



NATIONAL PBM BULLETIN

DEPARTMENT OF VETERANS AFFAIRS
VETERANS HEALTH ADMINISTRATION
PHARMACY BENEFITS MANAGEMENT STRATEGIC HEALTHCARE GROUP,
MEDICAL ADVISORY PANEL, OFFICE OF THE CHIEF CONSULTANT FOR OPHTHALMOLOGY AND
CENTER FOR MEDICATION SAFETY (VA MEDSAFE)
Off Label use of bevacizumab (Avastin®) for intravitreal injection

I. ISSUE – Safety concerns with the use of bevacizumab (Avastin®) intravenous preparation for intravitreal injection in the treatment of Age Related Macular Degeneration (AMD)

II. BACKGROUND – Why use bevacizumab for off label prescribing in the treatment of AMD?

The off label use of bevacizumab is being used as an option in the treatment of choroidal neovascularization **CNV**/AMD.^{1,2} The theoretical support of bevacizumab regards its vascular endothelial growth factor (**VEGF**) inhibition and its mechanism as an antiangiogenesis agent. Available information on the off label use of bevacizumab in AMD includes systemic intravenous administration, animal trials, retrospective case series, prospective interventional case series and open label therapy.³⁻¹¹ Currently; there are no published randomized, blinded, controlled trials of intravitreal bevacizumab in the treatment of AMD.

There are currently three FDA approved products for the treatment of AMD; verteporfin which is used in conjunction with photodynamic laser therapy (PDT), pegaptanib which is an anti-VEGF agent injected intravitreally and ranibizumab which is a humanized antibody fragment that binds to VEGF-A. These agents have proven safety and efficacy in select populations of patients with AMD. For some patients, none of these therapies have proven beneficial nor have succeeded in stabilizing the progression of their disease. Other treatment options have been explored, such as off label use of available anti-VEGF therapy (bevacizumab).

III. DISCUSSION - REVIEW OF WARNING

An internet survey described physician reported adverse effects from 70 centers in 12 countries. The reports included 7,113 intravitreal injections performed on 5,228 patients. Reported events included corneal abrasion, lens injury, endophthalmitis, retinal detachment, inflammation / uveitis, cataract progression, acute vision loss, central retinal artery occlusion, subretinal hemorrhage, retinal pigment epithelium tears, blood pressure elevation, transient ischemic attack, cerebrovascular accident and death. None of the rates exceeded 0.21%.¹²

Concerns exist regarding the compounding of intravitreal injections from an intravenous product. Intravenous bevacizumab is packaged in a single entry vial containing α,α -trehalose dihydrate, sodium phosphate

(monobasic, monohydrate), sodium phosphate (dibasic, anhydrous), polysorbate 20, and Water for Injection, USP. In preparing this formulation for intravitreal use, several methods may be employed. There is no standard that has been defined which describes the stability and sterility of the compounded preparation. Several signals have been reported in the FDA AERS database documenting severe adverse events in elderly patients receiving compounded bevacizumab, intravitreally. These reports include vitritis, vitreous hemorrhage, endophthalmitis, iritis and keratitis. Additionally, VA Med Safe is aware of reports of endophthalmitis within the VA system. It should be noted that a lag time exists between identification of a severe adverse event and a final report housed in a central database such as AERS or the VA databases. Thus, at the present time, the actual number of reported adverse events associated with increased “off label use” of bevacizumab may be greatly underestimated. Given the paucity of data regarding the long term safety of intravitreal bevacizumab; patients must be carefully screened prior to institution of therapy and be fully informed of the risks of using off label therapy.

IV. VA MEDSAFE RECOMMENDATIONS

1. Use of intravitreal bevacizumab is restricted to retinal specialists or those who are trained in intravitreal injections and AMD diagnosis
2. Use only in patients have failed to show benefit or stabilization after therapy with an FDA approved agent for treatment of AMD (i.e.; pegaptanib, ranibizumab or verteporfin/PDT)
3. Patients with active periocular or ocular infections, a history of gastrointestinal perforation, wound healing complications, arterial thromboembolic events, uncontrolled hypertension or recent history of myocardial infarction (< 1 year) should not receive bevacizumab
4. Patients must clearly understand the risks and benefits of off label bevacizumab therapy as documented with an informed consent
5. Actual dosage used, the lot number of the vial, method of preparation, date and time of administration and any unusual reactions must be clearly documented in the medical record
6. Continued monitoring/surveillance of potential ADEs associated with intravitreal bevacizumab administration by VAMedSAFE

V. REFERENCES

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