

CONFIDENTIAL

Important Information for Patients in the UK and Republic of Ireland

HOLOCLAR[®] ▼

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

PATIENT INFORMATION GUIDE

***This Patient Information Guide should be read in
conjunction with the Package Leaflet for Holoclar[®]***

▼ 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 of the Holoclar[®] Package Leaflet and/or this Patient Information Guide for how to report side effects.

What is the purpose of this Patient Information Guide?

This Patient Information Guide is an information resource for patients who wish to be treated with Holoclar®. This Guide contains important information about the safe and effective use of Holoclar®. Therefore it is advised that this Guide is read carefully before receiving Holoclar® treatment.

The key elements of this Guide include:

- The need to avoid use of eye drops containing benzalkonium chloride.
- The side effects of treatment with antibiotics and anti-inflammatory (steroid) medicines that you will receive after the operation.
- How to report suspected side effects.
- Information about the Holoclar® Registry and why it is encouraged that eligible patients participate.

This Patient Information Guide should always be read in conjunction with the Package Leaflet for Holoclar®.

What is Holoclar® and what is it used for?

Holoclar® is a medicine consisting of a layer of your own (autologous) cells cultured from a small sample of cells taken from your eye during a biopsy. Holoclar® is used in adults to repair the surface of an eye damaged due to physical or chemical burns. When the eye is badly compromised by physical or chemical burns, lots of scarring can occur and vision may be affected. Scarring can affect the limbus, the portion of the eye surrounding the cornea (see Figure 1.), which is normally responsible for maintaining the health of the eye and for repairing damaged cells. When the limbus becomes scarred, damage to the eye is not properly repaired.

By taking some healthy cells from the limbus of one of your eyes, a new layer of healthy tissue is grown in the laboratory. This layer of healthy tissue is then implanted by a surgeon into the damaged eye helping it to heal. In case of a partial bilateral problem, the healthy cells will be taken from a spared portion of your less damaged eye.

What does the treatment involve?

You will need to attend the clinic/hospital on a number of occasions for tests to determine your suitability to receive this treatment as well as for the surgery itself. The surgery will be carried out in 2 stages:

1. A biopsy surgery. This will be performed from your healthy eye (in the case of a unilateral problem) or from a spared portion of the damaged eyes (in the case of a bilateral problem) to extract healthy cells. The cells obtained during the biopsy will then be transported to a special laboratory where they will be prepared and grown in a special culture in order for you to have your second surgery.
2. During the second surgery, which will take place at least 50 days after the first surgery, the prepared cells (Holoclar®) will be implanted into your affected eye. Your surgeon will either use a local or general anaesthetic for the implant operation. The eye that is treated will remain closed for three days after the surgery. You will be treated with medicines to prevent infections and to minimise swelling. Sutures will be removed around 14 days later.

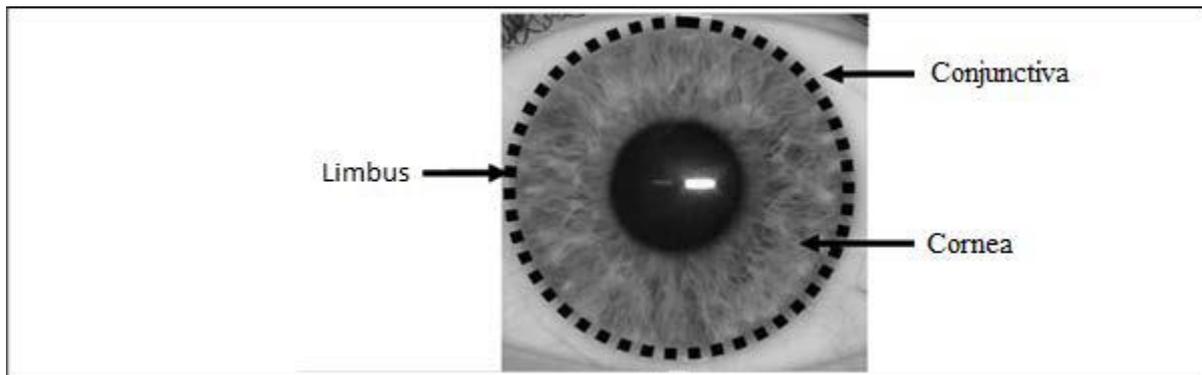


Figure 1.

What tests will I need to have?

First of all you will have a general examination, eye tests and blood tests to check for the presence of any infections and to determine that you are suitable for treatments.

What does the biopsy operation involve?

If the above assessments show that your general condition and your eye are suitable for the surgery, the surgeon will plan a date to take a sample (biopsy) from a healthy area in your eye. The biopsy surgery is usually performed under local anaesthetic, i.e. you are awake during the procedure. The biopsy sample will then be transported from the hospital to a dedicated laboratory where your cells are grown and prepared for the implant with Holoclar®.

After the biopsy has been taken, your surgeon will prescribe a course of antibiotics for you to reduce the chance of an infection occurring. It is important that you take all of these antibiotics according to the instructions given to you by your surgeon.

What does the implant operation involve?

The implant operation will usually take place several weeks after the biopsy operation (at least 50 days after). The precise time required to prepare Holoclar® for the implant operation is not always the same for everyone.

Your surgeon will agree with you a range of dates on which you will be asked to be available at the hospital for the implant operation. The implantation date may be adjusted 2-3 days prior to the estimated date of implantation, with the date being moved backwards up to 1 day before or 2 days after the initially confirmed date. This adjustment depends solely on your cells growth speed.

Sometimes, the implant operation may not be possible because the quality of the cells taken during the biopsy operation was inadequate to allow Holoclar® manufacturing. Under these circumstances a second biopsy operation may be required.

The surgery to implant Holoclar® into the affected eye may last up to about 45 minutes or more, depending on the conditions. The surgery will be performed under local or general anaesthetic. Your surgeon will agree with you the kind of anaesthesia to be applied. Your surgeon will remove the damaged tissue from your affected eye and replace it with the Holoclar® implant made by your own cells. Stitches (sutures) will be applied in order to secure the implant in place and a plaster will be applied to the eyelids to keep them closed for 3 days after surgery. The surgeon may suggest that the operation should be performed either at a Day Hospital or as in-patient treatment. For about two weeks after the implantation, the eye should be kept bandaged.

What happens after the implant operation?

It is expected that 3 days after the implant you will have the first check-up visit, during which the surgeon will remove the plaster from the eyelid and will make the first assessment of the eye treated with Holoclar®.

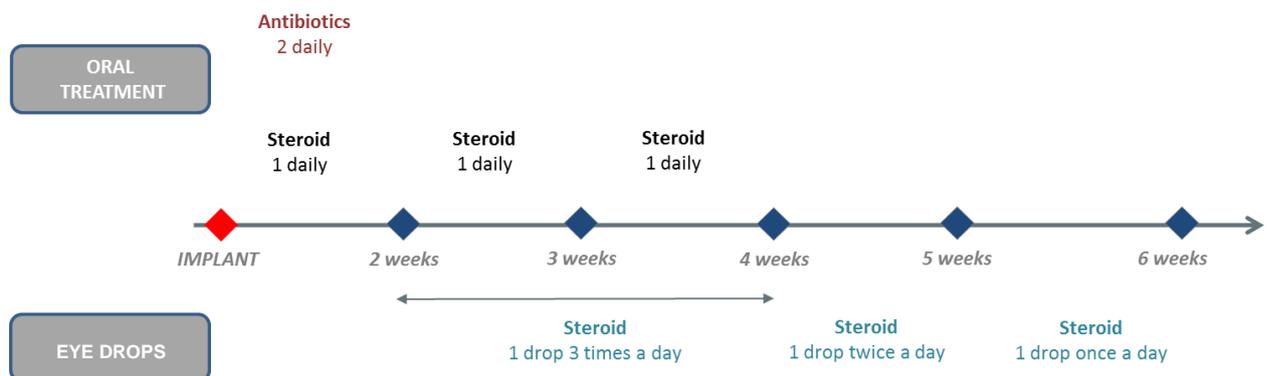
About 14 days after the implant you will have the second check-up visit, during which the surgeon will re-assess the condition of the eye. Stitches (sutures) placed in the eye during the implant operation will be removed.

Subsequent check-ups will occur around 6 weeks after implantation as well as at 6 months, 12 months and once a year for the subsequent 4 years.

What medicines will I need after surgery?

After the implant operation, your doctor or surgeon will prescribe you oral antibiotics and anti-inflammatory (steroid) medicines. This is to minimise the chance of an infection occurring and to keep swelling under control. ***It is very important that you take all the medicines prescribed to you by your doctor or surgeon; otherwise Holoclar® may not work.***

Around 2 weeks after implant you will also start anti-inflammatory (steroid) eye drops, one drop three times per day for the initial two weeks, twice a day for the third week and once a day for the fourth week. In case of continuing inflammation in the eye your doctor or surgeon may decide to prolong this treatment.



Are there any medicines I have to avoid?

Some eye drops contain a preservative called 'benzalkonium chloride'. This ingredient can damage cells and so could damage your Holoclar®.

Do not use any eye drops containing benzalkonium chloride unless your doctor or surgeon tells you to do so.

What are the possible side effects from Holoclar®?

Like all medicines, use of Holoclar® may be associated with side effects, although not everybody gets them and some are to be expected with eye surgery. Most side effects are related to the eye, are mild and usually disappear in the weeks after surgery.

Information about the side effects of Holoclar® can be found in the section on 'Possible side effects' contained in the Package Leaflet for Holoclar®. Please ensure that you read the Package Leaflet so you know what can occur. Ask your doctor or surgeon if you have any further questions or if there is anything that you do not understand.

What should I do if I get a side effect from Holoclar®?

If you get any side effects, you should tell your doctor or surgeon. This includes any possible side effects not listed in the Package Leaflet. ▼Holoclar® 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. You can also report side effects directly via:

- **For the UK:** report side effects using the Yellow Card Scheme at www.mhra.gov.uk/yellowcard
- **For the Republic of Ireland:** report side effects to HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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

What are the possible side effects from the other medicines given with Holoclar®?

Please note that possible side effects belonging to other medicines used or you are using may vary depending on their exact nature, for example whether the medicine is an antibiotic or an anti-inflammatory medicine. Based on the exact name of the medicine you are taking you should read the Package Leaflet that is supplied with it for a full list of possible side effects and other relevant safety information.

- Antibiotics given orally (e.g. doxycycline or amoxycillin tablets)

Do not take the medicine and discuss with your doctor or surgeon what to do if you have a known allergy or have experienced any previous reaction to the medicine or to other antibiotics (e.g. penicillin, streptomycin).

Take special care if you have liver or kidney problems, severe allergies or sensitivity to sunlight or if you take other medicines such as anticoagulants (medicines that thin the blood to prevent clotting), antacids (which may reduce absorption of the antibiotic and lessen its beneficial effects), oral contraceptives or medicines used in epilepsy, which could be less effective than expected. If you are taking doxycycline, avoid drinking alcohol during the antibiotic course.

Possible side effects can include nausea, headache, diarrhoea and thrush. You must contact a healthcare professional at once in case of more severe side effects such as sensitivity to light, severe skin rash, wheezing, swelling in the face, tongue or throat or if you get severe watery diarrhoea.

- Anti-inflammatory medications given orally (steroid tablets, e.g. prednisone)

Do not take the medicine and discuss with your doctor or surgeon if you have a known allergy to the medicine or to steroids.

You must take special care and inform your doctor or surgeon if you have other eye diseases (glaucoma) or injuries or ulcers on your cornea (the transparent front of the eye that covers the iris and pupil). You need to also take special care if you suffer from diabetes, bone problems (e.g. osteoporosis), stomach ulcers or bowel inflammation (colitis), infections, hepatitis, tuberculosis (TB), high blood pressure, heart problems, mental illness or sleep problems.

You must also tell your doctor or surgeon if you have recently had (within the last 2 weeks) or plan to have (within the next 8 weeks) a vaccination.

You must also take special care if you are taking other medicines at the same time including those for the heart and blood pressure, diabetes, vaccinations, non-steroidal anti-inflammatory drugs (NSAIDs) used to treat pain and inflammation and oral anticoagulants (blood thinning medications) such as warfarin.

Side effects can include clouding of the lens of the eye (cataract) and increased pressure in the eye (glaucoma) with or without eye pain, acne, hormonal effects and weight gain, raised blood pressure, high blood sugar, worsening of diabetes, infections, stomach ulcers including risk of bleeding, stretch marks, bruising or red marks on the skin or in the mouth, thinning of the skin, muscle wasting and weakness, bone wasting resulting in an increase risk of bone fractures (osteoporosis), difficulty in sleeping, headache and rarely psychiatric problems, irritability and depression.

- Anti-inflammatory eye drops (steroid eye drops, e.g. dexamethasone)

Do not take the medicine and discuss with your doctor or surgeon if you have a known allergy to the medicine or to steroids or if you have eye infection or glaucoma (increased eye pressure). Wearing of contact lenses during treatment must be avoided.

Most people will not suffer from any side effects from the use of these eye drops. Use may occasionally lead to stinging, burning, redness or watering of the eye which tends to be temporary. Any changes in eyesight should be reported to your doctor or surgeon.

Some eye drops contain a preservative called 'benzalkonium chloride'. This ingredient can damage cells and so could damage your Holoclar®.

Do not use any eye drops containing benzalkonium chloride
unless your doctor or surgeon tells you to do so.

What should I do if I get any side effects from the other medicines given with Holoclar®?

If you get any side effects, you should tell to your doctor or surgeon. This includes any possible side effects not listed in the relevant Package Leaflet(s) of the medicines you have been given.

You can also report side effects directly via:

- **For the UK:** report side effects using the Yellow Card Scheme at www.mhra.gov.uk/yellowcard
- **For the Republic of Ireland:** report side effects to HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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

What is the Holoclar® Registry and should I enrol in it?

Similar to most medicines when they are first made available in the market, Holoclar® has been studied in a relatively small number of patients. Whilst the information that is already known about the benefits and risks of treatment is sufficient to allow Holoclar® to be prescribed, it would be helpful to collect additional information about the use Holoclar®.

To increase what is known about Holoclar®, all patients are therefore encouraged to enrol in the Holoclar® Registry, which collects information about the effects of treatment. All information collected in the Registry will be anonymised and shared for research purposes. The anonymised information may be analysed from time to time and the results used to

better understand the benefits and risks of Holoclar[®]. This will ultimately help other patients just like you.

Participation in the Registry is entirely voluntary and if you choose not to participate in the Registry, this will not affect your treatment with Holoclar[®] or the care that you will receive.

If you agree to participate in the Registry, more information about the Registry will be provided to you. Your doctor or surgeon will ask for your written consent in order to collect your data for a research purpose and no data will be collected without your consent.

For further information about the Holoclar[®] Registry or to take part in the Registry, please speak to your doctor or surgeon.