RIBOCROSS TE - RIBOFAST

in Corneal Cross-linking Treatments

Instruction for use

Rev. 1.2023

SERVImed

RIBOCROSS TE and RIBOFAST:

RIBOCROSS TE 1.5 ml - riboflavin 0.1%, Vit E TPGS (penetration enhancer), dextran 10%, Sodium phosphate dibasic dodecahydrate, Sodium phosphate monobasic monohydrate, Sodium chloride. Purified water.

RIBOFAST 1.5 ml - riboflavin 0.1%, Vit E TPGS (penetration enhancer), Sodium phosphate dibasic dodecahydrate, Sodium phosphate monobasic monohydrate, Sodium chloride, Purified water.

CORNEAL CROSS-LINKING TREATMENT:

INDICATIONS

- Keratoconus
- Iatrogenic ectasia (after LASIK, PRK, RK)
- Pellucid Marginal Degeneration
- Infectious Keratitis
- Refractive defects and stabilization treatment: Combi SMILE-CXL, Combi FEMTOLASIK-CXL.

INCLUSION CRITERIA:

- Diagnosis of developmental keratoconus (Kmax range: 46 - 62 D)
- Central corneal thickness > 400 microns at the thinnest point
- Increase in the apical curvature of the cone by at least 1 D in the previous 6 months
- Clear cornea on biomicroscopy
- Absence of Vogt's striae

EXCLUSION CRITERIA:

- Presence of central or paracentral corneal opacity
- Central corneal thickness < 400 microns in the thinnest point
- History of herpetic keratitis
- Severe dry eye
- Corneal infections
- Autoimmune diseases
- Lens or retinal diseases
- Use of rigid contact lenses in the 4 weeks preceding the baseline assessment
- Cuts or wounds in the eye to be treated
- Chemical damage or delayed epithelial healing in the eye to be treated
- Pregnancy (including its planning) or breastfeeding
- Aphakic patients and pseudophakic patients whose implanted lenses are free of UV blocking
- Herpes simplex, herpes zoster keratitis, recurrent corneal erosion, corneal dystrophy
- Disorders of epithelial healing
- Refractive keratotomies
- Intra-stromal ring
- Post Lasik secondary corneal ectasias, with extremely irregular and inhomogeneous surfaces and central flattening

EQUIPMENT

- Cross-linking device
- Riboflavins (Ribocross TE/Ribofast)
- Pachymeter
- Operating table and instrument table
- EBK Epi Bowman Keratectomy device (for epi-off)
- Slit lamp
- Speculum
- Gauze, adhesive tape, lasik sponge,sterile tissue
- Therapeutic contact lens
- Pilocarpine 2%
- Topical anaesthetic (oxybuprocaine orbenoxinate drops)
- Topical antibiotic with large spectrum eye drops
- Lubricant eye drops
- Postoperative medication
- BSS
- Sucking ring
- Sterile dryers
- Single use and sterile clothes.
- Informed consent

PREPARATION AND PRE-OP HOME THERAPY

The patient has to remove contact lenses 7 days before the treatment. From 2 days before the treatment, the therapy includes:

- Topical antibiotic therapy, with large spectrum eye drops (i.e.one drop every 6 hours).
- Lubricant and protective therapy, with eye drops based on hyaluronic acid. It is preferrable to use preservatives free drops.

It is possible, always with the consent of the ophthalmologist, to use tranquillizers for anxious patients, the night before and the morning of the treatment.
The patient must be instructed to show up on treatment day without having applied chemicals (make-up, cosmetic creams, perfumes, etc.) during the last three days, and bringing a pair of sunglasses.

Before performing the treatment, it is suggested to measure the following parameters:

- Topography
- Corneal thickness (thinnest point)
- Kmax and its coordinates (x,y)
- K1, K2
- Astigmatism at 3,5 and 7 mm
- Corrected and uncorrected visual acuity (BSCVA, UCVA)
- Aberrometry: total corneal aberration coefficient, coma, spherical aberration

Pre- and post-treatment acquisitions should be carried out with the same diagnostic tool, to keep uniformity in the evaluations. Set the Kmax in diopters, with Cartesian reference system.

TREATMENT

1) PATIENT PREPARATION

The doctor verifies that the patient followed the prescribed therapy, and a clinical check is made to exclude possible inflammatory and/or infective processes.
The patient goes to the pre-treatment room, dressed with single use, sterile clothes. The preparation starts 30 minutes before

treatment, and consists in:

- Intra-ocular structures protection from UV-A rays using a single drop of pilocarpine 2% 15 minutes before the treatment.
- Topical anesthesia, with oxybuprocaine or benoxinate drops, every 5 minutes 15 minutes before the treatment. To reduce blinking reflex, instill one drop in the other eye.
- Prophylactic therapy with disinfectant eye drops.

The different drops have to be used with few minutes between one another, to avoid reciprocal wash-out.

Finally, the patient is accompanied in the treatment room, where he/she has to lay on the bed. If the doctor prefers, the eye not subject to CXL can be blindfolded.
Periocular skin is disinfected with an iodine povidone 10% based solution. Then, a sterile surgical mask, preferably adhesive, is applied, along with a speculum. Immediately before starting the treatment, it may be useful to instill a few drops of anesthetic eye drops and eye rinsing with BSS to eliminate residues of previously inoculated drugs.

2) CROSS-LINKING PROTOCOL: how to use RIBOCROSS TE and RIBOFAST

The following tables list the suggested indications for use of **RIBOCROSS TE** and **RIBOFAST** for every CXL protocol and corneal ectasia stage, according to ***Krumeich classification (Stage 1-3)***:

Ectasia Stage 1 - Krumeich classification

EPI ON CXL	STANDARD EPI OFF CXL	ACCELERATED CXL	CUSTOM FAST CXL	THINNEST CORNEAS
RIBOCROSS RIBOFAST	RIBOCROSS RIBOFAST	RIBOCROSS RIBOFAST	RIBOCROSS RIBOFAST	RIBOFAST swelling RIBOCROSS procedure

Ectasia Stage 2 - Krumeich classification

EPI ON CXL	STANDARD EPI OFF CXL	ACCELERATED CXL	CUSTOM FAST CXL	THINNEST CORNEAS
RIBOCROSS RIBOFAST	RIBOCROSS	RIBOCROSS	RIBOCROSS RIBOFAST	RIBOFAST swelling RIBOCROSS procedure

Ectasia Stage 3 - Krumeich classification

EPI ON CXL	STANDARD EPI OFF CXL	ACCELERATED CXL	CUSTOM FAST CXL	THINNEST CORNEAS
RIBOCROSS	RIBOCROSS	RIBOCROSS	RIBOCROSS RIBOFAST	RIBOFAST swelling RIBOCROSS procedure

Refractive Surgery combined with CXL

COMBI CXL
RIBOCROSS RIBOFAST

EPI-OFF CXL PROTOCOLS

STANDARD EPI-OFF 3 mW/cm² - 30 minutes (DRESDEN)

Indicated for corneal thickness > 400 µm (after epithelial removal).

1. Apply the speculum on the eye to be treated.
2. Remove the corneal epithelium with spatula after BAK application, around 8-9 mm diameter and eye rinsing with BSS to eliminate residues of the BAK.
3. SOAKING PHASE:

Instill **RIBOCROSS TE/RIBOFAST** solution: 1 drop every 1 minute for 30 minutes.

4. PATIENT POSITIONING:

Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.

5. IRRADIATION PHASE:

- Start UV irradiation at 3 mW/cm2 for 30 minutes (6 step di 5 minutes), fluence 5.4 J/cm2.
- Adjust UV beam to clear cornea diameter, excluding the limbus.
- Instill riboflavin 1 drop every 2 minutes for 30 minutes.

ACCELERATED EPI-OFF 9 mW/cm² - 10 minutes

Indicated for corneal thickness > 400 µm (after epithelial removal).

1. Apply the speculum on the eye to be treated.
2. Remove the corneal epithelium with spatula after BAK application, around 8-9 mm diameter and eye rinsing with BSS to eliminate residues of the BAK.

3. SOAKING PHASE:
4. Instill **RIBOCROSS TE/RIBOFAST** solution: 1 drop every 1 minute for 30 minutes.
5. PATIENT POSITIONING:
Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
6. IRRADIATION PHASE:
- Start UV irradiation at 9 mW/cm2 for 10 minutes, fluence 5.4 J/cm2.
- Adjust UV beam to clear cornea diameter, excluding the limbus.
- Instill riboflavin 1 drop every 1 minute for 10 minutes.

ACCELERATED EPI-OFF 18 mW/cm² - 5 minutes

Indicated for corneal thickness > 400 µm (after epithelial removal).
1. Apply the speculum on the eye to be treated.
2. Remove the corneal epithelium with spatula after BAK application, around 8-9 mm diameter and eye rinsing with BSS to eliminate residues of the BAK.
3. SOAKING PHASE:
4. Instill **RIBOCROSS TE/RIBOFAST** solution: 1 drop every 1 minute for 30 minutes.
5. PATIENT POSITIONING:
Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
6. IRRADIATION PHASE:
- Start UV irradiation at 18 mW/cm2 for 5 minutes, fluence 5.4 J/cm2.
- Adjust UV beam to clear cornea diameter, excluding the limbus.
- Instill riboflavin 2 drop every 1 minute for 5 minutes.

ACCELERATED EPI-OFF 30 mW/cm² - 3 minutes

Indicated for corneal thickness > 400 µm (after epithelial removal).
1. Apply the speculum on the eye to be treated.
2. Remove the corneal epithelium with spatula after BAK application, around 8-9 mm diameter and eye rinsing with BSS to eliminate residues of the BAK.
3. SOAKING PHASE:
4. Instill **RIBOCROSS TE/RIBOFAST** solution: 1 drop every 1 minute for 30 minutes.
5. PATIENT POSITIONING:
Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
6. IRRADIATION PHASE:
- Start UV irradiation at 30 mW/cm2 for 3 minutes, fluence 5.4 J/cm2.
- Adjust UV beam to clear cornea diameter, excluding the limbus.
- Instill riboflavin 2 drop every 30 seconds for 3 minutes.

EPI-ON CXL PROTOCOLS

IONTOPHORESIS 10 mW/cm² - 9 minutes

Epi-on protocol, no epithelium removal.
1. SOAKING PHASE:
Instill **RIBOCROSS TE/RIBOFAST** in the specific Iontophoresis electrode applied on the eye, until the grid is completely covered. Then set the electric field generator and keep it running until the complete absorption.Then, remove the electrode and proceed with the UV-A irradiation.
2. IRRADIATION PHASE:
- Start UV irradiation at 10 mW/cm2 for 9 minutes, fluence 5.4 J/cm2.
- Adjust UV beam to clear cornea diameter, excluding the limbus.

EPI-ON 3 - 9 - 18 mW/cm²

1. Apply the speculum on the eye to be treated.
2. SOAKING PHASE:
3. Instill **RIBOCROSS TE/RIBOFAST** solution: 1 drop every 1 minute for 30 minutes.
5. PATIENT POSITIONING:
Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
6. IRRADIATION PHASE:
- Start UV irradiation (fluence 5.4 J/cm2) at:
  - 3 mW/cm2 for 30 minutes. Instill riboflavin 1 drop every 2 minutes for 30 minutes.
  - 9 mW/cm2 for 10 minutes. Instill riboflavin 1 drop every 45 seconds for 10 minutes.
  - 18 mW/cm2 for 5 minutes. Instill riboflavin 1 drop every 15 seconds for 5 minutes.
  - Adjust UV beam to clear cornea diameter, excluding the limbus.

*CUSTOM FAST CXL**

In the CUSTOM FAST EPI-ON protocol, the treatment parameters (UV intensity, irradiation time and beam diameter) are calculated directly by the software available on the CF-X Linker device and regulated by the mathematical model of the consumption rate of the riboflavin; by entering the patient's topographic and pachymeter data (Thinnest corneal thickness, the coordinates of Kmax and Kmax) UV intensity, duration and diameter of the single treatment are calculated and set by the software.

1. Apply the speculum on the eye to be treated.
2. SOAKING PHASE:
Fixed at 15 minutes. Instill a drop of **RIBOCROSS TE/RIBOFAST** every 5 -10 seconds; the whole riboflavin syringe must be used in this phase. In the end of the phase, a corneal wash-out is recommended using BSS solution.
3.PATIENT POSITIONING:
Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
4. IRRADIATION PHASE:
- Start UV irradiation and adjust UV beam to the calculated value.
- Additional riboflavin instillation is not required in this phase.

** Only available on CF X-Linker device. For more detail on Custom Fast CXL procedure refer to Custom Fast instructions for use.*

CXL PROTOCOLS FOR THIN CORNEAS < 400 µm

RIBOFAST solution is indicated for the swelling of thin corneas with the following CXL protocols:

- EPI-OFF protocol (Dresden and 9 mW accelerated protocol) - not less than 350 µm
- EPI-ON protocol (Custom Fast CXL) - not less than 350 µm

EPI-OFF: DRESDEN or ACCELERATED PROTOCOL at 9 mW/cm²

1. Apply the speculum on the eye to be treated.
2. Remove the corneal epithelium with spatula after BAK application, around 8-9 mm diameter. Rinse the eye with BSS to remove residual BAK.
3. Check the depithelized corneal thickness at the thinnest point using ultrasound pachymetry.
4. SOAKING PHASE:
   Instill **RIBOFAST** solution every 20 seconds. Take five repetitive measurements in multiple points of the cornea and at the thinnest point every 2 minutes using ultrasound pachymetry, in order to swell the cornea.
   Perform **RIBOFAST** instillation until reaching 450/500 µm, according to patient case and surgeon evaluation, for maximum 10 minutes. Continue with **RIBOCROSS TE** to perform protocol soaking phase.

5. PATIENT POSITIONING:
Align the optical head on the patient's eye by using the focus system. The patient must be in lying position.
6. IRRADIATION PHASE:
- Start UV irradiation according to the indicated Epi-Off protocol and instill riboflavin during UV irradiation following the protocol's instruction (see previous paragraphs).

*EPI-ON: CUSTOM FAST CXL**

CUSTOMIZED EPI-ON Protocol suitable in the treatment of thin corneas (not less than 350 µm)

In the CUSTOM FAST EPI-ON protocol, the treatment parameters (UV intensity, irradiation time and beam diameter) are calculated directly by the software available on the CF-X Linker device and regulated by the mathematical model of the consumption rate of the riboflavin; by entering the patient's topographic and pachymeter data (Thinnest corneal thickness, the coordinates of Kmax and Kmax) UV intensity, duration and diameter of the single treatment are calculated and set by the software.

1. Apply the speculum on the eye to be treated.
2. SOAKING PHASE:
Fixed at 15 minutes. Instill a drop of **RIBOCROSS TE/RIBOFAST** every 5 -10 seconds; the whole riboflavin syringe must be used in this phase. In the end of the phase, a corneal wash-out is recommended using BSS solution.
3.PATIENT POSITIONING:
Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
5. IRRADIATION PHASE:
- Start UV irradiation and adjust UV beam to the calculated value.
- Additional riboflavin instillation is not required in this phase.

** Only available on CF X-Linker device. For more detail on Custom Fast CXL procedure refer to Custom Fast instructions for use.*

REFRACTIVE DEFECTS AND STABILIZATION TREATMENT:

COMBI SMILE-CXL - 15 mW/cm^2 (total energy 1.8 J/cm2)

1. Apply the speculum on the eye to be treated and perform SMILE refractive surgery procedure as usual.
2. Proceed with CXL treatment.
3. SOAKING PHASE:
   Instill **RIBOCROSS TE** solution on cornea with epithelium for 2 minutes using the whole vial.
4. PATIENT POSITIONING:
   Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
5. IRRADIATION PHASE:
   Start UV irradiation phase of 2 minutes with an intensity of 15 mW/cm2 (total energy 1.8 J/cm2). UV Beam diameter of 9 mm.

COMBI SMILE-CXL - 30 mW/cm^2 (total energy 2.7 J/cm2)

1. Apply the speculum on the eye to be treated and perform SMILE refractive surgery procedure as usual.
2. Proceed with CXL treatment.
3. SOAKING PHASE:
   Instill **RIBOFAST** solution into the corneal pocket obtained with SMILE method for 90 seconds using the whole vial.

4. PATIENT POSITIONING:
   Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
5. IRRADIATION PHASE:
   Start UV irradiation phase of 90 seconds with an intensity of 30 mW/cm2 (total energy 2.7 J/cm2). UV Beam diameter of 9 mm.

COMBI FEMTOLASIK-CXL - 15 mW/cm² (total energy 1.8 J/cm2)

1. Apply the speculum on the eye to be treated and perform LASIK refractive surgery procedure as usual.
2. Proceed with CXL treatment.
3. SOAKING PHASE:
   Instill **RIBOCROSS TE** solution on cornea with epithelium (LASIK flap on) for 2 minutes using the whole vial, to ensure greater stability of the flap to the stroma. After soaking, perform a BSS wash-out.
4. PATIENT POSITIONING:
   Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
5. IRRADIATION PHASE:
   Start UV irradiation phase of 2 minutes with an intensity of 15 mW/cm2 (total energy 1.8 J/cm2). UV Beam diameter of 9 mm.

COMBI FEMTOLASIK-CXL - 30 mW/cm² (total energy 2.7 J/cm2)

1. Apply the speculum on the eye to be treated and perform LASIK refractive surgery procedure as usual.
2. Proceed with CXL treatment.
3. SOAKING PHASE:
   Instill **RIBOCROSS TE** solution on cornea with epithelium (LASIK flap on) for 90 seconds using the whole vial, to ensure greater stability of the flap to the stroma. After soaking, perform a BSS wash-out.
4. PATIENT POSITIONING:
   Use the device focus system to align the optical head on the patient's eye. The patient must be in lying position.
5. IRRADIATION PHASE:
   Start UV irradiation phase of 90 seconds with an intensity of 30 mW/cm2 (total energy 2.7 J/cm2). UV Beam diameter of 9 mm.

3) PATIENT MEDICATION AND POST-OP THERAPY

After the treatment, use 2 drops of the antibiotic used in the preliminary phase and 1 cycloplegic drop (cyclopentolate or tropicamyde) can be used to decongest ciliary bodies, with an anti-inflammatory and antalgic effect. Do not use corticosteroids in Epi-off treatments, until total corneal re-epithelialization is achieved.
A protective bandage is recommended for the first 24 hours after treatment.
Therapeutic contact lens should be applied immediately after Epi-off and Epi-on high-energy protocols and left until the epithelium is intact.
The patient is accompanied in the post-treatment room, where the sterile clothes are removed. After one hour, he/she is checked on the slit lamp.

The patient is then dismissed with the following therapy:

- Topical antibiotic with large spectrum eye drops 5mg/ml, a drop every 6 hours, for 5/7 days;
- Hyaluronic acid-based eye drop, 4 times per day. It can be auto-administered more times in case of burning or foreign body sensation.
- Anti-inflammatory systemic therapy, in case of intense pain.
- Sterile tissues to clean eyelids and eye contour;

The topical therapy uses the same eye drops used during pre-operatory phase.

Refractive contact lens should be applied after total clinical recovery and generally 1 month after an epi off treatment and 15 days after an epi on treatment.

POST TREATMENT CHECK

The first follow-up check must be made after 24 hours from the treatment, to see if there is any complication, andincludes a slit lamp exam. If everything is ok, the patient is dismissed. Another follow-up check has to be madeafter 7 days. The doctor will evaluate if the therapy can be confirmed or modified, depending on the patient's clinical response.
The next checks will be planned case by case. Anyways, is recommended to evaluate corneal curvature, thickness, natural and corrected visual acuity, endothelial cell count, tonometry and corneal hysteresis after one month.
Further exams can be performed depending on clinical situation.
The required follow-up checks will be made at 3,6 and 12 months after the treatment.

For a complete analysis of the results, the parameters to be measured in all post-treatment checks are:

- Topography
- Corneal thickness (thinnest point)
- Kmax and its coordinates (x,y)
- K1, K2
- Astigmatism at 3,5 and 7 mm
- Corrected and uncorrected visual acuity (BSCVA, UCVA)
- Aberrometry: total corneal aberration coefficient, coma, spherical aberration

AFTER THE CROSS-LINKING TREATMENT

After any cross-linking protocol, it is common for the patient to experience, in the first days, a sensation of watery eye, blurred vision, sensation of a foreign body. The eyelids may appear swollen and the eye red. Vision may appear worse than before treatment even for prolonged time. If contact lens was used before treatment, it can only be resumed after authorization by the ophthalmologist. It may be necessary for the patient to change glasses and contact lenses after treatment, and to strictly follow the prescribed therapy for as long as necessary indicated by the ophthalmologist. Work, sports and driving a car are not recommended for a limited period of time which will be defined by the eye doctor.
During the first one or two years after the procedure, changes in refraction can be observed with the need to adjust glasses and contact lenses several times.

Recovery of sight

Improvement of vision cannot be guaranteed. If this happens, it is conditioned by the preoperative state of the eye. The presence of other eye injuries can limit vision recovery.
If the checks are not carried out according to the prescriptions of the ophthalmologist, the result of the intervention may be compromised.
ATTENTION: manipulation and rubbing of the treated eye determines the progression of ectasia.

Adverse events

Although the majority of cases are followed by excellent results, the CXL treatment does not escape the rule that there is no risk-free medical act. For this reason, it is not possible for the ophthalmologist to guarantee the successof the intervention or guarantee that no adverse events occur before, during and after the surgery.
The patient who subscribes to the information and consent model for the treatment necessarily assumes the risks foreseen for the procedure and also those not foreseen since they have never been reported in the scientific literature.

The following are the known, predictable but not preventable adverse events that may appear before, during and after CXL surgery. Among the adverse events mentioned there are some that can be controlled with medical therapy, others that require further surgery. In any case, the onset of an adverse event can delay or prevent complete functional recovery.
Preparation for treatment:
redness of the eye due to hypersensitivity or allergy to the drugs needed for the preparation
reduction of visual acuity due to the pharmacological myosis necessary to perform the treatment

During the treatment:
- corneal caustication
- irreversible damage to corneal endothelial cells and consequent corneal decompensation
- iris injury
- lesion of the lens
- retinal caustication

After the treatment:
- external or internal infection of the eye; both can lead, in extreme cases, to functional and anatomical loss of theeye
- melting of the corneal stroma
- delayed re-epithelialization
- corneal scar formation (haze and / or corneal grinding)
- corneal edema
- cataracts
- retinopathy
- maculopathy
- increased eye pressure (hypertonus)
- decrease in eye pressure (hypotonus)
- chronic uveitis
- astigmatism
- fluctuation and / or decrease in vision
- chronic inflammation of the ocular surface from dry eye with photophobia and chronic irritation symptoms
- unknown or unexpected side effects can also occur.

Particular Cases:

There are systemic and ocular conditions that make corneal cross-linking UV-A surgery at a greater risk of the occurrence of adverse events.
Systemic conditions: arterial hypertension, diabetes, depression of the immune system, alterations in the healing processes (keloids) create greater risks of complications especially in epi-off procedures.
Ocular conditions: sunken eye, narrow eyelid rim, dry eye, chronic allergic conjunctivitis, corneal opacity, lowendothelial count, endothelial dystrophy, reduced corneal thickness, low anterior chamber, previous eye laser or surgical procedures.
There are no known side effects of crosslinking in pregnancy, however it is preferable to carry out the treatment after pregnancy if there is a worsening of the visual conditions due to the evolution of ectasia.