Package leaflet: Information for the patient

HOLOCLAR®

79,000 - 316,000 cells/cm² living tissue equivalent *ex vivo* expanded autologous human corneal epithelial cells containing stem cells.

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your surgeon.
- If you get any side effects, talk to your surgeon. This includes any possible side effects not listed in this leaflet. See section 4.

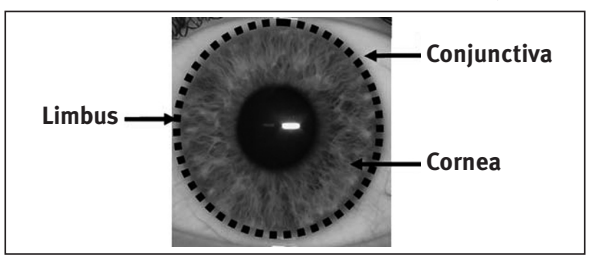
What is in this leaflet

1. What Holoclar is and what it is used for

Holoclar is a medicine used for replacing damaged cells of the cornea (the clear layer that covers the coloured iris at the front of the eye) including limbal cells which normally help to maintain the health of your eye.

Holoclar consists of a layer of your own cells which have been grown (ex vivo expanded) from a sample of limbal cells taken from your eye during a small surgical procedure called a biopsy. Each preparation of Holoclar is made individually and is for a single treatment only, although treatments can be repeated. The cells used to make Holoclar are known as autologous limbal cells:

- **Autologous** means that they are your own cells.
- The **limbus** is part of the eye. It is the rim surrounding the coloured centre (iris) of your eye. The picture shows where the limbus is in your eye.
- The limbus contains **limbal cells** which normally help to maintain the health of your eye and some of these are **stem cells** which can make new cells. These new cells can replace the damaged cells in your eye.



Holoclar is implanted to repair the damaged surface of the eye in adults. When the eye is badly damaged by physical or chemical burns, lots of scarring can occur and the limbus can be damaged. Damage to the limbus stops normal healing, which means that the damage to your eye is never properly repaired.

By taking some healthy limbal cells, a new layer of healthy tissue is grown in the laboratory on a supporting layer of fibrin, a protein scaffold. This layer of tissue is then implanted by a surgeon into the damaged cornea helping your eye to heal normally.

2. What you need to know before you are given Holoclar

You must not be given Holoclar:
- if you are allergic to any of the ingredients of this medicine (listed in section 6) or to bovine serum and mouse cells

Warnings and precautions
Talk to your surgeon before you are given Holoclar.

Holoclar is prepared individually from your own cells to match you, and must not be used for anyone other than yourself.

If you have an acute eye infection or swollen, red (inflamed) eyes, your treatment should be delayed until you have recovered.

When Holoclar is made, two ingredients from animals are used. One is foetal bovine serum which is from cows and is used to help grow your cells. The other ingredient is a special kind of inactivated mouse cell which is used to grow your limbal cells. If you are allergic to either of these ingredients, you will not be able to be given this medicine (see above under 'You must not be given Holoclar').

If you have any of the following problems with your eyes, they should be treated before this medicine is used:
- Uneven eyelids
- Scarring of the conjunctiva (the protective layer over the white of your eye) with damage where it joins to the inside of the eyelids (fornix shortening)
- Inability for your eye to sense pain (anaesthesia of the cornea or conjunctiva or hypoaesthia)
- Growth of the conjunctiva over the cornea (pterygium)
- Severe dry eye.

Other cases in which Holoclar cannot be used
Even if the surgeon has already taken a small sample of limbal cells (a biopsy) needed to produce the medicine, it is possible that you will not be able to have treatment with Holoclar. This is the case if the biopsy is not good enough to make Holoclar, the cells cannot be grown in the laboratory or the grown cells do not meet all the quality requirements. Your surgeon will inform you about this.

Children and adolescents
Only a very small number of children have been treated so far, so there is limited data on whether the treatment is safe for use in children or how effective it may be.

Kidney and liver problems
Please talk with your surgeon before the start of treatment if you have liver or kidney disease.

Other medicines and Holoclar
Some eye-drops contain a preservative called 'benzalkonium chloride'. This ingredient will damage the cells of which Holoclar is made. Do not use eye-drops containing benzalkonium chloride and/or other preservatives. Ask your doctor or pharmacist for advice.

Pregnancy and breast-feeding
If you are pregnant, think you might be pregnant or you are breast-feeding, treatment with this medicine should be delayed.

Driving and using machines
Holoclar is given by surgery on your eye and this will impact on your ability to drive and use machines. Therefore, do not drive or use machines after having Holoclar put in your eye until your surgeon tells you that it is safe to do so. Follow their advice carefully.

3. How Holoclar is given

Holoclar can only be prescribed and given by an eye surgeon in a hospital.
Treatment with Holoclar is a two-step procedure.

Visit 1: Biopsy taken
On the first visit, the surgeon will carry out a biopsy, which means removing a very small amount of tissue containing limbal cells (from your eye). Before the biopsy, the surgeon will give you eye-drops to anaesthetise your eye and surgically take the biopsy. This biopsy will then be used to make Holoclar. After biopsy has been taken, your surgeon will prescribe a course of antibiotics for you to reduce the chance of an infection.
It will take several weeks to produce Holoclar.

Visit 2: Holoclar implantation
On the second visit the surgeon will:
- Anaesthetise your eye
- Remove the scarred surface of the cornea
- Replace it with Holoclar

On the day of surgery, the surgeon will anesthetise your eye and then will attach the edge of your new cornea with stitches to make sure that Holoclar stays in place. Your eyelid will be taped closed for three days and your eye will be bandaged for 10 to 15 days after the implantation.

After surgery, you will be prescribed a course of medicines to ensure full healing: antibiotics to reduce the chance of an infection and steroids to reduce swelling and irritation. It is **very** important that you take all the medicines prescribed by your surgeon, otherwise Holoclar may not work.
Please read the package leaflets for the individual medicines you are given for further information on these medicines.

Ask your surgeon if you have any further questions about the treatment with Holoclar.

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4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most side effects affect the eye, some of which are caused by the surgery or associated pharmacologic treatment. Most side effects are mild and disappear in the weeks after surgery.

The most serious side effects are problem with cornea (erosion) and perforation of the cornea, caused by treatment failure, which may occur within the 3 months from Holoclar implantation. In such a case, please contact your surgeon.

Very common: may affect more than 1 in 10 people
- Inflammation of the eyelids (blepharitis)

Common: may affect up to 1 in 10 people
- Bleeding around the site of the operation where Holoclar was inserted
- Problems with cornea (erosion)
- Increased pressure in the eye (glaucoma)
- Eye pain
- Inflammation of the cornea
- Inflammation of the eyelids (blepharitis)
- Eye complications due to the operation

Uncommon: may affect up to 1 in 100 people
- Eye disorders - stickiness of the eyelid, bloodshot eyes, swelling and inflammation of the eye, perforation, thinning and opacity of the cornea, eye irritation, turning of the eyelid, inwards growth of the eyelashes, dilation of the pupil and lacrimation
- Sensitivity to light
- Overgrowth around the implant (metaplasia)
- Sensation of foreign body in the eye
- Infection of the cornea
- Conjunctivitis
- The stitches break
- Fainting
- Headache
- Nausea
- Vomiting
- Bleeding from the eye lid skin
- Allergic dermatitis

Reporting of side effects
If you get any side effects, talk to your surgeon. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How Holoclar is stored

The following information is intended for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Do not store above 25°C or below 15°C.
Do not refrigerate or freeze.
Keep Holoclar within the steel container in the plastic bag until surgery. This is to protect it from contamination by bacteria.
Holoclar must not be irradiated or sterilised.

Since this medicine will be used during your surgery, the hospital staff are responsible for the correct storage of the medicine before and during its use, as well as for the correct disposal.

6. Contents of the pack and other information

What Holoclar contains
- The active substance consists of 300,000 - 1,200,000 of your living eye cells, on average 3.5% of which are stem cells. Each square centimetre of Holoclar contains 79,000 - 316,000 cells.
- There are two excipients: one is fibrin - a clear supportive layer used to keep Holoclar intact, the other one is a liquid containing amino acids, vitamins, salts and carbohydrates to store the cells in the vial called Dulbecco's Modified Eagles Medium supplemented with L-glutamine.

What Holoclar looks like and contents of the pack
Holoclar is a layer of cells for implantation into your eye. The cells are kept alive in a small sterile container.
The medicine is put in several layers of packaging which protect the medicine from bacteria and ensures that Holoclar is kept at a stable temperature for 36 hours, if stored at room temperature (15-25°C).

Each package contains an individual treatment dose which is large enough to cover your cornea.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu.

The following information is intended for healthcare professionals only

<u>Precautions to be taken before handling or administering the medicinal product</u>

Holoclar must be transported within the facility in closed, break-proof, leak-proof containers.

This medicinal product contains human corneal epithelial cells. Healthcare professionals handling Holoclar must take appropriate precautions wearing gloves, protective clothing and eye protection to avoid potential transmission of infectious diseases.

<u>Preparation prior to administration</u>

Holoclar is an advanced therapy medicinal product ready to be implanted.
Holoclar must be administered by an appropriately trained and qualified surgeon.

<u>Administration</u>

Implantation
Holoclar is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Holoclar must not be administered if the information on the product labels and lot number do not match the patient's identity.
Holoclar should be administered under aseptic conditions in conjunction with limbal peritomy, undermining of the conjunctiva and excision of the corneal fibrovascular tissue in preparation of the defect bed. Next, the cultured tissue is fitted under the undermined conjunctiva. The excess of insert is trimmed, and the edge covered with the conjunctiva applying 2 or 3 stitches (sutures) of vicryl or silk 8/0 in order to form a physical seal of the lesion and to secure the implant. The eyelids are kept closed over the insert with a steri-strip band.

Holoclar is generally implanted under topical retrobulbar or parabulbar anaesthesia. Other anaesthesiology procedures may be followed at the discretion of the surgeon, excluding the use of lidocaine local anaesthesia or anaesthetics containing adrenaline must be avoided.

Concomitant use of Holoclar with eye-drops containing benzalkonium chloride, and/or other preservatives is not recommended.

The procedure of Holoclar administration includes the use of antibiotics and corticosteroids.
Following implantation, an appropriate regimen of topical and systemic anti-inflammatory and prophylactic antibiotic treatment must be given.

The implantation must be followed by an appropriate monitoring schedule.

<u>Measures to take in case of accidental exposure</u>

In case of accidental exposure local guidelines on handling of human-derived material must be followed. Work surfaces and materials which have potentially been in contact with Holoclar must be decontaminated with appropriate disinfectant.

<u>Precautions to be taken for the disposal of the medicinal product</u>

Unused medicinal product and all material that has been in contact with Holoclar (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

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