



JUL 16 1998

Ms. Annmarie Petraglia  
Vice President, Regulatory Affairs  
Bio-Technology General Corp.  
70 Wood Avenue South  
Iselin, New Jersey 08830

Re: P960011  
BioLon™ 1% Sodium Hyaluronate Viscoelastic Surgical Aid Fluid  
Filed: May 1, 1996  
Amended: May 16, June 27, August 7 and 15, and October 25, 1996; March 7, April 24,  
June 5, July 16, September 24, and November 10 and 20, 1997; January 26,  
June 16, and July 15, 1998

Dear Ms. Petraglia:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for BioLon™ 1% Sodium Hyaluronate Viscoelastic Surgical Aid Fluid. This device is indicated for use as a surgical aid to protect corneal endothelium during cataract extraction (extra-capsular), intraocular lens implantation and anterior segment surgery. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 3 years when stored at 4°C or 1 month when stored at 25°C.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/pmapage.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420

Parklawn Dr., Rm. 1-23, Rockville, MD 20857. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

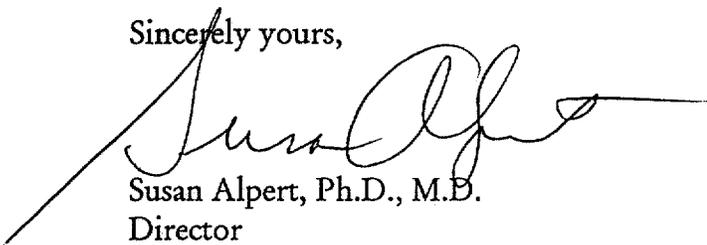
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Blvd.  
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Ashley A. Boulware at (301) 594-2053.

Sincerely yours,



Susan Alpert, Ph.D., M.D.  
Director  
Office of Device Evaluation  
Center for Devices and Radiological Health

Enclosure

Issued: 3-4-98

#### CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effectuated" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effectuated" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effectuated." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

- (1) May have caused or contributed to a death or serious injury; or
- (2) Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc. Any written report is to be submitted to:

Food and Drug Administration  
Center for Devices and Radiological Health  
Medical Device Reporting  
PO Box 3002  
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at

800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

## Summary of Safety and Effectiveness Data

### I. General Information

Device Generic Name: Intraocular Fluid (Sodium Hyaluronate)  
Device Trade Name: BioLon™ 1% Sodium Hyaluronate Viscoelastic Surgical Aid Fluid  
Applicant's Name and Address: Bio-Technology General Corporation  
70 Wood Avenue South  
Iselin, New Jersey 08830

Date of Panel Recommendation: None  
Premarket Approval Application (PMA) Number: P960011  
Date of Good Manufacturing Practice (GMP) Inspection: December 4, 1997  
Date of Notice of Approval to the Applicant: JUL 16 1998

### II. Indications

BioLon™ Sodium Hyaluronate (hereinafter called BioLon™) is indicated for use as a surgical aid to protect the corneal endothelium in cataract extraction (extra-capsular), intraocular lens implantation and anterior segment surgery.

When introduced in the anterior chamber of the eye during these surgical procedures, BioLon serves to maintain a deep anterior chamber.

In addition, BioLon™ helps to push back the vitreous face and prevent formation of a post-operative flat chamber.

### III. Contraindications

There are no known contraindications to the use of BioLon.

### IV. Warnings and Precautions

The following warning and precautions can be found in the BioLon™ labeling (Attachment 1).

#### Warning

Mixing of quaternary ammonium salts such as benzalkonium chloride with sodium hyaluronate results in the formation of a precipitate. The eye should not be irrigated with any solution containing benzalkonium chloride if BioLon™ is to be used during surgery.

#### Precautions

The BioLon™ syringe should be used only with the single-use cannula provided in the package.

Cannulas are intended for single patient use only. If reuse becomes necessary on the same patient during the surgical procedures, rinse the cannula thoroughly with sterile distilled water to remove all traces of residual material.

Verify that the cannula is properly locked to the Luer Lock Adaptor. Do not overtighten the Luer Lock Adaptor; this can lead to loosening of the Luer Lock Adaptor from the barrel.

Use only if the solution is clear.

Care should be taken to avoid trapping air bubbles behind BioLon™.

Instilling excessive amounts of BioLon™ into the anterior segment of the eye may cause increased intraocular pressure.

Pre-existing glaucoma or compromised outflow and operative procedures and sequelae thereto, including enzymatic zonulysis, absence of an iridectomy, trauma to filtration structures, and blood and lenticular remnants in the anterior chamber may increase postoperative intraocular pressure. Therefore:

- Do not overfill the eye chamber with BioLon™.
- Remove all remaining BioLon™ by irrigation and/or aspiration at the close of surgery.
- Carefully monitor the intraocular pressure, especially during the immediate postoperative period. If a significant rise is observed, treat appropriately.

On rare occasions, viscoelastic products containing sodium hyaluronate have been observed to become slightly opaque or to form a slight precipitate upon instillation into the eye. The clinical significance, if any, of this phenomenon is not known. The physician should, however, be aware of this possibility, and, should it be observed, the cloudy precipitated material should be removed by irrigation and/or aspiration.

BioLon™ is a highly purified substance extracted from bacterial cells. However, physicians should be aware of immunological, allergic, and other potential risks of the type that can occur from the injection of any biological substance since the presence of minute quantities of impurities (e.g., proteins) cannot be totally excluded.

## V. Device Description

BioLon™ is a sterile, non-pyrogenic, optically clear, viscoelastic preparation of highly purified, non-inflammatory, high molecular weight sodium hyaluronate. BioLon™ consists of a sterile, 2.25 ml syringe containing either 0.5 ml or 1.0 ml 1% sodium hyaluronate in phosphate-buffered salt solution.

Each milliliter of BioLon™ contains: sodium hyaluronate, 10 mg; sodium chloride, 8.5 mg; disodium hydrogen phosphate dodecahydrate, 0.56 mg; sodium dihydrogen phosphate dihydrate, 0.045 mg; and water for injection q.s. BioLon™ has a pH of 6.8 - 7.6, an osmolality of 260-380 mOsm/kg, and a viscosity of approximately 100,000 cps at a shear

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rate of 0.1 sec<sup>-1</sup> (25 °C). The average molecular weight of the sodium hyaluronate in BioLon™ is approximately 3 million daltons.

This polymer, a highly purified substance extracted from bacterial cells, is made of repeating disaccharide units of N-acetyl-glucosamine and sodium glucuronate linked by β-1,3 and β-1,4 glycosidic bonds. This polysaccharide is a physiological material that is widely distributed in the connective tissues of both animals and humans. Chemically identical in all species, hyaluronate can be found in the vitreous and aqueous humor of the eye, the synovial fluid, the skin, and the umbilical cord.

VI. Alternative Practices or Procedures

Prior to the development of viscoelastics for ophthalmic use, air or irrigation fluids such as saline solutions were the most commonly used anterior chamber maintainers or surgical aids. Today, viscoelastic materials are exclusively used. The alternatives to BioLon™ are other viscoelastics that have gained marketing approval, beginning in 1983.

VII. Marketing History

BioLon™ has been marketed in the following countries: Spain and Greece, since April 1993; Israel and Canada, since June 1993; Korea, since October 1993; Mexico, since December 1993; India, since May 1994; and, France, since January 1995. The following table (Table 1) states the registration status of BioLon™ in several countries. More than 150,000 syringes have been marketed. BioLon™ has not been removed from the market in any of the following countries for reasons related to safety or effectiveness.

Table 1. BioLon™ Registration Status

Country	Status	Registration Definition	Approval Date
Israel	Approved/marketed	Medical Device	6/92
Greece	Approved/marketed	Drug	1/95
Mexico	Approved/marketed	Medical Device	11/93
France	Approved/marketed	Drug	8/94
Italy	Approved	Drug	9/95
Korea	Approved/marketed	Drug	8/93
Canada	Approved/marketed	Medical Device	9/93
India	Approved/marketed	Import License	6/94
Colombia	Approved	Drug	9/95
Singapore	Approved	Drug	9/95
Netherlands	Approved	Drug	4/95
Turkey	Approved	Drug	10/95
Chile	Approved	Drug	10/95
EC Countries*	Certified as Medical Device by a European notified body (mdc.)	Medical Device	6/95

\*EC Countries: Germany, Austria, United Kingdom, Ireland, Spain, Portugal, and Denmark

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Alternate names for BioLon™ manufactured by Bio-Technology General (Israel) Ltd. (for overseas market) include: OphtHA, Biovisc, 1% sodium hyaluronate, and 1% NaHA.

VIII. Potential Adverse Effects of the Device on Health

In the clinical trials conducted by the sponsor, adverse events were reported in 26% of the patients receiving BioLon™ and 23% of the patients receiving the control substance (a commercially available sodium hyaluronate solution). The majority of the events reported included raised intraocular pressure (IOP) requiring treatment, capsule rupture, posterior capsular opacity, anterior chamber hemorrhage, ocular hemorrhage, and corneal-scleral leak. These events are common post-operative complications for cataract extraction surgery.

All device-related adverse events were increases in IOP. In most of the seven clinical studies conducted by the sponsor, an IOP greater than or equal to 28 mm Hg was considered to be an adverse event. Most of these patients received medications to lower their IOPs.

No patient was discontinued from the study due to a device-related adverse event.

The following table summarizes the ophthalmological adverse events observed at a rate of 1% or higher during the clinical study:

Table 2. Ophthalmological Adverse Events > 1%

Adverse Event	BioLon™	Control	Adverse Event	BioLon™	Control
Intraocular Pressure Increase (Requiring treatment)	22	17	Uveitis	3	3
Conjunctivitis	3	3	Synechiae	2	2
Corneal Erosion	3	0	Capsule Rupture	2	4
Suture-related ADE	2	2	Posterior Capsule Opacity	8	10
Hemorrhage Anterior Chamber	1	2	Vitreous Loss	1	4
Subconjunctival hemorrhage	1	4	Sphincter Damage	3	1
Seidel phenomenon	4	4	Cystoid Macular Edema	8	2
Superficial and Conjunctival Punctate Keratitis	12	5	Corneal Ulceration	1	2
Corneal edema	3	0			

Other ophthalmological adverse events that occurred at a rate of less than 1% include: eye pain, ocular hemorrhage, eyelid edema, ptosis, xerophthalmia, corneo-scleral leak, vitreous in anterior chamber, iris prolapse, hyphema, hyphema and haematic Tyndall, clot in pupil, haematic Tyndall, blood in anterior chamber and vitreous humor, anterior chamber hardness - reoperated, iris hernia - reoperated, vitreous filament in anterior chamber, anisekonia, iritis, iridocapsular synechiae, cyclitic membrane, vitreous bulge, vitreous hemorrhage, macula lutea degeneration, retinal hemorrhage, retinal detachment, subretinal fluid, choroidal hemorrhage, conjunctival hyperemia, keratitis filamentosa, blepharitis (infectious etiology),

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anterior uveitis, blurring opposite incision, cutaneous callus on eyelid, lachrymation, conjunctival filtration, caruncula tumefaction, papillary conjunctivitis and conjunctival cyst.

**IX. Summary of Preclinical Studies**

**Toxicological and Pharmacokinetic Studies**

All pre-clinical tests were performed according to good laboratory practices (21 CFR 58). All test protocols were found acceptable to FDA.

Results from the following tests demonstrated that BioLon™ is biocompatible and non-toxic:

<b>Toxicological Studies</b>					
<b>Study Type</b>	<b>Study Title</b>	<b>Species</b>	<b>Dose (vol)*</b>	<b>#Animals per dose</b>	<b>Outcome</b>
Single Dose Toxicity	Acute Intraperitoneal Toxicity in Mice	Mouse (CD-1)	400 mg/kg (40 ml/kg)	10	400 mg/kg not a toxic dose
	Acute Intravenous Toxicity in Mice	Mouse (CD-1)	6.25, 8.36, 10, 12.5 mg/kg (20 ml/kg volumes of 0.03-0.06% concentrations)	10	LD <sub>50</sub> = 9 mg/kg
	Acute Intravenous Toxicity in Rats	Rat (OFA)	7.5, 9, 10, 11.5, 12.5, 15 mg/kg (5 ml/kg volumes of 0.15-0.30% concentrations)	10 (5M, 5F)	LD <sub>50</sub> = 9.5 mg/kg (males), 10.5 mg/kg (females)
Repeated Dose Toxicity	Subacute Toxicity in Rats (14 days by intraperitoneal injection)	Rat (OFA)	10 mg/kg (5.6 ml/kg of 0.18% concentration)	10	No deleterious effects
	Subacute Toxicity in Rabbits (14 days by intraperitoneal injection)	Rabbit (NZW)	10 mg/kg (1 ml/kg)	6	No deleterious effects
Local Tolerance	Acute Intraocular Toxicity in Rabbit Eyes (aqueous humor)	Rabbit (NZW)	2 mg (0.2 ml)	6	Predictable rise in intraocular pressure; no other effects
	Acute Intraocular Toxicity in Cat Eyes (aqueous humor)	Cat (Iva:Fec)	2 mg (0.2 ml)	6	Same as in rabbit
	Acute Eye Irritation (administered into lower everted lid)	Rabbit (NZW)	0.2 mg (0.1 ml of 2% concentration)	3	No deleterious effects
Mutagenicity	NaHA Bacterial Mutation Assay (Ames Test)	<i>S. typhim.</i>	25-5000 µg/plate	N/A	No mutagenic effects.

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Study Type	Study Title	Species	Dose (vol)*	#Animals per dose	Outcome
Immuno-genicity	Delayed Sensitization in Guinea Pigs (Magnusson-Kligman test)	Guinea Pig	<ul style="list-style-type: none"> <li>• 5.0 mg NaHA intradermal</li> <li>• 500 mg NaHA topical twice</li> <li>• 5 mg NaHA intradermal</li> </ul>	20	No immunogenic effects
	Immunogenicity of BioLon™ in Rabbits (Onchterlong and Ring Tests)	Rabbit (NZW)	0.2% Intradermal	2	No immunogenic effects
Hemolysis	Preparation and Monitoring of Master Cell Bank (of NaHA-producing bacteria)	Hyaluronate-producing culture	1 lyophil	N/A	Non-hemolytic
	Hemocompatibility	N/A	1 ml of 0.5%, 0.25%, 0.125% BioLon™ in 1 ml citrated blood	N/A	Non-hemolytic
Pyrogenicity	Limulus Amoebocyte Lysate (LAL) Assay (Gel Clot Method)	N/A	1 ml	N/A	≤ 0.25 EU/ml

\* The volume of administration given is of 1% BioLon™, unless otherwise indicated.

The pharmacokinetic studies included the following:

NaHA Absorption, Distribution, Metabolism, and Excretion (ADME) studies using radiolabeled NaHA as follows:

- a. intravenous studies in rabbits and rats, which showed that the radioactivity levels in the serum declined with time, but increased in the liver, suggesting metabolism of the material
- b. excretion studies in rats, which showed that most of the radioactivity was excreted via respiration and some through the urinary tract
- c. intraocular studies in rabbits indicating that most of the radioactivity levels from the anterior chamber disappear within 72 hours

#### X. Summary of Clinical Studies

This section provides a brief summary of the clinical studies performed to evaluate the safety and effectiveness of BioLon™. There were seven individual clinical studies, which are also summarized below.

##### **Study Objective**

The endpoint of the investigational studies was to evaluate the safety and effectiveness of BioLon™ in the protection of the corneal endothelium and its capacity to facilitate surgery

during extracapsular cataract extraction procedures followed by the placement of an intraocular lens in the posterior chamber of the eye.

### Study Design

Seven (7) BioLon™ clinical studies were conducted in the period of 1989-1994. Five (5) of the 7 studies were comparative, using an FDA-approved sodium hyaluronate solution (hereafter referred to as SH) that has been marketed for more than 5 years as the control substance. The other 2 studies were non-comparative. In all of the studies, the patient follow-up period was 3 months. The studies were not conducted in the United States; however, they were conducted in accordance with the Declaration of Helsinki, 21 CFR §814.15(b), and the laws of the country in which the study was conducted. The following table summarizes the study types and the patient population enrolled in each study.

Table 3. Clinical Investigational Studies for BioLon

Study	Study Type	Country and Study Dates	No. of Investigators	No. of Patients (Drug group and gender)*				Age (years)
				Drug	M	F	Total	
1	Phase II, comparative, open label, controlled, randomized	United Kingdom 09/91-06/92	One	B	18	32	50	51-94
				SH	26	24	50	
2	Phase III, multicenter, comparative, open label, controlled, randomized	France 11/91-07/92	Three (One at each of three sites)	B	21	34	55	31-94
				SH	24	27	51	
3	Phase II, open label	Israel 10/89-11/90	One	B	13	18	31	54-88
				SH	0	0	0	
4	Phase II, comparative, open label, controlled, randomized	Israel 06/90-02/93	One	B	15	34	49	23-88
				SH	24	24	48	
5	Phase III, multicenter, comparative, open label, controlled, randomized	Italy 06/92-02/93	Three (One at each of three sites)	B	16	32	48	39-88
				SH	29	22	51	
6	Phase IV, comparative, open label, controlled, randomized	Israel 05/92-09/94	One	B	8	17	25	52-84
				SH	10	14	24	
7	Phase IV, open label	Israel 07/92-07/93	One	B	17	23	40	47-84
				SH	0	0	0	

\* B = BioLon, SH = Control group, M = Males, F = Females

Comparative - Involving two treatment groups, BioLon™ and a control substance.

Open label - Involving only treatment using BioLon™ (no control group).

### Patient Population and Demographic Data

The patient population for these studies included subjects over 18 years of age scheduled for extracapsular cataract extraction with lens implantation. A total of 522 patients were included in the studies. BioLon™ was used in 298 patients and SH in 224 patients. Patients with intraocular infection, corneal disease, or a history of anterior segment disease, significant

pathology, or any other disease that could interfere with the study, were excluded from the study at the time of pre-operative evaluation. In some studies, monocular patients and patients with previous ocular surgery or laser treatment in the cataractous eye were excluded from the studies. Table 4 shows the distribution of patients by group, age, and gender.

Table 4. Patient Population Demographics

Study Number <sup>1</sup>	Gender	BioLon™		SH	
		Total Patients	Mean Age ± SD <sup>2</sup>	Total Patients	Mean Age ± SD
Comparative (1, 2, 4, 5, 6)	Females	149 (65.6%)	71 ± 11	111 (49.6%)	70 ± 12
	Males	78 (34.4%)		113 (50.4%)	
	Total	227		224	
Non-comparative (3, 7)	Females	41 (57.7%)	73 ± 9	—	—
	Males	30 (42.3%)		—	
	Total	71		—	

A total of 8 patients in the BioLon™ group and 9 patients in the SH group were lost-to-follow-up or withdrew from the study. Due to protocol deviations, the numbers of evaluable patients in several of the studies were significantly lower than the numbers if patients treated. However, except for those patients who were lost to follow-up, data from all treated patients were analyzed and were found to be consistent with the data reported in this document.

### Safety and Efficacy Assessment

The safety parameters assessed in the studies were raised intraocular pressure (IOP) requiring treatment, and inflammation. Additional clinical adverse events were noted separately, based on other safety parameters set by the individual studies.

The efficacy parameters assessed in the studies were anterior chamber depth (ACD), visual acuity (VA), endothelial cell count (ECC) (in all studies except study 7), and corneal thickness (studies 1, 2, and 5 only).

### Data Analysis and Results

Due to the differences in study protocols, population characteristics, and/or post-operative measurement techniques and variables, the data from the individual studies were not combined for an overall statistical analysis.

#### 1. Safety data analysis

Post-operative increases in IOP are common occurrences following surgical procedures where viscoelastic ophthalmic aids have been used. Even though the substance is removed from the anterior chamber of the eye prior to completion of the procedure, some material

<sup>1</sup> Refer to Table 3.

<sup>2</sup> SD = Standard Deviation

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may be left behind that may obstruct the outflow of aqueous, consequently producing an elevated intraocular pressure.

Throughout the studies, transient increases in IOP (from pre-operative values) were observed for all patients 3-9 hours post-operatively. IOP increases greater than 28 mmHg were generally treated with medication and considered to be adverse events in most studies. A total of 22 BioLon™ and 21 SH patients received medication to lower the IOP. However, most of the patients had IOP values close to baseline from 24 hours to 3 months following surgery. No statistically significant differences were observed between the two treatment groups with respect to elevations in IOP (mean IOP values). Also, the changes in mean IOP from baseline values were similar for both treatment groups.

Table 5 summarizes the mean IOPs reported for the evaluable patients in each study. Of all patients treated, those whose IOP exceeded 30 mmHg at any time in the study are reported in Table 6.

Table 5. Summary of Mean IOPs

Study No.	Sample Size*		Mean IOP** (mmHg)	
	B***	SH	B	SH
1	48	44	16	17
2	42	38	17.4 (4-8 hrs)	17.7 (4-8 hrs)
3	19	--	25	--
4	20	16	21	21
5	48	50	18.3 (4-8 hrs)	18.5 (4-8 hrs)
6	21	21	22	18
7	40	--	16 (1 day)	--

\* Evaluable patients

\*\* Measured at 9 hours post-operatively, except where time is stated

\*\*\* B = BioLon, SH = Control group

Table 6. Summary of IOPs Exceeding 30 mm Hg\*

Study No.	Sample Size**		IOP > 30 mmHg	
	B	SH	B	SH
1	50	50	3	7
2	55	51	8	3
3	31	--	9	--
4	49	48	8	11
5	48	50***	0	0
6	25	24	7	4
7	40	--	3	--

\*Patients with multiple measurements greater than 30 mmHg were counted once.

\*\* All patients who were treated

\*\*\* One patient withdrew from the study just before surgery.

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The majority of patients developed mild to moderate inflammatory reactions, which regressed by Month 3 in most cases. Some patients developed transient corneal abnormalities (epithelial edema, stromal edema, or Descemet's folds); most of these disappeared by Month 3. Other patients had pre-existing corneal abnormalities that persisted after surgery.

Ophthalmoscopic examinations of the vitreous, retina, macula, choroid, and optic nerve head were performed pre- and postoperatively. Some patients had pre-existing conditions which were unnoticed preoperatively due to the presence of cataracts; however, no differences were observed between the two treatment groups.

## 2. Efficacy data analysis

Most of the studies reported that both treatment devices maintained normal anterior chamber depth during surgery, except for one patient in Study 3 who had a pre-existing shallow anterior chamber depth. A small, but statistically significant, difference between SH and BioLon™ (favoring SH) was observed in study 6 for the maintenance of full aphakic anterior chamber depth. However, since this analysis was based on a subjective rating of anterior chamber depth, the statistical difference was not considered clinically significant.

In the five comparative studies, no statistically significant differences in endothelial cell loss were reported after 3 months of follow-up between treatment groups, although differences were reported at earlier postoperative evaluation times. In all of the studies, the results indicate that BioLon™ was able to adequately protect the endothelial cells.

Corneal thickness was reported as increasing in both treatment groups immediately after surgery. Most values returned to baseline after 3 months. No statistically significant differences were observed between the two treatment groups with respect to mean changes in corneal thickness.

Mean visual acuity (VA) was reported using the decimal system with correction to the tenth. As expected due to the removal of the cataract and introduction of an intraocular lens, VA improved significantly from baseline values in all studies. VA was measured to detect any differences in postoperative outcomes between treatment groups that may be related to the viscosurgical device. Within each of the studies, no statistically significant differences in mean VA were observed between the two treatment groups at 3 months postoperatively.

Table 7 below, summarizes results from the measurement of the primary efficacy endpoints in all evaluable patients.

Table 7. Summary of Primary Efficacy Endpoints

Study #	Sample Size		% Decrease in ECC* at 3 months		ACD** (n = normal)		Corneal Thickness (mm) (preop/3 months postop)		
	B***	SH	B	SH	B	SH		B	SH
1	48	44	11	12	n	n	preop postop	0.52 ± 0.02 0.53 ± 0.02	0.53 ± 0.02 0.54 ± 0.02
2	42	38	8.6	6.0	n	n	preop postop	0.53 ± 0.08 0.55 ± 0.09	0.53 ± 0.08 0.54 ± 0.09
3	20	---	6	---	n	---		N/A†	N/A
4	24	22	9	11	n	n		N/A	N/A
5	48	50	5.9	3.5	n	n	preop postop	0.52 ± 0.03 0.52 ± 0.03	0.52 ± 0.03 0.52 ± 0.02
6	21	21	7	9	n	n		N/A	N/A
7	40	---	N/A	N/A	n	---		N/A	N/A

\* Endothelial cell count

\*\* Anterior chamber depth

\*\*\* B = BioLon, SH = Control group

† N/A = Not available

### Device Failures and Replacements

There were no device failures or replacements during the clinical studies.

### C. Summaries of Each Individual Clinical Study

#### Study 1 - United Kingdom Dates: 09/91-06/92

Study 1 was a phase II, comparative, open label, controlled, randomized study. The study population consisted of 100 patients, 50 in the BioLon™ group and 50 in the SH group. However, 7 patients were enrolled in violation of the protocol and 1 patient withdrew prematurely. Therefore, 92 patients were enrolled appropriately for evaluation (48 in the BioLon™ group and 44 in the SH group).

The study sample size was based on the safety parameter of IOP, with the assumption that it would be analyzed using a one-sided two-sample t-test and a significance level of 0.05. Based on data and standard deviations obtained from the scientific literature on commercially available ophthalmic viscosurgical devices, a sample size of 47 in each group was calculated to provide a 90% probability to detect a statistically significant difference in an IOP increase of 5.6 mm Hg from baseline values.

The viscoelastic material was injected for the duration of the operation and removed prior to closing of the corneal incision. The follow-up evaluation time was 3 months. The study was conducted by one investigator, and the follow-up evaluations were performed by one co-investigator (at one site).

There were no statistically significant differences in gender and age distribution between the control and study groups. Past medical events and preoperative findings were recorded for the operative eye of each patient; the findings in the two treatment groups were comparable.

The two treatment groups were evaluated for maintenance of anterior chamber depth, loss of endothelial cells, corneal thickness changes, IOP increases, ocular tissue abnormalities, visual acuity and adverse events. There were no statistically significant differences between the two treatment groups in the evaluation of these postoperative safety and efficacy parameters, except for visual acuity, where trends toward improved acuity were observed in the control group at weeks 2 and 6. This trend was not evident at week 12.

**Study 2 - Paris**  
**Dates: 11/91-07/92**

This was a phase III, multicenter, comparative, open label, controlled, randomized study. The study population consisted of 106 patients, 55 in the BioLon group and 51 in the SH group. One patient in the SH group was lost to follow-up; 3 patients in the BioLon™ group withdrew prematurely from the study. A total of 21 protocol violations were reported; they were due to missing data (8), exams performed outside the specified timeframe (6), the IOL was implanted in the anterior chamber rather than the posterior chamber (6), or more than one viscoelastic was used during surgery (1). Therefore, there were 80 evaluable patients (42 BioLon™ and 38 SH).

The study was conducted by 3 investigators at three different sites. Postoperative evaluations were masked. The study duration was 3 months.

The statistical analyses performed between investigational sites indicate that there were no differences between gender and age distribution. The two treatment groups were not statistically different when pre-surgical parameters were evaluated.

Patients were evaluated postoperatively for endothelial cell density, corneal thickness, maintenance of anterior chamber depth, surgical assessment of the viscoelastic, visual acuity, IOP increase, ocular tissue abnormalities and adverse events. The cell density in the corneal endothelium decreased significantly with time in both treatment groups; however the difference between groups was not significant. No statistically significant differences were observed between the two treatment groups in the evaluation of safety and efficacy parameters.

**Study 3 - Israel**  
**Dates: 10/89-11/90**

This was a phase II, open label study with no control population. A total of 31 patients were enrolled. Eight protocol violations were reported; 2 patients withdrew from the study prematurely and 1 patient was lost to follow-up. The protocol violations were missing data and exams performed outside the specified timeframe. There were 20 evaluable patients.

BioLon™ was injected into the anterior chamber for the duration of the operation and removed prior to the completion of the surgical procedure. The study was conducted by one investigator (one site). The follow-up evaluations were performed by 2 co-investigators. Patients were followed for 3 months.

Patients were evaluated for IOP increase, anterior chamber abnormalities, corneal abnormalities and VA. The anterior chamber depth was effectively maintained during surgery in all patients but one, who had a preexisting shallow anterior chamber. There were statistically significant changes from baseline values in endothelial cell counts at one month postoperatively and intraocular pressure in the first 24 hours postoperatively. However, the loss in endothelial cells appeared to be transient as cell counts were increasing towards normal at 3 months postoperatively. The IOP increases were also transient as all but 3 patients had returned to normal at the end of the first 24 hour period. The remaining three patients were treated with medication. All patients had returned to normal by 3 months postoperatively. Most patients developed a moderate inflammatory reaction by Day 1; however, the most severe reactions had subsided by Week 1 and all reactions disappeared by Month 1. All other safety and efficacy parameters evaluated were acceptable at 3 months.

**Study 4 - Israel**  
**Dates: 6/90 - 2/93**

This was a phase II, comparative, open label, controlled, randomized study. The study population consisted of 97 patients, 49 in the BioLon™ group and 48 in the SH group. There were 44 protocol violations (most missing data or exams performed outside the specified timeframe), 1 patient who withdrew prematurely and 6 patients who were lost to follow-up. Only 46 patients (24 BioLon™ and 22 SH) met the protocol. The study was conducted at one site, but follow-up evaluations were performed by 2 co-investigators.

The sample size was determined according to the same rationale as described for Study 1 above.

No statistically significant differences in age or gender were observed between the two treatment groups. The two groups were also comparable regarding occurrences of past medical events and preoperative findings.

The patients were evaluated for IOP increase, iritis, appearance of the cornea, maintenance of anterior chamber, endothelial cell loss, VA, performance in the eye (amount used, ease of aspiration, etc.) and ocular tissue abnormalities.

Both groups showed a statistically significant decrease in mean endothelial cell counts 3 months postoperatively as compared to baseline values. However, there was no statistically significant difference between the treatment groups. No statistically significant differences between the two groups were obtained in the postoperative evaluation of the other safety and efficacy parameters.

**Study 5 - Italy**  
**Dates: 06/92-02/93**

This is a phase III, comparative, open, controlled, randomized study conducted by three investigators at three different sites. A total of 99 subjects were enrolled in the study; however, one subject withdrew (from the SH group). A total of 48 patients in the BioLon™ group and 51 in the SH group were enrolled.

The sample size for each treatment group was calculated using referenced methods that predict that 98% of the surgeries will be successful and that estimate that there is a 10% difference between the two treatment substances.

There was a statistically significant difference between gender distribution among the two groups, but no differences were found between groups regarding preoperative safety and effectiveness parameters (IOP, pachymetry and endothelial cell counts) of the surgical eye.

The patients were evaluated for IOP, endothelial cell counts, pachymetry, VA, biomicroscopy findings, ophthalmoscopy findings, maintenance of the anterior chamber depth, presence of iridoptosis, rupture of the capsule, loss of vitreous, quantity applied, and ease of removal.

No statistically significant differences were observed between the two treatment groups in the evaluation of postoperative safety and efficacy parameters.

**Study 6- Israel**  
**Dates: 05/92-09/94**

This was a phase III, comparative, open label, controlled, randomized study. The investigation was conducted in one site. All surgical procedures were performed by one investigator and the follow-up evaluations performed by two co-investigators. A total of 49 patients were enrolled in the study, 25 receiving BioLon™ and 24 receiving SH. Due to 6 protocol violations (missing data and exams performed outside the specified timeframe) and 1 premature withdrawal, only 42 patients (21 in each group) were evaluable in accordance with the protocol.

The number of patients enrolled was not determined based on statistical analyses; it was based on patient availability. The only requirement was that an equal number of patients be enrolled in each treatment group.

No statistically significant differences were observed in gender and age distribution between the two study groups. Past medical events and preoperative findings in the surgical eye were recorded and the two groups were comparable.

The patients were evaluated postoperatively for IOP, anterior chamber abnormalities, corneal abnormalities, VA, endothelial cell loss, and maintenance of anterior chamber depth.

No statistically significant differences were obtained between the two groups regarding the safety and efficacy parameters evaluated postoperatively, except for the maintenance of anterior chamber depth. The anterior chamber depth was sufficiently maintained by both treatments; however, there was a statistically significant difference favoring the control substance for maintenance of full aphakic anterior chamber depth.

**Study 7 - Israel**  
**Dates: 07/92-07/93**

This was a phase IV, open label study. One investigator participated in the study; the postoperative evaluations were performed by two co-investigators. A total of 40 patients were enrolled in the study in accordance with the protocol. This study did not have a control population. Patients were followed for 12 weeks.

The patients were evaluated for maintenance of anterior chamber depth, IOP increase, iritis, appearance of the cornea, VA, and evaluation of other corneal tissue. A surgical assessment included observations of any occurrences of iris prolapse, vitreous bulge, and vitreous loss. Endothelial cell loss was not evaluated because the hospital facilities where the study was conducted did not have adequate instrumentation for this measurement.

Anterior chamber depth was well maintained by BioLon™; based on the grading system used by the investigator, 13 patients had a moderately full aphakic depth and 26 patients had full aphakic depth. Transient rises in IOP were observed at 24 hours postoperatively; however, the mean IOP returned to the baseline value by the second postoperative week. Anterior chamber and corneal abnormalities were observed on the first postoperative day, but disappeared or returned to normal by the twelfth week. Visual acuities improved significantly from baseline, as expected. A total of 16 adverse events were reported in 13 patients. Other than three occurrences of elevated IOP (above 28 mm Hg and requiring treatment), the adverse events were not considered to be device related. In conclusion, the safety and efficacy parameters evaluated postoperatively were acceptable.

**XII. Conclusions drawn from the clinical studies**

The clinical studies indicate that:

- a. BioLon™ is safe and effective for the maintenance of the anterior chamber depth and protection of the corneal endothelium during cataract extraction and intraocular lens implantation;
- b. only a transient increase in intraocular pressure was observed in all studies;
- c. the rate of adverse events obtained with the use of BioLon™ was not statistically different from that obtained in the control group; and,
- d. in most of the safety and efficacy parameters evaluated throughout the studies, the results obtained for BioLon™ were not statistically different from those obtained for the control group.

Therefore, the benefits of using BioLon™ outweigh any potential risks to the patient, which are common postoperative complications with cataract extraction surgery and intraocular lens implantation procedures.

XIII. Panel Recommendation

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CDRH Decision

The Center for Devices and Radiological Health (CDRH) reviewed the PMA and concluded that the PMA contained sufficient valid scientific evidence to provide reasonable assurance of the safety and effectiveness of the device under the prescribed indications for use. The applicant's manufacturing facility was inspected on December 4, 1997 and was found to be in compliance with the device Good Manufacturing Practice regulations. FDA issued an approval order on July 16, 1998.

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# BioLon™

## Sodium Hyaluronate

### Product Information

#### Description

BioLon™ is a sterile, nonpyrogenic, *optically clear*, viscoelastic preparation of highly purified, high molecular weight sodium hyaluronate. BioLon™ contains 10 mg/ml of sodium hyaluronate dissolved in a physiological sodium chloride phosphate buffer (pH 6.8 - 7.6). This high molecular weight polymer is made up of repeating disaccharide units of N-acetyl-glucosamine and sodium glucuronate linked by  $\beta$ -1,3 and  $\beta$ -1,4 glycosidic bonds.

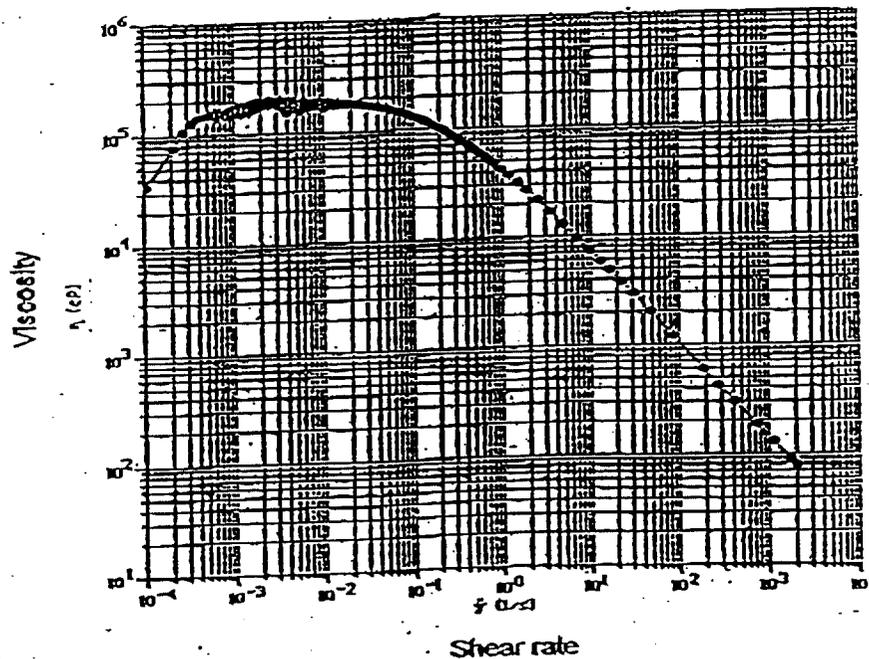
Sodium hyaluronate is a physiological material that is widely distributed in the connective tissues of both animals and man. Chemically identical in all species, hyaluronate can be found in the vitreous and aqueous humor of the eye, the synovial fluid, the skin and the umbilical cord.

BioLon™ has the following properties:

- High molecular weight (mass average molecular weight approximately 3 million daltons)
- High viscosity

Each milliliter of BioLon™ contains: sodium hyaluronate, 10 mg; sodium chloride, 8.5 mg; disodium hydrogen phosphate dodecahydrate 0.56 mg; sodium dihydrogen phosphate dihydrate 0.045 mg; water for injection q.s. BioLon™ has an osmolality of 260-380 mOsm/kg and a viscosity of approximately 100,000 cps at a shear rate of 0.1 sec<sup>-1</sup>(25°C).

BIOLON viscosity at different shear rates



BioLon™ Sodium Hyaluronate  
Product Information

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### Indications

BioLon™ is indicated for use as a surgical aid to protect corneal endothelium during cataract extraction (extra-capsular) procedures, intraocular lens (IOL) implantation and anterior segment surgery. When introduced in the anterior segment of the eye during these surgical procedures, BioLon™ serves to maintain a deep anterior chamber.

In addition, BioLon™ helps to push back the vitreous face and prevent formation of a post-operative flat chamber.

### Contraindications

When used as recommended there are no known contraindications to the use of BioLon™.

### Warnings

Mixing of quaternary ammonium salts such as benzalkonium chloride with sodium hyaluronate results in the formation of a precipitate. ***The eye should not be irrigated with any solution containing benzylalkonium chloride if BioLon is to be used during surgery.***

### Precautions

- ***The BioLon™ syringe should be used only with the single-use cannula provided in the package.***
- Cannulas are intended for single patient use only. If reuse becomes necessary on the same patient during the surgical procedures, rinse the cannula thoroughly with sterile distilled water to remove all traces of residual material.
- Verify that the cannula is properly locked to the Luer Lock Adaptor. Do not overtighten the Luer Lock Adaptor; this can lead to loosening of the Luer Lock Adaptor from the barrel.
- Use only if the solution is clear.
- Care should be taken to avoid trapping air bubbles behind BioLon™.
- Instilling excessive amounts of BioLon™ into the anterior segment of the eye may cause increased intraocular pressure.
- Pre-existing glaucoma or compromised outflow and operative procedures and sequelae thereto, including enzymatic zonulysis, absence of an iridectomy, trauma to filtration structures, and by blood and lenticular remnants in the anterior chamber may increase post-operative intraocular pressure. Therefore,
  - ⇒ Do not overfill the eye chamber with BioLon™.
  - ⇒ Remove all remaining BioLon™ by irrigation and/or aspiration at the close of surgery.
  - ⇒ Carefully monitor the intraocular pressure, especially during the immediate post-operative period. If a significant rise is observed, treat appropriately.

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- On rare occasions, viscoelastic products containing sodium hyaluronate have been observed to become slightly opaque or to form a slight precipitate upon instillation into the eye. The clinical significance, if any, of this phenomenon is not known. The physician should, however, be aware of this possibility, and, should it be observed, the cloudy or precipitated material should be removed by irrigation and/or aspiration.
- BioLon™ is a highly purified substance extracted from bacterial cells. However, physicians should be aware of immunological, allergic and other potential risks of the type that can occur from the injection of any biological substance since the presence of minute quantities of impurities (e.g. proteins) cannot be totally excluded.

### Adverse Reactions

In clinical trials, 298 patients were treated with BioLon™ and 224 patients were treated with sodium hyaluronate, an approved comparative device on the U.S. market for more than five years. The incidences of adverse experiences that were reported in >1% of the patients are shown in Table I.

Table I\*

	BIOLON		CONTROL	
	n=298	(%)	n=224	(%)
Increased Intraocular Pressure Requiring Treatment*	22	(7.4)	17	(7.6)
Superficial & Conjunctival Punctate Keratitis	12	(4.0)	5	(2.2)
Cystoid Mascular Edema	8	(2.7)	2	(0.9)
Posterior Capsule Opacity	8	(2.7)	10	(4.5)
Seidel Phenomenon	4	(1.3)	4	(1.8)
Conjunctivitis	3	(1.0)	3	(1.3)
Corneal Edema	3	(1.0)	0	(0)
Corneal Erosion	3	(1.0)	0	(0)
Sphincter Damage	3	(1.0)	1	(0.4)
Uveitis	3	(1.0)	3	(1.3)

\*There is no statistically significant difference in the number of adverse events between the two treatment groups.

\*Mean IOP BioLon™ = 36.7 mm Hg (30 mm Hg - 52 mm Hg)

\*Mean IOP Control = 33.6 mm Hg (28 mm Hg - 48 MM Hg)

Adverse events which occurred in <1% and in at least 2 patients include: ocular hemorrhage, corneo-scleral leak, suture related adverse events, vitreous in anterior chamber, hyphema and hematic Tyndall, synechiae, capsule rupture, and cyclytic membrane.

BioLon™ Sodium Hyaluronate  
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**Dosage/Applications**

**Cataract Surgery and Intraocular Lens Implantation**

Refrigerated BioLon™ should be allowed to attain room temperature (approximately 20 - 30 minutes) prior to use. The usual dose required is 0.2 to 0.5 ml of BioLon™. BioLon™ should be slowly and carefully introduced into the anterior segment of the eye using the provided cannula.

Injection of BioLon™ can be performed either before or after delivery of the lens.. BioLon™ may also be used to coat surgical instruments and the intraocular lenses prior to insertion.

Additional BioLon™ can be injected during surgery to replace any BioLon™ lost during surgical manipulation (see Precautions section).

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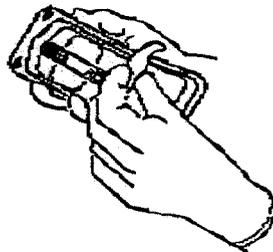
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BioLon™ Sodium Hyaluronate  
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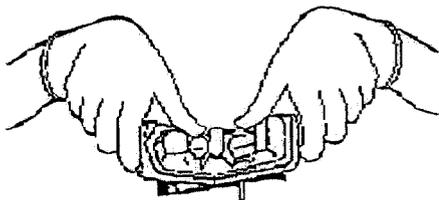
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### Syringe Operating Instructions

1. Twenty to thirty minutes before use, remove the product box from the refrigerator, remove the blister pack from the box and allow the syringe to reach room temperature.

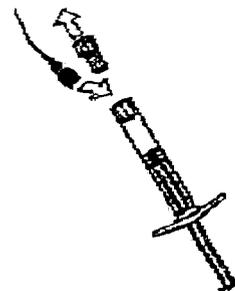


2. Peel off the blister Tyvek backing.

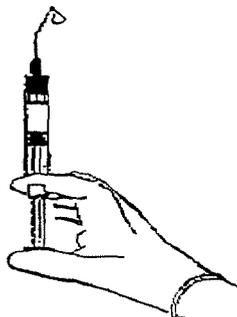


3. While holding the blister open side down, bend the blister and allow the syringe to fall gently onto the sterile surface. (Alternatively, hold the blister open side up and bend back the blister until the barrel's luer end is exposed. Gripping the luer end of the barrel, remove the syringe from the blister. **Do not remove the syringe from the plunger end**).

4. Remove the tip cap from the syringe and attach the cannula. **Attention:** Do not apply pressure to the plunger rod while the cannula is being affixed.



5. Apply gentle pressure to the plunger in order to expel air from the cannula and verify that the syringe is operating properly.



6. The syringe is ready for use.

BioLon™ Sodium Hyaluronate  
Product Information

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**How Supplied**

BioLon™ is supplied in sterile, disposable 2.25 ml syringes containing either 0.5 ml or 1.0 ml of 1% sodium hyaluronate in phosphate-buffered salt solution. Each product package contains a blister-packed syringe, a sterile, single-use ophthalmic cannula (anterior chamber irrigator) and a package insert.

**Storage Instructions**

Store in a cold dark place (2° - 8°C; 36° - 48°F). May be kept at 25°C(77°F) for up to one month. Protect from freezing. Bring to room temperature prior to use.

**Caution**

Federal law restricts this device to sale by or on the order of a physician.

**Manufactured by:**

Bio-Technology General, (Israel) Ltd., Kiryat Weizmann,  
Rehovot 76326, Israel

**Distributed by:**

Bio-Technology General Corp.  
70 Wood Avenue South  
Iselin, New Jersey 08830

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