P960033

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name: Intraocular Fluid (Sodium Hyaluronate)

Device Trade Name: STAARVISC™ Sodium Hyaluronate

Applicant's Name and Address: STAAR Surgical Company
1911 Walker Avenue
Monrovia, CA 91016

Date of Panel Recommendation: October 19, 1988*

Premarket Approval Application (PMA) Number: P960033

Dates of Good Manufacturing Practice (GMP) Inspections:

Bulk Material Processing Site: STAAR Surgical AG
27121 Aliso Creek Road
Aliso Viejo, CA 92656

Aseptic Filling of Syringes: Chesapeake Biological Laboratories
1111 South Paca Street
Baltimore, MD 21230

Syringe Tray Packaging, Final Packaging Site: STAAR Surgical AG
Hauptstrasse 104
CH-2650 Nidau, Switzerland

Conclusion: The sites were found to be in compliance with applicable Good Manufacturing Practices after inspections by FDA on December 10, 1997, June 18, 1999, and November 13, 1997, respectively.

Date of Notice of Approval to the Applicant: JUL - 2 1999

II. Indications

STAARVISC™ is indicated is indicated for use as a surgical aid in ophthalmic anterior and posterior segment surgery including:

- Cataract extraction with or without implantation of an intraocular lens;
- Corneal transplant surgery;
- Glaucoma filtering surgery; and
- Secondary lens implantation.

---

* See Section XIII, CDRH Decision, for additional details.

STAARVISC™ aids in maintaining a deep anterior chamber during surgery, protecting corneal endothelial and surrounding tissues from touch by instruments or intraocular lenses, inflating the capsular bag after cataract extraction and lubricating surgical instruments.

III. Contraindications

There are no known contraindications for the use of STAARVISC™ sodium hyaluronate when used as recommended.

IV. Warnings and Precautions

Warnings

There are no warnings for the use of STAARVISC™ sodium hyaluronate.

Precautions

Those precautions normally considered during ophthalmic surgical procedures are recommended. Transient increases in intraocular pressure following surgery because of pre-existing glaucoma or due to the surgery itself may occur. For these reasons the following precautions should be considered:

- An excess quantity of STAARVISC™ should not be used and all STAARVISC™ should be removed from the anterior chamber by irrigation or aspiration after surgery.
- The intraocular pressure of patients receiving STAARVISC™ should be carefully monitored. Patients in the clinical study reported a maximum mean IOP of 19.2 mm Hg at approximately 9-12 hours postoperative. At 24 hours postoperative, mean IOP had decreased to 15.6 mm Hg. If the postoperative intraocular pressure increases above expected values, appropriate therapy should be administered.
- Denaturation and particulate formation in viscoelastics with the repeated use of reusable cannulae has been reported in some studies. It is recommended that a single use cannula such as the one provided in this package be used when instilling STAARVISC™ into the eye. Reuse of the cannula should be avoided.
- STAARVISC™ is prepared from a biological source. It is a highly purified fraction extracted from avian tissues and may contain minute amounts of protein. The physician should be aware of potential risks that can occur with the injection of biological material into the eye. Each batch of STAARVISC™ is tested to demonstrate that it is essentially non-inflammatory.

V. Device Description

STAARVISC™ is a sterile, non-pyrogenic, non-inflammatory, viscoelastic solution of highly purified sodium hyaluronate dissolved in buffered saline to produce a 1.1 - 1.5% solution. The viscosity of this solution is approximately 140 cP at a shear rate of 1000 sec^{-1} @ 25°C.

The molecular weight of STAARVISC™ is between 800,000 and 1,000,000. The refractive index of STAARVISC™ is 1.3353 @ 35°C.

The sodium hyaluronate is a naturally occurring linear glycosaminoglycan with a repeating disaccharide unit of sodium glucuronate and n-acetyl glucosamine linked by a beta 1-3 glucosidic bond. These disaccharide units are linked together by beta 1-4 linkages to form a long unbranched chain. This sodium hyaluronate is prepared from avian tissues using a unique process, which removes contaminating material to yield a product essentially devoid of protein and nucleic acids.

STAARVISC™ is supplied as a 0.65 ml sterile preparation of sodium hyaluronate in a physiological buffered solution (pH = 6.9 - 7.5). Each ml of STAARVISC™ contains 13 mg of sodium hyaluronate.

VI. Alternative Practices or Procedures

Air or other gases, isotonic solutions such as Ringer's Lactate Solution (RLS) or Balanced Salt Solution (BSS), methylcellulose, sodium chondroitin sulfate, potassium salt of hyaluronic acid, or a combination of chondroitin sulfate and sodium hyaluronate are the articles most commonly used as surgical aids in ophthalmic surgery. BSS, RLS, air or sodium hyaluronate constitute the commonly used articles for restoration of the volume of the eye.

VII. Marketing History

STAARVISC™ has been distributed for commercial use outside the United States in countries of the European Union, Switzerland, and South Africa.

VIII. Potential Adverse Effects of the Device on Health

STAARVISC™ is derived from biological sources and, therefore, has the potential to contain minute amounts of protein or other matter at levels which may put the patient at risk for allergic reactions in certain susceptible individuals. Although no reports of these types of reactions have been received for STAARVISC™ , there may still be reactions that may range from mild inflammatory reactions or fever to anaphylaxis. With any viscoelastic substances used during ocular surgery, there is also the potential that small amounts of the material may be inadvertently left in the eye, which could cause complications, most notably an increase in intraocular pressure. This type of complication was not noted in the clinical study of STAARVISC™ ; however, if it occurs, it is generally transient.

The clinical study of STAARVISC™ demonstrates that the aforementioned risks are rare and that the potential benefits to the patient resulting from the use of the device exceed the risks associated with its use.

IX. Summary of Preclinical Studies

Preclinical studies were performed on STAARVISC™ in both the bulk and finished form. These studies were conducted using both in-vivo and in-vitro test systems, using acceptable

protocols, in conformance with Good Laboratory Practices (21 CFR 58) except where noted.

Study Type	Study Title	Outcome
Immunogenicity	Complement Activation Analysis	Nonimmunogenic
Cytotoxicity	Agarose Overlay, Direct Contact	Nontoxic
Cytotoxicity	Inhibition of Cell Growth	See note below
Cytotoxicity	MEM Elution	Noncytotoxic
Hemolysis	In Vitro Hemolysis	Nonhemolytic
Systemic Toxicity	Systemic Toxicity Study in the Mouse	Nontoxic
Mutagenicity	Ames Test	Nonmutagenic
Sensitization	Dermal Sensitization in the Guinea Pig	Nonsensitizing
Irritation	Intraocular Irritation in the Rabbit	Nonirritating
Pyrogenicity	Limulus Amebocyte Lysate (LAL)	Nonpyrogenic

Note: The inhibition of cell growth test showed clear evidence of cell growth inhibition. The applicant explained that that cell growth inhibition is not a suitable test for cytotoxicity for hyaluronic acid, and provided literature references that demonstrated that hyaluronic acid modulates cell proliferation. Because the results of other biocompatibility studies, and the clinical studies, demonstrate that the device is safe and effective for its intended use, the applicant's explanation for these test results was considered satisfactory.

In addition, the sponsor conducted the following testing to demonstrate that STAARVISC™ is identical to the material (IVISC) used in the clinical trial: pH, hyaluronate content, UV absorbance, viscosity, osmolality, residual proteins, product purity, and toxicity testing (see above).

X. Summary of Clinical Studies

This section provides a brief summary of the clinical studies performed to evaluate the safety and effectiveness of STAARVISC™ .

Study Objectives

The sponsor conducted clinical studies to establish that STAARVISC™ is a safe and effective surgical aid that can:

- maintain the anterior chamber depth and volume of the globe during intraocular surgery;

- serve as an aid in performing selected surgical procedures, namely, cataract extraction and IOL implantation;
- serve as an aid in facilitating IOL insertion through coating the IOL; and
- protect the endothelial cells during IOL insertion.

Study Design

The sponsor conducted a single-armed, non-randomized, prospective trial of STAARVISC™ to investigate its safety and efficacy as a surgical aid in cataract extraction, IOL implantation, and intraocular surgery.

The follow-up period was 14 days with the investigator selecting postoperative visits at 1 day, 4 - 8 days, and 14 days.

The sponsor also conducted two special subgroup studies:

Endothelial Cell Loss

The sponsor studied endothelial cell loss on 51 patients using the reporting schedule described above, with an additional examination for endothelial cell count at a minimum of 4 weeks postoperatively.

Intraocular Pressure

The sponsor monitored immediate postoperative intraocular pressure in 60 patients at 1 hour, 3 hours, 6 hours, and 24 hours.

Patient Selection Criteria

All patients over the age of 18 undergoing cataract removal and intraocular lens implantation were eligible for inclusion in this study. Patients with the following conditions were excluded:

- Chronic iritis
- Aniridia
- Chronic uveitis
- Any other condition which would disqualify a prospective patient from the investigator's standpoint.

Data Analysis and Statistical Methods

Statistical analyses were performed to evaluate the safety and effectiveness parameters and to identify possible risk factors. Means and proportions were the primary descriptive statistics used. When subgroup comparisons were made, the statistical test used was the Student's t

distribution. In this summary, all references to statistical significance mean a P-value of less than 0.001, unless otherwise noted.

Controls

No concurrent control patients were required. Patients treated with STAARVISC™ were compared to published data where appropriate.

Study Population and Characteristics

Patient Accountability

No. Patients Enrolled	213	
No. Eyes Enrolled	214	(1 patient had bilateral use of the device.)
No. Deaths	1	(Cause of death was due to medical problems unrelated to the surgery.)
No. Lost to follow-up	3	1.4% lost to follow-up rate (2 patients, 1 of them bilateral)

Demographics and Preoperative Pathologies

Of the 214 patients enrolled in the STAARVISC™ study, 91 (42.5%) were male and 123 (57.5%) were female, with 13.1% of the patients (28/214) 60 years of age or younger. The study group underwent various surgical procedures, including intracapsular and extracapsular cataract extraction with IOL implantation, secondary IOL implantation, IOL repositioning, and IOL removal and replacement.

The majority of the extraction procedures were by phacoemulsification (87.4%). Posterior chamber PMMA IOLs were predominately implanted (165/214). Of the remaining surgeries involving primary IOL implantation, 34 received silicone posterior chamber IOLs and 5 received PMMA anterior chamber IOLs.

Preoperatively, the following conditions were recorded: corneal clarity, corneal disease, previous inflammatory disease, previous glaucoma, and the general health of the patient. A total of 43 patients (20.1%) were considered to have at least one pre-existing condition that could affect the outcome of the surgery.

Preoperative intraocular pressure (IOP) was also recorded. The mean preoperative pressure for all patients was 16 mm Hg. Patients with preoperative glaucoma also had a mean preoperative pressure of 16 mm Hg.

Conclusion

Patient accountability is adequate. Additionally the demographic and preoperative pathology profiles reported for STAARVISC™ indicate that this is a normal population for cataract extraction and IOL implantation.

Safety and Effectiveness Summary

Surgical Procedure

STAARVISC™ was evaluated for three criteria: maintenance of the anterior chamber depth, ability to facilitate IOL implantation, and overall performance of the product. These were subjective assessments required for each surgery performed. In all cases, STAARVISC™ was reported to have performed as required with the exception of it not facilitating IOL implantation. The investigator reported that it did maintain the anterior chamber depth and performed as expected.

Corneal Edema

Corneal edema was evaluated at the second (4-8 days) and third (14 days) postoperative examinations. Within the expected variability, due to the subjective nature of the assessments and preoperative conditions of the patients, STAARVISC™ performed equivalently to competitive products (95.2% clear at 3 months postoperatively).

Iritis

The overall rate of iritis (cells and flare) at the 4-8 day postoperative period was 58.8%. At the 14 day examination, the rate had decreased to 21.4%. The rate of iritis was judged to be equivalent to competitive products. Direct comparison was difficult due to the highly subjective nature of the surgeons' reporting criteria and the variability of the surgical procedure.

Intraocular Pressure Response

Tonometry readings were performed preoperatively and at three postoperative examinations. Mean preoperative pressures for the operative and fellow eyes were 16 and 15 mm Hg, respectively.

At one day postoperatively, the mean IOP was 17 mm Hg for all patients. At the 4-8 day and 14 day postoperative periods, the mean IOP was 15 mm Hg for patients with pre-existing glaucoma and 14 mm Hg for patients without preoperative glaucoma. The mean value for IOP was measured during the preoperative and postoperative periods and did not vary to a significant extent during the postoperative periods. The profile or distribution of the patients within certain IOP ranges did vary. At the 1 day postoperative period, IOP changed 10 mm Hg or less

from the preoperative value for 85.9% of the patients (n = 176). This included a rise or fall in IOP from the preoperative measurement.

IOP Substudy

This study was conducted to evaluate IOP response during the first 24 hours. A total of 60 patients were enrolled in this substudy.

The mean and standard deviation of IOP measurements were calculated for the patients enrolled in the IOP subgroup study. The results of this study were analyzed by comparison of the mean values at the required postoperative time periods with preoperative values. Statistical significance was determined by calculation of t-values and comparison of those t-values using the standard t-test.

At p = 0.001, no statistically or medically significant differences were noted at any of these postoperative intervals. This holds true for the entire substudy population (n = 60) and for the glaucoma exclusion group (n = 55).

A study of the IOP responses to Viscoat and Healon was reported in the literature. This study compared the effects of these two competitive viscoelastic materials on IOP in patients undergoing uncomplicated extracapsular cataract extraction and posterior chamber IOL implantation.

As with the STAARVISC™ study, the investigators removed the material by aspiration. The study showed a significant postoperative increase in IOP for Healon and Viscoat but no significant difference between the two materials.

The data from this published report were compared at the corresponding postoperative time intervals with those of STAARVISC™ obtained in the IOP substudy. There was consistently less change in IOP and a generally lower standard deviation with STAARVISC™ than reported with either Viscoat or Healon.

Although the raw data were not available to calculate statistical significance, a review of the data reveals that there are, for all practical purposes, no changes in IOP during the first day postoperatively with STAARVISC™ . This is in comparison to both Viscoat and Healon which produced a peak rise of 50% and 75%, respectively, during the first 24 hours postoperatively.

Endothelial Cell Loss

When evaluating endothelial cell loss, several factors must be taken into account, particularly patient age and type of surgery. In the sponsor's study, 88% of the cases involved cataract extraction by phacoemulsification. Those that were performed by intracapsular extraction or planned extracapsular extraction were due to surgical difficulties or complications encountered. Both of these biases would be expected to yield a higher cell loss rate. In spite of this bias, when comparing published studies of surgeries using saline, the data compare favorably for ages under 70 years with a

reported cell loss of –4.5% STAARVISC™ vs. 13.8% for saline. For the group 70 years of age and older the data were comparable (12.5% STAARVISC™ vs. 16.61% saline).

These data demonstrate that STAARVISC™ provides protection for endothelial cells during cataract extraction and IOL implantation

Note: In the preceding paragraph, negative values for the mean cell loss are reported. While it is not medically possible to observe an increase in endothelial cell counts (a negative cell loss), it is possible because of the error involved in the method for endothelial cell determinations to have a higher value for a postoperative period compared to the preoperative value.

Thus, if a patient was reported as having a net gain of cells, the percent cell loss was reported as negative.

XI. Conclusions Drawn from the Clinical Studies

The data in the PMA demonstrate that, when used as directed, STAARVISC™ is safe and effective for use as a surgical aid in anterior segment procedures including cataract extraction and intraocular lens implantation.

XII. Panel Recommendation

At an advisory meeting held on October 19, 1988 (see notes under Section XIII, CDRH Decision), the Ophthalmic Devices Panel recommended that the PMA P880030 for IVISC (STAARVISC™) be approved subject to submission of the following:

- Clarification of medications used in the study;
- Review of Investigator #6 reporting results (if results are inaccurate then the results will be eliminated from the study);
- Clarification of labeling regarding intraocular pressure rises after surgery; and
- Assurance that the amount of material used in the IOP substudy was representative.

The applicant has addressed the Panel's recommendations in this PMA. The information was reviewed by CDRH and found to comply with the Panel's recommendations and FDA's requests.

XIII. CDRH Decision

The device was initially clinically studied by International Pharmaceutical Products, Inc. (IPPI), under the tradename IVISC. IPPI submitted a PMA, P880030, for IVISC. The clinical data for P880030 were evaluated by the Ophthalmic Devices Panel on October 19, 1988, and found approvable.

Ownership of the PMA was subsequently transferred to Norbrook Laboratories, Ltd., who withdrew P880030 in 1993. In 1995, Norbrook transferred all rights to the PMA to STAAR Surgical Company.

With preclinical testing, STAAR Surgical Company has demonstrated that STAARVISC™ is the same product that was clinically studied by IPPI under the tradename IVISC. See Section IX, Summary of Preclinical Studies, for a description of the comparative testing done by STAAR Surgical Company to demonstrate that STAARVISC™ is the same product as IVISC.

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. CDRH approved this PMA in a letter to the PMA applicant dated JUL - 2 1999 and signed by the Director, Office of Device Evaluation.