Primary & Secondary
Healthcare Department

SO(DC) 9-1/2024
GOVERNMENT OF PUNJAB
DRUGS CONTROL WING, P&SH DEPARTMENT
48/1, KACHA LAWRENCE ROAD, LAHORE

Dated Lahore, the 28th June, 2024

NOTIFICATION

No.SO(DC)9-1/2024. Pursuant the approval of the Chief Minister and the recommendations of a Committee of the Technical Experts, the Competent Authority has been pleased to notify the SOPs regarding off-label intravitreal usage of injection Bevacizumab for hospitals in Punjab (*copy enclosed*). All Health Facilities under the administrative control of P&SH Department are hereby directed to implement and follow the said SOPs in letter and spirit, to ensure the safe dispensing and administration of the said drug in the best of public interest. The Chief Drugs Controller, Punjab is also directed to ensure implementation of the instant SOPs in letter and spirit.

SECRETARY
GOVERNMENT OF THE PUNJAB
PRIMARY & SECONDARY HEALTHCARE DEPARTMENT

NO. AND DATE EVEN:

Copy of the above is forwarded for information & necessary action to the:

1. Director General Health Services, Punjab.
2. Director General, Directorate of Drugs Control, Punjab.
3. Secretary, Provincial Quality Control, Punjab.
4. Chief Drugs Controller, Punjab.
5. Chief Executive Officers (District Health Authority) Punjab with the request to ensure circulation and implementation of the subject SOPs in the healthcare facilities of concerned District.
6. Medical Superintendents of all Non-Teaching DHQ Hospitals and THQ Hospitals in Punjab.
7. Deputy Director HISDU, with the request to share the said notification in the official groups of CEOs (DHAs), Punjab & Medical Superintendents of Non-Teaching DHQ Hospitals and THQ Hospitals.
8. P.A to Minister, P&SH Department.
9. P.S.O to Secretary, P&SH Department.
10. P.A to Special Secretary (Ops.), P&SH Department.
11. P.A to Additional Secretary (Drug Control/ Technical), P&SH Department.
12. P.A to Deputy Secretary (Drugs Control), P&SH Department.

SECTION OFFICER (DRUGS CONTROL-II)

OFF-LABEL USAGE OF INJECTION BEVACIZUMAB (AVASTIN)

Unapproved use of an approved drug is often called "**off-label**" use. This term can mean that the drug is used for a different disease or medical condition given in an unusual way (such as by a different route), given in a different dose than in the approved label. Off-label prescribing is when a physician gives you a drug that the U.S. Food and Drug Administration ("**FDA**") has approved to treat a condition different than your condition. This practice is legal and common.

Bevacizumab (Avastin) was originally FDA-approved for cancer treatment, its off-label use for eye complications has been supported by numerous studies since 2005. The off-label indications of Intravitreal Injection Bevacizumab (Avastin) are Diabetic Retinopathy, Retinal Vein Occlusion, Age-Related Macular Degeneration, Eale's Disease, Retinopathy of prematurity, Neovascular Glaucoma, Choroidal Neo Vascularization, Corneal Graft Rejection. The common Adverse Drug Reactions ("**ADRs**") include eye redness, dryness, discomfort, and temporary blurred vision. Severe ADRs are rare and include eye pain, infections, detached retina, cataracts, endophthalmitis, etc.

STANDARD OPERATING PROCEDURE FOR INTRA-VITREAL INJECTION BEVACIZUMAB (AVASTIN)

The following Standard Operating Procedure ("**SOP**") is hereby suggested to be adopted keeping in view the best international practices to ensure the safe dispensing and administration of off-label Intravitreal Injection Bevacizumab (Avastin) under aseptic conditions, prioritizing patient well-being and regulatory compliance.

i. **Authorized Distribution:** The distributor/authorized agent of the manufacturer/importer shall be responsible for the distribution of Injection Bevacizumab for dispensing, exclusively to pharmacies having valid Pharmacy licenses, government sector health facilities, and the registered ophthalmologists, who shall keep records of the purchase & utilization. Registered pharmacies, government sector health facilities, and registered ophthalmologists after receiving the sealed injection must store the vial at the desired temperature of 2-8°C, as per product specifications.

ii. **Preparation and Dispensing:** Aseptic dispensing (draw from the vial into unit doses) of Injection Bevacizumab should be conducted in either a sterile compounding pharmacy within the hospital/clinic or a dedicated clean room equipped with Laminar Air Flow System classified as ISO Class 5 or

better in the vicinity of Operation Theatre ("OT"). This dispensing should be conducted by the qualified registered pharmacy technician/dispenser/nurse under the in-person supervision of qualified registered pharmacists. The compounding Pharmacy or a separate room adjacent to the OT with a dedicated sterile area should fully implement a Quality Management System ("QMS") that adheres to dispensing protocols in line with aseptic guidelines compliant with international standards, notably USP Chapter <797>.

a. **Personnel:** The Personnel involved in the preparation of Intravitreal Injection Bevacizumab, must be able to demonstrate proficiency in performing the sterile manipulations and maintaining appropriate environmental conditions. The personnel must be trained in Hand hygiene, garbing, cleaning and disinfection, calculations and measurements, aseptic technique, maintaining sterility, use of equipment, documentation of the process, principles of High-Efficiency Particulate ("HEPA")-filtered unidirectional airflow within the ISO Class 5 area and proper use of laminar flow hood. The competency of the personnel must be evaluated every 12 months in the above-mentioned areas. For the personnel involved in the sterile preparation area, medical fitness should be assessed at the time of hiring, and periodical medical surveillance be made at least biennially.

b. **Workplace/Area:** All the classified areas including the ante room, buffer room, and sterile compounding area must follow the air quality standards as defined in the USP Chapter <797>. The compounding/dispensing Pharmacy sterile area must be validated initially and revalidated every 6 months including the following parameters: Air changes per hour, HEPA filter integrity, Total particle count (ISO Classification) and smoke pattern testing, etc., as defined in USP <797>.

c. **Method of Preparation:** The area shall be cleaned before the dispensing of Intravitreal Bevacizumab. It shall be ensured that no other product/activity is being performed during Bevacizumab preparation. Ultraviolet lamps in the Biological Safety Cabinet must be turned on 15 minutes before the Intravitreal Bevacizumab preparation. The Injection Bevacizumab vial safety cap should be opened inside the Biological

Safety Cabinet away from the air grid, and the rubber seal must be cleaned with Isopropyl Alcohol (70%). The required dose of 1.25mg/0.05 ml (as per Prescription) should be prepared preferably in Intravitreal syringe/equivalent syringes/as per physician recommendation. Each unit dose is filled carefully concerning the accurate dose and maintaining aseptic techniques. All the individual syringes should be immediately labeled with the required labels. The individual prepared dose should be placed in safety packing and sealed with the preparation date and time accordingly. The details of the preparation procedure must be recorded in the worksheet log.

d. **Labelling:** The label shall contain the prescriber and patient details, drug name (Generic and brand), dose and strength, dosage form, route of administration, preparation date, time, storage temperature, expiry/stability after preparation and instructions for use (if any).

iii. **Microbiological Air & Surface Monitoring:** All microbiological air and surface monitoring procedures, the test results, and the corrective actions must be documented, and the records must be maintained in accordance with the USP Chapter <797> requirements i.e., for area monitoring at least on every 6 monthly bases while the Surface sampling of all classified areas must be conducted at least on monthly basis.

iv. **Proper Disposal:** The remnant vials shall be discarded within the same day as per guidelines and a proper record of disposal should be maintained.

v. **Informed Consent:** Owing to the critical and sensitive nature of the matter, ophthalmologist must obtain informed consent from each patient in the local language using the consent form prescribed by Technical wing of SHC&ME Department, prior to administrating Intravitreal Injection Bevacizumab. Important risks to be covered during the informed consent process include all ADRs with the said drug and post-procedural complications including Endophthalmitis. The Ophthalmologist must take videographic consent or written consent form with CNIC/ B-Form along with the thumb impression of patient and witness of Guardian/Attendant of patient.

vi. **Administration:** In public sector hospitals, the Head of the Ophthalmology Department (**"HOD"**) will have the authority to schedule one or more days for the administration of Intravitreal Injection

Bevacizumab based on the needs of the health facility. The procurement and administration of Intravitreal Injection Bevacizumab shall only be allowed in the private sector hospitals, registered with the Punjab Healthcare Commission ("**PHC**"). The affiliated Consultant ophthalmologists either PMDC Level II (MCPS/DOMS) or PMDC Level III (MS, FCPS, FRCS, American Board or equivalent) with at least three years of experience shall administer the Intravitreal Inj. Bevacizumab to the patients under sterile and aseptic protocol applicable to any minor/Cataract surgery. The 3rd/4th year Post Graduate Residents certified by University/CPSP may assist ophthalmologists in teaching hospitals. The Intravitreal Injection Bevacizumab shall be administered to only one eye at a time. Simultaneous bilateral injections should not be given except in cases of Retinopathy of Prematurity (**"ROP"**). A minimum one-week interval must be maintained between injections for both eyes. The injection once drawn from the vial, must be administered within a maximum time limit of 4-6 hours.

vii. **Surveillance:** The video of preparation and injection administration may be run in every monthly clinical meeting held in different units of various cities as a mandatory component of the meeting.

viii. **Measures for Ocular Infection:** In case of any sign of infection, the treating ophthalmologist shall administer Intravitreal injections of antibiotics immediately or perform immediate vitrectomy himself or by another ophthalmologist frequently performing vitreoretinal surgeries, if deemed appropriate.

ix. **Reporting Adverse Events:** If an adverse event ("**AE**")/ Adverse Drug Reaction ("**ADR**")/ Suspected Unexpected Serious Adverse Reaction ("**SUSAR**")/ Endophthalmitis is observed with Intravitreal Injection Bevacizumab (Avastin), it should be reported immediately to Provincial Pharmacovigilance Centre either via Medicine Surveillance System ("MSS") using URL **mss.pshealthpunjab.gov.pk** or **Suspected ADR Reporting Yellow Form.** The report must have complete information.

a. **The drug/Therapeutic Good;** Its generic name and brand name, batch number, dosage form, strength, and proof of purchase.
b. **The event;** Exact diagnosis and cause of suspected reaction (signs and symptoms, lab investigations, physical examination and history, co-morbidities, and any other clinical information).

c. **The Patient & Reporter;** Correspondence information of patient & reporter for further follow-up/investigation.

x. **Bulk Supply or Inter-City Transportation:** The compounded and aseptic preparations are meant for individual patients provided on prescription, drugs in syringes should not be transported out of the premises of the hospital/clinic from its operation theatre or Pharmacy. Moreover, bulk supply or inter-city transportation of such preparations is hereby banned with immediate effect.

xi. **Record Keeping:** Ophthalmologists and healthcare facilities must ensure the purchase of Injection Bevacizumab from licensed pharmacies or authorized distributors. The sale invoices/warranty for these products must include the details of injection, batch, price, and date of dispensing items along with the stamp and signature by the warrantor. The ophthalmologist should keep records of all the patients.

xii. All Healthcare Establishments providing Intravitreal Inj. Avastin should prominently display the charges. However, these charges should not exceed the maximum limit notified by the Punjab Healthcare Commission ("**PHC**") from time to time.

xiii. All the eligible ophthalmologists and healthcare professionals involved in the purchase, dispensation, and administration of Intravitreal Injection Bevacizumab shall not deviate from these SOPs.

xiv. The PHC is required to incorporate the above-mentioned dispensing protocol for Inj. Bevacizumab (Avastin) in their Minimum Service Delivery Standards ("**MSDS**") as a mandatory provision for all the healthcare facilities/clinics across Punjab (Public and private).