ANNEX I

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 16%) 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/cm^2, corresponding to 1 cm^2 of product/cm^2 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	Uncommon

	perforation, eye irritation, photophobia	
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 national reporting system listed in Appendix V.

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

Holostem Terapie Avanzate s.r.l.
Via Glauco Gottardi 100
41125 Modena
Italy
Telephone: +39 059 2058070
Telefax: +39 059 2058115

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: 15/01/2019

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Holostem Terapie Avanzate s.r.l.
Via Glauco Gottardi,100, Modena, 41125, Italy

Name and address of the manufacturer responsible for batch release

Holostem Terapie Avanzate s.r.l.
Via Glauco Gottardi,100, Modena, 41125, Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being

reached.

- **Additional risk minimisation measures**

The following additional risk minimisation measures are necessary for the safe and effective use of the product:

Educational material for healthcare professionals to provide training on the appropriate use of the product and to minimise risks, addressing the key elements of:

- Patient selection
- Traceability of patients and use of identifiers
- Biopsy, implant and follow up care
- Contraindicated use of eye drops containing benzalkonium chloride
- Risk of glaucoma and blepharitis
- Encouraging enrolment in the registry
- Reporting suspected side effects

The education material should also include both an Educational Manual and a training programme which will incorporate verification of physicians' comprehension of the training provided.

Educational material for patients and/or carers to address the following key elements:

- Contraindicated use of eye drops containing benzalkonium chloride
- Side effects of post-transplant treatment with antibiotics and corticosteroids
- Inform patients of the registry
- Reporting suspected side effects

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
Multinational, multicentre, prospective, open-label, uncontrolled interventional study (HLSTM03) to assess the efficacy and safety of autologous cultivated limbal stem cells grafting for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns	Final CSR June 2022

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

ZIPPED SEALABLE BAG

1. NAME OF THE MEDICINAL PRODUCT

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

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

This medicine contains cells of human origin.
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 16%) 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.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Living tissue equivalent.
Each container contains 3.8 cm^2 of autologous human corneal epithelium attached to a fibrin support and immersed in transport medium.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
For implantation.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Potentially infected biological material.
Handle with care, avoid, any shaking, inverting or other mechanical stress.
For autologous use only.

8. EXPIRY DATE

EXP : Day / Month / Year
At time: Hour / Minute (CET)

9. SPECIAL STORAGE CONDITIONS

Store between 15 °C – 25 °C
Keep the steel primary container tightly closed in order to protect from bacterial, fungal and viral contamination
Do not freeze
Do not sterilise
Do not irradiate (e.g. X-rays)
Each batch is shipped in a temperature-controlled thermally insulated box for organ transplant.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Holostem Terapie Avanzate s.r.l., Via Glauco Gottardi 100, 41125 Modena, Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/987/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<Not applicable.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable.>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PLASTIC BAG (TERTIARY)

1. NAME OF THE MEDICINAL PRODUCT

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

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

This medicine contains cells of human origin.
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 16%) 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.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Living tissue equivalent.
Each container contains 3.8 cm^2 of autologous human corneal epithelium attached to a fibrin support and immersed in transport medium.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
For implantation.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Potentially infected biological material.
Handle with care, avoid any shaking, inverting or other mechanical stress.
For autologous use only.

8. EXPIRY DATE

EXP : Day / Month / Year
At time: Hour / Minute (CET)

9. SPECIAL STORAGE CONDITIONS

Store between 15 °C - 25 °C
Keep the steel primary container tightly closed in order to protect from bacterial, fungal and viral contamination
Do not freeze
Do not sterilise
Do not irradiate (e.g. X-rays)
Each batch is shipped in a temperature-controlled thermally insulated box for organ transplant.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Holostem Terapie Avanzate s.r.l., Via Glauco Gottardi 100, 41125 Modena, Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/987/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Batch
Patient’s Forename and Surname:
Patient’s Date of Birth:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<Not applicable.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<Not applicable.>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SCREW-CAP CONTAINER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Holoclar

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:
DATE:
HOUR: (Time zone)

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

M.A.H: Holostem Terapie Avanzate s.r.l.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Holoclar 79,000 – 316,000 cells/cm2living 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

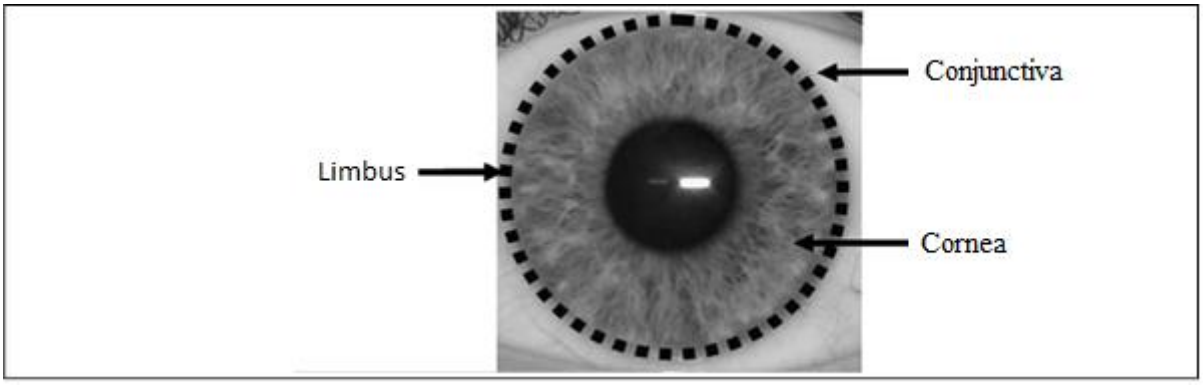
1. What Holoclar is and what it is used for
2. What you need to know before you are given Holoclar
3. How Holoclar is given
4. Possible side effects
5. How Holoclar is stored
6. Contents of the pack and other information

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 it is not known whether the medicine 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 can 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.

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. 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, 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

Uncommon: may affect up to 1 in 100 people
- Eye disorders - stickiness of the eyelid, bloodshot eyes, swelling of the eye, perforation of the cornea and eye irritation
- Sensitivity to light
- Overgrowth around the implant (metaplasia)
- Infection of the cornea
- The stitches break
- Fainting
- Bleeding from the eye lid skin

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

5. How Holoclar is stored

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.

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.

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

Marketing Authorisation Holder and Manufacturer

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

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

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The following information is intended for healthcare professionals only:
(The complete SmPC will be provided as a separate document in the medicine pack)