SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Holoclar 79,000 - 316,000 cells/cm^2 living tissue equivalent

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Ex vivo expanded autologous human corneal epithelial cells containing stem cells.

2.2 Qualitative and quantitative composition

Holoclar consists of a transparent circular sheet of 300,000 to 1,200,000 viable autologous human corneal epithelial cells (79,000 - 316,000 cells/cm^2), including on average 3.5% (0.4 to 10%) limbal stem cells, and stem cell-derived transient amplifying and terminally differentiated cells, attached on a supportive 2.2 cm diameter fibrin layer and maintained in the transport medium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Living tissue equivalent.
Transparent, circular sheet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with moderate to severe limbal stem cell deficiency (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.

4.2 Posology and method of administration

This medicinal product is intended for autologous use only.
Holoclar must be administered by an appropriately trained and qualified surgeon and is restricted to hospital use only.

Posology
The amount of cells to be administered is dependent on the size (surface in cm^2) of the corneal surface.

Each preparation of Holoclar contains an individual treatment dose with sufficient number of cells to cover the entire corneal surface. The recommended dose of Holoclar is 79,000 - 316,000 cells/cm², corresponding to 1 cm² of product/cm² of defect. Each preparation of Holoclar is intended as a single treatment. The treatment may be repeated if considered indicated by the treating physician.

The administration should be followed by an appropriate antibiotic and anti-inflammatory treatment schedule, as recommended by the physician (see section 4.4).

Special populations

Elderly

Data on the use of Holoclar in elderly populations are limited. No recommendation on posology can be made (see sections 4.8 and 5.1).

Hepatic and renal impairment

Data on the use of Holoclar in patients with hepatic and renal impairment are not available.

Paediatric population

The safety and efficacy of Holoclar in children and adolescents aged 0 to 18 years has not yet been established. Currently available data are described in section 4.8 and 5.1, but no recommendation on posology can be made.

Method of administration
For implantation.

Full technical details on the procedures associated with the use of Holoclar are provided in the educational manual.

Biopsy

For the manufacture of Holoclar, a biopsy of 1 - 2 mm^2 of undamaged limbus is required. The biopsy is performed using topical anaesthesia. The eye is subjected to ocular surface lavage with sterile balanced salt solution for eye irrigation followed by detachment of the conjunctiva from the limbus to expose the sample collection site of the cornea. An incision of 2 x 2 mm is made to remove the biopsy.
The biopsy is placed in the sterile test tube supplied containing transport medium. The biopsy must be received by the manufacturer within 24 hours from the procurement.

Post-biopsy treatment
Following the biopsy, an appropriate regimen of prophylaxis with an antibiotic treatment must be given.

In some cases it may be possible that the source limbal stem cells of the patient are not expandable or that the release criteria are not met, due to poor biopsy quality, patient characteristics, or manufacturing failure. Therefore, it can occur that Holoclar cannot be delivered. The surgeon will be informed as early in the process as possible and should hence select an alternative treatment for the patient.

Implantation

Holoclar is intended solely for use in autologous limbal stem cell regeneration in line with the approved therapeutic indication and 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 insert 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.

Post-operative treatment
Following implantation, an appropriate regimen of topical and systemic anti-inflammatory and prophylactic antibiotic treatment must be given.

The following regimen is suggested: Doxycycline 100 mg tablets twice daily (or amoxicillin 500 mg twice daily) and prednisone orally at a daily dose of 0.5 mg/kg (to a maximum dose of 25 mg) per day should be administered from the day of surgery for 2 weeks. After 2 weeks the systemic antibiotic administration should be stopped and the daily dose of prednisone should be tapered to 0.25 mg/kg (maximum 12.5 mg) per day for 1 week, to 0.125 mg/kg (maximum 5.0 mg) per day for the following week and then stopped.

Two weeks after surgery, a topical corticosteroid treatment should be started with preservative-free dexamethasone 0.1% eye-drops, 1 drop three times per day for 2 weeks, then reduced to 1 drop twice daily for 1 week and 1 drop once daily for a further week. The topical corticosteroid can be maintained in case of persistent ocular inflammation.

The implantation must be followed by an appropriate monitoring schedule.

For information on the preparation and handling of Holoclar, please refer to section 6.6.

4.3 Contraindications

Hypersensitivity to any of the excipients listed in section 6.1 or to bovine serum and murine 3T3-J2 cells.

4.4 Special warnings and precautions for use

General
Holoclar is an autologous product and should under no circumstances be administered to anyone other than the donor patient.

Holoclar contains lethally-irradiated murine 3T3 fibroblast cells and may contain traces of foetal bovine serum. Patients with a known hypersensitivity to mice or foetal bovine serum must not be treated (see section 4.3).

Holoclar could contain potentially infected biological material. Although the risk is considered to be low and controlled in the manufacturing.

Precautions for use
Concomitant eyelids malposition, conjunctival scarring with fornix shortening, corneal anaesthesia and/or conjunctival anaesthesia or severe hypoaesthesia, pterygium and severe dry eye are potential complicating factors. When possible, concomitant eye problems should be corrected prior to Holoclar implantation.

Patients with acute ocular inflammation or infections should be deferred until recovery has been documented since inflammation may compromise treatment success.

The procedure of Holoclar administration include the use of antibiotics and corticosteroids (see section 4.2). For relevant safety information, physicians should consult the SmPC of these medicinal products.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Eye-drops containing benzalkonium chloride, and/or other preservatives, must be avoided. Benzalkonium chloride (as well as other quaternary ammonium compounds) is cytotoxic and eye-drops containing this preservative may damage the newly-regenerated corneal epithelium. Other cytotoxic agents must be avoided.

No interactions between Holoclar and the post-biopsy/post-operative treatment suggested in section 4.2 have been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data for the use of Holoclar in pregnant women.

Animal studies are not available with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, and in light of the requirement of the post-operative pharmacological treatment, it is preferable to avoid the use of Holoclar during pregnancy.

Breast-feeding
As a precautionary measure, Holoclar is not recommended for implant during breast-feeding.

Fertility
No clinical data on the effects of Holoclar on fertility are available.

4.7 Effects on ability to drive and use machines

The surgical nature of the underlying procedure for the implantation of Holoclar has a major influence on the ability to drive and use machines. Therefore, following treatment with Holoclar, driving and using machines must be limited and patients should follow the advice of their treating physician.

4.8 Undesirable effects

Summary of the safety profile
The most serious adverse reactions are corneal perforation and ulcerative keratitis, which may occur within the 3 months from Holoclar implantation and are related to the corneal epithelial instability, and syncope vasovagal occurring in the first day after surgery due to eye pain. The most common adverse reactions are eye disorders. The most frequently occurring reaction related to the surgical procedure was conjunctival haemorrhage (5%) which appears mostly during the first day after surgery and tends to be mild in intensity and disappears within a few days without treatment.

Tabulated list of adverse reactions
Adverse reactions reported in patients implanted with Holoclar are provided in the table.
The following categories are used to rank the adverse reactions by frequency of occurrence: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System / organ class	**Adverse reaction**	**Frequency**
Infections and infestations	Corneal infection	Uncommon
Nervous system disorders	Syncope vasovagal	Uncommon
Eye disorders	Blepharitis	Very common
	Conjunctival haemorrhage, eye haemorrhage, corneal epithelium defect, eye pain, glaucoma/intraocular pressure increased, ulcerative keratitis	Common
	Conjunctival adhesion, conjunctival hyperaemia, corneal oedema, corneal perforation, eye irritation, photophobia	Uncommon
Skin and subcutaneous tissue disorders	Haemorrhage subcutaneous	Uncommon
General disorders and administration site conditions	Metaplasia of the implant	Uncommon
Injury, poisoning and procedural complications	Suture rupture	Uncommon

Description of selected adverse reactions
Blepharitis (10.5%), and corneal epithelium defect (3.5%) were the most common individual adverse reactions not related to the surgical procedure. Glaucoma (3.5%) was the most frequent adverse reaction considered related to the corticosteroid treatment (see sections 4.2 and 4.4). Reports of glaucoma included adverse reactions of intraocular pressure.

Paediatric population
There is no information on the safety of Holoclar in children up to 7 years of age and only limited information in patients 8 - 17 years of age. In the paediatric patients included in the studies HLSTM01 (age 13, 14 and 16 years) and HLSTM02 (age 8 and 14 years) the profile of adverse reactions was not different from the adult population.

Elderly
There is only limited information in elderly (n=12, >65 year old) and very elderly (n= 2, 75-84 year old) patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard. Or in Ireland 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.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other ophthalmologicals, ATC code: S01XA19

Mechanism of action and pharmacodynamic effects
The mechanism of action of Holoclar is the replacement of corneal epithelium and lost limbal stem cells in patients in which the limbus has been destroyed by ocular burns. During the corneal repair process, the administered stem cells are intended to partially multiply, differentiate and migrate to regenerate corneal epithelium, as well as maintaining a reservoir of stem cells that can continually regenerate the corneal epithelium.

Conventional pharmacodynamic studies for Holoclar have not been performed.

Clinical efficacy and safety
The efficacy of the medicinal product was evaluated in a multi-centre, case-series, non-controlled, retrospective cohort study in 106 patients (HLSTM01 study) of both genders, treated for the presence of a moderate to severe limbal stem cell deficiency (LSCD). Moderate to severe LSCD was defined according to an invasion of at least two quadrants of the corneal surface by superficial neo vessels. A total of 104 patients, aged between 13 and 79 years (mean 46.8 years) were included in the primary efficacy analysis. At the time of product administration, the mean duration of the condition since the injury was 18 years (median 10 years), 99% of patients had corneal opacity and 90% of them had a severe impairment in visus ($1/10^{th}$ or less at Snellen chart). Success of the procedure was evaluated based on the presence of a stable corneal epithelium (i.e. absence of epithelial defects) without significant recurrence of neovascularisation (no more than one quadrant without central corneal involvement) at 12 months post-intervention. A total of 75 (72.1%) treatments were reported with a successful outcome. These results were confirmed in a sensitivity analysis where superficial neovascularisation was evaluated by an independent assessor from blinded photos of patients' eyes taken before and after Holoclar implantation.

Additional clinically-relevant parameters were evaluated as secondary efficacy assessments.

The proportion of patients with symptoms (pain, burning or photophobia) significantly decreased from pre-surgery (40 patients with at least one symptom; 38.5%) to one year after the procedure (12 patients; 11.5%).

Fifty-one patients (49.0%) had an improvement in visual acuity of at least one full line on a Snellen chart (or one category for the severely impaired cases). The proportion of patients with improvement in visual acuity was higher among those without a scar of the corneal stroma (15/18 patients, 83.3%) than in those with scarring (36/81 patients, 44.4%). When categorical values for visual acuity were converted into the Logarithm of the Minimum Angle of Resolution (LogMAR), 47% of cases (40 over 85 with non-missing values) experienced an improvement equal or greater than 3 Snellen line equivalents.

Fifty-seven patients underwent a keratoplasty after the use of the product with a success rate of 42.1% (N=24) one year after the corneal transplantation (i.e. with a stable corneal epithelium without significant recurrence of neovascularisation).

Elderly
The HLSTM01 study enrolled a total of seven patients (6.7% of the study population) with an age at baseline of 65 years or above, and seven additional patients (24.1%) were included in HLSTM02. Although limited with regard to the number of subjects, data from both studies showed a success rate around 70% of treated cases in the elderly population. This level of efficacy is similar to that observed in the treated patients overall.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Holoclar in one or more subsets of the paediatric population in the treatment of limbal stem cell deficiency due to ocular burns (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The product is implanted locally.
The nature and intended clinical use of Holoclar are such that conventional pharmacokinetic studies on absorption, biotransformation and elimination are not applicable. Immunohistochemical analysis of cornea taken from patients receiving keratoplasty after Holoclar treatment demonstrated that the transplanted stem cells establish a normal layer of stratified corneal epithelium, which do not migrate or invade basal ocular structures.

5.3 Preclinical safety data

Non-clinical safety data were limited to in vitro testing of tumorigenicity of the human autologous cell cultures. These tests included cell karyotype, cell growth in soft agar and growth factor-dependent proliferation. In vitro studies have revealed no evidence of anchorage-independent growth indicative of tumorigenic potential.

The safety of Holoclar is demonstrated in the results obtained from the two retrospective clinical studies.

Conventional non-clinical reproductive and developmental toxicity studies are not considered relevant, given the nature and the intended clinical use of the autologous product.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Transport medium (Dulbecco's Modified Eagles Medium supplemented with L-glutamine)
Fibrin support.

6.2 Incompatibilities

There have been no formal compatibility studies with Holoclar therefore this medicinal product should not be used with other medicinal products during the post-surgical period until the corneal epithelium integrity is fully restored. Exceptions include non-topical antibiotics for prophylaxis and corticosteroids during the immediate post-operative period.

6.3 Shelf life

36 hours.
Holoclar must be applied no later than 15 minutes after opening the primary container.

6.4 Special precautions for storage

Store between 15°C – 25°C
Do not refrigerate or freeze
Do not irradiate (e.g. X-rays)
Do not sterilise
Keep the steel primary container tightly closed to protect from bacterial, fungal and viral contamination.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Holoclar is supplied as one individual treatment dose contained in a screw-cap container. Each container contains 3.8 cm^2 of autologous human corneal epithelium attached on a fibrin support and covered with transport medium.

The container is put in a secondary plastic container which is then put in a sealed sterile plastic bag. The sealed bag is put in a non-sterile, thermally insulated box for organ transportation with a temperature monitor. Finally, the thermally insulated box is put in a zipped sealable bag for transportation.

6.6 Special precautions for disposal and other handling

Holoclar is intended solely for autologous use. Prior to implantation the patient's name should be carefully checked with the patient/donor identification on the shipment documentation and product container.

Any shaking, inverting or other mechanical stress of the Holoclar container should be avoided.

See the educational material for further information.

Holoclar must not be sterilised. The container and closure should be carefully visually inspected for any derogation. If the Holoclar primary container is damaged, the visual appearance of the product is affected, visual particulates are identified, the product must not be used and must be returned to the manufacturer. If the temperature monitored in the insulated box deviates from the storage conditions, contact the manufacturer.

Any unused medicinal product or waste material must be returned to the manufacturer.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/987/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17/02/2015

Date of latest renewal: 10/12/2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.