. However, the number of patients who have received Holoclar is not large enough for such a risk to be ruled out. |
| Risk of unapproved use in: <ul style="list-style-type: none">• patients with milder forms of limbal stem-cell deficiency | Safety and benefits of Holoclar have not been evaluated in these patients. |

| Risk | What is known |
|---|---------------|
| <ul style="list-style-type: none"> patients with limbal stem-cell deficiency due to causes other than burns patients under 18 years | |

Missing information

| Risk | What is known |
|-------------------------------|--|
| Pregnancy and breastfeeding | No patients included in the two clinical trials were pregnant or breastfeeding. Treatment with Holoclar should be delayed if the patient is pregnant or breastfeeding. |
| Children (limited data) | Only limited data are available on the use of Holoclar in children and adolescents under 18 years. Holoclar should not be used in children or adolescents under the age of 18. It is not known whether the product is safe for use in children or how effective it may be. |
| Older people (limited data) | Only limited data are available on the use of Holoclar in the older people (over 65 years). The precautions to be taken for the older people are the same as those for adults in general. |
| Re-administration of Holoclar | Only limited data are available concerning patients who have received Holoclar more than once, although no specific risks related to re-administration of the product have been observed. |
| Long-term safety and efficacy | Follow-up data available from patients treated with Holoclar do not raise any particular concern with respect to the long-term effectiveness or safety of Holoclar. However, more long-term follow-up data are required and a new clinical trial is to be conducted to look at Holoclar's long-term effects. |

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Holoclar can be found on [Holoclar's EPAR page](#).

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Holoclar's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Glaucoma

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| Risk minimisation measure: educational material for healthcare professional and patient information guide |
| Objective and rationale: <ul style="list-style-type: none">• To increase healthcare professionals' understanding of the required treatment procedures, including the use of antibiotics and corticosteroids after the implantation of Holoclar• To remind users about the risk of increased pressure in the eye and to provide key information for safe use of concomitant medications following the surgery |
| Description: <ul style="list-style-type: none">• The educational manual will be given to healthcare professionals and will provide full technical details on the procedures associated with the implantation, including post-implant treatment with anti-inflammatory drugs, as well as information on the possible risk of increased pressure in the eye.• The patient information guide will provide details of the anti-inflammatory treatment required post-implant and key information for the safe use of concomitant medications. |

Lack of effect manifesting as corneal epithelium defects

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| Risk minimisation measure: educational manual for healthcare professionals |
| Objective and rationale: To increase healthcare professionals' understanding of eye conditions which should not be present or should be corrected prior to Holoclar administration and to advise them that corneal epithelial defects are a common side effect |
| Description: The educational manual will provide full technical details on the procedures associated with the implantation, including details of eye conditions which should be corrected prior to implantation in order to increase the chance of a successful implant |

Inflamed eyelids (blepharitis)

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| Risk minimisation measure: educational manual for healthcare professionals and patient information guide |
| Objective and rationale: To increase the healthcare professionals' and patients' awareness that inflamed eyelids are a common adverse event |
| Description: <ul style="list-style-type: none">• An educational manual will be given to healthcare professionals, providing full technical details on the procedures associated with the implantation, including common adverse reactions such as blepharitis.• A patient information guide will provide details of common side effects, including inflamed eyes. |

Use of eye drops containing benzalkonium chloride

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| Risk minimisation measure: educational manual for healthcare professionals and patient information guide |
| Objective and rationale: To increase the healthcare professionals' and patients' awareness that eye drops containing the preservative benzalkonium should be avoided because this ingredient can damage cells and could damage the implant. |
| Description: <ul style="list-style-type: none">• An educational manual will be given to healthcare professionals, providing them with full technical details on the procedures associated with the implantation, and advising them that eye drops containing benzalkonium must be avoided.• A patient information guide will advise patients not to use any eye drops containing benzalkonium chloride because it can damage cells and could damage the implant. |

Post-implant infection

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| Risk minimisation measure: educational manual for healthcare professionals and patient information guide |
| Objective and rationale: <ul style="list-style-type: none">• To increase the healthcare professionals' and patients' understanding of required post-implant treatment with antibiotic drugs to prevent corneal infection, which is an uncommon side effect of Holoclar |
| Description: <ul style="list-style-type: none">• An educational manual will be given to healthcare professionals, providing them full technical details on the procedures associated with the implantation including post-implant treatment with antibiotic drugs to prevent the uncommon side effect of corneal infection.• A patient information guide will provide details of the antibiotic treatment that is required post-implant to reduce the risk of an eye infection. |

Errors administering Holoclar

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| Risk minimisation measure: educational manual for healthcare professionals |
| Objective and rationale: To inform healthcare professionals of procedures to be followed by in order to prevent medication errors |
| Description: An educational manual will be given to healthcare professionals, providing them with full technical details of the procedures associated with the implantation that are to be followed in order to prevent medication errors. |

Planned post-authorisation development plan

List of studies in post-authorisation development plan

| Study/activity (including study number) | Objectives | Safety concerns /efficacy issue addressed | Status | Planned date for submission of (interim and) final results |
|---|--|---|---------------|---|
| Study HLSTM03 Clinical study to determine the efficacy and safety of Autologous Cultivated Limbal Stem Cells transplants (ACLST) for restoration of the eye surface (corneal epithelium) in patients with Limbal Stem-Cell Deficiency (LSCD) due to eye burns. | To determine the effect and safety of one or two ACLSCTs in restoring the eye surface in patients suffering from moderate to severe LSCD due to eye burns. Patients from 2 years of age and adults will be included in the study. | To confirm the efficacy and safety of the product in restoring the eye surface in patients suffering from moderate to severe LSCD due to eye burns using the current method for performing ACLSCT (including performing more than one transplant if needed and using current treatments after the operation). | Planned | December 2020 (planned) |

Studies which are a condition of the marketing authorisation

Study HLSTM03 is a condition of the marketing authorisation

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 02-2015.