



RIBOFLAVIN

OPHTHALMIC MEDICAL DEVICE

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RICROLIN

(RIBOFLAVIN 0,1%)

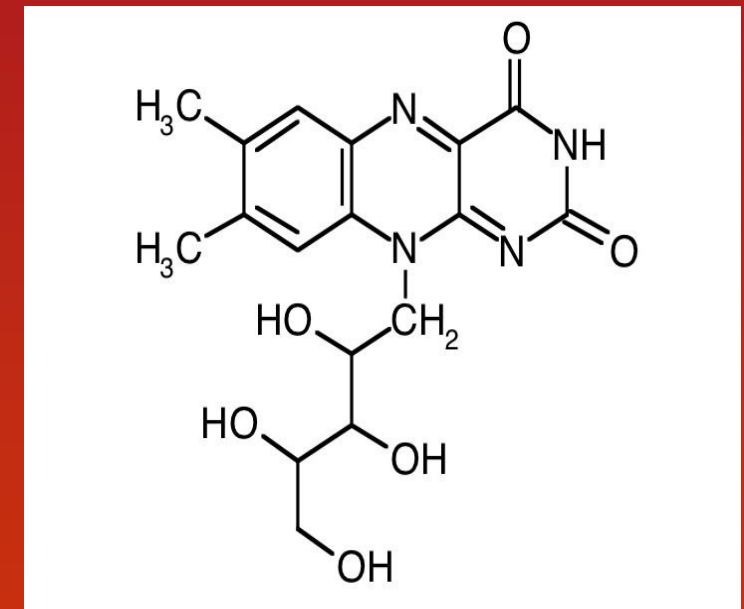
RICROLIN is an ophthalmic drug (drops) used for a new therapeutical procedure: the corneal collagen **cross-linking** for the treatment of ***keratoconus*** and secondary corneal ***ectasias***



RIBOFLAVIN

(VIT. B2)

- Was discovered in 1927 by Paul Gyorgy and it was synthesized by Richard Kuhn in 1935.
- Initially it was called Lactoflavin, because of its high concentration in milk.
- Successively a ribitol molecule was found and the name of Vit. B2 was changed in Riboflavin.



RIBOFLAVIN

(VIT. B2)

- Riboflavin is an heterocyclic mixture derived from an isoalloxazine molecule linked with a ribitol chain.
- It's a yellow substance barely soluble in water, it is heating resistant and highly fluorescent when excited by UV light.



RIBOFLAVIN

(VIT. B2)

- Riboflavin is widely represented in nature, and is found in mammalian tissues as a coenzymatic form.
- Riboflavin is involved in many metabolic reactions.
- **It loses its vitaminic properties** (riboflavin radical detachment) during a light exposure **when a photolytic reaction occurs.**

RICROLIN

(RIBOFLAVIN 0,1%)

- **Composition:**

100 ml of solution contains:

Riboflavin phosphate 0,125 g

Dextran T500 20 g

Excipient : dihydrate monobasic phosphate sodium, dihydrate dibasic phosphate sodium, sodium chloride, water for injectable solution q.b. a 100 g

- **Tonicity:**

slightly hypotonic ophthalmic solution (290 mOsm/l)

- **pH: 7,25.**

- **RICROLIN is preservative free**

RICROLIN

RIBOFLAVIN 0,1%

Stability

Accelerated stability tests at 5 months (20 months of ordinary stability) show a **Riboflavin titre above 97%, in accordance with the Good Laboratory Practice.**

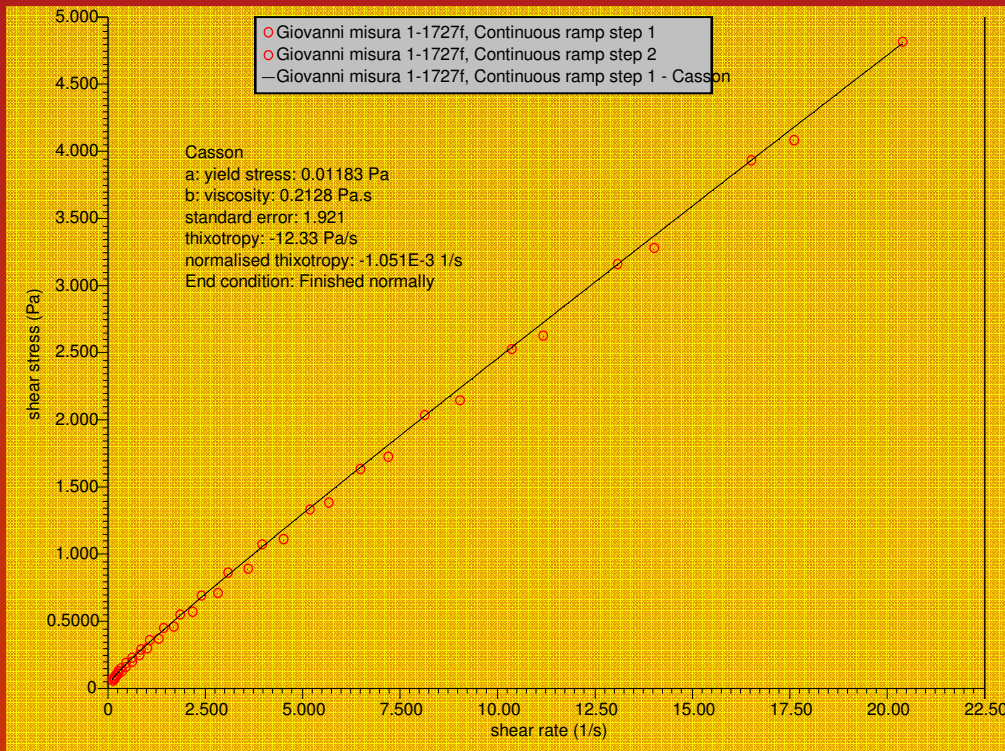
RICROLIN

RIBOFLAVIN 0,1%

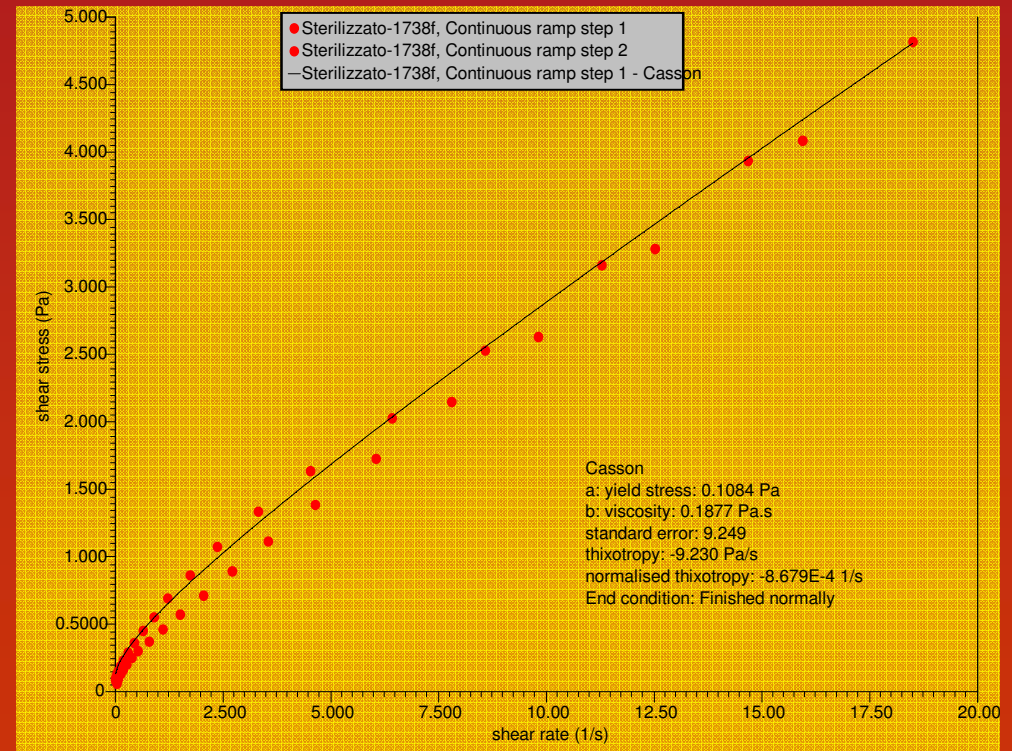
- **RICROLIN** ophthalmic solution is **sterile**, according to current GLP rules.
- **RICROLIN** is a Medical Device (**CE 0373**)



Ricrolin is a viscous ophthalmic solution that has photo-polymerizing properties



Dextran not sterilized



Dextran sterilized

RICROLIN

(RIBOFLAVIN 0,1%)

Properties

Riboflavin, combined with UV-A light, generate a **photo-polymerizing effect** on corneal collagen. The **increase in rigidity of the corneal structure** is due to the formation of new links between collagen fibers. This is the base of cross-linking treatment.

The Cross-Linking of collagen

- In 90' started research of the “*biological glue*” activable by thermic or light sources and able to increase the resistance of stromal collagen. These studies showed that the linking action was due to an oxidative mechanism induced by the release of oxyhydrilic free radicals.

- **The clinical evidence that diabetic patients are rarely affected by keratoconus supported these studies. In affected patients the natural cross-linking effect of glucose produces an increase of corneal resistance (Maillard's reaction).**
- **An increase in corneal resistance, due to natural collagen glycosilation, occurs also with ageing.**

Cross-Linking types

- **Enzymatic Cross-linking:**
 - the physiological cross-linking is performed by Lysyl-oxidase enzyme
 - the AGEs (Advanced Glycation Endproducts) are liable for cross-linking in diabetes
- **Chemical Cross-linking:**
 - glutaraldehyde, formaldehyde
- **Photochemical Cross-linking:**
 - UV rays, ionizing radiation
- **Photo-oxidative Cross-linking:**
 - RIBOFLAVIN - UVA**

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ROLE OF RIBOFLAVIN in Cross-Linking treatment

1. Absorption of UV radiation
2. Photo-sensitizing agent: production of reactive oxygen species
3. Corneal endothelium and other eye structures protection



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ROLE OF RIBOFLAVIN in Cross-Linking treatment

The parameters currently used does not lead to **any risk to the corneal endothelium** [0,1% Riboflavin reduces UV intensity up to 95% (0,15 mw/cm²)]

Without Riboflavin the UV absorption of almost 30% by the endothelium and 50% by the lens was measured.

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ROLE OF RIBOFLAVIN in Cross-Linking treatment

Cross-linking effects are directed to the anterior cornea because of Riboflavin high UV-A absorption capacity.

Thus corneal endothelium, lens and retina will be protected

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ROLE OF T 500 DEXTRAN

**RICROLIN contains Dextran T 500 20%
(500.000 D) that:**

1. Maintains the osmolarity:

- **Corneal stroma: 380-420 mosmol/l**
- **Riboflavin solution 0,1% - Dextran T 500 20%:
400 mosmol/l**



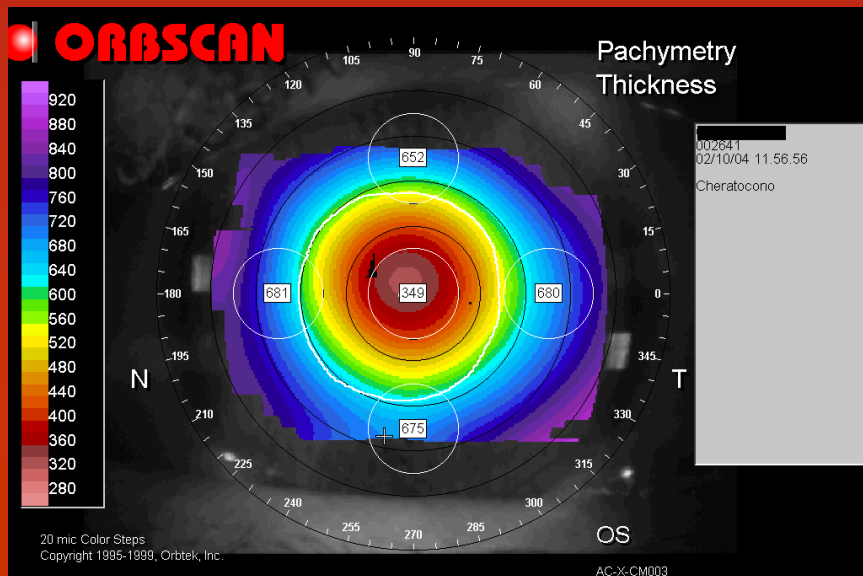
**2. Avoids corneal soaking and swelling during
the treatment**

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Indication

RICROLIN associated to an UV-A rays source is suitable for the parasurgical treatment of:

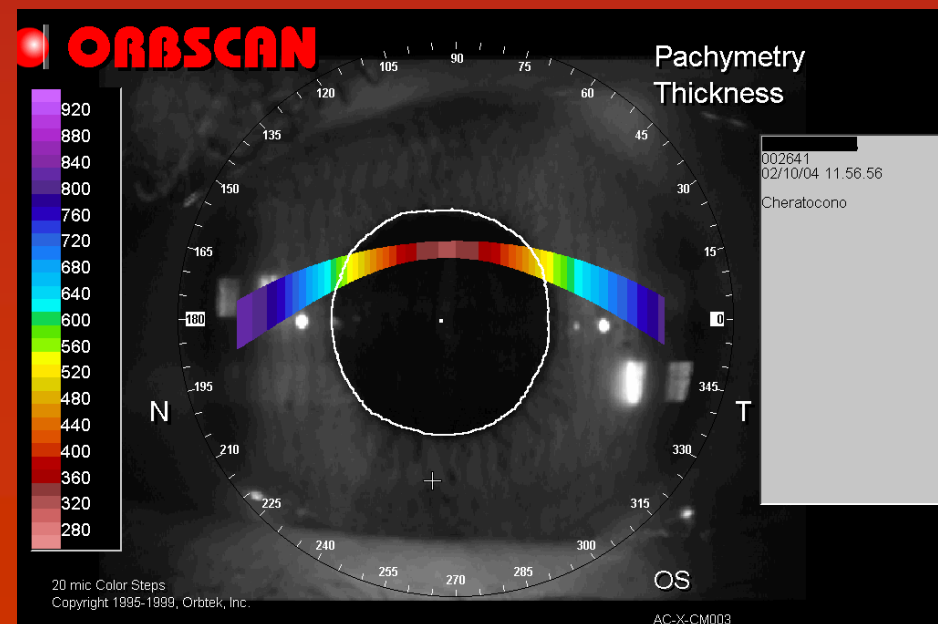
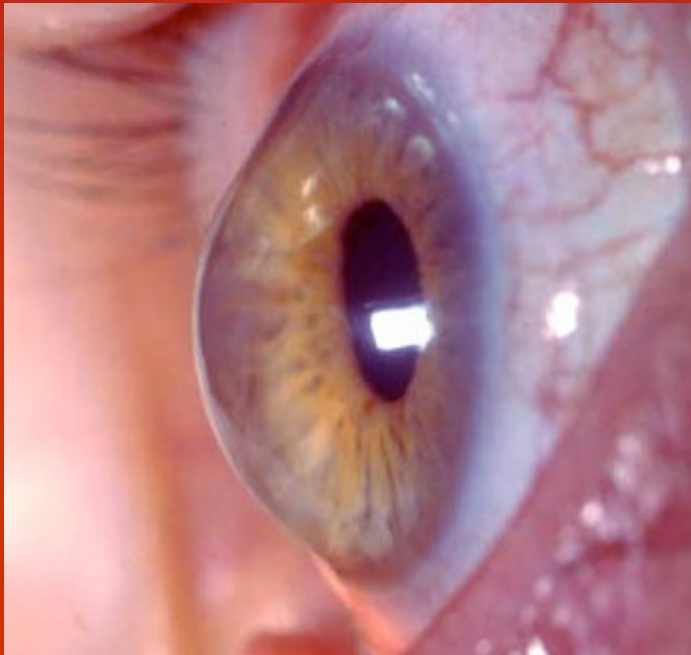
- **Progressive keratoconus**
- **Corneal ectasias**



RICROLIN

Indication

The administration of both Ricrolin and UV-A rays induces a **decrease in keratoconus progression**, thus preventing a corneal transplantation
(however not excluded in future)



RICROLIN

Methods of use

- **5-10 minutes before irradiation**, instill several times RICROLIN ophthalmic solution with the proper syringe-dispenser
- During the treatment with UV-A, administer RICROLIN **every 5 minutes, for an overall time of 30 minutes.**



RICROLIN

Side effects and contraindications

- **RICROLIN** is contraindicated in case of hypersensitivity to any drug component or any chemically correlated substances.
- **No side effects** (neither ocular nor systemic) **have been reported**
- **No systemic toxic side effects have been reported** in case of exceeding or prolonged intake. The absorption of riboflavin is indeed a saturable biological system (up to 25 mg) and, moreover, it exists a maximum treshold for its body storage.

RICROLIN

Precautions

- **RICROLIN** should be stored with a temperature range between **+4 and +8 °C**.
- **RICROLIN** is **sterile** and **disposable**.
- **RICROLIN** is a product for external ocular usage

RICROLIN

Precautions

- **Don't touch ocular surface with the needle to avoid any risk of contamination**
- **Don't use the product 1 hour after the opening.**
- **Keep away from light.**
- **Don't use the drug after its expiration date or if the container is damaged.**



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