



GUIDELINES FOR INTRAVITREAL INJECTIONS

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GUIDELINES FOR INTRAVITREAL INJECTIONS OF AVASTIN (BEVACIZUMAB)

The incidence of post-injection endophthalmitis though low, is of great concern as there is a dramatic increase in the number of injections performed annually in India.

The risk of cluster endophthalmitis is high as multiple patients may receive injections from the same vial in a single session.

Cluster Endophthalmitis occurs due to:

Contaminated surgical supplies, Sterilization failure or Improperly performed technique. Commonest cause of contaminated surgical supplies is a Counterfeit Avastin (Bevacizumab) vial.

Following draft has been developed jointly by AIOS and VRSI along with the 4 member expert subcommittee.

We understand that there may be techniques, other than the ones enunciated in this draft, and working well in hands of some retina surgeons in India. However the recommendations made in this draft are based on the Best Practices followed and published worldwide. Our aim is to allow each one of us in India to achieve safe intravitreal injection for our patients with an endpoint of zero infection.

{Please remember, this is only a Best Practice Guidelines Document and has no legal binding whatsoever, nor can it be used for legal purposes.}

Background of this Document:

Based on the recent meeting held on 8th February 2016 between Dr V G Somani Joint DCGI, a panel of experts from all over India, representatives of the All India Ophthalmological Society (AIOS), Vitreoretinal Society of India (VRSI) and representatives from the Roche Products (India) Pvt. Ltd it was decided that Ophthalmologists in India can use Avastin as an off label drug for Intravitreal injection. This should be done after taking an informed consent from the patient who should be informed about the options available. The injection should be performed in a sterile environment and should be done by Ophthalmologists, who have the knowledge and training of performing safe intravitreal injections and

have the ability and the facilities to manage any adverse events that may arise after such an injection.

ROCHE COMPANY, who is the manufacturer and supplier of Avastin in India, will be responsible for delivering pure and sterile Avastin Vials with a documented cold chain to its distributor.

Once procured from the distributor it is the duty of the Ophthalmologist to maintain the sterility and cold chain of the Bevacizumab vial and to deliver it safely in a sterile environment to his/her patients.

Following document discusses the recommended way Bevacizumab should move from the Distributor into doctor's clinic/hospital and further used as an intravitreal injection. It will help you achieve the goal of safe delivery of sterile Bevacizumab.

A) Procurement and Intravitreal Injection Procedure

D) Post Injection Patient Monitoring and reporting of Adverse Events

A. PROCURING & STORING THE BEVACIZUMAB VIAL

1. Purchase drug from a ROCHE authorized distributor (List will become available on www.rocheindia.com or the dcgi website) only on a proper bill that documents the lot number and matches with the lot number on the carton.
2. Please ensure he/she is an authorized Roche Distributor. It is best to avoid switching dealers for the sole purpose of discounted price. Check the authorization letter of the dealer. We can inspect the authorization and bills from Roche periodically. We are working to get the label modified so that the drug can be purchased on the prescription of an Ophthalmologist or an oncologist.
3. Check the Cold chain log record (from Roche to the Final Distributor). This may not be possible for each vial but should be asked for and checked periodically.
4. Bevacizumab carton may preferably be stored in an airtight

- (screwable) clean plastic container to prevent wetting of the carton at 2–8°C. Once purchased, transport the drug in a dry ice pack.
5. It should be stored at the hospital in an exclusive refrigerator at 2–8°C with temperature display, power backup, and a temperature log. Do not store any non-drug related items, such as food and beverages, microbiology or pathology samples, blood and blood products, in the same refrigerator. Electronic data loggers are available in the market to monitor the temperature. The refrigerator should ideally be lockable and access to this should be possible only to few certified people.
 6. A separate register should be kept to keep record of Bevacizumab usage. This should have following information
 - a) Name of the Person who transferred the vial to the refrigerator
 - b) Record of Utilization of the vial with the lot number, aliquot preparation date and samples sent for culture and their reporting.
 - c) In case the culture comes positive, report to the distributor and inform on the national registry with the lot number (this registry is being developed)

Fractionation procedure guidelines (For a complete understanding, please refer to the video on the VRSI website www.vrsi.in/ Bevacizumab. This video will soon become available,

B. HOW TO USE THE BEVACIZUMAB VIAL

There are options to ensure safe injections of Bevacizumab into the vitreous which are listed below. The person (paramedical staff/doctor) who removes the vial from the refrigerator should enter his /her name in the Bevacizumab register

To ensure authenticity of the Bevacizumab vial please check that the carton has not been tampered with and then use the Kezzler code on the carton. This is an alphanumeric code that needs to be sent as an sms to the number

indicated on the vial. You will get an instantaneous reply from ROCHE about the authenticity of the vial. Use the vial only after authenticating it. If the code is not correct do not open the carton and use the vial. Return it with the proof of the message you have got to the distributor.

Once the authenticity is confirmed, carefully open the vial and check that the lot number and expiration date on the vial matches that on the carton. Also ensure the vial does not look tampered and look at the contents of the vial for anything unusual.

OPTIONS FOR PREPARING BEVACIZUMAB

Option 1:

Prepare aliquots in class 1000 environment under a class 10 laminar flow hood and thermosealed.

Option 2:

Fractionation and Aliquoting:

Place of Fractionation

We suggest opening a vial and preparing the required number of injections in 1ml syringes under sterile conditions (ideally under ISO class 5 conditions):

- Clean Room with Laminar flow Hood
- Compounding Isolator
- Sterile Operation Theatre with HEPA filter or Laminar flow with filter.

Steps of Aliquoting

- Open the cap of the vial. Clean the Rubber Stopper with Sterilium/ 70% Isopropyl Alcohol. The swab used for cleaning also must be sterile. A 20/23 G needle / mini spike device is inserted in the rubber stopper of the vial by a scrubbed paramedical staff / ophthalmologist in the operation theatre with mask and cap. The scrubbing and gowning should be as for any intra-ocular surgery. The vial must be held upside down

- by non-scrubbed personnel in the operation theater wearing a cap and mask.
- Do not talk while the procedure is being done.
 - The scrubbed staff should withdraw 0.2 ml of Bevacizumab in a 1 ml disposable syringe without injecting any air in the vial. All other aliquots are similarly prepared.
 - Cap it with a 30 G needle. Ensure there is no remnant air in the syringe. The needle could be optionally bent/ capped by a sterile cap.
 - Do not withdraw less than 0.2 ml per syringe. All syringes should be prepared by withdrawing drug from a single puncture of 20/23 G needle.
 - The prepared capped syringes with the drug must be stored in ETO sterilized sealed pouches and then placed in a sterile autoclavable container. Each sterile box should have a label with name of the drug, batch number, date of preparation of the syringe and date of expiry, (which is 2 weeks from the date of preparation). Each sealed cover of the syringe must have an individual label of the batch number and date of expiry of the syringe. The sterile autoclavable box is to be kept at 2-8°C. On the day of consumption the required number of syringes can be taken out in the OT, in sterile environment and the rest transferred to another sterile autoclavable box and restored.
 - Even if all the injections are to be consumed the same day by different surgeons in the same hospital, they should be maintained between 2-8°C.
 - Two of the aliquotted syringes should be sent on day 1 for microbiological culture.
 - All the boxes be kept at 2-8 C
 - A freshly opened 29/30/31 G needle should be used at the time of performing the Intravitreal injection.

A separate register for maintaining a log of usage of Bevacizumab must be maintained in the operation theater. This includes medical record

number, name of the patient, name of surgeon, and indication for use, and the batch number with expiry of the syringe.

Two syringes must be sent for culture and sensitivity testing. If there is no growth on culture after 48 hours, the batch of syringes can be released for use in patients.

It is preferable to keep the vial for a month before destroying it. The vial should be destroyed rather than just discarded to prevent its misuse. Destroy the labeling sticker on the vial with a permanent marker or remove it physically before discarding the vial.

Option 3:

Withdraw Bevacizumab directly from the vial using a 30G needle by strict aseptic technique (after having cleaned the rubber stopper with Sterilium or 70% Isopropyl alcohol) in a sterile OT and inject. **Ensure that before you start injecting the first aliquot, send a sample for culture and sensitivity, wait 48 hrs to obtain a negative culture. The injection can be done only if the culture is clear.** This technique has limited published data and hence has to be followed with caution and at the discretion of the ophthalmologist under very strict aseptic conditions. The vial should always remain stored after use in its carton and in an airtight plastic container at 2-8°C.

It is recommended that both for technique 2 and 3, a culture is to be sent on day 1, wait for 48 hours for culture report before using the aliquots or the vial. The 30G needle used for injection should be a new one and not the one with which the aliquot was stored. The vial or the aliquots can be stored, kept and used for a maximum duration of two weeks.

Discard the empty vial after one month– it is NOT to be re-used

C. Intravitreal injection guidelines (Please see video at www.vrsi.in/ Intravitreal injection).

I. Pre-op preparation and precautions:

- **Patient screening & precautions:**

- The need and choice of Intravitreal injection should be tailored to the individual patient according to the best clinical judgment of the attending/injecting eye specialist.
- All patients should be screened to ensure a patent nasolacrimal duct and negative regurgitation test.
- Patients with active infection of the ocular adnexa (blepharitis, meibomitis) or a blocked nasolacrimal duct/ positive regurgitation test are at high risk for endophthalmitis and should be treated for the active infection first. Injection should be scheduled after the active infection is treated.
- Surgical/procedural time-out to verify the patient's name, Intravitreal agent and laterality should be practiced before injection for each patient.
- Bilateral injections are **NOT** recommended and injection for the other eye should be planned at least one week later.
- Patients with uncontrolled systemic conditions like uncontrolled diabetes should first be treated for it.
- Antibiotics: Routine use of topical antibiotics for a day prior and three days post injection may be of help.
- **Patient preparation:**
 - **Consent:** An informed written consent should be taken from all patients undergoing the injection after explaining the procedure and the risks involved. Off label use of Bevacizumab should be included in the consent and explained to the patient.
 - Each patient should be given a cleaned OT gown, protective cap and booties before entering the preoperative holding area/operating room.

Time of Using the Aliquoted Bevacizumab

- While the Aliquots are waiting to be used they should be maintained in sterile ,packed pouches in a sterile container at 2-8 C. Local logistics need to be worked out by the

injecting surgeons

- The drug is not to be stored for more than 15 days.

2. Steps of Injection

1. It is recommended to do the injection procedure in an operation theater or a sterile room designated for such procedures taking all precautions as are taken for any intraocular surgery. We do not recommend Intravitreal injection Bevacizumab in an office setting.
2. Evidence suggests that prophylactic antibiotics are not better than the use of povidone iodine 5% drops. We recommend mandatory cleaning and draping. Use 10% povidone-iodine to clean the skin and periocular adnexa and 5% povidone iodine drops to be instilled in the conjunctival sac for a contact period of 3 minutes
3. Please instill one drop of proparacaine eye drops in the eye before instilling povidone-iodine drop.
4. Patients with known povidone allergy can have fluoroquinolone eye drop instilled 3 times in the eye starting 30 minutes prior to the injection.
5. The surgical area should be draped using sterile linen and a separate plastic sticking eye-drape for each patient to isolate the field.

A sterile speculum should be used to prevent contact of the eyelashes and eyelid margins with the injection site and needle.

Topical anesthetic drops should be preferred over anesthetic gel as the latter may interfere with povidone-iodine contact with the conjunctiva/injection site.

Reapply povidone-iodine after anesthetic drop use. Before the injection, povidone-iodine (5%) should have been the last agent applied to the intended injection site.

Routine anterior chamber paracentesis is NOT recommended.

6. The injecting physician must scrub, and wear cap and mask. Talking should be minimal during the injection procedure.
7. Draping should be done after a minimum of 2-3 minutes of povidone iodine painting. This is to provide adequate exposure time for the povidone iodine to act against pathogens.
8. During the waiting time of 2 minutes, one can prepare the caliper marking, and make the final adjustment of volume of Bevacizumab with a fresh 29/30 G needle.
9. Do not hesitate to re-drape if eyelashes have not been completely tucked under the drape.
10. Take a final time-out to confirm the name of the patient and the correct eye to be injected.
11. It is preferable to inject under an operating microscope. .
12. Any quadrant can be chosen for injection. Sterile calipers should be used to mark 3– 4 mm from limbus (depending on lens status) to mark the injection site.
13. Post injection the cul de sac can again be flushed with povidone iodine or the injection site dabbed with a povidone iodine soaked sterile swab.
14. The eye can be patched with povidone iodine 5% drops for 2 hours after injection.
15. Post-injection antibiotic and its use is left to the discretion of the Ophthalmologist treating the case. However, in patients with poor lid hygiene, or debilitating systemic status, topical antibiotic eye drops for 5 days are recommended.

3. Post-operative precautions:

- Proper lid hygiene should be maintained in the post-op period
- Post-injection IOP should be monitored and topical antiglaucoma may be prescribed for post-injection IOP spike as and when warranted.

- All patients should be given a discharge card mentioning the injection details, postoperative instructions, symptoms of infection (pain, redness, dimness of vision, swelling, discharge, etc.) and 24-hour emergency contact information.
- Patients should be instructed to avoid washing of eyes for 24 hours
- After each day, all the instruments and linen after thorough cleaning and drying should be autoclaved for the next day.
- Follow-up of each patient should be tailored as per the indication for the Intravitreal injections.

D. Postoperative Management

1. Patients may be examined within 3 days after injection. If the patient is unable to come for any reason, the patient must be asked to report to the nearest ophthalmologist immediately if there is unusual pain, redness, or drop in vision at any time. These instructions must be given in writing to the patient and it must be ensured that they, or the accompanying attendant have understood it.
2. We suggest a good examination of anterior segment using slit lamp for any cells in the anterior chamber or anterior vitreous. Fundus should be examined using indirect ophthalmoscopy for any exudates, floaters, or new onset peripheral retinal hemorrhages or vasculitis.
3. Please check the intra-ocular pressure at each visit.
4. Patients should be instructed to avoid head bath for 1 day post injection and swimming for 3 days post injection.
5. In case the patient is due for injection in both eyes, it should be done at an interval of 3 days

Cautions

- Injections for ROP are not covered in these guidelines.
- Anti-VEGF injections should be deferred in pregnant women.

- Caution should be exercised in patients with increased risk of thromboembolic phenomenon or recent history of stroke or myocardial infarction, as for any other intra-ocular surgery.
- Injections should be deferred in patients with uncontrolled blood sugar levels as it may increase the chances of endophthalmitis. However, there is no evidence-based guideline for a cut-off of blood sugar or HbA1c level.
- Patient should be informed about higher risk of endophthalmitis in uncontrolled diabetes. If the patient wishes to proceed with the injection due to unavoidable circumstances, the above discussion should be documented in the consent prior to the injection. Such patients may be given pre and post-injection topical antibiotics as an additional precaution.

Don'ts

Do not buy Avastin from a Non Roche Distributor

Do not use the Bevacizumab Vial if not Authenticated by Kezzler Code

Do not inject Bevacizumab in OPD. Considering the varied circumstances in India we have taken a conscious decision of injecting Bevacizumab in sterile setting of an operating room or similar area.

Do not transport partially used vials in ice packs. Do not transport Aliquoted syringes of Bevacizumab. If a surgeon is practicing at multiple centers, it is recommended that each center be equipped to fractionate Bevacizumab. If this is not feasible, it is recommended that the patient be taken to the nearest center where Bevacizumab is available.

Do not store an Bevacizumab vial for re-use once it's seal is broken

Do not re-use the Bevacizumab vial by puncturing it multiple times.

These guidelines may be updated as and when new evidence is gathered by us or any other Indian / Western scientific body. Visit www.vrsi.in for any update and to report adverse events.



Informed Consent For Avastin Tm (Bevacizumab) Intravitreal Injection

INDICATIONS:

Abnormal growth of new blood vessels beneath the macula (area of fine central vision in the retina) can occur in conditions such as Age-related macular degeneration (AMD), myopia, histoplasmosis, angioid streaks, and eye injury. Sometimes there is no known reason for the abnormal blood vessels. These abnormal blood vessels leak fluid, blood and protein beneath the retina resulting in vision loss that may become severe and permanent without treatment.

Swelling of the central retina (macular edema) can occur in many conditions such as diabetic retinopathy, retinal vein occlusion etc. The swelling can result in vision loss that can progress and become permanent without treatment.

POSSIBLE BENEFITS AND “OFF-LABEL” STATUS:

Avastin™ was not initially developed to treat your eye condition but for treatment of metastatic colorectal cancer. Avastin has been extensively used as an “off-label” drug in ophthalmology. “Off-label” in regards to usage of avastin in your eye means that avastin was not developed for use in the eye. But based on existing sound medical evidence, your ophthalmologist considers that usage of avastin will benefit your eye condition and hence suggests it as an option for treating your eye.

POSSIBLE LIMITATIONS AND ADMINISTRATION:

The goal of treatment is to prevent further loss of vision. Although some patients have regained vision, the medication may not restore vision that has already been lost, and may not ultimately prevent further loss of vision caused by the disease.

After the pupil is dilated and the eye is numbed with anaesthesia, the medication is injected into the vitreous, the jelly-like substance in the back chamber of the eye. Avastin is administered by an injection into your eye as needed at regular intervals (about every four to six weeks); your ophthalmologist will tell you how often you will receive the injection, and for how long.

ALTERNATIVES:

You do not have to receive treatment for your condition, although without treatment, these diseases can lead to further vision loss and blindness.

The approved options as of now for treating your eye condition are Lucentis and Accentrix (Novartis), Eyelea (Bayer), Razumab (Intas). Some patients with macular edema may also benefit from Ozurdex (Allergan) a steroid implant.

COMPLICATIONS FROM THE MEDICATION AND INJECTION: Complications when Avastin is given to patients with cancer:

When Avastin is given to patients with metastatic colorectal cancer, some patients experienced serious and sometimes life-threatening complications, such as gastrointestinal perforations or wound healing complications, hemorrhage, arterial thromboembolic events (such as stroke or heart attack), hypertension, proteinuria, and congestive heart failure. Patients who experienced these complications not only had metastatic colon cancer, but were also given 400 times the dose you will be given, at more frequent intervals, and in a way (through an intravenous infusion) that spread the drug throughout their bodies.

Risk when Avastin is given to treat patients with eye conditions:

Ophthalmologists believe that the risk of these complications for patients with eye conditions is low. Patients receiving Avastin for eye conditions are healthier than the cancer patients, and receive a significantly small dose, delivered only to the cavity of their eye. Two large trials and a large compilation of data comparing Avastin to other similar drug have found Avastin to be as safe as the other FDA approved drug.



3 ✂

Known risks of intravitreal eye injections:

Possible complications and side effects of the procedure and administration of Avastin include but are not limited to retinal detachment, cataract formation (clouding of the lens of the eye), glaucoma (increased pressure in the eye), hypotony (reduced pressure in the eye), damage to the retina or cornea (structures of the eye), and bleeding.

There is also the possibility of a serious eye infection (endophthalmitis). Any of these rare complications may lead to severe, permanent loss of vision, particularly endophthalmitis, which may rarely result in loss of the eye as well. Patients receiving an injection of Avastin may experience less severe side effects related to the pre-injection preparation procedure (eyelid speculum, anesthetic drops, dilating drops, antibiotic drops, povidoneiodine drops and the injection of the anesthetic). These side effects may include eye pain, sub-conjunctival hemorrhage (bloodshot eye), vitreous floaters, irregularity or swelling of the cornea, inflammation of the eye, and visual disturbances.

PATIENT RESPONSIBILITIES:

I will immediately contact my ophthalmologist if any of the following signs of infection or other complications develop: pain, blurry or decreased vision, sensitivity to light, redness of the eye (compared to immediately after the injection), or discharge from the eye. I have been instructed NOT to rub my eyes or swim for three days after each injection. I will keep all post-injection appointments so my doctor can check for complications.

_____ Patient initials

3 ✂

Although the likelihood of serious complications affecting other organs of my body is low, I will immediately contact my primary care physician or go to the Emergency Room if I experience abdominal pain associated with constipation and vomiting, abnormal bleeding, chest pain, severe headache, slurred speech, or weakness on one side of the body. As soon as possible, I will also notify my ophthalmologist of these problems.

_____ Patient initials

I will inform my ophthalmologist if I need to have any surgery, and I will inform any other surgeon, including dentists, that I am on a medication that needs to be stopped before I can have surgery.

_____ Patient initials

PATIENT CONSENT:

The above explanation has been read by/to me. The nature of my eye condition has been explained to me and the proposed treatment has been described. The risks, benefits, alternatives, and limitations of the treatment have been discussed with me. All my questions have been answered.

- I understand that Avastin was approved by the FDA for the treatment of metastatic colorectal cancer, and has not been approved for the treatment of eye conditions. Nevertheless, I wish to be treated with Avastin, and I am willing to accept the potential risks that my physician has discussed with me.

_____ Patient initials

- I hereby authorize Dr. _____ to administer the intravitreal injection of Avastin in my _____ (“right” or “left”) eye at regular intervals as needed. This consent will be valid until I revoke it or my condition changes to the point that the risks and benefits of this medication for me are significantly different.

Patient’s Signature & Date

Witness’s Signature & Date

Doctor’s Signature & Date





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