




ATC codes: **S01LA08**

Indication	Age related macular degeneration ICD11 code: 9B75.0Z
INN	Bevacizumab
Medicine type	Biological agent
List type	Complementary
Formulations	Parenteral > Locoregional injections > Intravitreal: 25 mg per mL
EML status history	First added in 2013 (TRS 985) Changed in 2017 (TRS 1006)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org  Read more about patents. 


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Expert Committee recommendation

The Expert Committee did not recommend the deletion of bevacizumab for intravitreal administration for the treatment of neovascular age-related macular degeneration. The Expert Committee noted that the reported cases of infection presented in the application were associated with sub-optimal compounding and administration practices. No additional clinical evidence relating to the overall benefit-harm ratio of intravitreal bevacizumab was provided. The Committee reiterated the importance of compounding and administering intravitreal bevacizumab under sterile conditions.

Background

The application from F. Hoffman-La Roche Ltd requested the deletion bevacizumab for ophthalmic use from the EML or amendment of the current listing for bevacizumab to indicate that the product was not developed or approved by regulatory authorities for ocular use and that potential harm may be caused to patients by inappropriate handling and storage. Bevacizumab was added to the EML in 2013 for intravitreal administration for the treatment of neovascular age-related macular degeneration (nAMD). In making its recommendation, the 2013 Expert Committee concluded that, on the basis of the CATT (1, 2) and IVAN (3) comparative trials of bevacizumab and ranibizumab and the observational safety data, intraocular bevacizumab was effective and safe for the treatment of nAMD. The Committee noted that bevacizumab does not have regulatory approval for use in nAMD and highlighted the need for its safe preparation and intravitreal administration (4).

Harms

The application stated that sterility could be compromised during the process of compounding bevacizumab for intravitreal administration from its preservative-free, single-use vial, when multiple intravitreal doses are prepared from the same single-use vial. The application described recent cases from Egypt, India and the Islamic Republic of Iran, in which some patients experienced adverse ocular events after intravitreal administration of bevacizumab. The same cases were described, and a similar request was made to add clarifying language to the EML listing of bevacizumab, in correspondence from Roche to the Director-General of WHO, Dr Margaret Chan, in 2016. The application referenced United States Pharmacopoeia standards for the manufacturing of IV drug formulations and ophthalmic solutions. The Pharmacopoeia states that the manufacturing requirements for IV drug formulations allow higher sub-visible particle counts than those for ophthalmic solutions and that bevacizumab is therefore not manufactured in accordance with the more stringent requirements for particulate matter in ophthalmic solutions.

Additional evidence

2015 Expert Committee consideration of ranibizumab Bevacizumab was considered again by the Expert Committee in 2015 as part of its consideration of an application requesting the addition of ranibizumab to the EML for treatment of nAMD, visual impairment due to diabetic macula oedema (DME), visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO), visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) and visual impairment due to choroidal neovascularization (CNV) secondary to pathological myopia (PM) (5). The results of a Cochrane review of 12 randomized controlled trials (RCTs) including a total of 5496 participants with nAMD indicate that anti-VEGF agents (ranibizumab, bevacizumab and pegaptanib) are effective in terms of maintaining visual acuity; ranibizumab and bevacizumab were also shown to improve visual acuity (6). Comparative efficacy for visual acuity (gain of 15 letters or more of visual acuity at one year) of ranibizumab compared with the currently EML-listed bevacizumab, expressed as risk ratio (RR), was 0.90 (95% CI: 0.73–1.11). The results of a Cochrane review of 18 RCTs indicate that anti-VEGF agents (ranibizumab, aflibercept, bevacizumab and pegaptanib) are effective in terms of maintaining and improving visual acuity in patients with DME when compared with control treatments (i.e. no anti-VEGF agents) (7). Regarding absolute benefit, 100 participants need to be treated with antiangiogenic therapy to allow 20 more people (95% CI: 13–29) to have markedly improved vision after one year. No significant subgroup difference between bevacizumab, ranibizumab and aflibercept was demonstrated. The comparative efficacy for visual acuity (a gain of three or more lines at one year) of ranibizumab compared with the currently EML-listed bevacizumab, expressed as relative odds ratio (OR), was 1.15 (95% CI: 0.67–2.08). This analysis was based on direct and indirect comparisons, taking advantage of all available evidence. More recently, a multicentre RCT of 660 patients with DME found aflibercept to be more effective than ranibizumab and bevacizumab at improving vision in patients with lower visual-acuity letter scores at baseline (8). The Expert Committee considered that the results of this trial are of interest and that the comparative effectiveness of aflibercept in comparison with other anti-VEGF agents needs to be further explored. The results of a Cochrane review of six RCTs including a total of 937 patients with CRVO indicated that anti-VEGF agents (ranibizumab, aflibercept, bevacizumab and pegaptanib) are effective in maintaining and improving visual acuity (9). There were no statistically significant differences between the anti-VEGF agent subgroups. This comparison is limited by the paucity of studies and – in the absence of head-to-head randomized studies – the lack of direct comparison of anti-VEGFs. However, the Expert Committee considered that differences between bevacizumab and ranibizumab for this indication are unlikely, given the contextual evidence in similar diseases and the lack of a biological rationale for differences. Three additional RCTs compared ranibizumab and bevacizumab in patients with myopic choroidal neovascularization (mCNV) (10–12). Significant improvements in visual acuity were observed in both ranibizumab and bevacizumab groups. The differences in the final mean BCVA between the groups was not significant, although these studies had limited power. In a recent meta-analysis, the comparative efficacy for visual acuity (a gain of three or more lines at one year) of ranibizumab compared with the currently EML-listed bevacizumab, expressed as risk ratio, was 0.95 (95% CI: 0.67–1.32) (13). With regard to safety, the meta-analyses conducted for all antiangiogenic drugs compared with either sham therapy or photocoagulation showed no significant difference regarding all serious systemic adverse events, specific serious systemic adverse events such as arterial thromboembolic events (including myocardial infarction, stroke or cerebral infarction, ischaemic cardiomyopathy), and overall mortality (6, 7, 9). Ocular inflammation and increased intraocular pressure after intravitreal injection were the most frequently reported serious ocular adverse events. Endophthalmitis was reported in less than 1% of anti-VEGF treated participants. The occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups. In addition, a recent Cochrane systematic review assessing the systemic safety of intravitreal bevacizumab compared with ranibizumab in patients with nAMD in non-industry-sponsored RCTs found no relevant difference for deaths, serious adverse events, or specific

subsets of serious adverse events, with the exception of gastrointestinal disorders, in the first two years of treatment (14). Based on the event rates in the studies, the risk of death with ranibizumab is 3.4% and with bevacizumab 3.7% (95% CI: 2.7–5.3%), and the risk of serious adverse events with ranibizumab is 22.2% and with bevacizumab 24% (95% CI: 20–29.1%). These results suggest that if a difference does exist, it is likely to be small. Ranibizumab is more expensive than bevacizumab, with each injection costing several hundred US dollars and less than 100 US dollars, respectively (15). In a large independent RCT based in the United Kingdom, the mean total cost per patient over the 2-year trial ranged from £18 590 (US\$ 29 119) for monthly ranibizumab to £3002 (US\$ 4702) for as-needed bevacizumab (16). Drug cost accounted for 80–88% of the total cost for patients randomized to ranibizumab and 21–30% of the cost for patients randomized to bevacizumab. Recent economic analyses investigated the cost-effectiveness of as-needed ranibizumab versus monthly bevacizumab: as-needed ranibizumab was more costly and produced negligible or no health gains compared with monthly bevacizumab (15, 16). The Expert Committee noted that currently available formulations of bevacizumab are not specifically formulated for intravitreal injection. Bevacizumab is available as a sterile solution of 25 mg/mL (i.e. 1.25 mg per 0.05 mL) and therefore does not need to be diluted or reconstituted in any way for intravitreal injection. The Committee considered that reports of adverse events (such as endophthalmitis) resulting from compounding of doses from the currently available bevacizumab vial sizes for multiple intravitreal injections, had been traced to inadequate sterility in the compounding process. The Committee noted that there was substantial evidence from well-conducted independent studies showing bevacizumab and ranibizumab to be similarly effective and safe. Again, the Expert Committee acknowledged that bevacizumab is not specifically formulated for intravitreal administration and noted reports of adverse events, including endophthalmitis, resulting from administration of compounded bevacizumab. The Committee considered that the safe use of bevacizumab (as currently formulated) may require use to be restricted to a single patient per vial, or any alternative approach to comply with safe and sterile injection practices, and appropriate storage conditions, to prevent any possibility of contamination. While recognizing the importance of effective management strategies for neovascular eye diseases, and that ranibizumab is registered in many countries for these indications while bevacizumab is used off-label, the Expert Committee decided not to add ranibizumab to the EML.

Other considerations

The Expert Committee acknowledged the potential risk of infection associated with non-sterile compounding and intravitreal injection of bevacizumab from single-use vials, and recalled the findings of the Expert Committee in both 2013 and 2015 of the need for safe and sterile compounding and administration techniques for intravitreal bevacizumab.

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