HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
7 JULY 2021

The legally binding text is the original French opinion version

ranibizumab
LUCENTIS 10 mg/ml solution for injection in pre-filled syringe
LUCENTIS 10 mg/ml solution for injection

Re-evaluation

Key points

Favourable opinion for reimbursement only in the treatment of visual impairment due to diabetic macular oedema (DME), in the event of diffuse forms or leakages close to the centre of the macula, in adults with a visual acuity of less than or equal to 5/10 and in whom diabetes management has been optimised.

Unfavourable opinion for reimbursement in other situations.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

Optimisation of diabetes management and its risk factors (glucose, blood pressure and lipid balance and quitting smoking) is a prerequisite to any treatment for visual impairment due to diabetic macular oedema (DME). Control of blood glucose and blood pressure, within the limits required by learned societies, can make it possible to control progression of the retinopathy or DME.

Among the other types of management available, focal laser photocoagulation, which is the standard treatment, is reserved for focal forms of macular oedema located away from the fovea, and possibly cases of severe DME involving the central region, where there are leaks from micro-aneurysms accessible via laser treatment and when visual acuity is normal. This technique does not improve visual acuity.
Medicinal treatments include anti-VEGF intravitreal injections (ranibizumab and aflibercept) and corticosteroid intravitreal implants [OZURDEX (dexamethasone), and ILUVIEN, (fluocinolone acetonide)].
Anti-VEGF [ranibizumab (LUCENTIS) and aflibercept (EYLEA)] intravitreal injections are first-line treatments when the visual impairment is associated with a diffuse form of DME or leakages close to the centre of the macula.
The MA for OZURDEX (dexamethasone) limits its use, firstly, to patients who are pseudophakic or who are unsuitable for non-corticosteroid therapy - subpopulations in which it is considered to be a first-line treatment - and, secondly, to patients insufficiently responsive to non-corticosteroid therapy, i.e. as second-line treatment.
For anti-VEGF therapies, as for OZURDEX (dexamethasone), the Committee recommends that these treatments be used when visual acuity has decreased to less than or equal to 5/10 and diabetes management has been optimised.
The choice between anti-VEGF therapies [ranibizumab (LUCENTIS) and aflibercept (EYLEA)] and OZURDEX (dexamethasone) in pseudophakic patients is left to the decision of the ophthalmologist, who should take into account the ophthalmological characteristics of the treated eye, the diabetic retinopathy stage, as well as the patient's cardiovascular and cerebrovascular history and capacities to comply with treatment.

In chronic DME, a fluocinolone acetonide intravitreal implant (ILUVIEN) is a therapeutic option, in the event of failure of other treatments, particularly anti-VEGF therapies, OZURDEX (dexamethasone) and laser therapy, if management of diabetes is optimised, taking into account its safety profile (risk of glaucoma, cataract).

DME associated with vitreomacular traction is the only clinical form for which surgery remains the treatment of choice. This form of DME is rare: it is estimated to concern less than 5% of oedemas.

Role of LUCENTIS (ranibizumab) in the care pathway:

LUCENTIS (ranibizumab) anti-VEGF remains a first-line treatment of visual impairment due to diabetic macular oedema (DME), in the event of diffuse forms or leakages close to the centre of the macula, in adults with a visual acuity of less than or equal to 5/10 and in whom diabetes management has been optimised.

The choice between anti-VEGF therapies [ranibizumab (LUCENTIS) and aflibercept (EYLEA)] and OZURDEX (dexamethasone intravitreal implant) in the first-line treatment of pseudophakic patients is left to the decision of the ophthalmologist, who should take into account the ophthalmological characteristics of the treated eye [history of glaucoma or ocular hypertonia, lens status (phakic or pseudophakic), history of vitrectomy], the diabetic retinopathy stage, as well as the patient's cardiovascular and cerebrovascular history, age and capacities to comply with treatment.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Diabetic macular oedema (DME) is a complication of diabetic retinopathy. It is asymptomatic but progresses gradually to visual impairment and blindness, resulting in disability and a marked deterioration in quality of life.

◗ The medicinal product LUCENTIS (ranibizumab) is a curative medicine for visual impairment due to DME.

◗ Its efficacy/adverse effects ratio remains high.

◗ There are therapeutic alternatives to this medicinal product.

◗ This medicinal product is a first-line treatment of visual impairment due to diabetic macular oedema (DME) in the event of diffuse forms or leakages close to the centre of the macula, in adults with a visual acuity of less than or equal to 5/10 and in whom diabetes management has been optimised.

Public health impact

Considering:

- the seriousness of DME, which causes visual impairment and is the leading cause of blindness in patients under the age of 50;
- the prevalence of DME in diabetics, estimated to be 3%;
- the partially met medical need in the treatment of visual impairment due to DME, particularly in the event of diffuse forms or leakages close to the centre of the macula, which cannot benefit from laser photocoagulation;
- the partial response to the identified partially met need in view of:
  - the results of the prospective cohort in the BOREAL-DME observational study after 36 months of follow-up, below the clinical significance threshold (5 letters) and lower than that observed in clinical studies (+4.1 letters in the BOREAL-DME study, +8.0 letters in the RESTORE extension study and +11.4 letters in the RIDE study) but given improvements ≥ 10 letters or ≥ 15 letters, which are maintained in more than a third of patients (40% and 30% respectively) and the percentage of patients exceeding the level of 70 letters (5/10) increasing from 31.4% to 55.5% between 12 and 36 months;
  - the lack of a demonstrated additional impact in terms of quality of life, a particularly important aspect in this disabling disease,
  - the lack of a demonstrated additional impact on the organisation of care and the patient's care or life pathway, particularly in terms of the number of follow-up visits and injections.

LUCENTIS (ranibizumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of LUCENTIS (ranibizumab) 10 mg/ml solution for injection remains substantial in the treatment of visual impairment due to diabetic macular oedema (DME), in the event of diffuse forms or leakages close to the centre of the macula, in adults with a visual acuity of less than or equal to 5/10 and in whom diabetes management has been optimised.

It remains insufficient in the other situations.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use only in the treatment of visual impairment due to diabetic macular oedema (DME), in the event of diffuse forms or leakages close to the centre of the macula, in adults with a visual acuity of less than or equal to 5/10 and in whom diabetes management has been optimised, and at the MA dosages.

The Committee issues an unfavourable opinion for reimbursement in other situations.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

- **In the treatment of visual impairment due to diabetic macular oedema (DME), in the event of diffuse forms or leakages close to the centre of the macula, in adults with a visual acuity of less than or equal to 5/10 and in whom diabetes management has been optimised:**

Considering:
- **the long-term results of the available clinical studies, in particular those from the phase 3 RESTORE study (36 months); improvement in visual acuity of +8.0 letters and RIDE study (48 months); improvement in visual acuity of + 11.4 letters, suggesting maintenance of the efficacy and safety profile of ranibizumab intravitreal injections in patients with visual impairment due to DME;**

but considering:
- **data from the prospective cohort in the BOREAL-DME observational study suggesting, after 36 months of follow-up, a lower efficacy in routine practice (below the clinical relevance threshold of 5 letters), than that observed in the phase 3 RESTORE and RIDE clinical studies (mean change in BCVA of +4.1 letters in the BOREAL-DME study, +8.0 letters in the RESTORE extension study and +11.4 letters in the RIDE study);**
- **the absence of a demonstrated improvement in terms of quality of life;**
- **the absence of randomised comparative studies having compared the efficacy and safety of ranibizumab 0.5 mg (LUCENTIS) with those of aflibercept (EYLEA) and the dexamethasone intravitreal implant (OZURDEX), in the medium and long term;**

the Committee considers that LUCENTIS (ranibizumab) provides no clinical added value (CAV V) in the care pathway, including EYLEA (aflibercept) and OZURDEX (dexamethasone), in the treatment of visual impairment due to DME, in the event of diffuse forms or leakages close to the centre of the macula, in adults with a visual acuity of less than or equal to 5/10 and in whom diabetes management has been optimised.