SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

A. Premarket Approval Application (PMA) Number: P000046
Date Filed: November 6, 2000
Date Approved: APR 18 2001

B. Generic Name of Device: Sodium Hyaluronate

C. Trade Name of Device: Staar Surgical Company
STAARVISC™ II Sodium Hyaluronate

D. Applicant's Name and Address: Anika Therapeutics, Inc.
236 West Cummings Park
Woburn, MA 01801

E. Good Manufacturing Practice (GMP) Inspection: February 17, 2000

F. Ophthalmic Devices Panel: June 8, 1981 and March 18, 1983

II. INDICATIONS

STAARVISC™ II Sodium Hyaluronate is intended for use during surgery in the anterior and posterior segments of the human eye. Procedures include:

- Cataract extraction
- Intraocular lens (IOL) implantation
- Corneal transplantation surgery
- Glaucoma filtering surgery
- Surgical procedures to reattach the retina.

STAARVISC™ II is designed to create and maintain anterior chamber depth and visibility, protect corneal endothelial cells and other intraocular tissues, minimize interaction between tissues during surgical manipulation, and act as a vitreous substitute during retinal reattachment surgery. STAARVISC™ II also preserves tissue integrity and good visibility when used to fill the anterior and posterior segments of the eye following open sky procedures.

III. CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH) DECISION

The application includes by reference the data in PMA P810025 for the Amvisc™ sodium hyaluronate by Med-Chem Products, Inc. (PMA now owned by Bausch & Lomb Surgical, Inc.) and approved by FDA on October 31, 1983. Bausch & Lomb Surgical has authorized Anika Therapeutics, Inc to incorporate by reference the information contained in its approved PMA to manufacture the lenses.

CDRH approval of the Anika Therapeutics, Inc. PMA is based on (1) the safety and effectiveness data contained in PMA P810025 and (2) the results of the FDA inspection of the manufacturing facility. A summary of safety and effectiveness data for the Amvisc™ sodium hyaluronate appears in Attachment A.

On June 8, 1981, the Ophthalmic Device Section of the Ophthalmic; Ear, Nose, Throat; and Dental Devices Panel reviewed the PMA for the Amvisc™ Sodium Hyaluronate (P810025) and unanimously recommended approval of the PMA subject to the condition that all administrative requirements be met and that the applicant be in compliance with the device Good Manufacturing Practice regulations. On March 18, 1983 the Ophthalmic Device Section reviewed the applicant's amended PMA requesting additional indications for use and unanimously recommended approval of the application for anterior chamber surgery including the use of Amvisc™ as an aid in glaucoma filtration surgery and ophthalmic surgical procedures to implant an IOL, extract a cataract, and transplant the cornea.

CDRH concurred with the Panel recommendation and approved this application (P810025) and final labeling on October 31, 1983. In accordance with CDRH's announced policy (04/18/86 PMA Guidance Memorandum #86-4), this licensing PMA was not taken to the Panel. CDRH approved this application (P000046) and final labeling on APR 18 2001. In an on-site inspection on _____, the manufacturing facility was found to be in compliance with the device Good Manufacturing Practice regulations.

The device's shelf-life has been established and approved as 24 months.

Attachment

Summary of Safety and Effectiveness Data

I. General Information

A. Device Generic Name: sodium hyaluronate

B. Device Trade Name: AMVISC™

C. Applicant's Name and Address: Med-Chem Products, Inc.
236 West Cummings Park
Woburn, Massachusettes 01801

D. Premarket Approval Application (PMA) Number: P810025

E. Date of Panel Recommendations: June 8, 1981 and March 18, 1983

F. Date of Notification to Applicant: OCT 31 1983

II. Indications

AMVISC™ is indicated for use as an aid in posterior and anterior chamber surgeries including glaucoma filtering surgery and surgical procedures to reattach the retina, implant an intraocular lens (IOL), extract a cataract, and transplant the cornea.

Actions

AMVISC™ aids in surgery by acting as a lubricant and space-filling agent. Following use, the device is replaced by the body's natural processes of dissolution and restoration. In retinal reattachment surgery, AMVISC™ aids in the realignment of the retina to its anatomical position and holds it in place for reattachment. In IOL implantation, AMVISC™ aids by facilitating insertion of the lens with the result that ocular tissues are less damaged by the implantation procedure. In cataract extraction and glaucoma surgery, AMVISC™ aids by maintaining depth in the anterior chamber during surgery. In corneal transplant procedures, AMVISC™ aids in the placement, suturing and maintenance of shape of the donor graft.

III. Device Description

Sodium hyaluronate (NaHA), a naturally occurring polymer present in all the tissues of the body, is composed of sodium glucuronate and N-acetylglucosamine. These two constituents are linked alternately by beta 1-3 and beta 1-4 glycosidic bonds.

AMVISC™ is a highly purified preparation of NaHA obtained from rooster combs. AMVISC™ contains 10 milligrams per milliliter (mg/ml) of NaHA dissolved in a physiological sodium chloride solution. The molecular

weight (MW) of the NaHA is greater than 1,000,000 based on viscosity measurements. The combination of MW and NaHA concentration in AMVISC™ yields a viscoelastic solution that is able to function as an aid because of its lubricating and space filling properties.

Because the NaHA in AMVISC™ is prepared from avian tissues and is known to contain minute amounts of protein the physician should be aware of the potential for immune response of the types that can occur with the injection of any biological material. The labeling contains precautions to this effect.

IV. Alternative Practices or Procedures

Air or other gases, isotonic solutions such as Ringer's Lactate Solution (RLS) or balanced salt solution (BSS) and other NaHA devices are the products most commonly used as surgical aids in ophthalmic surgery. BSS, RLS and/or air constitute the most commonly used products for restoration of the volume of the eye.

V. Summary of Studies

A. Preclinical Toxicological Studies:

These studies were conducted to evaluate the safety of AMVISC™ when the device was implanted in different tissue locations in four different species of animals.

1. Immune Effects

The immunogenicity of AMVISC™ was studied by toe pad injections in rabbits. No immunogenic effects were observed. Intraocular injections of AMVISC™ in owl monkeys and intraarticular injections of AMVISC™ in horses also support this observation.

2. Intravitreal Injections

The safety of AMVISC™ for use as an aid in retinal reattachment surgery was evaluated by aspirating the vitreous of owl monkey eyes and injecting AMVISC™ to replace the removed vitreous. These studies, employing both single and multiple injections, demonstrated that AMVISC™ is non-toxic and non-immunogenic when used in situ as an aid in posterior segment surgical procedures, and that AMVISC™ is removed from the eye by outflow into the aqueous.

3. Intraarticular and Intradermal Injections

Following arthrocentesis, AMVISC™ was injected into different horse joints, and was also evaluated by intradermal injection into guinea pigs. The NaHA was removed from the joints after AMVISC™ injection. No adverse local or systemic effects were observed, macroscopically or microscopically, after single and multiple injections.

The intradermal injection study in guinea pigs was performed to compare the inflammatory responses obtained with isotonic saline and histamine, used as negative and positive controls, and another NaHA product (HEALON®). The inflammatory response obtained with isotonic saline was mild and associated with the trauma of injection. The inflammatory responses obtained with AMVISC™ and HEALON® were mild and comparable to the response obtained with isotonic saline.

Conclusion

The results from the above toxicological studies provide reasonable assurance that the device is non-toxic and non-immunogenic.

B. Microbiological Testing:

This testing was performed to provide a high level of assurance that the device is sterile and non-pyrogenic. The sterilization process used by the manufacturer involves a series of procedures designed to kill and remove contaminating bacteria. The procedures are validated by determining bioburden of the starting material, at stages during the manufacturing process and on the finished device, before and after packaging. Sterility tests, performed according to the United States Pharmacopeia XX (U.S.P. XX) have shown that the finished device is sterile. The U.S.P. pyrogen tests have shown that the device is non-pyrogenic.

The sponsor has submitted data adequate to establish a shelf-life expiration date of 2 years.

Conclusion

The results of these tests provide reasonable assurance that the device is safe from a microbiological standpoint. The sponsor has demonstrated product stability and sterility for a period of 2 years.

C. Clinical Studies:

Objectives

The sponsor conducted studies to demonstrate whether AMVISC™ is safe and effective as a device that can:

1. serve as an aid in holding tissues in place during and after surgical procedures to reattach the retina;

2. serve as an aid to fill space left by the loss of ocular fluid or tissue during or after surgery in the anterior chamber and after removal of the vitreous in vitrectomy and open sky procedures; and

3. serve as an aid in performing selected surgical procedures, namely, cataract extraction, IOL implantation and corneal transplant surgery.

At the time clinical studies were initiated by the sponsor, there were no alternate products that had been approved by FDA as safe and effective for any of the uses being investigated. The use of AMVISC™ was, therefore, evaluated by the surgeons with respect to the device's safety and effectiveness for the uses described above. AMVISC™ was investigated for those uses because the device offered the advantages of high viscosity and a refractive index that minimized distortion, thus enabling the surgeon to observe the area of surgery clearly.

In certain instances the surgeons were able to compare their experience with the device with their experience with air and saline. BSS has been shown to be safe and effective and is the subject of an approved New Drug Application for use in ophthalmic surgery. Gases and salt solutions, however, are not specifically approved as aids for the uses that the sponsor proposed for AMVISC™.

FDA determined that the study designs are adequate and that the data obtained from the studies constitute valid scientific evidence from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of the device under its conditions of use. FDA acknowledges that at the time these studies were performed there were no products of proven safety and effectiveness for the uses proposed for AMVISC™. FDA believes, however, that the data obtained in the studies, together with the data from the preclinical studies, establishes the safety of AMVISC™ in that the surgeons did not observe any adverse reactions or complications indicating that AMVISC™ interfered with healing or adversely affected the tissues subjected to the trauma of surgery.

Safety

The data from the studies in which the effects of AMVISC™ on ocular tissues were investigated was assessed collectively to allow an evaluation of the device's safety under various surgical procedures or use conditions. FDA concludes that this collective assessment is appropriate because although AMVISC™ was studied as an aid in a variety of surgical procedures, the underlying mechanism of action of the device is the same in each procedure and the same major complications, e.g., increased intraocular pressure (IOP), corneal thickening, and other adverse effects on ocular tissue, were monitored or reported upon by the investigators in these studies. For example, IOP was monitored in the anterior segment uses of AMVISC™ because of a concern that increased IOP might be associated with the use of NaHA and that the increases could be sight-threatening. IOP measurements also were performed following use of AMVISC™ in retinal reattachment procedures. Assessing the

information collectively also permitted an evaluation of the device's safety under a variety of conditions of use. Finally, this approach allowed for an aggregating of the reports of complications associated with the use of AMVISC™ to assure that no significant finding would be lost due to a small number of observations.

Although IOP monitored in these studies was evaluated by each investigator using slightly different criteria, such as definitions of when IOP has increased, FDA concluded that these differences do not preclude an assessment of the incidence of clinically significant increases in IOP or its possible effect on the sight of the patient or the outcome of the surgery. These postoperative elevations in IOP were observed when AMVISC™ was used during anterior segment surgery. The rates and amount of rise in IOP were not clinically significantly different from the elevated IOP observed when anterior segment surgery was performed without the use of the device. There were no reports of poor surgical outcome or visual loss which could be attributed to AMVISC™. Many of the surgical techniques, and the reasons for the surgery itself, can contribute to the occurrence of increased IOP or to the eventual surgical outcome. In the case of retinal reattachment surgery or cataract extraction surgery, for example, successful outcome is not a simple definition and is affected by the type, nature, and extent of the surgery and resulting trauma to the tissues, the general condition of the eye and of the patient, and the particular surgical technique employed by the surgeon.

There were no reports of intraocular infection, severe inflammatory response, or any adverse reactions in any patient receiving AMVISC™. No problems other than the reported mild, transient inflammatory responses were encountered during surgery that could be attributable to AMVISC™.

AMVISC™ was neither associated with nor demonstrated to be a causative factor in any undue increase in IOP following anterior segment surgery. While there are reports of postoperative rises in IOP, these occurred early and cannot be distinguished from increases in IOP associated with surgical trauma. The rises disappeared spontaneously or responded to conventional therapy. The labeling contains precautionary statements that postoperative IOP should be carefully monitored.

Conclusion

FDA concludes that the collective data from all these studies constitute valid scientific evidence that can be evaluated to assess the safety of AMVISC™ for the indications proposed by the sponsor.

Based upon these findings, and after a review of the deliberations and recommendations of the Ophthalmic Device Section of the Ophthalmic; Ear, Nose, Throat; and Dental Devices Panel, FDA concludes that AMVISC™ is safe for the indications in the labeling

submitted by the applicant.

Effectiveness

The studies described in Section C (Objectives) also were intended to gather data to allow an evaluation of the effectiveness of AMVISC™ as an aid in a variety of ophthalmic surgical procedures. The data supporting each specific proposed use were evaluated, and, as appropriate, the data also were evaluated collectively in assessing the effectiveness of AMVISC™ as an aid in anterior and posterior surgical procedures.

FDA concluded that the success rate of the surgery in which AMVISC™ was used as an aid is not an appropriate criterion for the effectiveness of AMVISC™ because the patient's final outcome is affected by preoperative severity, surgical techniques, general health of the patient, and other therapeutic measures that may be used, such as drugs to treat glaucoma. Furthermore, as an aid, AMVISC™ is intended to help the physician perform the surgery through AMVISC™'s characteristics, such as viscosity and transparency, which allow the device to remain in the surgical area or to hold tissues in place during and after surgery and also allow the surgeon to observe the area of surgery clearly. In some cases, investigator experiences or evaluations of AMVISC™'s usefulness as an aid in performing specific surgical procedures were considered by FDA and are discussed where appropriate.

1. Retinal Reattachment Surgery

The sponsor supplied information from a 6-year clinical study of 286 patients in whom AMVISC™ was used as an aid during retinal reattachment surgery.

AMVISC™ was injected into the vitreous cavity in order to push the retina into the required position and to hold it in place during and after surgery. The device was used as an aid in the management of vitreoretinal disease of 294 eyes of 286 patients. In 76 scleral buckling procedures to repair rhematogenous retinal detachments, AMVISC™ was injected into the vitreous following release of subretinal fluid, to maintain IOP and to realign the retina by a tamponade. In 175 other eyes with massive preretinal retraction and retinal detachments, open-sky vitrectomy procedures were performed. In these cases AMVISC™ was used to maintain the shape and clarity of the vitreous space during the operation and at the end of vitrectomy the posterior and anterior segments were filled with AMVISC™. In 45 open-sky vitrectomy procedures, corneal transplants were performed where the corneal button was replaced and the replacement was held in place and sutured using AMVISC™ as an aid. In other procedures AMVISC™ was used to reform a flat anterior chamber in the correction of glaucoma (5 cases), and in the management of a dislocated IOL (1 case).

During 81 closed vitrectomies, AMVISC™ also was applied extraocularly between the surgical contact lens and the cornea to improve visualization during surgery. AMVISC™ was injected intraocularly once in 149 patients, twice in 54 patients and three times in 3 patients.

Investigators involved in this study concluded that the device aided in the surgical procedures. The viscoelastic properties of the device helped in maintaining the localization and separation of tissues. The lubricating properties of the device also were instrumental in allowing easy placement and manipulation of tissues for suturing. Additional advantage was gained by the visual clarity of the surgical field during the surgical procedure. During the course of the study, all the intraocular tissues were exposed to AMVISC™, and the surgeons did not observe any adverse reactions to AMVISC™ or any complications that arose from its use. Furthermore, there was no indication that AMVISC™ interfered in any way with healing or adversely affected the tissues subjected to the trauma of surgery.

2. Anterior Segment Surgery

A study was performed to evaluate the use of AMVISC™ as a device to aid in anterior segment surgery. A total of 18 patients was evaluated for any abnormal elevation of IOP or abnormal inflammatory response such as corneal edema and iritis. In 12 patients, phacoemulsification was followed by the implantation of a posterior chamber IOL. In three patients, extracapsular cataract extraction was followed by implantation of two posterior and one anterior chamber IOLs. Phacoemulsification with no IOL implantation was performed in one patient and keratoplasty procedures in two patients. The results of this study show no significant adverse effects that could be reasonably attributed to the use of AMVISC™. AMVISC™ also was effective as an aid in protecting ocular tissues, maintaining the depth of the anterior chamber, implanting IOLs, and placing and suturing of tissues. As discussed above, AMVISC™ also was an effective aid in 45 open-sky vitrectomy procedures, 5 anterior chamber reformation procedures, and in the management of a dislocated IOL.

Conclusion

FDA concludes that the data from these studies demonstrated, by valid scientific evidence, that AMVISC™ is an effective aid during posterior chamber surgical procedures. During retinal reattachment surgery, AMVISC™ fills the vitreous cavity, pushes the retina into its required (original) position, and holds the retina in position during and after surgery. In open-sky vitrectomy procedures and corneal transplant surgery, AMVISC™ is effective as an aid in transplanting and suturing of the cornea and protects ocular structures in general during the surgical procedures.

FDA also concludes that the data from these studies demonstrate, by valid scientific evidence, that AMVISC™ is effective as an aid in anterior chamber surgical procedures. During cataract extraction surgery and IOL implantation, AMVISC™ aids in maintaining the depth of the anterior chamber and in protecting the corneal endothelium and other ocular structures during surgery.

VI. Potential Adverse Effects of the Device on Health

Because AMVISC™ is derived from biological sources, it may contain protein or other matter which can cause allergic reactions in certain susceptible individuals. These reactions may range from mild rashes or fever to anaphylaxis. The device's labeling contains precautionary statements to physicians about potential risks from injection of AMVISC™.

Other potential adverse effects on health resulting from the use of this device are indicated in the package insert under "adverse reactions" and "precautions" (Attachment A).

VII. Panel Recommendation

On June 8, 1981, the Ophthalmic Device Section of the Ophthalmic; Ear, Nose, Throat; and Dental Devices Panel unanimously recommended approval of the PMA for AMVISC™ for use as an aid in posterior segment surgery including retinal reattachment procedures subject to the following conditions:

1. All administrative requirements must be met.

2. The applicant must be in compliance with the device Good Manufacturing Practice (GMP) regulations.

The sponsor subsequently amended the application to include other indications for use in addition to those considered during the June 8, 1981, Section meeting. On March 18, 1983, the Ophthalmic Device Section reviewed the applicant's amended PMA requesting additional indications for use. The Section unanimously recommended approval of the application for anterior chamber surgery including the use of AMVISC™ as an aid in glaucoma filtration surgery and ophthalmic surgical procedures to implant an IOL, extract a cataract, and transplant the cornea.

VIII. FDA Decision

FDA has determined that the conditions recommended by the panel during the June 8, 1981, meeting, and subsequently applied to the approval recommendation at the March 18, 1983, meeting, have been met.

FDA has reviewed the data in the PMA and the Section's recommendations and has determined that the data demonstrate, by valid scientific evidence, that AMVISC™ is safe and effective for use as an aid in posterior and anterior chamber surgeries including glaucoma filtration surgery and ophthalmic surgical procedures to reattach the retina,

implant an IOL, extract a cataract, and transplant the cornea. FDA believes that the probable benefits to health resulting from the use of the device for these indications outweigh any probable risks from use of the device.

FDA concurred with the Section's recommendation and approved the application and final labeling on OCT 31 1983 . The shelf-life has been established as 2 years. In an on-site inspection on the firm was found to be in compliance with the device GMP regulations.

IX. Conditions of Approval

In addition to the standard "Conditions of Approval" (Attachment B), the sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109. Copies of approved package insert, syringe labels, and syringe outer container labels (Attachment A) are available to interested persons for inspection at:

Food and Drug Administration
Office of Medical Devices
Document Control Center (HFK-20)
8757 Georgia Avenue
Silver Spring, Maryland 20910

Attachments A and B