Ranibizumab

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 21. Ophthalmological preparations > 21.6. Ophthalmological preparations > Anti-vascular endothelial growth factor (VEGF) preparations

ATC codes: S01LA04

Indication	Degenerative high myopia ICD11 code: 9B76
INN	Ranibizumab
Medicine type	Biological agent
List type	Complementary
Formulations	.
EML status history	Application rejected in 2015 (TRS 994)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Ranibizumab
DrugBank	Ranibizumab

Summary of evidence and Expert Committee recommendations

An application was submitted by Novartis Pharma AG, Basel, Switzerland for inclusion in the WHO Model List of Essential Medicines of ranibizumab for the treatment of neovascular (wet) age-related macular degeneration (nAMD), visual impairment due to diabetic macular 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). Expert reviews of the application were prepared by two members of the Expert Committee. Public comments on the application were received from e European Alliance for Access to Safe Medicines, from Professor Andrzej Stankiewicz, President of AMD Association Poland, from e Hellenic Retina Society, from Professor Wojciech Omulecki, Head of the Department of Ophthalmology, Medical University of Lodz, Poland, and from the Chairmen of the Polish Ophthalmological Society, Retina Hong Kong and the Irish Patients' Association. At its 19th meeting, the Expert Committee, while noting the absence of stringent regulatory authority approval for use for the indication of nAMD, recommended inclusion of bevacizumab (an alternative vascular endothelial growth factor (VEGF) inhibitor) in the EML for treatment of nAMD on the grounds of public health need, demonstrated safety and effectiveness, and favourable cost–effectiveness (1). The pooled prevalence of nAMD, a progressive and chronic disease of the retina, at any stage is 8.7% (95% credible interval (CrI): 4.3–17.4%) and the prevalence of late-stage nAMD is 0.4% (95% CrI: 0.2–0.8%). Higher prevalence is observed in European than in Asian or African populations (2). The condition is the leading cause of irreversible blindness in people over 50 years of age in developed countries (3). As a result of increased life expectancy and the growth of the elderly

population, the number of cases of nAMD is expected to increase drastically by 2020 (4). Diabetic retinopathy is one of the most frequent and severe complications of diabetes mellitus. DME is caused by the exudation and accumulation of extracellular fluid and proteins in the macula and is associated with blindness in the working-age population in developed countries (5). Visual impairment due to DME has been reported to affect approximately 1–3% of the diabetic population (6). Retinal vein occlusion involves the narrowing or blockage of a retinal vein. It is classified by the site of venous occlusion as either central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO). Approximately 16.4 million adults are affected worldwide, 13.9 million with BRVO and 2.5 million with CRVO; annual incidences of BRVO and CRVO are 0.12% and 0.03–0.04%, respectively (7–9). Pathological myopia is a leading cause of vision loss, especially in a younger population (<50 years of age). Population-based studies reported the prevalence of PM to be 0.9–3.1% and of visual impairment attributable to PM to range from 0.1% to 0.5% in European studies and 0.2% to 1.4% in Asian studies (10). The prevalence of choroidal neovascularization in individuals with PM has been reported to be 5.2–11.3%; development of CNV is associated with visual impairment. Numerous studies document the efficacy of ranibizumab for the treatment of nAMD, DME, BRVO, CRVO, CNV and PM. In nAMD, the MARINA (11), ANCHOR (12) and FOCUS (13) trials reported mean increases in visual acuity in the subgroups receiving intravitreal injections of 0.5 mg ranibizumab compared with sham photodynamic therapy (PDT), sham intravitreal injections and active verteporfin PDT. 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 (14). 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 RESOLVE and RESTORE studies assessed the efficacy and safety of ranibizumab in patients with visual impairment due to DME. The RESOLVE study showed that ranibizumab is effective in improving best corrected visual acuity (BCVA) and is well tolerated (15). In the RESTORE study, ranibizumab monotherapy and ranibizumab combined with laser therapy proved to be superior to standard laser therapy in improving visual acuity (16). Over three years, BCVA was maintained and the occurrence of ocular and non-ocular adverse events was limited (17). The results of a Cochrane review of 18 RCTs indicate that anti-VEGF agents (ranibizumab, a ibercept, 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) (18). 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 (19). e 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 BRAVO study, a multi-centred RCT of 397 patients with macular oedema secondary to BRVO, compared monthly intravitreal ranibizumab injections (0.3 mg and 0.5 mg) with sham injections (20). e study reported that ranibizumab appears to have a favourable effect on visual function. However, approximately 50% of the ranibizumab 0.3 mg group and 45% of the ranibizumab 0.5 mg group in the trial also received rescue laser photocoagulation therapy, which may have had a significant effect on the primary outcome (21). The CRUISE RCT followed a similar design to BRAVO, randomizing 392 patients with macular oedema secondary to CRVO to monthly intravitreal ranibizumab injections (0.3mg and 0.5mg) or sham injections (20). The proportions of patients gaining three lines or more in BCVA were 46.2% in the 0.3 mg ranibizumab group, 47.7% in the 0.5 mg ranibizumab group, and 16.9% in those receiving sham injections. e ROCC study of 32 patients with macular oedema secondary to CRVO, randomized to monthly intravitreal ranibizumab (0.5 mg/0.05 mL) or sham injections for three consecutive months, also reported increased BCVA in the ranibizumab group compared with the sham injection group (22). 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 e ective in

maintaining and improving visual acuity (23). 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. The 12-month randomized RADIANCE trial, including 277 patients with myopic CNV, assessed the efficacy and safety of ranibizumab, administered under two different schedules, guided by visual acuity stabilization or disease activity, compared with verteporfin PDT. Ranibizumab treatment provided superior BCVA gains compared with verteporfin PDT in the first three months (24); patients in the verteporfin PDT arm of the study were switched to ranibizumab thereafter. Three additional RCTs compared ranibizumab and bevacizumab in patients with myopic choroidal neovascularization (mCNV) (25–27). 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) (28). 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 (14, 18, 23). 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 (29). 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. In consideration of costs, the Expert Committee noted that the National Institute for Health and Care Excellence (NICE) considers ranibizumab to be cost–effective for nAMD (20 000 – 25 000 patients/year in the United Kingdom) but not affordable for DME (100 000 patients/year) (30). Ranibizumab is more expensive than bevacizumab, with each injection costing several hundred US dollars and less than US$ 100 US respectively (31). 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 (32). 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 (31, 32). Ranibizumab is currently registered in more than 100 countries worldwide for nAMD, DME, BRVO and CRVO and in more than 80 countries for mCNV. It is recommended by NICE as a possible treatment for these conditions (30, 33–35). Ranibizumab must be administered under aseptic conditions by a qualified ophthalmologist experienced in intravitreal injections. Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the skin, eyelid and ocular surface should be administered before the injection. Following intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection and tonometry within 30 minutes following the injection. Patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or uorescein angiography) (36). 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 25mg/mL (i.e. 1.25mg 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 therefore noted that safe use of bevacizumab as currently formulated requires that use may need to be restricted to a single patient per vial, notwithstanding the wastage. Any alternative approach to using a single vial for multiple patients would have to comply with appropriate safe and sterile injection practices, including any requirements for storage of the product, to ensure that there would be no possibility of contamination. Bevacizumab is already included in the EML. The Expert Committee noted that the evidence resulting from well-conducted independent studies comparing ranibizumab and bevacizumab, critically appraised in several independent systematic reviews, is substantial. Overall, the evidence shows ranibizumab and bevacizumab to be similarly effective in nAMD, DME and mCNV. There was no direct comparative evidence for bevacizumab and ranibizumab in BRVO and CRVO, but the Expert Committee considered that differences have not been demonstrated, as the contextual evidence in similar diseases supports similar effectiveness and safety of the two medicines. In cost– effectiveness analyses, as might be expected, bevacizumab is the preferable option since ranibizumab costs significantly more but offers no greater benefits. The Committee was also concerned that inclusion of ranibizumab on the Model List for treatment of eye diseases might divert relevant resources from other interventions at country level. The Committee considered the option of adding a square box to the existing listing of bevacizumab, thereby allowing selection of ranibizumab as a pharmacological alternative VEGF inhibitor. However, given the difference in current prices of the two products and the legislation relating to “off-label” use of medicines in many countries, the Committee decided that indicating interchangeability could well result in considerable additional expenditure at country level, without additional clinical benefit. The Committee considered that inclusion only of the less expensive bevacizumab on the EML might serve to facilitate its use (albeit off-label) for this indication. 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. References: 1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children). 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