CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218010Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 30, 2023

To: Lois Almoza, Senior Regulatory Health Project Manager, Division of Regulatory Operations for Specialty Medicine (DROSM)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for iDose® TR (travoprost intraocular implant), for intraocular administration

NDA: 218010

Background:
In response to DROSM's consult request dated November 17, 2023, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original NDA submission for iDose® TR (travoprost intraocular implant), for intraocular administration.

PI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on November 29, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on November 28, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at carrie.newcomer@fda.hhs.gov.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE A NEWCOMER
11/30/2023 10:39:01 AM

HUMAN FACTORS RESULTS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 3, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 218010
Product Name, Dosage Form, and Strength:	iDose TR[a] (travoprost) intraocular implant, 75 mcg
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Glaukos Corporation (Glaukos)
FDA Received Date:	February 22, 2023
TTT ID #:	2023-3781 and 2023-3782
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Human Factors Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director:	Jason Flint MBA, PMP

[a] The proprietary name for this NDA, iDose TR was found conditionally acceptable on June 5, 2023.

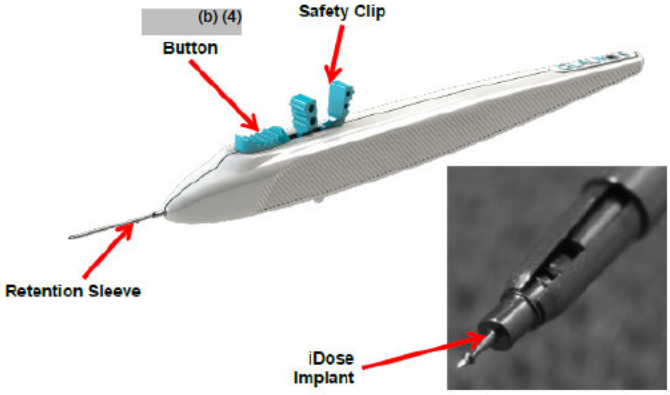
1 REASON FOR REVIEW

This review evaluates a human factors (HF) validation study report, container label, carton labeling, device peel lid (blister tray) labeling, and prescribing information (PI) submitted under NDA 218010 for travoprost intraocular implant.

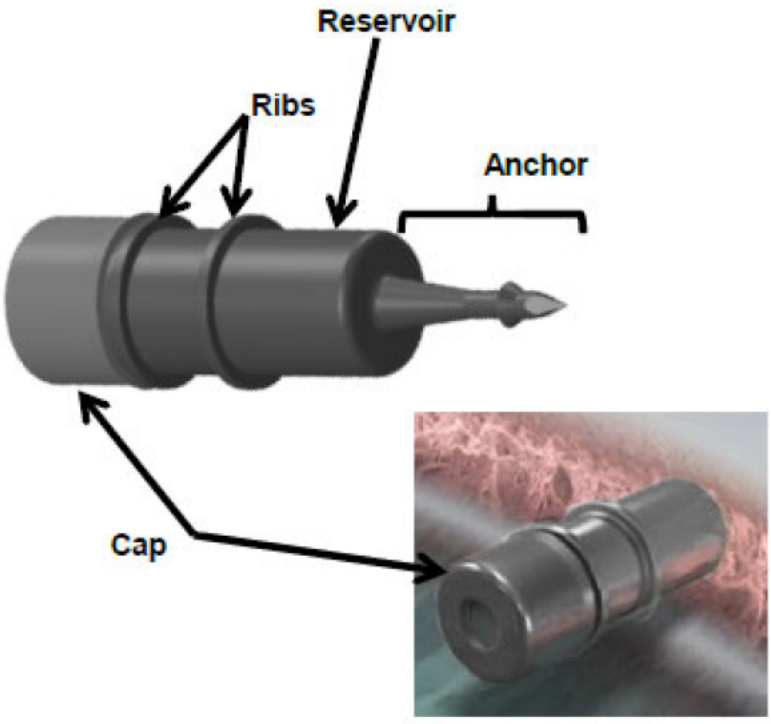
1.1 PRODUCT INFORMATION

Table 1. Relevant Product Information for Listed Drug and iDose TR		
Product Name	Travatan	iDose TR
Application Type and Number	NDA 021257	NDA 218010
Initial Approval Date	March 1, 2001 (Withdrawn FR effective on March 26, 2018 – was not withdrawn for safety or effectiveness reasons)	N/A
Active Ingredient	Travoprost	
Indication	For the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.	For the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).
Route of Administration	Ophthalmic	Intraocular
Dosage Form	Ophthalmic solution	Intraocular implant
Strength	0.004%	75 mcg
Dose and Frequency	One drop in the affected eye(s) once daily in the evening.	iDose TR is a travoprost delivery system consisting of a travoprost releasing implant pre-loaded in a sterile, (b) (4) inserter. iDose TR is administered intracamerally through a small, clear corneal incision and is anchored into the sclera at the iridocorneal angle. (b) (4)
How Supplied	2.5 mL solution in a 4 mL and 5 mL solution in a 7.5 mL natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene or	iDose TR (travoprost intraocular implant) (NDC 25357-100-01) is provided sterile and preloaded in a sterile, (b) (4) inserter that is packaged in a blister tray sealed with a Tyvek lid. (b) (4)

	high-density polyethylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.	(b) (4). Implants are individually serialized, and the serial number is provided on the tray lid. The tray is sealed inside of a transparent plastic pouch along with an oxygen scavenger packet, which is packaged inside a unit carton. Tamper evidence is provided by a seal on both ends of the carton.
Storage	Store at 2°C to 25°C (36°F to 77°F).	Store at 2°C to 25°C (36°F to 77°F). Do not freeze.
iDose TR Intended Users	Ophthalmic surgeons	
iDose TR Intended Use Environment	Sterile field environment.	
iDose TR Container Closure/Device Constituent (including figure)	Travoprost intraocular implant is a combination product proposed as a sterile implant preloaded in a sterile, (b) (4) inserter that is packaged in a blister tray sealed with a Tyvek lid. (b) (4). Implants are individually serialized, and the serial number is provided on the tray lid.   	


(b) (4)
Button
Safety Clip
Retention Sleeve
iDose
Implant

(b) (4)


Reservoir
Ribs
Anchor
Cap

	(b) (4)

1.2 REGULATORY HISTORY

New Drug Application (NDA) 218010 is a 505(b)(2) NDA and the listed drug product is Travatan, NDA 021257.

1.3 RELEVANT HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On June 1, 2023, we searched for previous DMEPA reviews and FDA/Glaukos interactions relevant to this current review using the terms, "iDose TR", "IND 120955." Our search identified one meeting package in which we provided human factors comments. See details below.

- On October 17, 2022, Glaukos submitted a Type B Pre-NDA meeting request under IND 120995 to discuss the development program for Travoprost intraocular implant, 75 mcg. The meeting package included a question, requesting feedback from the Agency on the adequacy of the HF Validation testing to support their NDA submission. [b] We granted the request as a teleconference meeting. In the preliminary meeting document dated November 18, 2022[c], we provided HF comments stating that, *"it is premature to assess the adequacy of the testing. Therefore, please submit the complete test reports in your future submission for our review. In addition, please provide a Use-Related Risk Analysis (URRA)."*

[b] Type B Meeting Background Materials: Pre-NDA CMC for Travoprost Intraocular Implant IND 120995. Aliso Viejo (CA): Glaukos Corporation; 2022 OCT 17. Available from: \\CDSESUB1\EVSPROD\ind120995\0073\m1\us\meet-materials-pre-nda-cmc.pdf

[c] Ballard, K. Meeting Preliminary Comments for Travoprost Intraocular Implant. Silver Spring (MD): FDA, CDER, OSE (US); 2022 NOV 18. IND 120995

- On November 29, 2022, we had the meeting with Glaukos. In response[d] to the preliminary meeting comments Glaukos stated that, *"The Human Factors Usability Engineering validation study results report will be submitted in the NDA and placed in eCTD section 5.3.5.4 – Other Study Reports and Related Information. A Use-Related Risk Analysis, which complies with the methodologies and qualitative levels defined in IS0 14971 and IEC TIR 62366-2, has been performed and will be submitted as part of the NDA. No further discussion is necessary."*[e]
- On February 22, 2023, Glaukos submitted a new drug application under NDA 218010. This submission included HF validation study results report, container label, carton labeling, device peel lid (blister tray) labeling, and PI, which are the subject of this review. We note Glaukos did not submit the HF validation study protocol for review prior to commencing their HF Validation Study.

1.4 MATERIALS REVIEWED

Table 2. Materials Considered for this Label and Labeling Review

Material Reviewed	Section/ Appendix
Product Information/Prescribing Information	Section 1. 1
Background Information Previous DMEPA Reviews	Sections 1.2 and 1.3
Human Factors Validation Study Results Report and HF-Related Supporting Documents	A
Information Requests Issued During the Review	B
Labels and Labeling	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, and our evaluation of the study methodology to determine if study has been appropriately designed to support evaluate the safe and effective use of the proposed product.

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[d] Correspondence Regarding Meetings – Sponsor Minutes Type B Pre-NDA Meeting. Aliso Viejo (CA): Glaukos Corporation; 2022 DEC 21. Available from: \\CDSESUB1\EVSPROD\ind120995\0077\m1\us\gkos-meet-mins-pre-nda-cmc.pdf

[e] Ballard, K. Meeting Minutes for Travoprost Intraocular Implant. Silver Spring (MD): FDA, CDER, OSE (US); 2023 JAN 05. IND 120995.

2.1 SUMMARY OF HUMAN FACTORS VALIDATION STUDY DESIGN

Table 3 presents a summary of the HF validation study design. See Appendix A for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	Practicing ophthalmic surgeons – a total of 16 participants were included in the HF validation study: 15 participants from the US 1 participant from the Philippines[f]
Training	All participants were trained using a training slide deck and were asked to watch the iDose TR training video (referred to as dry lab demonstration). The participants were also provided a copy of the Instructions for Use (IFU) which is embedded in the PI, for reference.
Test Environment & Materials	This validation study was performed with representative use environment and used production equivalent device, IFU, primary and secondary packaging. The testing room included sterile surgical environment, with surgical microscope in a generic room with the following items: • Surgical microscope (free standing or bench top model) • Gloves (equivalent in function/performance to those found in their operating room, ambulatory surgical center, or other sterile environment) • Gonioprism • Viscoelastic • Use of a fake eye with synthetic implantable meshwork to represent the patient's eye and targeted implantation site, the trabecular meshwork.

[f] We noted that the HF validation study inclusion criterion stated that, *"participants in the summative evaluation test shall reside and practice in the US."* However, one participant in the study, participant (b) (6), location of practice is Makati City, Philippines. As such, since this participant did not meet the aforementioned inclusion criterion, we did not include this participant's results in our evaluation. Additionally, we note the study include 15 participant which is in alignment for HF validation studies per the FDA Guidance *Applying Human Factors and Usability Engineering to Medical Devices* [f]; FDA generally recommends that each distinct user group includes at least 15 participants for HF validation studies. Therefore, our evaluation of the HF validation study focused on the 15 participants that reside and practice in the US.

	Table 9. Summative Evaluation Supplies and Materials **#** / **Number** / **Description** 1. N/A — Synthetic eye with implantable meshwork 2. N/A — GonioVisc fake visco material for Visualization 3. N/A — Dispensing Needle, Blunt Tip 22 ga x 1/2" Tip 4. N/A — Syringes 3ml (for phak-I demo purposes) 5. N/A — Syringe Caps (for phak-I demo purposes) 6. 90-0053 — Forceps, Technik 3-SA 7. 90-0068 — Beaver Blade, Micro Knife, 5.0mm, 15deg 8. 90-0054 — Dental Bib Polyback Towel, 2-Ply Tissue + Poly, 13" x 18" 9. N/A — Surgical Gloves 10. iPrism SX — iPrism SX 11. 90-0079 — Universal Training Mount 12. 50-0077 — Weck-cel Sponge
Sequence of Study	1. Training 2. 1 hour training decay 3. Written Exam (hereafter called knowledge task questions) 4. Simulated procedure (hereafter called simulated use scenario) using fake eye with synthetic implantable meshwork 5. Post-Summative evaluation/Debriefing interview

2.2 DISCUSSION OF METHODOLOGY

Our review of the study identified the following issues in the study methodology, which are discussed in detail below:

2.3 EVALUATION OF IMPLANT REMOVAL AND RE-ADMINISTRATION

During the course of our review of the HF validation study, we noted that the Prescribing Information (PI) *Section 2.1 General Dosing Information* states that, (b) (4) However, the HF validation study did not evaluate the removal and re-administration of the implant. (b) (4) (b) (4) To inform our assessment we reached out to the Division of Ophthalmology (DO) clinical team to inquire on the timeline (b) (4). The DO clinical team indicated Applicant's (b) (4)

The removal and the re-administration of the implant after implantation was not evaluated in the HF validation study; therefore, we are unable to evaluate these tasks. We note that simulated use human factors studies would not adequately assess these tasks given that this product is implanted into human tissue. As such, we defer to the Division of Ophthalmology (DO) to determine the additional information or data needed (b) (4) (b) (4)

2.4 THE STUDY SEQUENCE

We note that Glaukos evaluated the knowledge task questions before conducting the simulated use scenario. We generally expect knowledge tasks to be conducted after simulated use scenario as asking participants the knowledge task questions before the simulated use scenario may bias the simulated use scenario results. However, we find evaluating the knowledge task question prior to conducting the simulated use scenario reasonable in this case since the proposed use of the product is likely to include training prior to use. Additionally, we note that Glaukos clarifies *"the intended users, typically clinicians and surgeons trained in ophthalmic practice, extensive background in procedures similar to the iDose procedure*" as such users will have familiarity of the proposed product. Therefore, the bias of conducting the knowledge task prior to simulated use scenario may reasonably minimized in this case.

2.5 TRAINING DECAY PERIOD

We note Glaukos included a decay time of one hour, as a rationale Glaukos cited the *Guidance for Industry: Applying Human Factors and Usability Engineering to Medical Devices (2016)*. Glaukos cites per the Guidance, *"because retention of training decays over time, testing should not occur immediately following training; some period of time should elapse. In some cases, giving the participants a break of an hour (e.g., a "lunch break") is acceptable; in other cases, a gap of one or more days would be appropriate, particularly if it is necessary to evaluate training decay as a source of use-related risk."* Additionally, Glaukos provides the rationale that *"given the intended users, typically clinicians and surgeons trained in ophthalmic practice, extensive background in procedures similar to the iDose procedure and the ease of use and design of the iDose product, a one-hour decay period from end of training to beginning of the summative evaluation (starting with the knowledge tasks followed by the simulated procedure) was deemed a sufficient training decay versus an extended decay period needed for complex surgical devices."*[g] We acknowledge Glaukos' rationale for selection of one hour decay time. We find that one hour decay time to be reasonable

3 HUMAN FACTORS RESULTS AND ANALYSES

Notwithstanding the concerns above, we reviewed the study results. In this section, we have carefully reviewed each reported issue (i.e., use error, close call, use difficulty), Glaukos' URRA, the participants' subjective feedback, and Glaukos' comments to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product. We provide a discussion of the identified use tasks in table 4 below where we agree with the Applicant's conclusions and have no further recommendation or comment.

[g] Response to HF Information Request Dated 21 August 2023 (NDA 218010 and iDoseTR). Aliso Viejo (CA): Glaukos Corporation; 2023 AUG 23. Available from: \\CDSESUB1\EVSPROD\nda218010\0017\m5\53-clin-stud-rep\535-rep-effic-safety-stud\reduce-iop-oag-oh\5354-other-stud-rep\hfue-0007\hf-response-21-aug-2023.pdf

Table 4. Focused Analysis of Use Errors, Use Difficulties and Close Calls and DMEPA's Recommendations

Legend: UE = use error; CC = close call; UD = use difficulty; URRA = use-related risk analysis; RCA = root cause analysis; HFVS = Human Factors Validation Study;
Participants ID: (b) (4) (total of 15 participants)

Summary of Information Supplied by Applicant	DMEPA's Identified Areas of Dissent and Recommendations
This icon is displayed on the Patient ID Card, which Glaukos' submitted as part of the labeling. The Patient ID Card is supposed to be given to the patients once the implant is administered. The card is intended to be completed after the procedure with information of the "*implant date," "Implant location," and "MRI Safety Information*." The card includes an icon "  ," which is supposed to describe that the implant is MRI conditional. The meaning of the icon was assessed in the study with the knowledge task question below. Knowledge Task Question: "What does this icon mean?  ", The correct answer is "MRI Conditional" Reported Issues: Participant Type: UE (n=1): P11	We contacted the DO clinical team to ask who completes this patient ID card. The DO clinical team clarified that the patient ID card is primarily filled out by other staff in the establishment such as nurses and not necessarily by the providers who perform the procedures. See second row below for more discussion regarding this task.
Observed error(s): The participant responded, "approved for MRI."	
Relevant RCA/Subjective Feedback: Glaukos did not collect subjective feedback.	
Based on the Applicant's URRA, performing this task incorrectly or not at all may result in: trauma as a result of implant heating or movement, iris or corneal touch with product, and intraocular trauma and associated sequelae.	

Applicant's Comments and Proposed Post- HFVS Mitigations: none	We issued an information request (IR) asking Glaukos to clarify their rationale for not collecting subjective feedback for this task. On May 31, 2023, Glaukos responded[h] that *"While most participants (15 of 16, 93.75% of participants) gave the labeling definition provided for the MRI symbol (i.e., "MRI conditional"), participant 11 responded "approved for MRI." The scale for MRI safety includes MRI unsafe, MRI conditional and MRI safe in order of decreasing restrictions. Glaukos' interpretation of the participant's answer deemed it to be closer to MR conditional than to MRI unsafe or MRI safe. The participant's knowledge of the Information for Use (IFU) was tested by presenting the test participant with open-ended and neutrally worded questions (in accordance with FDA's Guidance Applying Human Factors and Usability Engineering to Medical Devices, Section 8.1.5.2 Knowledge Task Data). Given the open-ended nature of the question that was asked of the participant ("What does this icon mean?"), it is Glaukos' interpretation that the participant answered in a sufficiently appropriate manner. Therefore, the answer was considered sufficiently correct to not trigger probing question of the participant, and a root cause analysis was not performed."* We considered Glaukos' explanation, the utilization of the MRI icon, and we reached out to the DO clinical team to clarify who fills out the patient ID card in actual use situations. The DO clinical team clarified that the patient ID card is primarily filled out by other staff in the establishment such as nurses and not necessarily by the providers who perform the procedures. Based on this information we note that the appropriate intended users (other staff such as nurses) of the Patient ID card were not evaluated in the study. Therefore, this limits our ability to comment on the use error observed in this task. However, our review of the user interface and labels and labeling indicates that the PI (*Section 5.7 MRI Conditional*) contains instructions to support this task. Based on our review of the user interface we did not identify areas of improvement and have no recommendations at this time.

[h] Response to HF Information Request (NDA 218010 iDose TR). Aliso Viejo (CA): Glaukos Corporation; 2023 May 31. Available from: \\CDSESUB1\EVSPROD\nda218010\0009\m5\53-clin-stud-rep\535-rep-effic-safety-stud\reduce-iop-oag-oh\5354-other-stud-rep\hfue-0007\response-info-request-hr-2023-05-26.pdf

Task: Insertion of the Implant

Reported Issues	Participant Type:
UD (n=2)	(b) (4)

Observed event(s):
With one participant, *"the stents moved while attempting to back away with prongs opened. The participant regrasped and successfully implanted in location one clock hour over:"*
The other participant, *"reseated the implant to ensure it was firmly in position."*

Relevant RCA/Subjective Feedback:
Glaukos stated, *"Both repeated attempts (two separate doctors) involved the doctor placing the implant into position within the implantable meshwork in the synthetic eye and then, feeling as if the implant was not seated securely, regrasped the implant and finally implanted the implant firmly in position in a different location."*

Based on the Applicant's URRA, performing this task incorrectly or not at all may result in: Anterior uveitis/iritis, corneal edema, corneal endothelial cell loss, hyphema, inflammation, intraocular tissue damage, IOP increase, iris damage, keratitis, no therapeutic effect or reduced/loss of therapeutic effect, trabecular meshwork damage, and vision loss-moderate (blurred vision).

Applicant's Comments and Proposed Post- HFVS Mitigations: none

We noted that the PI includes instruction to the user, (b) (4) Based on our review of the user interface, we did not identify any additional mitigations to address these use difficulties and have no recommendations at this time.

4 LABELS AND LABELING ANALYSES

The prescribing information, carton labeling, container labels, device peel label, and instructions for use can be improved to promote safe use of the product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and the proposed recommendations to minimize the risk for medication error in Tables 4 and 5.

5 CONCLUSIONS AND RECOMMENDATIONS

Our review of the HF study identified that the removal and re-administration of the implant after implantation was not evaluated. We note that this limits our ability to interpret the study data and (b) (4) (b) (4); the development of fibrotic tissue around the implant was not evaluated in the HF validation study. Therefore, our ability to assess the (b) (4) effects of fibrotic tissue development around the implant are limited. We are concerned that simulated use human factors would not adequately assess (b) (4) this product given that this product is implanted into human tissue. As such, we defer to the Division of Ophthalmology (DO) to determine the additional information or data needed (b) (4) (b) (4).

Additionally, our review of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations in Table 4 for DO and Table 5 for Glaukos. We ask that DO convey Table 5 in its entirety to Glaukos. We advise these recommendations are implemented during this review cycle of NDA 218010.

These labeling changes can be implemented without submitting additional HF validation testing data for Agency review.

6 RECOMMENDATIONS FOR THE DIVISION OF OPHTHALMOLOGY

Table 4. Identified Issues and Recommendations for Division of Ophthalmology (DO)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
1.	As currently presented the package type term, (b) (4) is used throughout the prescribing information (PI), Tyvek lid label, and	(b) (4) is not considered an appropriate package type term[i]. In discussion with our Office of Pharmaceutical Quality colleagues, we determined	Regarding the implant, remove reference to a package type term. For example, revise (b) (4) to "implant". Regarding the inserter, revise the package

[i] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient -Use Containers for Human Use. 2018 Available from: https://www.fda.gov/media/117883/download

Table 4. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	carton labeling to describe the inserter as well as separately describe the implant.	that the implant which eludes drug over a period of time, does not need a package type term and can be simply referred to as "implant". However, for the inserter, OPQ recommends revising (b) (4) to "single-dose inserter."	type term to "Single Dose" throughout the labeling. For example, revise (b) (4) to "single-dose inserter".
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, we note the statement (b) (4) . Additionally, information is not included that specify the duration of the implan (b) (4)	(b) (4) clarifying the duration of the implant will minimize the risk of (b) (4) wrong duration medication errors.	(b) (4) Additionally, we recommend including information that clarifies the duration of the implant and when the implant is recommended to be removed.

7 RECOMMENDATIONS FOR GLAUKOS CORPORATION

Table 5. Identified Issues and Recommendations for Glaukos Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Tyvek lid Label and Carton Labeling			
1.	The route of administration is not present on the principal display panel.	Failure to include the route of administration on the principal display panel may lead to wrong route errors.	Add the route of administration "For intracameral administration" in accordance with 21 CFR 201.100(b)(3).
2.	As currently presented, the format for expiration date is not defined.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to separate the portions of the expiration date.
3.	The intended location of the linear barcode is not specified.	Required by 21 CFR 201.25(c)(2). The drug barcode is often used as an	Include the product's linear barcode as required by 21 CFR 201.25(c)(2).

Table 5. Identified Issues and Recommendations for Glaukos Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		additional verification before drug administration in the hospital setting therefore it is an important safety feature that should be part of the label.	
4.	The root name 'TR' appears in a smaller font compared to the device name 'iDose'. (b) (4) Additionally, the graphic above the root name distracts from the proprietary name. Furthermore, the (b) (4) (b) (4) font color against the white background decreases readability.	Required label statements must be displayed in a manner consistent with FDA regulations 21 CFR 201.15(a)(6), taking into account all pertinent factors, including typography, layout, contrast, and other printing features.	Revise the root name "TR' to appear in the same font size as the commensurate with the remainder of the proprietary name. Additionally, we recommend relocating the graphic to appear away from the proprietary name. Lastly, we recommend revising the (b) (4) font color within the proprietary name to a color (b) (4) that provides more contrast against the white background.
5.	As currently presented, the dosage statement reads (b) (4)	The terminology (b) (4) is not consistent with the terminology used to describe current labeling (i.e., Prescribing Information).	For clarity and consistency revise the dosage statement to *"Dosage: See Full Prescribing Information."*
Tyvek lid label			
1.	As currently presented, the manufacturer's name graphic 'GLAUKOS®' competes in prominence with the proprietary name, established name	The proprietary name, established name and strength statements, along with other critical product information should be presented as the most	We recommend decreasing the prominence of the manufacturer name (e.g., decreasing the font size) and relocating away from the product name.

Table 5. Identified Issues and Recommendations for Glaukos Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	and strength statements. (b) (4)	prominent information on the container label.[j]	

[j] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors | FDA

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. HUMAN FACTORS RELATED SUBMISSION DOCUMENTS

- The HF validation study results report is accessible in EDR via: \\CDSESUB1\EVSPROD\nda218010\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\reduce-iop-oag-oh\5354-other-stud-rep\hfue-0007\study-hfue-0007.pdf

APPENDIX B. INFORMATON REQUESTS ISSUED DURING THE REVIEW

On April 22, 2023, we issued an information request (IR) to request the following information:

- We note the inclusion of "Table 10. Hazard-Related Use Scenarios Covered Within This Summative Evaluation" which lists Risk Analysis from Document RM-049. However, the Use Related Risk Analysis (URRA) and Human Factors Protocol are not included with your submission. As such, we are unable to conduct a comprehensive review of your submission. Submit the following:
    - your URRA that includes a comprehensive and systematic evaluation of all steps involved in using your product and the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. Please see an example of how to present some of the key information for a URRA below from our draft guidance titled Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications
    - your HF Validation Study Protocol
- We note your proposed Prescribing Information (PI) includes color graphics under Sub Section *2.2 Administration*, which show users the instruction on how to use the device and insert the implant. Please clarify if your proposed PI with the color graphics is the intend to market PI which will be included in the carton.

On April 25, 2023 Glaukos provided a response to the IR that can be accessible in EDR via: \\CDSESUB1\EVSPROD\nda218010\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud\reduce-iop-oag-oh\5354-other-stud-rep\hfue-0007\response-info-request-hr.pdf

On May 26, 2023, we issued and information request (IR) to request the following:

- We reference our information Request dated April 22, 2023, in which we recommended your Use-Related Risk Analysis categorize tasks as critical or non-critical. Although your Use- Related Risk Analysis (i.e., your Risk Assessment) did not include a categorization of tasks as critical or non-critical, we note your Usability Engineering Report included a categorization of all "summative evaluation tasks" as critical. However, the "summative exam questions" were not categorized as non-critical or critical. Per our guidance: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, "Critical tasks are user tasks that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user,

where harm is defined to include compromised medical care". Revise your Usability Engineering Report to include the categorization of each summative exam question as non-critical or critical.

- We note in your Usability Engineering Report, you did not include the root cause analyses for summative exam questions in which incorrect answers were given. Specifically, for the Summative Exam Question 7, "What does this icon mean?", we note that the root cause analysis was not included.

    - Participant Serialization (b) (6), answered the question as "approved for MRI." However, it is not clear why the participant answered the question incorrectly. Please provide any additional information as to whether the moderator asked any other probing questions as to why the participant did not answer the question correctly. If the moderator asked other probing question, please provide the participant's response to the probing questions.

- We note your Usability Engineering Report did not include the moderator's script. Please provide the interviewer/moderator scripts that was used in your study.

On May 31, 2023 Glaukos provided a response to the IR that can be accessible in EDR via: \\CDSESUB1\EVSPROD\nda218010\0009\m5\53-clin-stud-rep\535-rep-effic-safety-stud\reduce-iop-oag-oh\5354-other-stud-rep\hfue-0007\response-info-request-hr-2023-05-26.pdf

On August 16, 2023, we issued an information request (IR) to request the following information:

- We note in your Usability Engineering Report, Section A.6.2.3 states that, "participant will be provided with the G2-TR product and all accompanying documentation during both the written exam and simulated procedure." However, it is unclear if the participants had access to the training materials and the prescribing information during the simulated procedure. If participants did have access to the training materials and the prescribing information during the simulated procedure, please specify how many participants referenced the training materials and the prescribing information, during the simulated procedure of the study.

On August 18, 2023 Glaukos provided a response to the IR that can be accessible in EDR via: \\CDSESUB1\EVSPROD\nda218010\0016\m5\53-clin-stud-rep\535-rep-effic-safety-stud\reduce-iop-oag-oh\5354-other-stud-rep\hfue-0007\hf-response-16-aug-2023.pdf

On August 21, 2023, we issued an information request (IR) to request the following information:

- We note inconsistencies with regards to when the study participants completed the written exam (hereafter, referred to as knowledge tasks). Specifically in your usability engineering report Appendix D you stated, "Record the time in which training ended and the start time of the written exam on the raw user data sheet". However, in your information response dated August 18, 2023, you stated, "In the next step during the summative evaluation, participants performed a simulated procedure and knowledge tasks." Please clarify when the study participants completed the knowledge tasks. Was it before or after the simulated procedure?
- Additionally, we note there was a one-hour decay period after the training session. However, you did not provide a rationale as to why the "1-hour" decay period was selected for your summative evaluation. Please provide a rationale as to why "one hour" decay period was selected for your summative evaluation.

On August 23, 2023, Glaukos provided a response to the IR that can be accessible in EDR via: \\CDSESUB1\EVSPROD\nda218010\0017\m5\53-clin-stud-rep\535-rep-effic-safety-stud\reduce-iop-oag-oh\5354-other-stud-rep\hfue-0007\hf-response-21-aug-2023.pdf

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following iDose TR labels and labeling submitted by Glaukos Corporation on February 22, 2023, July 19, 2023, and August 30, 2023.

- Tyvek Lid Label
- Carton Labeling
- Implant card and card labeling
- Prescribing Information (Image not shown),
    - Annotated version available from: \\CDSESUB1\EVSPROD\nda218010\0001\m1\us\annotated-draft-labeling-text.docx
    - Clean version available from: \\CDSESUB1\EVSPROD\nda218010\0001\m1\us\draft-labeling-text.docx

C.2 Label and Labeling Images

Tyvek Lid Label received July 19, 2023

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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VALERIE S VAUGHAN
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OLUWAMUREWA OGUNTIMEIN
11/04/2023 02:21:09 PM

JASON A FLINT
11/06/2023 08:32:57 AM

Clinical Inspection Summary

Date	October 23, 2023
From	Roy Blay, Ph.D. Michele Fedowitz, M.D. Jenn Sellers, M.D., Ph.D. Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	William Boyd, M.D., Deputy Division Director Rhea Lloyd, M.D., Clinical Team Leader Martin Nevitt, M.D., Reviewing M.O. Lois Almoza, P.M. Division of Ophthalmology
NDA	218010
Applicant	Glaukos Corporation
Drug	iDose TR (travoprost intraocular implant, 75 mcg)
NME	No
Therapeutic Classification	Prostaglandin analogue
Proposed Indication(s)	The reduction of intraocular pressure (IOP)
Consultation Request Date	28 Mar 2023
Summary Goal Date	22 Nov 2023
Action Goal Date	22 Feb 2024
PDUFA Date	22 Feb 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Protocols GC-010 and GC-012 were submitted to the Agency in support of NDA 218010 for the use of iDose TR for the reduction of intraocular pressure (IOP). Two clinical investigators, Drs. Sarkisian and Parkhurst, were inspected in support of this NDA.

Based on the results of these inspections, Protocols GC-010 and GC-012 appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the proposed indication.

II. BACKGROUND

The Applicant submitted this NDA to support the use of iDose TR, a prostaglandin analogue (travoprost), for the reduction of intraocular pressure (IOP).

Inspections were requested of the following protocols in support of this application:

Protocol Numbers and Titles: GC-010 and GC-012 are both entitled "Prospective, Randomized Phase 3 Study Comparing Two Models of a Travoprost Intraocular Implant to Timolol Maleate Ophthalmic Solution, USP, 0.5%"

Protocols GC-010 and GC-012

These protocols are essentially identical and whose objectives were to evaluate the safety and efficacy of two models of the Travoprost Intraocular Implant Models G2TR-063 and G2TR-125, two intraocular implants that elute travoprost at high and low rates, respectively.

These protocols were Phase 3, prospective, randomized, double-masked, active-controlled, parallel-group, multi-center clinical trials comparing the efficacy and safety of the Model G2TR-063 and G2TR-125 Travoprost Intraocular Implants to topical timolol, a nonselective beta-adrenergic antagonist, in subjects with open angle glaucoma (OAG) or ocular hypertension (OHT).

At Visit 1, subjects were screened for eligibility. At Visit 2 (baseline), subjects were further screened regarding continuing eligibility including completing appropriate washout periods and qualifying IOPs. At Visit 3, remaining qualifying subjects were randomized in a 1:1:1 ratio to implantation with the high-eluting implant, the low-eluting implant, or a sham procedure. At subsequent visits through Visit 19 (Month 36, end-of-study), IOPs were measured at designated times.

The primary efficacy measure was the change from baseline IOP, measured in the study eye at 8:00 AM ± 30 minutes and 10:00 AM ± 30 minutes. The primary efficacy endpoint was based on the difference in mean IOP, between each test group (G2TR-063 and G2TR-125) and the control group, for each diurnal IOP measurement time at Visit 5 (Day 10), Visit 7 (Week 6), and Visit 8 (Month 3) follow-up visits.

Study GC-010 was conducted at 45 study sites (44 U.S., 1 Philippines) from 22 May 2018 (first subject screened) to 05 April 2022 (last subject, last visit for 12-month analysis). A total of 583 subjects were included in the per-protocol analysis set.

Study GC-012 was conducted at 50 study centers (49 U.S., 1 Armenia) from 02 August 2018 (first subject screened) to 10 June 2022 (last subject, last visit for 12-month analysis). A total of 555 subjects were included in the per-protocol analysis set.

III. RESULTS:

1. **Sarkisian, Steven, M.D.**
   Dean A McGee Eye Institute
   608 Stanton L Young Blvd
   Oklahoma City OK 73104

Site: 232: Protocol GC-010
Inspection Dates: 31 Jul-4 Aug 2023

Dr. Sarkisian was inspected for the conduct of Protocol **GC-010.** This was the second inspection of Dr. Sarkisian; the first inspection was in 2018 and did not yield any significant findings. At this site, 73 subjects were screened, 63 subjects were enrolled, 42 subjects completed the study, and 16 subjects remained ongoing in the study.

The study files of 30 subjects who completed or were ongoing in the study were reviewed**,** including verification of the visual assessments and examinations that contributed to the determination of the primary efficacy endpoint as well as the reporting of adverse events. Subject records reviewed included study eligibility, protocol adherence, and the reporting of protocol deviations. The records of all 73 screened subjects were reviewed for appropriate informed consent.

Study related documents reviewed included Form 1572s, IRB, sponsor, and monitor correspondence, training documentation, delegation logs, investigational product (IP) receipt, storage, accountability, and dispensation records, electronic records including access controls and audit trails, and financial disclosures.

The following protocol deviations regarding investigational product treatment randomization and administration occurred at the site:

1. Subjects (b) (6) and (b) (6) had IP/sham implantation procedures performed on September 26, 2018, however, the randomization assignment and actual treatment received were reversed between these two subjects. Specifically, Kit 10101/Bottle 20095 (IP) was assigned to Subject (b) (6) but used for Subject (b) (6). Kit 10100/Bottle 20106 (Sham) was assigned to Subject (b) (6) but used for Subject (b) (6). The randomization assignments and inventory kits numbers were corrected for these two subjects to reflect treatments actually received and were reported to the IRB and the Sponsor.

2. Subject (b) (6) was assigned bottle kit 20091 but received bottle kit 20097 which had been assigned to Subject (b) (6). This was discovered within one day; therefore, Subject (b) (6) did not use bottle kit 20097 instead having used the second bottle from a previous visit. Incidentally, both bottle kits were investigational product and would not have changed the subject's treatment. This was reported as a protocol deviation.

3. Subject (b) (6) was assigned bottle kit 21039 but was dispensed bottle kit 21309; both kits were from the same treatment arm and did not change the subject's treatment. The sponsor corrected EDC to accurately reflect the actual dispensed kit bottle number, and this was reported as a protocol deviation.

4. Subject (b) (6) was assigned bottle kit 21283 but was dispensed bottle kit 21108; both kits were from the same treatment arm and did not change the subject's treatment. This was reported as a protocol deviation.

The following protocol deviation regarding eligibility occurred at the site:

Subject (b) (6) was randomized and enrolled into the study but did not meet the inclusion criteria requiring a 28-day washout period for the use of a beta-blocker (Timolol). The subject's washout period was only 20 days. This was reported as a protocol deviation in the submission.

Reviewer's Note: The clinical investigator accepted responsibility for the protocol deviations that occurred at the site in his August 22, 2023, response. These deviations were discovered during the trial and were reported in the NDA submission. A CAPA was started at the time of occurrence and appears acceptable though rare incidents of improper dispensation were still observed. The changes in IP administration were either of the same treatment arm or recorded appropriately and do not appear to have a significant impact on subject safety or efficacy considerations.

The inspection compared the source documents and electronic case report forms (eCRFs) with the data listings. Other than the protocol deviations described above, adherence to the regulations and the investigational plan appeared adequate.

2. Parkhurst, Gregory, M.D.
Parkhurst Nuvision
3900 Essex Lane, Suite 101
Houston, TX 77027

Site:321: Protocol GC-012
Inspection Dates: 28 Aug–1 Sep 2023

Dr. Parkhurst was inspected for the conduct of Protocol **GC-012.** This was the first inspection of Dr. Parkhurst. At this site, 86 subjects were screened, 49 subjects were screen failures, 38 subjects were enrolled in the study with two subjects withdrawing consent, one subject being lost to follow up, and one subject discontinuing due to explantation of the study device. To date, 23 subjects have completed the study and 11 subjects remain on study.

The study files of 25 of the implanted subjects were reviewed, including verification of the visual assessments and examinations that contributed to the determination of the primary efficacy endpoint as well as the reporting of adverse events. Informed consent forms were reviewed for all 86 screened subjects. Subject records also reviewed included medical histories, study eligibility, randomization treatment with the investigational product (IP), and concomitant medications.

Study related documents reviewed included Form 1572s, IRB correspondence and approvals, training documentation, delegation logs, IP shipment, receipt, storage, accountability, and dispensation records, sponsor and monitor correspondence, electronic records including access controls and audit trails, and financial disclosures.

The inspection verified the primary efficacy endpoints as well as the adverse event reporting and no significant discrepancies were reported. Adherence to the regulations and the investigational plan appeared adequate.

{See appended electronic signature page}

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DO/Deputy Director/William Boyd
DO/Medical Team Leader/Rhea Lloyd
DO/MO/Martin Nevitt
DO/Project Manager/ Lois Almoza
OSI/Office Director/David Burrow
OSI/Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Michele Fedowitz
OSI/DCCE/GCPAB Reviewer/Roy Blay
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/s/

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MICHELE B FEDOWITZ
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JENN W SELLERS
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