



P960034

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 12 1998

Ms. Toni D. Elliott
Manager, Regulatory Affairs
Pharmacia & Upjohn Company
592 Ceresia Court
Pickerington, OH 43147

Re: P960034
CeeOn™ Heparin Surface Modified (HSM) Ultraviolet-Absorbing
Polymethylmethacrylate (PMMA) Posterior Chamber Intraocular Lenses (IOLs)
Filed: October 1, 1996
Amended: November 14 and December 6, 1996; March 12, June 6, July 28, August 18,
August 26, and September 24, 1997; February 12, May 12, June 23, July 9, and
July 15, and August 12, 1998

Dear Ms. Elliott:

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) which requests approval for lens models with the heparin surface modification applied to all your single-piece PMMA lenses approved in P810055. These models will be specified with a "C" following the number designation for the corresponding non-HSM PMMA model. The lenses will be marketed under the trade name CeeOn™ HSM PMMA IOLs. This device is indicated for primary implantation for the visual correction of aphakia in adults in whom a cataractous lens has been removed by an extracapsular cataract extraction (ECCE) or phacoemulsification. They are intended to be placed in the capsular bag. 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 devices upon receipt of this letter.

The sale, distribution, and use of these devices 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 devices, the devices are 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.

CDRH approval is subject to full compliance with the conditions described in the enclosure and the following:

1. Registration of all patients receiving the above-reference intraocular lens must be continued and the data base shall be maintained indefinitely, or until the applicant is otherwise notified.
2. A way of facilitating adverse reaction reporting, such as an 800 telephone number, must be maintained.
3. Advertising and other printed materials prepared by your firm or its distributors may not include indications or claims not included in the FDA-approved labeling for the device, e.g., that the use of this lens results in reduced incidence of adverse events associated with inflammatory reactions or similar claims.

Expiration dating for this device has been established and approved at 3 years 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, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. 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.

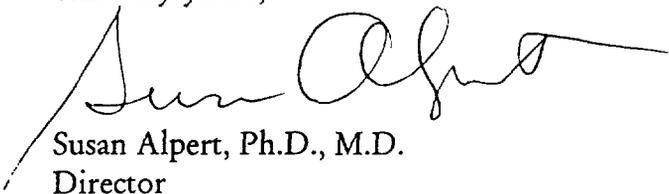
All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

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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. Claudine Krawczyk at (301) 594-2053.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Susan Alpert", with a long horizontal flourish extending to the right.

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 Effected" 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 Effected" 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 Effected." 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

- A. Premarket Approval Application (PMA) Number: P960034
Date Filed: October 1, 1996
Date Approved: AUG 12 1998
- B. Generic Name of Device: Heparin Surface Modified (HSM) Ultraviolet-Absorbing Posterior Chamber Intraocular Lens (IOL)
- C. Trade Name of Device: CeeOn™
- D. Applicant's Name and Address:
Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001
- E. Good Manufacturing Practice (GMP) Inspection Dates:
Date of Inspection (Groningen, The Netherlands): October 31, 1997
Conclusion: The manufacturing site was found to be in compliance with device GMP requirements.
- F. Ophthalmic Devices Panel (Panel):
Date Reviewed: October 20, 1997
Recommendation: Approvable

II. INDICATIONS

CeeOn™ HSM IOLs are indicated for primary implantation for the visual correction of aphakia in adults in whom a cataractous lens has been removed by an extracapsular cataract extraction (ECCE) or phacoemulsification. They are intended to be placed in the capsular bag.

III. SUMMARY

Several clinical investigations of the CeeOn™ HSM lenses were conducted to investigate the safety and effectiveness of the HSM posterior chamber IOLs. The first study was in Models UB89H, 720H, and 810H to evaluate the safety and the effectiveness of the lenses for the visual correction of aphakia (411 cohort patients). The cohort population of 411 represents the total number of completely followed patients. The core population of 686 represents the total number of

patients enrolled in the study. Data from the first study on 411 patients followed postoperatively for 12-14 months were clinically and statistically evaluated against historical controls(1). The population at risk for developing visually-disabling cataracts and needing cataract surgery is typically elderly; the elderly population has a slightly higher proportion of females to males. The average age of the 411 cohort patients was 72.5 years at the time of surgery; 54.3% of the 411 cohort patients were female and 45.7% were male. The inclusion/exclusion criteria did not exclude patients on the basis of gender or gender-related pathology. The study population was 94.6% Caucasian for the 411 cohort; 3.6% African-American, and 1.7% other. In this study, which began in 1990, all patients who met the inclusion criteria were included in the study.

Most CeeOn™ patients achieved a visual acuity of 20/40 or better. The rates for both overall and best-case visual acuity of 20/40 or better for the 411 cohort exceed the FDA grid values.

A second study was conducted in Model 815HS HSM IOLs to evaluate the effectiveness of the lenses in reducing the postoperative inflammatory response (assessed from the presence of giant cells and/ or cellular deposits as markers of inflammation) following cataract surgery in routine patients and in patients with diabetes or glaucoma. The postoperative inflammatory response was assessed from the occurrence of giant cells on the lens surface as determined by specular micrograph and from the presence of cell deposits on the lens surface as determined by slit-lamp. Patients in each group were randomized to receive either an HSM or non-HSM intraocular lens (same model) following cataract extraction. A total of 367 patients were enrolled in this study. For each group, the number of patients to receive an HSM or non-HSM lens are as follows: 112 routine patients received an HSM lens, and 108 received a non-HSM lens; 41 diabetic patients received an HSM lens, and 48 received a non-HSM lens; and 30 glaucoma patients received an HSM lens, and 28 received a non-HSM lens. The presence of giant cells or cellular deposits was evaluated for all patients seen at each visit, and comparisons between the HSM and non-HSM lenses were performed. The percentage of patients reported with giant cells on the lens surface demonstrated

(1) In 1983 Stark et. al. (*Ophthalmology*, 90(4): 311-317) published a grid of historical clinical data established from review of 45,543 eyes implanted with IOLs PMA-approved before 1982. FDA adopted the grid, which includes adverse reaction rates, sight-threatening complication rates and visual acuity results, for comparison to new lens models. Based on the analysis of the detailed data presented in the PMA, it was determined that the clinical performance of Models 720H, 810H, and UB89H compare favorably with the grid of historical data (refer to Section IV.B.1. Safety and Effectiveness Data). The cumulative rate of hyphema in the 411 cohort was higher than reported in the Stark grid; however, this complication did not persist. The rates for all the remaining sight-threatening complications and all the adverse reactions were less than the Stark grid.

that a statistically significant difference in favor of the HSM IOLs for the early postoperative months. For the routine patient population, this difference was statistically significant for up to 6 months. For the glaucoma patient population, the difference was statistically significant for up to 3 months. For the diabetic patient population, the difference was statistically significant for up to the first year. The percentage of patients reported with cellular deposits on the lens surface demonstrated that a statistically significant difference in favor of the HSM IOLs was only evident at the 3-month visit for all three patient populations. This difference was also evident at the 6-month visit in the glaucoma patient population. The results of this study demonstrate some reduction in the amounts of cellular deposits and giant cells for the CeeOn™ HSM IOLs compared to non-HSM PMMA lenses (refer to Section IV.B.2. Safety and Effectiveness Data). However, the effectiveness of the heparin surface modified lenses in reducing the incidence of complications or adverse events associated with inflammatory reaction has not been established.

Several “international” and “independent” studies were performed to evaluate the incidence of postoperative inflammation following cataract surgery in patients who received an HSM IOL. The analyses for several of these studies supported the results from the Model 815HS study in that trends were noted towards reduced cellular deposits and reduced presence of giant cells in patients with HSM IOLs as compared to those with non-HSM PMMA IOLs (refer to Section IV.B.3. Safety and Effectiveness Data). However, variability in the effectiveness results and, in some cases, small sample sizes and the absence of controls rendered the data confirmatory in nature rather than pivotal.

IV. SAFETY AND EFFECTIVENESS DATA

A. Nonclinical Studies

The applicant has performed nonclinical studies on this device in accordance with the FDA guidance document for testing intraocular lenses dated June 9, 1980. The applicant conducted a battery of in vivo and in vitro acute and chronic toxicity tests that establish the biocompatibility of the lens materials. These studies, combined with data from chemistry and engineering analyses, demonstrate the suitability of the material and overall device design for use in an intraocular lens. The adequacy of the manufacturing processes, including sterilization, was established through review of the manufacturing information in the PMA as well as through on-site inspections. Nonclinical testing demonstrates the safety and effectiveness of this device from microbiology, toxicology, engineering, and manufacturing perspectives. Five additional studies were performed to evaluate the toxicity and virus inactivation of the heparin, and the stability of the heparin modification on the surface of the IOLs. These studies demonstrated no signs of toxicity of the heparin or the HSM IOLs, successful reduction of pseudorabies and poliovirus in the heparin, and stability of the heparin modification on the surface of the IOL.

B. Clinical Studies

1. Study of Models UB89H, 720H, and 810H for correction of aphakia and safety

Overall Visual Acuity (20/40 or better)

	<u>Cohort=411</u>	<u>FDA Grid</u>
Age < 60 Years	97.0% [31/32]	93.7%
Age 60-69 Years	94.0% [97/103]	90.8%
Age 70-79 Years	92.0% [169/183]	88.6%
Age ≥ 80 Years	81.0% [75/93]	75.2%
All Ages Combined	91.0% [372/411]	88.0%
*Best Case, All Ages Combined	96.0% [277/290]	94.0%

Adverse Reactions

	<u>Core=686</u>	<u>FDA Grid</u>
Hypopyon	0.0% [0]	0.4%
Intraocular Infection	0.0% [0]	0.1%
Acute Corneal Decompensation	0.0% [0]	0.2%
Surgical Reintervention	1.2% [8]	2.0%

Postoperative Complications

	<u>Cohort=411</u>	<u>FDA Grid</u>
Cumulative Hyphema	4.4% [18]	1.0%
Cumulative Macular Edema	1.9% [08]	3.5%
Persistent Macular Edema	0.7% [03]	0.8%
Cumulative Pupillary Block	0.0% [00]	0.3%
Persistent Secondary Glaucoma	0.2% [01]	0.5%
Persistent Cyclitic Membrane	0.0% [00]	<0.1%
Persistent Vitritis	0.0% [00]	0.1%
Cumulative Retinal Detachment	0.0% [00]	0.5%
Cumulative Endophthalmitis	0.0% [00]	<0.1%
Persistent Corneal Edema	0.2% [01]	0.6%
Persistent Iritis	0.0% [00]	1.0%
Cumulative Lens Dislocation	0.0% [00]	0.4%

*Best Case: Excludes patients with preoperative ocular pathology, macular degeneration, abnormal cornea, or endothelial disease at any time.

2. Study in Model 815HS in routine, glaucoma, and/ or diabetic patients for reduction of cellular deposits and giant cells

Percent of Patients with Giant Cells and/ or Cellular Deposits

$N_{\text{routine}} = 220$ (112 with HSM and 108 with non-HSM)

$N_{\text{glaucoma}} = 58$ (30 with HSM and 28 with non-HSM)

$N_{\text{diabetic}} = 89$ (41 with HSM and 48 with non-HSM)

Visit	Routine		Glaucoma		Diabetic	
	HSM	Non-HSM	HSM	Non-HSM	HSM	Non-HSM
Giant Cells – Specular Micrography						
Week 1	2% (2/100)	*26% (26/101)	8% (2/24)	*28% (5/18)	11% (4/38)	*41% (19/46)
Month 1	7% (7/105)	*52% (49/95)	9% (2/23)	*28% (5/18)	13% (5/39)	*55% (24/44)
Month 3	11% (11/101)	*47% (42/90)	10% (2/20)	*48% (10/21)	3% (1/37)	*59% (26/44)
Month 6	8% (7/90)	*32% (27/85)	20% (3/15)	41% (7/17)	14% (5/35)	*42% (17/41)
Month 12	7% (4/62)	11% (8/71)	11% (1/9)	33% (5/15)	7% (2/31)	*26% (10/38)
Cellular Deposits – Slit Lamp						
Week 1	20% (22/108)	25% (26/103)	15% (4/27)	23% (6/26)	13% (5/39)	13% (6/48)
Month 1	13% (14/107)	23% (23/102)	11% (3/28)	20% (5/25)	10% (4/41)	15% (7/47)
Month 3	13% (14/105)	*27% (27/99)	8% (2/24)	*36% (9/25)	3% (1/38)	*17% (8/48)
Month 6	14% (13/93)	24% (21/87)	0% (0/21)	*33% (7/21)	0% (0/37)	7% (3/45)
Month 12	14% (11/78)	20% (16/79)	20% (3/15)	28% (5/18)	6% (2/34)	13% (6/45)

* Statistical significance ($p < 0.05$) in favor of HSM lens.

3. International and Independent Studies

Clinical Utility Variables by Study
International Pharmacia HSM IOL Studies

Study	Primary Effectiveness Variables	Secondary Effectiveness Variables
87IE01	Cellular and pigment deposits Capsular fibrosis Elschnig pearls Synechia Iritis	
87IE02	Iritis Synechia Cellular, pigment and fibrin deposits Capsular fibrosis Corticosteroid treatment	Complications Visual acuity Adverse reactions
88IE03	Corticosteroid treatment Iritis Cellular, pigment and fibrin deposits Synechia Capsular fibrosis Elschnig pearls	
89IE02	Blood-aqueous barrier breakdown	Corneal edema Posterior synechia Cellular, pigment and fibrin deposits
89IE03	Giant cells Fluorophotometry Laser cell flare meter	
90ES01	Giant cells Cellular deposits	Pigment and fibrin deposits Capsular fibrosis Visual acuity
90IE01	Giant and epithelioid cells Cellular deposits	Pigment deposits Fibrin deposits Capsular fibrosis Visual acuity
90IE02	Corticosteroid therapy Iritis Cellular, pigment and fibrin deposits Synechia Capsular fibrosis Elschnig pearls	

Summary of Clinical Results of Pharmacia Studies
Double-Blind, Randomized, Controlled, Minimum One-Year Follow up

Variables	Study 87IE02	Study 88IE03	Study 90IE01	Study 90IE02
Patients	267 (129 HSM; 138 non-HSM)	524 (260 HSM; 264 non-HSM)	239 (118 HSM; 121 non-HSM) (Glaucoma/Diabetes)	99 (51 HSM; 48 non-HSM) (Asian)
Lens Model	700	725	720	725
Follow-up	3 Years	2 Years	1 Year	1 Year
Cell Deposits	p<0.05 cumulative rate up to 1 year in favor of HSM; no difference at 2 and 3 years	p<0.05 at 3 to 6-month and 1-year visits in favor of HSM	p<0.05 at each visit (except 1 week) in favor of HSM	p<0.05 at 3 to 6 month and 1-year visits in favor of HSM
Pigment Deposits	p<0.05 cumulative rate up to 1 year in favor of HSM; no difference at 2 and 3 years	p<0.05 cumulative rate up to 1 year in favor of HSM	Incidence similar for HSM and PMMA	Incidence similar for HSM and PMMA
Fibrin	Incidence low and similar for HSM and PMMA	Trend shows higher incidence in PMMA at early visits; trend reversed later	p<0.05 at 1-year visit in favor of PMMA (non-HSM)	Incidence similar for HSM and PMMA
Capsular Fibrosis	Incidence similar for HSM and PMMA	Incidence similar for HSM and PMMA	Incidence similar for HSM and PMMA	Incidence similar for HSM and PMMA
Elschnig Pearls	P<0.05 at 1-year visit in favor of PMMA (non-HSM)	Incidence similar for HSM and PMMA	Not evaluated	Incidence similar for HSM and PMMA
Iritis	Incidence similar for HSM and PMMA	Incidence similar for HSM and PMMA	Not evaluated	Incidence similar for HSM and PMMA
Synechia	Incidence similar for HSM and PMMA	Incidence similar for HSM and PMMA	Not evaluated	Incidence similar for HSM and PMMA
Giant Cells	Not evaluated	Not evaluated	p<0.05 at each visit in favor of HSM	Not evaluated

Summary of Clinical Results of Pharmacia Studies
 Studies With Less Than One-Year Follow up OR No Control Group OR In a Specific
 Patient Population

Variables	Study 87IE01	Study 89IE02	Study 89IE03	Study 90ES01
Patients	73 (all HSM)	61 (34 HSM; 27 non-HSM)	54 (29 HSM; 25 non-HSM)	59 (27 HSM; 32 non-HSM) (Exfoliation Syndrome)
Lens Model	700	725	725	725
Follow-up	1 Year	6 Months	3 Months	1 Year
Blood Aqueous Barrier	Not evaluated	p<0.05 at 6 months in favor of HSM	Not evaluated	Not evaluated
Cell Deposits	Incidence increased over year	Incidence similar for HSM and PMMA	Not evaluated	p<0.05 cumulative rate up to one year in favor of HSM
Pigment Deposits	Incidence increased over year	Not evaluated	Not evaluated	Incidence similar for HSM and PMMA
Fibrin	Incidence decreased over year	Not evaluated	Not evaluated	Incidence similar for HSM and PMMA
Capsular Fibrosis	Incidence increased over year	Not evaluated	Not evaluated	Incidence similar for HSM and PMMA
Elschnig Pearls	Incidence increased over first 6 months, but dropped significantly by one year	Not evaluated	Not evaluated	Not evaluated
Synechia	Highest incidence reported at 3 and 6 months	Incidence similar for HSM and PMMA	Not evaluated	Incidence similar for HSM and PMMA
Corneal Thickness	Not evaluated	Incidence similar for HSM and PMMA	Not evaluated	Not evaluated
Intraocular Pressure	Not evaluated	Incidence similar for HSM and PMMA	Not evaluated	Not evaluated
Iritis	Reported incidence only at early postoperative visits	Not evaluated	Not evaluated	Not evaluated
Anterior Chamber Reaction (aqueous flare and cell)	Not evaluated	Not evaluated	Incidence similar for HSM and PMMA	Not evaluated
Giant Cells	Not evaluated	Not evaluated	p<0.05 at 1 and 3 months in favor of HSM; p<0.05 for small cells at 1 month	Incidence similar for HSM and PMMA

Summary of Clinical Results - Independent Studies

Variables	Study by Stavrou, P.	Study by Lin, C.L.	Study by Ravalico, G.	Study by Percival, S.	Study by Jones, N.
Patients/ Eyes	32 (all HSM) (Uveitis)	121 (73 HSM; 48 non-HSM) (Glaucoma, Diabetes, Uveitis)	40 (20 with pseudoexfoliation syndrome and 20 control; 10 HSM and 10 non-HSM in each group)	36 (all HSM) (Iridocyclitis)	20 (all HSM) (Fuch's Heterochromic Uveitis)
Lens Model	720	Not specified	720	720 & 725	728
Follow-up	16 Months (avg.)	3 Months	6 Months	Up to 2 Years	14.5 Months (avg.)
Blood Aqueous Barrier	Not evaluated	Not evaluated	p<0.01 reduction from preop for HSM and PMMA in patients with pseudoexfoliation syndrome	Acute postop fibrin reaction related to blood-aqueous barrier breakdown-25% incidence	Not evaluated
Cell Deposits	15.6%	Incidence similar for HSM and PMMA	Lower incidence of lenses with deposits in HSM group (no statistics) at 3 and 6 months	Incidence of 25% for fibrin deposits; incidence of 16.6% for implant precipitates	Incidence of 10% for fibrin deposits; incidence of 20% for significant giant cells (50% cumulative rate)
Synechia	25%	Incidence similar for HSM and PMMA	Not evaluated	Incidence of 8.3%	Not evaluated
Capsular Fibrosis	9.3% required YAG capsulotomy (50% reported haze)	Incidence similar for HSM and PMMA	Not evaluated	Incidence of 8.3%	Incidence of 35%
Iritis	Not evaluated	Not evaluated	Not evaluated	Not evaluated	Not evaluated
Anterior Chamber Reaction (aqueous flare and cell)	Not evaluated	Less clinically significant edema in HSM group at 1 week	Not evaluated	Not evaluated	Not evaluated
Corneal Edema	Not evaluated	Less clinically significant edema in HSM group at 1 week	Not evaluated	Not evaluated	Not evaluated

V. CONCLUSION

The Center for Devices and Radiological Health (CDRH) and the Panel 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. At an advisory meeting on October 20, 1997, the Panel recommended that Pharmacia & Upjohn's PMA for the CeeOn™ HSM IOLs be approved subject to submission to and approval by CDRH of labeling modifications as described by the Panel. CDRH concurred with the Panel's recommendation. In an amendment received by FDA on August 12, 1998, Pharmacia & Upjohn submitted the revised labeling. CDRH approved this PMA in a letter to the PMA applicant dated AUG 12 1998 and signed by the Director, Office of Device Evaluation.

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DRAFT - 08/98

CeeOn™
LENSES

PRODUCT INFORMATION

**HEPARIN SURFACE-MODIFIED
ULTRAVIOLET-ABSORBING PMMA
ONE-PIECE POSTERIOR CHAMBER
INTRAOCULAR LENSES**



Pharmacia & Upjohn

PRODUCT INFORMATION

PRESCRIPTION DEVICE

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

DEVICE DESCRIPTION

The CeeOn heparin surface-modified (HSM) ultra-violet (UV) light-absorbing posterior chamber intraocular lenses (IOLs) manufactured by Pharmacia & Upjohn Company are designed to be positioned posterior to the iris where the lens should replace the optical function of the natural crystalline lens. However, accommodation will not be replaced.

INDICATIONS

CeeOn HSM IOLs are indicated for primary implantation for the visual correction of aphakia in adults in whom a cataractous lens has been removed by extracapsular cataract extraction (ECCE) or phacocmulsification. They are intended to be placed in the capsular bag.

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Physicians considering lens implantation under any of the following circumstances should weigh the potential risk/benefit ratio:

1. Recurrent severe anterior or posterior segment inflammation or uveitis.
2. Patients in whom the intraocular lens may affect the ability to observe, diagnose or treat posterior segment diseases.
3. Surgical difficulties at the time of cataract extraction which might increase the potential for complications (e.g., persistent bleeding, significant iris damage, uncontrolled positive pressure or significant vitreous prolapse or loss).
4. A distorted eye due to previous trauma or developmental defect in which appropriate support of the IOL is not possible.
5. Special consideration should be given to the dimensions of lenses at the extreme ends of the power range () 34D, () 4D) in relation to the anatomical clearances in the patient's eye. The potential impact of the factors such as optic central thickness, optic edge thickness and overall lens size on a patient's long-term clinical outcome must be carefully weighed against the potential benefit associated with the implantation of an intraocular lens. The patient's clinical progress should be carefully monitored.
6. Patients in whom neither the posterior capsule nor zonules are intact enough to provide support.
7. Circumstances that would result in damage to the endothelium during implantation.
8. Suspected microbial infection.
9. Children under the age of 2 years are not suitable candidates for intraocular lenses.

In addition to the specific warnings listed above relating to preoperative and operative patient characteristics, the following warnings pertain to specific lens characteristics and must be considered by the physician prior to implantation:

9. Lenses (4D are not intended for correction of refractive error for phakic patients who do not have a cataract.
10. Small amounts of lens decentration occurring with an IOL having a narrow or small optic ((5.5 mm) may cause glare or other visual disturbances under certain lighting conditions. Surgeons should consider this potential complication before implanting an IOL with a small or narrow optic.
11. Since the clinical investigations of CeeOn HSM PMMA posterior chamber lenses were conducted with the lens being primarily in the capsular bag only, there are insufficient clinical data to demonstrate the safety and effectiveness of these lenses when placed in the ciliary sulcus.

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1. DO NOT resterilize. Most sterilizers are not equipped to sterilize PMMA without producing undesirable side effects. If the pouch or tray seal is inadvertently opened, contact Pharmacia & Upjohn Company, Ophthalmics Business regarding returned lens policy.
2. DO NOT store the lens in direct sunlight or at temperatures greater than 115°Fahrenheit.
3. DO NOT soak or rinse the lens in any solution other than sterile balanced salt solution or sterile normal saline.
4. Care should be taken when handling the optical portion of the lens as implantation forceps may damage the heparin surface modification, and some benefit of the modification may be compromised.
5. Nd:YAG capsulotomy may damage the heparin surface modification, and some benefit of the modification may be compromised.

ADVERSE EVENTS

The complications experienced by the Cohort patient population (411 patients) during the clinical trial of Models UB89H, 720H and 810H include (in order of frequency): hyphema, 4.4% (Grid 1.0%); abnormal corneal pathologies (guttata, Fuchs', corneal dystrophy, etc.), 2.4%; Elschnig pearls, 2.2%; macular edema, 1.9% (Grid 3.5%); secondary glaucoma, 0.2% (Grid 0.5%); and persistent corneal edema, 0.2% (Grid 0.6%). Additional complications documented as having occurred with the use of other one-piece PMMA IOLs may include, but are not limited to, the following: endophthalmitis, cyclitic membrane, pupillary block, retinal detachment, lens dislocation and persistent iritis.

Table 1 provides reports of adverse reactions at the end of the one-year postoperative follow up for all core patients enrolled in this study.

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Table 1
Adverse Reactions
All U.S. Study Patients
N = 686

Adverse Event	% of Total Patient Population*	Grid Value (%)
Hypopyon	0.0	0.4
Intraocular Infection	0.0	0.1
Acute Corneal Decompensation	0.0	0.2
Secondary Surgical Intervention	1.2	2.0
Repair of Iris Prolapse	(0.3)	
Retinal Detachment Repair	(0.3)	
Aspiration of Lens Material	(0.3)	
Vitreous Diagnostic Tap	(0.1)	
Wound Repair	(0.1)	

*Due to mathematical rounding, the sum of the percentages for specific conditions requiring secondary surgical intervention do not equal the total (1.2%).

CLINICAL TRIALS

A clinical trial of CeeOn HSM PMMA IOL Models UB89H, 720H and 810H was initiated on January 24, 1990. The results achieved by 411 patients (cohort) followed for one year provide the basis for the data which were used to support that CeeOn HSM PMMA IOLs can be used for the visual correction of aphakia. Of the 411 patients, 188 (46%) were male and 223 (54%) were female. Approximately 95% of the patients enrolled were reported as Caucasian, 4% were reported as Black and 2% were reported as "Other". Some percentages are rounded and may not total 100%.

VISUAL ACUITY

Table 2 presents the best case visual results reported for the patients in the 411-cohort patient clinical investigation of Models UB89H, 720H and 810H one year postoperatively. The information provided excludes patients reported with preoperative ocular pathologies or macular degeneration at any time during the investigation. Two hundred ninety (290) of the 411 patients met these criteria.

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Table 2
Final Visual Acuity
Best Case Cohort Patients
Models UB89H, 720H and 810H
N = 290

Age	N	Final Visual Acuity											
		20/40 or Better			20/41 to 20/80		20/81 to 20/100		20/101 to 20/200		Worse than 20/200		
		n	%	Grid %	n	%	n	%	n	%	n	%	
< 60	26	26	100	96.9	0	0	0	0	0	0	0	0	0
60 - 69	85	81	95	93.8	2	2	0	0	0	0	2	2	2
70-79	126	119	94	94.9	5	4	1	1	0	0	1	1	1
≥80	53	51	96	87.9	1	2	0	0	0	0	1	2	2
TOTAL	290	277	96	94.0	8	3	1	0	0	0	4	1	1

REDUCTION OF CELLULAR DEPOSITS AND GIANT CELLS

A second one-year study, randomized, double-masked, multicenter and controlled involving a total of 367 patients was conducted in the United States. All patients were enrolled between August 1994 and October 1996. Patients were divided into three groups: routine (220), glaucoma (58) and diabetes (89) patients. Within each group, patients were randomized to receive either an HSM or non-HSM intraocular lens following cataract extraction. The lens model used for both of the treatment groups was 815HS.

Data from this clinical investigation demonstrate that the amounts of cellular deposits and giant cells are reduced on CeeOn HSM lenses compared to non-HSM lenses (Table 3). This difference is observed during the first postoperative months. The effectiveness of HSM lenses in reducing the incidence of adverse events associated with inflammatory reactions has not been established.

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Table 3
 Percent of Patients with Giant Cells and/or Cellular Deposits
 Model 815HS

Giant Cells - Specular Micrography						
Visit	Routine Patients (112 - HSM; 108 - Non-HSM)		Glaucoma Patients (30 - HSM; 28 - Non-HSM)		Diabetic Patients (41 - HSM; 48 - Non-HSM)	
	HSM	Non-HSM	HSM	Non-HSM	HSM	Non-HSM
Week 1	2% (2/100)	*26% (26/101)	8% (2/24)	*28% (5/18)	11% (4/38)	*41% (19/46)
Month 1	7% (7/105)	*52% (49/95)	9% (2/23)	*28% (5/18)	13% (5/39)	*55% (24/44)
Month 3	11% (11/101)	*47% (42/90)	10% (2/20)	*48% (10/21)	3% (1/37)	*59% (26/44)
Month 6	8% (7/90)	*32% (27/85)	20% (3/15)	41% (7/17)	14% (5/35)	*42% (17/41)
Month 12	7% (4/62)	11% (8/71)	11% (1/9)	33% (5/15)	7% (2/31)	*26% (10/38)
Cellular Deposits - Slit Lamp						
Week 1	20% (22/108)	25% (26/103)	15% (4/27)	23% (6/26)	13% (5/39)	13% (6/48)
Month 1	13% (14/107)	23% (23/102)	11% (3/28)	20% (5/25)	10% (4/41)	15% (7/47)
Month 3	13% (14/105)	*27% (27/99)	8% (2/24)	*36% (9/25)	3% (1/38)	*17% (8/48)
Month 6	14% (13/93)	24% (21/87)	0% (0/21)	*33% (7/21)	0% (0/37)	7% (3/45)
Month 12	14% (11/78)	20% (20/79)	20% (3/15)	28% (5/18)	6% (2/34)	13% (6/45)

* Denotes statistical significance (p < 0.05) in favor of HSM lens.

DETAILED DEVICE DESCRIPTION

These single-piece lenses are manufactured from Pharmacia UVEX polymethylmethacrylate (PMMA), which contains an ultraviolet light absorbing chromophore. Pharmacia UVEX PMMA has a refractive index of 1.491. The modification of the lens surface is a two-step process in which polyethylenimine is adsorbed onto the lens surface followed by covalent endpoint attachment to nitrous acid degraded (NAD) heparin.

The haptics are angled anteriorly from the edge of the lens or extended in a planar fashion. Lens powers of 4.0 to 34.0 diopter in 0.5 diopter increments are available. The *in situ* dioptric power of the lens is indicated on the lens container. The overall lens length, the optic configuration and dimension are indicated in the addendum to this insert. Some lens models may be available in lens powers of -10.0 to 4.0 diopter and 35.0 to 40.0 diopter in 1.0 diopter increments.

Pharmacia UVEX PMMA with heparin surface modification is a non-toxic, synthetic, thermoplastic polymer. The spectral transmittance curve for Pharmacia heparin surface-modified UVEX PMMA is presented in the following graph.

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Curve #1: 4.0 diopter Pharmacia HSM UVEX
PMMA cutoff wavelength 370 nm.

Curve #2: 34.0 diopter Pharmacia HSM UVEX
PMMA cutoff wavelength 383 nm.

Curve #3: 53-year-old natural lens cutoff wavelength
407 nm.

(See Boettner EA, Wolter JR. Transmission of the Ocular
Media. *Investigative Ophthalmology*. 1:776-783, 1962.)

NOTE: The cutoff wavelengths (10% transmittance) and the
spectral transmittance curves represent the range of
transmittance values of the IOLs made with this material.

DIRECTIONS FOR USE

1. Prior to implanting, examine the lens package for type, power and proper configuration.
2. Open the peel pouch, peel back the Tyvek® lid, remove the tray lid by pressing on the lid and remove the lens in a sterile environment.
3. Visually examine the lens thoroughly to ensure particles have not become attached to it, and examine the lens optical surfaces for other defects.
4. The lens may be soaked in sterile balanced salt solution until ready for implantation.

Caution: Do not use the lens if the package has been damaged. The sterility of the lens may have been compromised.

LENS POWER CALCULATIONS

The physician should determine preoperatively the power of the lens to be implanted. Physicians requiring additional information on lens power calculation may contact Pharmacia & Upjohn Company, Ophthalmics Business.

PATIENT REGISTRATION SECTION

Pharmacia & Upjohn Company maintains a patient registration system in order to contact physicians or patients in the future if unrecognized long-term effects of the lenses are discovered.

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The lens package contains product identification labels for maintaining a record of lens usage and patient registration. At the time of surgery, the postage-paid implant registration card (Lens Accountability Form) included in the package is to be completed and returned to Pharmacia & Upjohn Company where a record of all implants is maintained in order to monitor long-term effects of implantation of these lenses. FDA REQUIRES THAT REGISTRATION BE COMPLETED FOR ALL PATIENTS.

An Implant Identification Card, to be supplied to the patient, is also included in the package. The patient should be instructed to keep the card as a permanent record of his/her implant and to show the card to any eye care practitioner he or she may see in the future.

REPORTING

Adverse reactions and/or potential sight-threatening complications that may reasonably be regarded as lens-related and that were not previously expected in nature, severity or degree of incidence should be reported to Pharmacia & Upjohn Company, Ophthalmics Business at the toll-free number (800-423-4866). This information is being requested from all implant surgeons in order to document potential long-term effects of intraocular lens implantation.

HOW SUPPLIED

CeeOn HSM IOLs are supplied STERILE in a dry heat-sealed package. The inner package is sterilized with ethylene oxide and should be opened only under sterile conditions (See DIRECTIONS FOR USE). CeeOn HSM IOLs should be stored at room temperature.

EXPIRATION DATE

The expiration date on the lens package is the sterility expiration date. This lens should not be implanted after the indicated sterility expiration date.

RETURN/EXCHANGE POLICY

Contact Pharmacia & Upjohn Company, Ophthalmics Business regarding the policy for returning a lens.

Manufactured by:

Pharmacia & Upjohn Company, Ophthalmics Business

Kalamazoo, Michigan 49001

Toll-free Telephone Number (800) 423-4866

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