



BioHance™

CROSS-LINKED
HYALURONIC ACID (HA)

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BIOHANCE™ TECHNOLOGY

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BioHAncTM
TECHNOLOGY

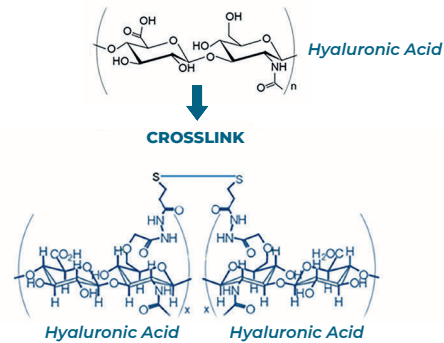


1

BIOHANCE™ CROSS-LINKED HYALURONIC ACID (HA)

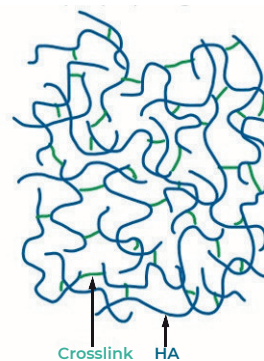
● A patented technology

BioHance™ is a patented technology which uses advanced bioengineering to create a molecular matrix of cross-linked hyaluronic acid (HA). **It produces a molecular scaffolding with unique physical and chemical properties, that enhances hydration, accelerates the body's own healing processes and extends duration on the ocular surface.**



● BioHance™ cross-linked HA properties

HA is a naturally occurring substance throughout the body of humans and animals that plays a key role in hydration, tissue lubrication, and healing processes. Before BioHance™, the rapid degradation of naturally occurring HA limited its clinical applications and efficacy in the real world. This patented technology makes it possible to chemically modify the HA so it is **more resistant to degradation, while providing an ideal environment to enhance natural healing processes and unique mucoadhesive properties that extend hydration and lubrication.** The concentration of BioHance™ may vary based on the intended use.



Cross-linked HA hydrogel

BioHance™ technology creates a matrix of cross-linked HA that enhances natural healing

● How our cross-linked HA compares to traditional cross-linked alternatives

Our BioHance™ cross-linked HA is a **purified product containing no residual crosslinkers or toxic by-products that can have a detrimental or irritating effect.**

Traditional cross-linking technologies use a process that can result in poor biocompatibility, trigger an elevated immune response, or inflammation.

● A platform technology

In addition, the chemically functionalized polymers (a molecule made from joining together many small molecules) in this **platform technology can be cross-linked to a variety of other molecules.**

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HOW IT IS MADE

BioHAnce™ is created by making two modifications to hyaluronic acid. We purchase medical grade linear hyaluronic acid made by a fermentation process, free of animal products, which is modified and purified prior to use in our ocular formulations. Following the final purification, the solution is sterile filtered and aseptically cross-linked to form the final HA gel product.



3

KEY BENEFITS OF BIOHANCE™ CROSS-LINKED HA

- Enhances hydration, lubrication, ocular comfort, and helps stabilize the tear film^{7,8}
- Increases residence time (vs linear HA): lasts 2-5 times longer than traditional artificial tears^{3,4}
- Requires less applications (BID), improving owner compliance
- Creates a thin barrier that soothes and protects the eye without blurring vision
- 0.75% BioHAnce™ cross-linked HA supports faster corneal healing compared to linear HA⁶ and amniotic drops⁵
- Shown to enhance tear film concentrations of some antibiotics¹
- Does not bind to antibiotics (unlike serum)⁷
- BioHAnce™ technology has been created specifically for animal health
- Well tolerated:
 - Preservative free
 - Thiol cross-linking allows for a purified end product (no residual crosslinker which can be irritating or cause inflammation)

4

AVOID THE “GLOB”

Comparison of cross-linked vs non cross-linked HA



Competitor A
Sticky glob on pet's eye



Ocunovis™
Sheer gel drop that spreads a clear, thin film across the eye after each blink

- **Cross-linking creates a more viscous lubrication at a lower concentration** and has mucoadhesive properties that a linear HA molecule does not. It stays on ocular surfaces longer and does not get cleared from the eye during blinking like traditional HA eye drops do.

- **Once you cross-link HA, it changes its chemical and physical properties** meaning you cannot compare the concentration of a linear HA

product to the concentration of a cross-linked HA product. The cross-linking process effectively creates an infinite molecular weight, meaning the physical properties are different.

- The higher the molecular weight of a product, the harder it is to get into solution. **Our cross-linked formulation nearly creates an infinite molecular weight but allows for scaling, purification and sterile filtration.**



STUDIES WITH
BioHAncTM

CROSS-LINKED HYALURONIC ACID (HA)





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the complete study



ENHANCED TEAR FILM CONCENTRATIONS OF CEFAZOLIN AND CHLORAMPHENICOL USING CROSS-LINKED HYALURONIC ACID IN CANINE EYES¹

Dikla Arad, Ella Margot Mordechai, Yulia Goncharov, Ron Ofri, Lionel Sebbag
25 FEBRUARY 2025 - VETERINARY OPHTHALMOLOGY

0.75% BioHance™ cross-linked HA increased the duration of antibiotics in the tear film of 10 healthy dogs. The tear film concentration of chloramphenicol and cefazolin were increased and higher tear film antibiotic concentrations were maintained longer (up to 8 hours) when mixed with 0.75% BioHance™ cross-linked HA compared to a 1.4% PVA.

● Purpose

To evaluate the impact of two excipients, 1.4% polyvinyl alcohol (PVA) and 0.75% cross-linked hyaluronic acid (XHA*), on tear film concentrations of cefazolin and chloramphenicol.

● Methods

Cefazolin and chloramphenicol were compounded into 5.5% and 0.5% ophthalmic solutions, respectively, using either 1.4% PVA or 0.75% XHA*. Ten dogs (20 eyes) were enrolled, including five brachycephalic and five non-brachycephalic dogs. In the first trial, each dog received cefazolin-PVA in one randomly assigned eye and cefazolin-XHA in the contralateral eye; one month later, the same design was repeated with chloramphenicol formulations. Tear fluid was collected at 0, 1, 5, 10, 15, 30, 60, 120, 240, 360, and 480 minutes after drop administration using 2 µL capillary tubes, and antibiotic concentrations were quantified using UV-Vis spectrophotometry against validated standard curves. Physicochemical properties of each formulation—including drop size, pH, viscosity, and stability—were also assessed to ensure consistent performance.

● Results

Tear film concentrations of cefazolin and chloramphenicol were significantly higher with XHA* compared to PVA at all time points ($p \leq 0.020$), except for baseline (both antibiotics), times 1 minute, 60 minutes, and 120 minutes for cefazolin. The tear film kinetics exhibited a biphasic pattern, with drug levels decreasing from 0 to 120 minutes, then slightly increasing between 120 and 360 minutes before declining again until 480 minutes. The area under the time-concentration curve (AUC_{0-480}) was significantly greater with XHA* versus PVA formulations ($p = 0.002$), with a median 2.4 and 4.2 times higher for cefazolin and chloramphenicol, respectively. Formulation characteristics: XHA-antibiotic drops were larger in volume than PVA drops ($\approx 46 \mu\text{L}$ vs. $40 \mu\text{L}$; $p < 0.001$) and maintained near-neutral pH, appropriate viscosity, and stability within 90–110% of initial drug concentrations for at least 30 days under refrigeration.

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● Discussion

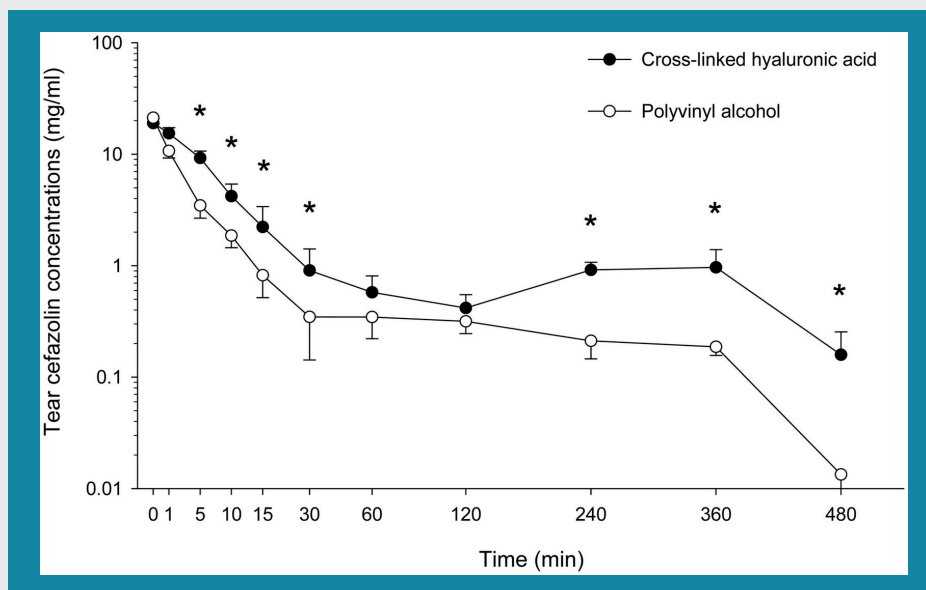
Cross-linked hyaluronic acid (XHA*) dramatically enhances ocular delivery of topical antibiotics, achieving higher and more sustained tear film concentrations than conventional PVA formulations. Chloramphenicol levels were elevated at all time points, while cefazolin was higher at most time points, reflecting XHA's ability to prolong precorneal residence and act as a potential drug reservoir. XHA* drops were stable, maintained optimal pH and viscosity, and exhibited a biphasic clearance pattern, supporting sustained drug release. Beyond improved pharmacokinetics, XHA offers potential clinical benefits noted in this study—including antibacterial activity, enhanced corneal healing, and improved tear film quality—making it a versatile excipient for ocular therapeutics.

¹Referenced as XHA in publication. Dômes Pharma brand product name is Oculenis™.

● Results Continued

5.5% CEFAZOLIN

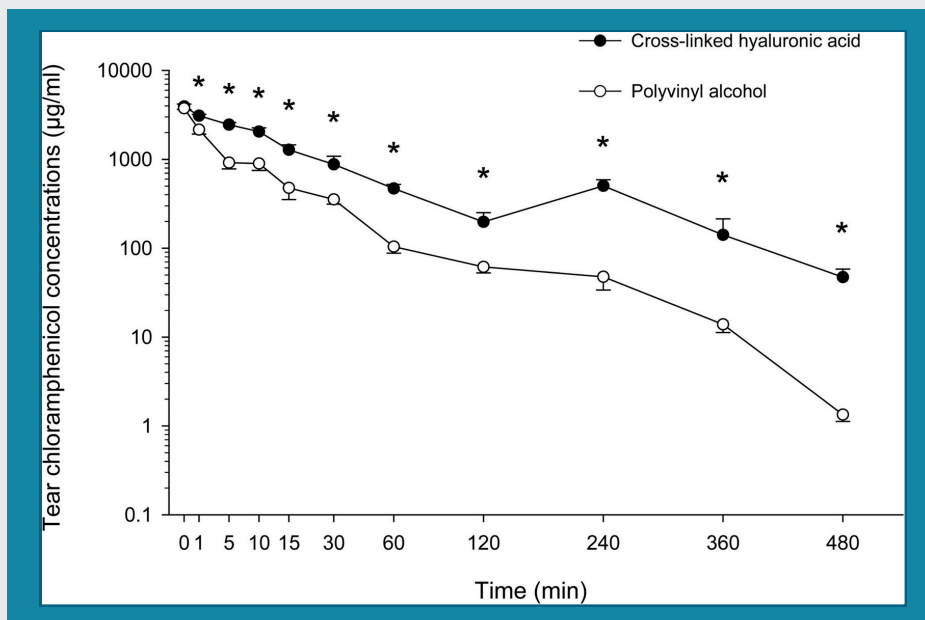
Formulation with 0.75% BioHance™ cross-linked HA consistently delivered higher tear film concentrations of cefazolin than PVA, achieving more than double the overall exposure (2.4-fold AUC increase) and sustained levels across all dogs.



Scatter plot depicting the median $\pm$ SEM of tear cefazolin concentrations over time in ten dogs receiving 5.5% cefazolin compounded in polyvinyl alcohol (one eye; white circles) or cross-linked hyaluronic acid (other eye; black circles). The y axis is displayed in logarithmic scale. Asterisks (*) indicate statistical differences ($p < 0.05$) between eyes at each time point.

0.5% CHLORAMPENICOL

0.75% BioHance™ cross-linked HA provided dramatically higher tear film concentrations of chloramphenicol than PVA at nearly every time point, resulting in a 4.2-fold greater overall exposure and a unique, sustained release profile.



Scatter plot depicting the median $\pm$ SEM of tear cefazolin concentrations over time in ten dogs receiving 0.5% chloramphenicol compounded in polyvinyl alcohol (one eye; white circles) or cross-linked hyaluronic acid (other eye; black circles). The y axis is displayed in logarithmic scale. Asterisks (*) indicate statistical differences ($p < 0.05$) between eyes at each time point.

CONCLUSIONS

The cross-linked hyaluronic acid significantly enhanced the retention and overall exposure of both cefazolin and chloramphenicol in the canine tear film. These findings suggest that XHA could serve as a superior delivery vehicle for ocular antibiotics, potentially improving treatment outcomes for ophthalmic infections.



2

EVALUATION OF CROSS-LINKED HYALURONIC ACID GEL DROPS AND THERAPEUTIC COMBINATIONS FOR OPHTHALMIC INFECTIONS²

S. K. Atzet, A. D. Fankhauser, E. K. Behan, B. K. Mann

ACVO 2022 POSTER SESSION - PALM SPRINGS, CA

The physical properties (viscosity, shear thinning, and concentration) of BioHance™ cross-linked HA were maintained when combined with certain antibiotics or antiviral drugs. In vitro results suggest that BioHance™ cross-linked HA does not bind active pharmaceutical ingredients and may enhance efficacy in some cases.

Purpose

To evaluate the *in vitro* efficacy and physical properties of combining antibacterial and antiviral drugs with a patented cross-linked hyaluronic acid (XHA*) based eye drops.

Methods

Several active pharmaceutical ingredients (Neomycin, Polymyxin B, Bacitracin, Gentamicin, Cefazolin, Ciprofloxacin, Gramicidin, Oxytetracycline, Tobramycin, Cidofovir, and Ganciclovir) were aseptically mixed with XHA*, which, with its unique extracellular matrix, serves both as a delivery vehicle and eye lubricant. The resulting combined hydrogels were then evaluated for changes in physical properties (e.g., viscosity and shear thinning). Tobramycin hydrogels were evaluated for antimicrobial activity using a zone of inhibition assay. Ganciclovir hydrogels were tested for antiviral efficacy using a cytopathic effect assay (CPE) with Feline Herpesvirus 1 (FHV-1). Both were compared with the same drugs diluted in saline serving as controls.

Results

The addition of active ingredients resulted in no significant changes to the viscosity or shear thinning profile of XHA* hydrogels. Tobramycin hydrogel and tobramycin control exhibited equivalent zone of inhibition against three strains of bacteria. XHA ganciclovir solution was found to have a 4.3 and 3.2 fold reduction of viral activity as compared with saline solutions of Ganciclovir.

Visual Analysis	CC ₅₀	EC ₅₀	SI
Ganciclovir Solution	>100	15	>6.7
Ganciclovir Hydrogel	>100	3.5	>29

This assesses antiviral activity by observing virus-induced damage to cells under the microscope and determining whether the drug prevents it.

Neutral Red	CC ₅₀	EC ₅₀	SI
Ganciclovir Solution	>100	8	>13
Ganciclovir Hydrogel	>100	2.4	>42

This quantifies cell viability using a dye retained only by living cells, providing a sensitive and objective measure of antiviral protection.

Ganciclovir showed a 3-4 fold increase in potency when combined with BioHance™ cross-linked HA.

CONCLUSIONS

In vitro results suggest that both the unique physical properties (viscosity, shear thinning, and concentration) of XHA* and efficacy of tested active pharmaceutical ingredients are maintained or improved in the case of Ganciclovir. Future work will include target animal efficacy and disease state clinical studies along with application and dosing requirements based on potential synergistic effects from the XHA's* increased residence time.

*Referenced as XHA in poster session. Dômes Pharma brand product name is Oculenis™.



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the complete study

3

COMPARATIVE FLUOROPHOTOMETRIC EVALUATION OF THE OCULAR SURFACE RETENTION TIME OF CROSS-LINKED AND LINEAR HYALURONIC ACID OCULAR EYE DROPS ON HEALTHY DOGS³

ANDRESSA LOPES GREGO, ANDY D FANKHAUSER, EMILY K BEHAN, SARAH K ATZET, D. J. HAEUSSLER, FRANZ RIEGLER MELLO, MARIZA BORTOLINI, FABIANO MONTIANI FERREIRA
23 SEPTEMBER 2024 - VETERINARY RESEARCH COMMUNICATIONS

BioHAnce™ cross-linked X-HA* exhibited a dual phase behavior: a broad microgel coverage first, followed by accumulation in tear film meniscus and medial canthus in the second phase, remaining in contact with ocular surface up to 180 minutes (3 hours).

● Purpose

This study evaluated and compare the retention time of 0.75% linear hyaluronic acid (L-HA), 0.75% cross-linked hyaluronic acid (X-HA*), and 0.9% saline on the ocular surface of healthy canine eyes.

● Methods

L-HA and X-HA* were covalently modified using Alexa Fluor 488 reactive moieties. Saline was combined with fluorescein salt. The study evaluated 35 client-owned dogs (17 brachycephalic, 13 mesocephalic and 6 dolichocephalic) that were split into groups which received either 1 drop of fluorescently labeled L-HA, X-HA*, or saline. Using a blue light filter (450-490 nm) in low-light conditions, digital images were obtained from instillation to 180 minutes at the same angle and under specific guidelines. The images masked and analyzed to assess the percent of the total ocular area covered with green fluorescence at various time points.

● Results

The X-HA* exhibited a dual phase behavior with the first phase occurring between 2 and 30 minutes and was characterized by initial microgel coverage. After 30 minutes, tear film accumulation was observed. The second phase, occurring between 90 and 180 minutes, was characterized by progressive X-HA* accumulation in the medial canthus up to 180 minutes. Meanwhile, coverage with L-HA and saline eye drops was initially broad (up to 30 minutes). After this, tear film accumulation was also observed but without the marked accumulation in the medial canthus like X-HA*. No traces of the fluorescent compounds were observed by 45 minutes in all 21 eyes treated with saline and by 120 minutes in all 20 eyes treated with L-HA.

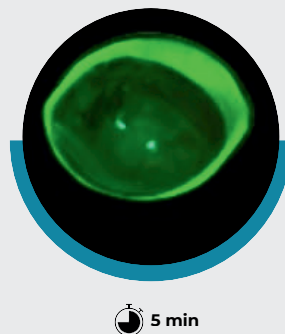
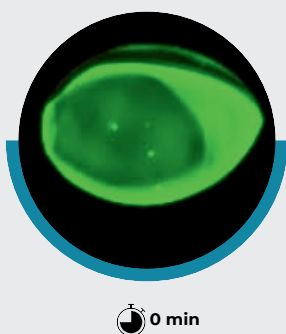
CONCLUSIONS

The X-HA* exhibited a broader ocular surface coverage and a significantly increased ocular surface contact time compared with linear HA. Not only could this indicate extended lubrication but, potentially, could be used as a topical sustained-release drug application method.

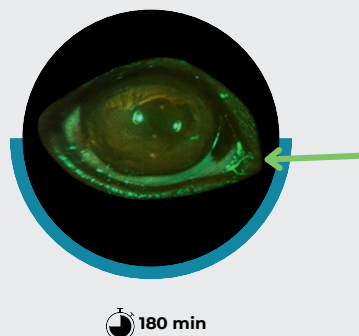
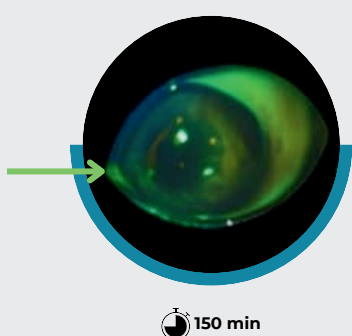
*Referenced as X-HA in publication. Dômes Pharma brand product name is Oculenis™.

BioHance™ cross-linked HA (X-HA*) outperformed L-HA and saline groups by remaining on the ocular surface for an extended period of time, providing prolonged lubrication. This finding may reduce the need for frequent reapplication and potentially serve as a vehicle for sustained topical drug release in future studies

1st PHASE: Wide Surface Coverage



2nd PHASE: Medial Canthus Deposit Phase (slow release)



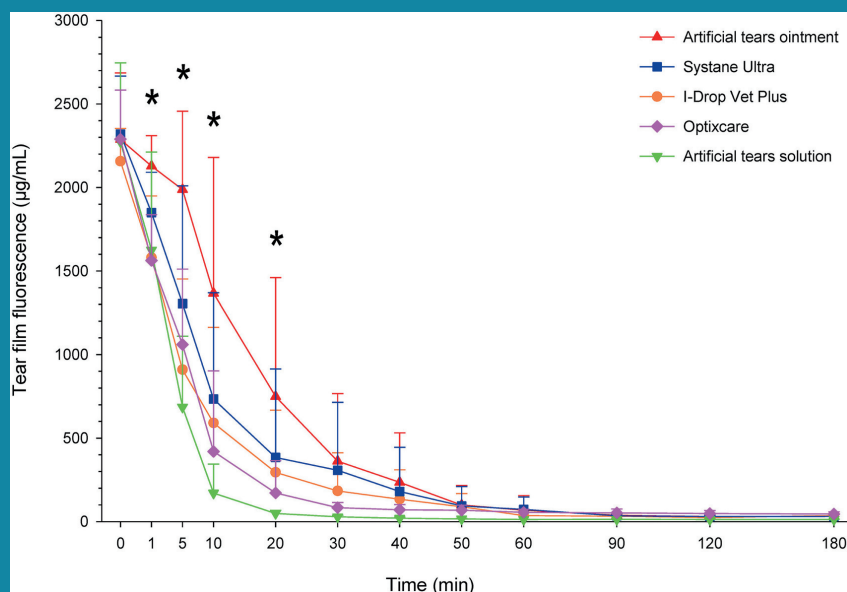
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4

PRECORNEAL RETENTION TIME OF OCULAR LUBRICANTS MEASURED WITH FLUOROPHOTOMETRY IN HEALTHY DOGS⁴

L. Bedos, R. A. Allbaugh, M. Roy, M. A. Kubai, L. Sebbag
20 JANUARY 2023 - VETERINARY OPHTHALMOLOGY

- This study did not contain any Dômes Pharma products, but was included for comparison
- 6 healthy dogs, 12 eyes
- Created 1% fluorescein solutions using Artificial Tears Ointment® (mineral oil/white petroleum), I-Drop® Vet Plus (0.25% HA), Optixcare® Plus (0.25% HA), Systane® Ultra (0.4% polyethylene glycol 400 and 0.3% propylene glycol), and Artificial Tears Solution® (1.4% PVA)
- Tear fluid was collected and fluorescein concentrations were measured
- Median retention times were significantly different: 40 mins for Artificial Tears Ointment®, 35 mins for Systane® Ultra, 30 mins for I-Drop® Vet Plus, 25 mins for Optixcare® Plus, and 10 mins for Artificial Tears Solution®.





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the complete study

5

COMPARATIVE STUDY ON CORNEAL EPITHELIUM HEALING: EFFECTS OF CROSSLINKED HYALURONIC ACID AND AMNIOTIC MEMBRANE EXTRACT EYE DROPS IN RATS⁵

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23 JULY 2024 - FRONTIERS IN VETERINARY SCIENCE

In this proof of concept study, BioHance™ cross-linked HA (X-HA*) significantly accelerated corneal healing, with complete re-epithelialization achieved faster than amniotic drops (AMEED). By 36–48 hours, ulcer size was markedly smaller in the X-HA* group, and treated eyes showed less tissue damage and cell death compared to AMEED and saline control.

● Introduction

Considering the importance of faster re-epithelialization in corneal repair and patient comfort, the aim of this study was to demonstrate and compare the efficacy of 0.75% BioHance™ cross- linked HA (X-HA*) and amniotic eye drops (AMEED) for corneal wound healing in rats. A control group (0.9% saline) of eyes was also included. Epithelization time, changes in the experimentally created ulcer area, and healing quality using histopathology were analyzed.

● Materials & Methods

Fifteen male Wistar rats (30 eyes) were selected for the study. After general and topical anesthesia, a superficial corneal ulcer was created bilaterally using a corneal trephine and it was polished using a diamond burr. The rats were randomly assigned to a treatment group: either X-HA* or AMEED. They received 1 drop (0.05 ml) of the respective treatment every 12h in one eye, while the contralateral eye received saline as a control for a duration of 72h. Corneal defects were then evaluated by fluorescein staining and imaged under a blue light at time 0, 12, 24, 36, 48, and 72h. The following re-epithelization scores were assigned based on the time taken for complete re-epithelization time: (1) 12h; (2) 24h; (3) 36h; (4) 48h; (5) 72h; and (6) incomplete re-epithelization in 72h. The fluorescein-stained area of the epithelial defect area was proportionally calculated and expressed individually as the percentage of the ulcerated area relative to the total corneal surface area at each time point, referred to as the median epithelial defect area (MEDA). Clinical vascularization scores (0–3) were analyzed using a modified Hackett-McDonald scoring system. After 72h, the rats were humanely euthanized, and the eyes were collected for histopathology and immunohistochemistry to assess cellularity, collagen organization, inflammation, and markers such as caspase-3 and cytokeratin. Quantitative and qualitative analyses were performed on multiple corneal sections to evaluate healing and tissue changes.



*Referenced as X-HA in publication. Dômes Pharma brand product name is Oculenis™.

● Results

The cornea was considered healed when there was no fluorescein uptake

Eye Drop Treatment (Group)	Evaluation Time (hours)					
	0	12	24	36	48	72
BioHAnce Crosslinked HA						
AMEED						
Saline						

Representative photographs of individual rats from each group at evaluated time points. Re-epithelialization occurred in this X-HA* eye at 36h while this AMEED eye showed incomplete re-epithelialization at 72h. Note the presence of loose epithelium margins surrounding the ulcer and fluorescein stain undermining its border. Note this eye in the saline group has a small fluorescein-positive lesion near the center of the cornea (white arrow) at 72h indicating incomplete re-epithelialization.

X-HA* treatment led to faster, more complete corneal healing than AMEED or saline controls. MEDA was significantly smaller at 36 and 48 hours, and total re-epithelialization time was shorter with X-HA*. Histopathology revealed minimal inflammation, vascularization, and epithelial-stromal separation, while immunohistochemistry showed markedly lower caspase-3 expression—indicating reduced apoptosis and healthier epithelial regeneration. Overall, X-HA* preserved corneal integrity and accelerated recovery compared to other treatments.

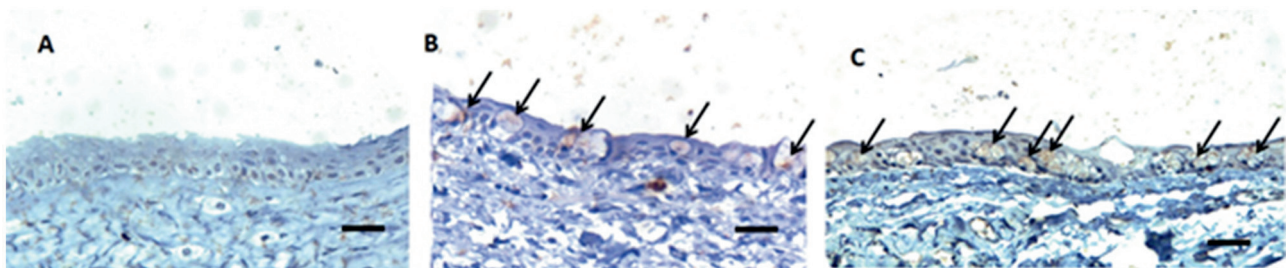


Figure 5. Immunohistochemistry revealed reduced caspase-3 expression in corneas treated with X-HA* and AMEED compared to saline, indicating less epithelial cell apoptosis and healthier tissue integrity.

● Discussion

Topical X-HA* has been shown to accelerate corneal epithelial healing. AMEED did not decrease corneal re-epithelialization time. X-HA* may also potentially be used as an adjunct therapy for treating corneal ulcers in clinical situations.

● Conclusion

X-HA* eye drops improved corneal epithelialization, as reflected in decreased re-epithelialization time and a smaller median ulcerated area. This improvement was consistent across all evaluation times compared to eyes from the AMEED- and saline- (control) treated groups in rats with experimental superficial corneal ulcers. AMEED did not decrease corneal re-epithelialization time and demonstrated mild signs of corneal epithelium toxicity in samples analyzed under light microscopy.

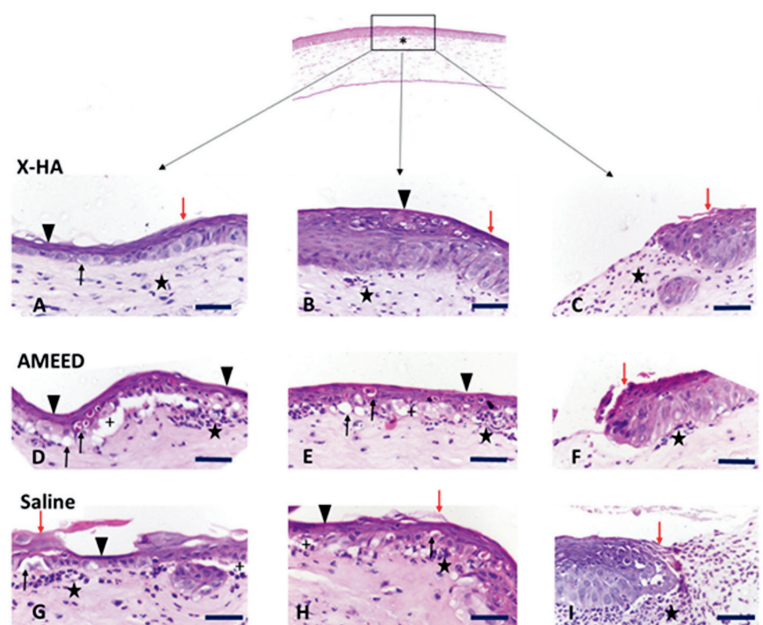


Figure 4. Top – asterisk (*) low magnification photomicrography showing the central corneal region (rectangle) where the epithelial defect was created and from where the samples were taken. Samples A, B, and C are from the X-HA group; samples D, E, and F from the AMEED group; and samples G, H, and I from the saline (control) group.



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the complete study

6

TOPICAL CROSS-LINKED HA-BASED HYDROGEL ACCELERATES CLOSURE OF CORNEAL EPITHELIAL DEFECTS AND REPAIR OF STROMAL ULCERATION IN COMPANION ANIMALS⁶

DAVID L. WILLIAMS, BARBARA M. WIROSTKO, GLENWOOD GUM, BRENDA K. MANN
25 JULY 2017 - INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE AN ARVO JOURNAL

0.75% BioHance™ cross-linked HA administered TID in addition to 0.5% chloramphenicol significantly accelerated the closure of acute corneal stromal ulcers in dogs and cats compared with a 0.3% linear HA solution. Furthermore, BID administration of the cross-linked HA aided in healing chronic (>2 weeks) corneal ulcers in dogs.



● Purpose

The purpose of this study was to determine the safety of topical ocular administration of a cross-linked, modified hyaluronic acid (xCMHA-S*) hydrogel, and its effectiveness in accelerating repair and closure of acute and nonhealing corneal ulcers in companion animals as a veterinary treatment and its utility as a model for therapy in human corneal ulceration.

● Methods

Two concentrations of xCMHA-S* (0.33% and 0.75%) were topically administered to the eyes of rabbits six times daily for 28 days to assess safety. Then, 30 dogs and 30 cats with spontaneous acute corneal ulcers were treated with either xCMHA-S* (0.75%) or a non-cross-linked HA solution (n = 15 per group for each species), three times daily until the ulcer had healed. Finally, 25 dogs with persistent nonhealing corneal ulcers were treated with xCMHA-S* (0.75%) twice daily until the ulcer had healed.

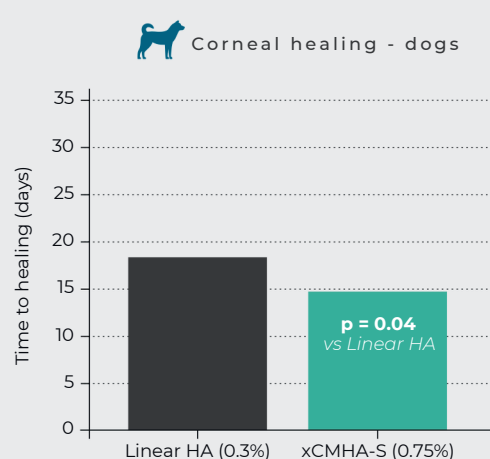
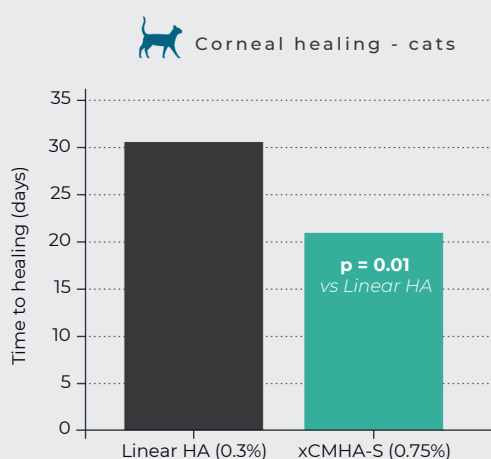
● Results

Both concentrations of the xCMHA-S* hydrogel were well tolerated, safe, and nontoxic in the 28-day exaggerated dosing study in healthy rabbits. Topically applied xCMHA-S* significantly accelerated closure of acute corneal stromal ulcers in dogs and cats compared with a non-cross-linked HA solution. Furthermore, topical administration of the xCMHA-S* aided in closure of nonhealing corneal stromal ulcers in dogs.

*Referenced as xCMHA-S 0.4% or 0.75% in publication. Dômes Pharma brand product names are Ocunovis™ & Oculenis™, respectively.

CONCLUSIONS

Hyaluronic acid has previously been shown to aid in corneal wound repair. This study demonstrates that a cross-linked, modified HA hydrogel provides further benefit by accelerating time to corneal wound closure compared to a non-cross-linked HA solution in companion animals, and therefore may be beneficial in fulfilling an unmet need in humans.



	xCMHA-S (0.75%)	iDrop linear HA (0.3%)	p
 CATS	n=15 21.0 +/- 11.0 days	n=14 31.8 +/- 10.3 days	0.01
 DOGS	n=15 14.8 +/- 4.1 days	n=15 18.3 +/- 4.9 days	0.04

Mean time to healing of acute corneal stromal ulcers in 30 dogs and 30 cats with topical chloramphenicol and three-times daily BioHance™ cross-linked HA (0.75%) or linear HA (0.3%)





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the complete study



EVALUATION OF TOPICALLY APPLIED CROSS-LINKED HYALURONIC ACID (REMEND®*) ON THE OCULAR SURFACE OF CLINICALLY HEALTHY DOGS⁷

C. E. Plummer, B. C. Martins, C. Bolch, P. S. Martinez, B. E. Carbia
ACVO 2022 POSTER SESSION - PALM SPRINGS, CA

Topically applied BioHance™ cross-linked HA (Remend®*) may improve tear quality, especially tear film stability, in dogs and was detected at one hour after topical application.

● Purpose

To evaluate effects of a topically applied cross-linked HA (Remend Eye Lubricating Drops® - Bayer Animal Health*) on the ocular surface of clinically normal dogs.

● Methods

Twenty dogs with normal ophthalmic examinations received tear ferning tests (TF-M7, TF-M5, and TF-R), Schirmer's tear test (STT-I), tear film breakup time (TFBUT), slit-lamp biomicroscopy, indirect ophthalmoscopy and rose Bengal dye staining (RB) on the first day of examination (day 0), 1 week after initial examination (day 7), and 2 weeks after examination (day 14). Following examination and baseline testing, subjects received cross-linked HA (Remend®*) two times a day (BID) on the right eye (OD). The left eye (OS) served as control and received saline BID. Tear fluid samples from both treated and control eyes were evaluated for HA levels by ELISA prior to and at several time points following treatment.

● Results

For the duration of the study, there was no statistically significant difference in aqueous tear production (STT-I) or rose Bengal retention between study and control eyes. There was a statistically significant improvement in TFBUT between study and control eyes on Day 7 ($p < 0.001$) and Day 14 ($p < 0.001$). There was a statistically significant improvement in TF-M7 scores ($p < 0.02112$) and TF-R scores by Day 14 ($p < 0.01097$). HA was present in measurable quantities in the tear fluid at 30 minutes and one hour after topical application in treated eyes.

CONCLUSIONS

Topically applied cross-linked HA (Remend®) may improve tear quality, especially tear film stability, in dogs. Cross-linked HA (Remend®) was present in the tear fluid 60 minutes after application.

*Referenced as Remend® in poster session. Dômes Pharma (US) brand product name is Ocunovis™



A CROSSLINKED HA-BASED HYDROGEL AMELIORATES DRY EYE SYMPTOMS IN DOGS⁸

D. L. Williams, B. K. Mann

06 JUNE 2013 – *International Journal of Biomaterials*

xCMHA-S* treatment led to meaningful improvements in clinical signs of KCS, including reduced ocular irritation, discharge, and hyperemia. In addition, pet owners strongly preferred the crosslinked formulation, citing easier administration, better tolerance, and the convenience of a twice-daily dosing schedule compared to more frequent treatments with conventional HA drops.

● Purpose

Keratoconjunctivitis sicca (KCS) is common in both humans and dogs that often requires lifelong topical therapy. Standard treatment includes lubricating eye drops, which may need to be administered four to six times daily, creating challenges for both patients and caregivers. To address this limitation, a novel crosslinked hydrogel based on thiolated carboxymethyl hyaluronic acid (xCMHA-S*) was developed and designed to extend ocular surface residence time and reduce the dosing burden. The purpose of this study was to characterize the rheological properties of xCMHA-S* compared with non-crosslinked HA solutions and to evaluate its clinical effectiveness as a tear supplement in dogs with KCS.

● Methods

The 0.4% xCMHA-S* hydrogel was synthesized from thiolated carboxymethyl hyaluronic acid and crosslinked as previously described. The formulation was verified for HA concentration and characterized by rheological testing, including viscosity and viscoelastic measurements, to compare its physical properties with those of a non-crosslinked 0.4% HA solution and a commercial HA eye drop. A clinical evaluation was then performed in 25 dogs diagnosed with KCS. Baseline assessments included Schirmer tear test values and then scored conjunctival hyperemia, ocular irritation, and ocular discharge. Clinical signs were scored as follows: normal (0), mildly impaired (1), or severely impaired (2). Dogs were treated twice daily with the xCMHA-S* hydrogel for two weeks, after which the same clinical parameters were reassessed. Outcomes were compared to previously published results from dogs treated with non-crosslinked HA eye drops.

● Results

Treatment with the xCMHA-S* hydrogel for two weeks in 25 dogs with KCS did not significantly change Schirmer tear test values, as expected for a tear supplement. However, clinical signs of disease including conjunctival hyperemia, ocular irritation, and ocular discharge were significantly improved following treatment. When compared with previously reported outcomes using a non-crosslinked HA eye drop, improvements in ocular surface health were consistently greater with the crosslinked formulation, with significant differences for conjunctival hyperemia and ocular discharge, and near-significant differences for ocular irritation. Pet owners also reported greater ease of use, better tolerance, and a preference for the twice-daily crosslinked hydrogel compared with their experiences using non-crosslinked HA products.

CONCLUSIONS

The 0.4% crosslinked HA hydrogel* provided clear clinical benefits in dogs with KCS despite being administered only twice daily, a reduced dosing frequency compared to many conventional tear supplements. While tear production itself was unchanged, ocular comfort and surface health improved significantly, and owners reported both greater satisfaction and preference for the product. These findings support xCMHA-S* as a promising longer-acting tear supplement for managing KCS in veterinary patients.

*Referenced as xCMHA-S in study. Dômes Pharma brand product name is Ocunovis™.



EFFICACY OF A CROSSLINKED HYALURONIC ACID-BASED HYDROGEL AS A TEAR FILM SUPPLEMENT: A MASKED CONTROLLED STUDY¹⁰

D. L. Williams, B. K. Mann
10 JUNE 2014 – PLOS One



Crosslinked CMHA-S* hydrogel outperformed standard HA drops by significantly improving ocular surface health in dogs with KCS and earning higher owner satisfaction scores. Its longer retention and reduced dosing make it a practical, effective option for managing chronic dry eye in veterinary patients.

● Purpose

Hyaluronic acid (HA)-based lubricants are well suited for use as tear supplements, but their efficacy depends on molecular weight, concentration, and viscoelastic properties. To improve ocular residence time and reduce dosing frequency, a novel crosslinked thiolated carboxymethyl hyaluronic acid (CMHA-S*) hydrogel was developed as a tear supplement. The purpose of this study was to evaluate the clinical performance of the CMHA-S hydrogel compared with a commercial non-crosslinked HA eye drop in dogs with KCS, using a randomized, masked design to assess efficacy and tolerability.

● Methods

0.4% CMHA-S* was synthesized, filter-sterilized, covalently crosslinked to form a hydrogel (xCMHA-S*), and aseptically packaged into sterile 10 mL bottles. Twenty dogs clinically diagnosed with KCS, for whom topical cyclosporine was ineffective or unavailable, were enrolled with informed owner consent. Dogs were randomly assigned in a masked fashion to receive xCMHA-S* or a commercial HA-based eye lubricant (iDrop® Vet Plus) three times daily for three weeks. Ophthalmic examinations included Schirmer tear test measurements and grading of conjunctival hyperemia, ocular discharge, and ocular irritation (0–3 scale), with owners also providing subjective ratings of treatment efficacy. The primary outcome was the composite post-treatment score compared to baseline using ANCOVA, with all analyses performed blinded to treatment.

● Results

In this masked, randomized trial, both treatment groups included dogs of breeds predisposed to KCS, with no significant differences in age, sex, or neuter status between groups. xCMHA-S* treatment produced a significantly greater reduction in composite ocular surface disease scores compared to the linear HA formulation (ANCOVA, $P=0.0003$), even after adjusting for pretreatment severity. Improvements were particularly notable for conjunctival hyperemia and ocular irritation. Schirmer tear test values remained unchanged across both groups, consistent with the supplements' non-lacrostimulant mechanism of action. Owner-reported satisfaction was markedly higher in the xCMHA-S* group, with 80% rating the treatment as highly effective, compared to lower ratings for the linear HA.

CONCLUSIONS

xCMHA-S* provided superior clinical benefit over standard linear HA eye drops, improving ocular surface health and being strongly preferred by owners for effectiveness and ease of use. While it did not stimulate tear production, its enhanced retention and reduced dosing frequency made it a more practical and effective adjunctive therapy for canine KCS. These findings support the clinical utility of crosslinked HA formulations as an important addition to the management of chronic ocular surface disease in veterinary medicine.

*Referenced as xCMHA-S in study. Dômes Pharma brand product name is Ocunovis™.



Scan here to view the complete study

10

A CROSS-LINKED HYALURONAN GEL ACCELERATES HEALING OF CORNEAL EPITHELIAL ABRASION AND ALKALI BURN INJURIES IN RABBITS¹¹

G. Yang, L. Espandar, N. Mamalis, G. D. Prestwich
03 MAY 2010 – Veterinary Ophthalmology

1% cross-linked hyaluronan hydrogel accelerates corneal wound healing and restores healthier tissue structure compared to standard care. Its proven efficacy in both abrasion and alkali burn models highlights its potential as a powerful solution for managing noninfectious corneal injuries.

● Purpose

To evaluate the efficacy of a chemically modified and cross-linked derivative of hyaluronan (CMHA-SX) for treatment of corneal epithelial abrasion and standardized alkali burn injuries in rabbits.

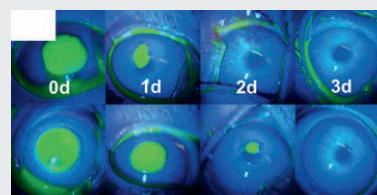


● Methods

Twelve female New Zealand white rabbits were divided into two groups: one received standardized 6-mm corneal epithelial abrasions and the other standardized 6-mm alkali burns. In each rabbit, the right eye was treated with 1% CMHA-SX four times daily for one week, while the left eye received PBS as a control. Wound healing was monitored by fluorescein staining and slit-lamp photography at defined timepoints, and corneas were collected for histological evaluation on day 7 (abrasion group) and day 12 (alkali burn group).

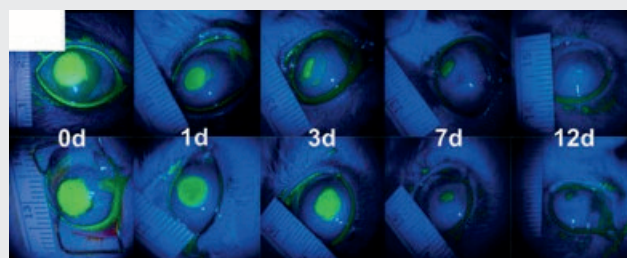
● Results

In the corneal abrasion model, CMHA-SX treatment significantly accelerated wound healing, with 83% closure at 24 hours compared to 49% in controls, and complete closure achieved by 48 hours versus 72 hours in PBS-treated eyes. Histologically, CMHA-SX-treated corneas had epithelial thickness closer to normal, while controls showed thinning.



Cornea epithelial abrasion model

In the alkali burn model, CMHA-SX also promoted faster healing, with significantly smaller wound areas from day 1 and highly significant differences by day 3 (74% vs. 28% closure). By day 12, CMHA-SX-treated eyes showed nearly complete closure and well-organized epithelium and stroma, whereas PBS-treated eyes remained edematous with incomplete re-epithelialization.



Corneal epithelial alkali burn model

CONCLUSIONS

This preliminary study demonstrated that 1% CMHA-SX significantly accelerated corneal wound healing in both abrasion and alkali burn models compared to PBS. CMHA-SX also resulted in thicker, more organized epithelium and improved stromal structure, suggesting enhanced tissue quality. These findings highlight CMHA-SX as a promising therapeutic for veterinary ophthalmology, warranting larger clinical trials and direct comparisons with unmodified HA to further define its advantages and mechanisms of action.



EVIDENCE IN
ACTION





LUIGI

PATIENT HISTORY:

On July 8, 2016, a 2-year-old cat, got a thorn in his eye after one of his late-night adventures. His Owners Immediately brought him to the veterinarian.

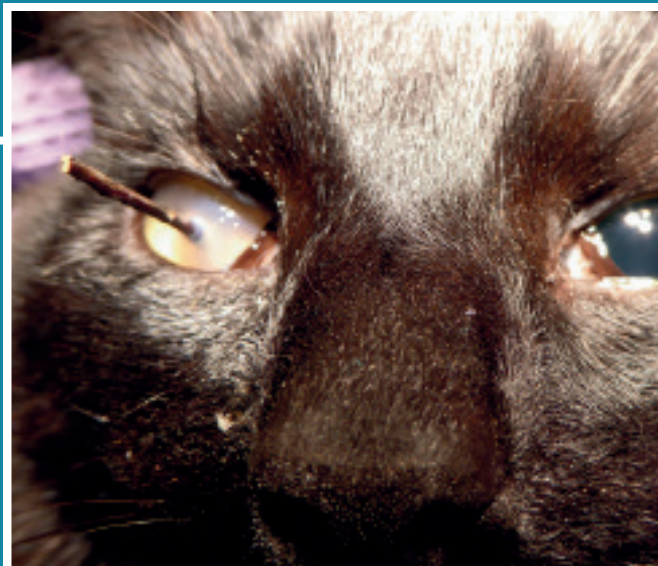
Weight: 10.9 lb

Species: Feline

Gender: Male (N)

Age: 2 yrs

Breed: European Shorthair



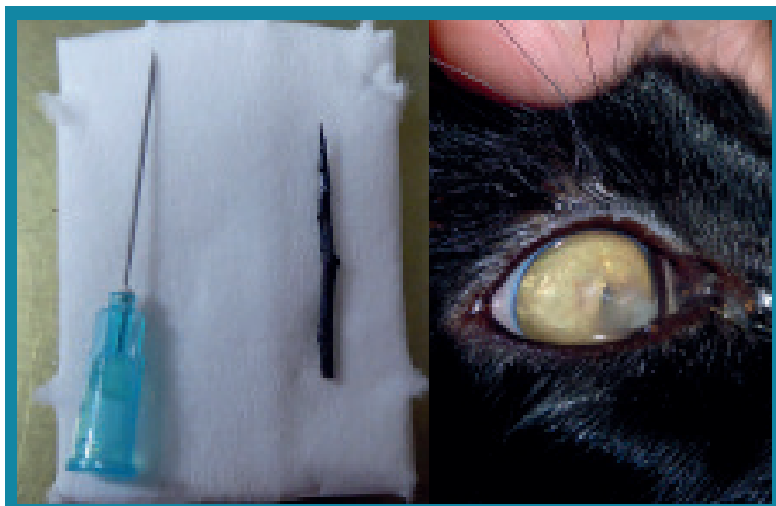
THE PROBLEM:

CORNEAL PERFORATION

A large mandrel completely perforated Luigi's cornea, and his entire cornea was clouded. After a general examination, the veterinarian gave Luigi injections of local anesthetics and sedatives.

The veterinarian then removed the mandrel and treated Luigi's perforated cornea with Oculenis BioHance Ocular Repair Gel* (0.75% BioHance cross-linked hyaluronic acid, twice daily until healed) to accelerate cell regeneration. To treat his infection, Luigi received a combination of antibiotics.

Eye injuries are so painful, so Luigi received analgesic care during his stay.

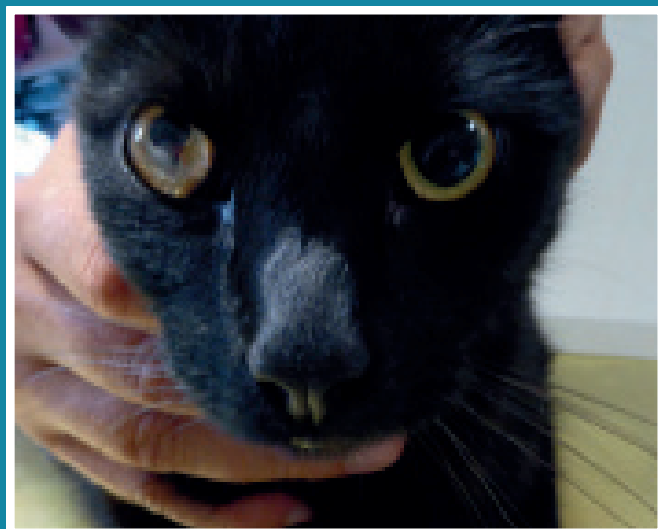


THE OUTCOME:

SUCCESSFUL APPLICATION OF BIOHANCE OCULAR REPAIR GEL

Starting on July 8, 2016, Luigi received twice daily drops of Oculenis BioHance Ocular Repair Gel until his eye healed. The next day, Luigi was ready to go home. He also received 2 NSAID pills for two days after going home to help with his pain.

At his next visit on August 5, 2016, Luigi's eye was almost completely healed. Because of the accelerated cell healing from applying Oculenis BioHance Ocular Repair Gel, only a tiny scar of the complete corneal perforation is visible. Luigi's visual acuity was fully preserved.



TESTIMONIALS



“It is a pleasure to improve patient care utilizing Ocunovis with cross-linked hyaluronic acid to improve corneal health in dogs and cats. Utilizing cross-linked hyaluronic acid improves corneal contact time and improves the overall ocular health and comfort of our patients. In addition, it is great to work with Domes Pharma as they truly have a passion to improve patient care.”

– **Dr. DJ Haeussler, DVM, MS, DACVO**



“Although highly effective, no antiviral drugs to date prevent conjunctival goblet cell depletion in cats with herpesvirus infection. That’s why I recommend concurrent use of topical hyaluronate in cats with herpetic disease. Due to its proven longer corneal contact time, Ocunovis Procure is a good choice.”

– **Dr. David Maggs, BVSc (hons), DAVO**



“The causes of ocular surface disease are often multifactorial. Accordingly, treatment needs to mirror this multifactorial approach. I choose Oculenis BioHAnce Ocular Repair Gel for my patients as not only does it provide long-lasting lubrication and comfort that doesn’t interfere with the use of antibiotics, It’s cross-linked hyaluronic acid provides a barrier matrix that promotes epithelial cell migration and ultimately faster healing.”

– **Dr. Patricia E. Mundy, VetMB MR CVS MA (hons) DACVO**



“Having healthy tear film is an important part of corneal healing. I have been impressed with how well some of my older, cushinoid equine patients have healed after corneal surgery when prescribed Oculenis BioHAnce repair gel (Remend 0.75) as part of their post operative treatment regimen. The cross-linked hyaluronic acid technology in this product has been shown to shorten corneal healing times, and I have personally seen this decrease in healing time especially in my older equine patients.”

– **Dr. Tara Richards BSc DVM DACVO PhD (Ontario)**



“I routinely prescribe my canine and feline patients with topical cross-linked hyaluronic acid (Ocunovis / Oculenis) to lubricate and soothe the ocular surface, reduce tear film instability from dry eye disease, corneal ulceration, viral/bacterial infections, and more. The cross-linked technology behind these lubricants is remarkable, benefiting our patients care by improving precorneal contact time and the overall health of the ocular surface.”

– **Dr Lionel Sebbag, DVM, PHD, DACVO**



“I choose Ocunovis Procure for quantitative and qualitative dry eye disease in dogs and cats. It is proven to have longer corneal contact time than linear hyaluronic acid products and can be given less frequently, which improves client compliance.”

– **Dr. Caroline Betbeze, DVM, MS, DACVO**

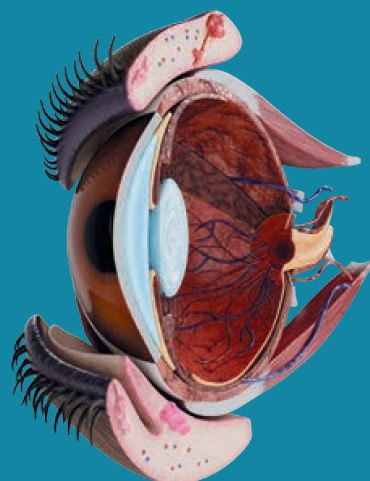
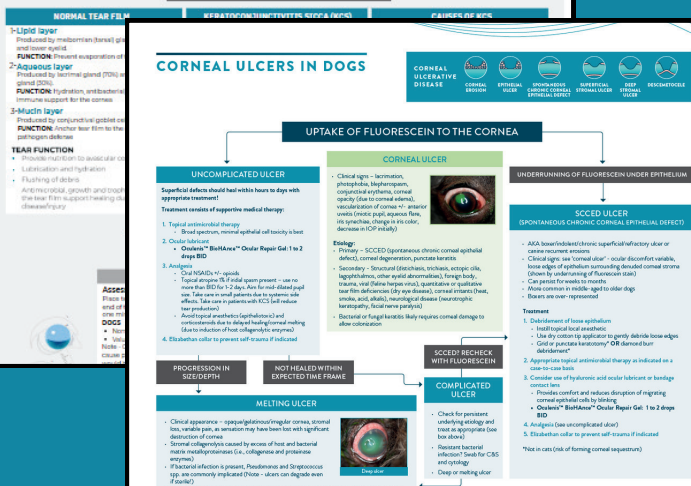


“I absolutely love the Oculenis and Ocunovis eye drops from Domes for me herpes kitties. The high-quality HA, soothing gel texture, and lack of preservatives make this the perfect eye drop to soothe irritated cat eyes and aid in the healing process. These products are definitely a game-changer for me!

– **Dr. Shelby Reinstein DVM, MS, DACVO**

DIAGNOSE AND TREAT DRY EYE

DIAGNOSIS AND TREATMENT OF QUANTITATIVE KERATOCONJUNCTIVITIS SICCA (DRY EYE)



OCULAR IMMERSION TOOL

3D eye ball

TREATMENT GUIDES & DIAGNOSTIC TOOLS

Fluorescein is an orange hydrophilic dye that turns green in basic media. It has a high affinity for the hydrophilic stroma but does not bind to the hydrophobic corneal epithelium. There are 4 diagnostic advantages for ophthalmology.



Clinical Management of Corneal Ulcers- Simple vs. Complicated

Dr. Lionel Sebbag



Diagnostics in Ophthalmology: Getting the Most out of These Minimally Invasive Tests



Puffy Eye... Maybe it's Feline Herpesvirus?

Dr. David Maggs



Practical Corneal Ulcer Management for General Practitioners

Dr. Alex Sigmund

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