Comparison of EU market access decisions for Visual Disorders based on the PRISMACCESS® DATABASE

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OBJECTIVES:

- Visual impairments (VI) have a huge impact on patient's quality of life. They restrict the work ability and daily life of patients and if untreated VI could cause blindness. The WHO counts worldwide 36 million blind people and 217 million people with visual impairment. Around 75% of these might be avoidable with (early) treatment. [1]
- In the last 10 years, various medications for visual impairments have been assessed by HTA authorities in the EU5. This study provides a comparison of benefit assessments for reimbursement by EU-5 HTA agencies using the Prismaccess®/Evalumade® database. Within that it uses its three-colored scale and shows the availability of therapies for patients.

METHODS:

The international HTA database Prismaccess® includes benefits assessments, including the UK (NICE England, SMC Scotland, AWMSG Wales), HAS France, G-BA Germany, TLV Sweden, ZIN Netherlands, NCPE Ireland and regional and national decisions from Italy and Spain. All decisions on therapies for VIs launched in these countries for the last 10 years were considered for a systematic reimbursement analysis. Excluded from this evaluation were re-assessments of older drugs and biosimilars.

- The international HTA database Prismaccess® includes over 20.000 decisions by market access authorities worldwide.
- This study includes the decisions of the following authorities (countries):
  - o France – Transparency Committee Haute Autorité de Santé – TC HAS / CEESP
  - o England – National Institute for Health and Care Excellence - NICE
  - o Scotland – Scottish Medicines Consortium - SMC
  - o Wales – All Wales Medicines Strategy Group – AWMSG
  - o Germany – Federal Joint Committee - G-BA
  - o Sweden – The Dental and Pharmaceutical Benefits Agency (Tandvårds-Läkemedelförmånsverket) - TLV
  - o Netherlands – The National Health Care Institute (Zorginstituut Nederland) – ZIN
  - o Ireland – National Centre for Pharmacoeconomics – NCPE
  - o Italy – Decisions on regional level of the Regions Emilia-Romagna & Veneto. Additionally, on a national level decisions of Italians Medicines Agency – AIFA were considered.
  - o Spain – Agencia Española de Medicamentos y Productos Sanitarios – AEMPS. Additionally, decisions on the level of the Hospital Network (GENESIS) and also regional decisions of Andalucia, Aragon, Basque, Catalonia (CAMHDA) were considered.
- All decisions on therapeutic areas labeled for VI launched between January 1st 2010 until October 15th 2019 were considered for a systematic analysis.
- Results are labelled according to the national rating. Table 1 explains the national reimbursement grading systems and additionally an overall comparable rating system, visualizing all decisions using a traffic light system. While green and red are self-explaining, yellow means a restriction from a clinical, but also from an economic point of view. As example for France and Germany, if there is an added benefit granted for the therapy in total, but at least in one subgroup, a "no proven added benefit" was granted, then the restriction is assumed ("yellow").
  - o Green – Recommended without limitation
  - o Yellow – Recommended with limitation
  - o Red – Not recommended
- The following five indications have been included in the analysis:
  - o Age-related macular degeneration (AMD),
  - o Visual impairment due to choroidal neovascularisation (CNV),
  - o Visual impairment to choroidal neovascularisation (CNV) secondary to pathologic myopia,
  - o Visual impairment due to to diabetic macular oedema (DMO) and
  - o Visual impairment due to macular oedema secondary to retinal vein occlusion (branch BRVO or central CRVO).

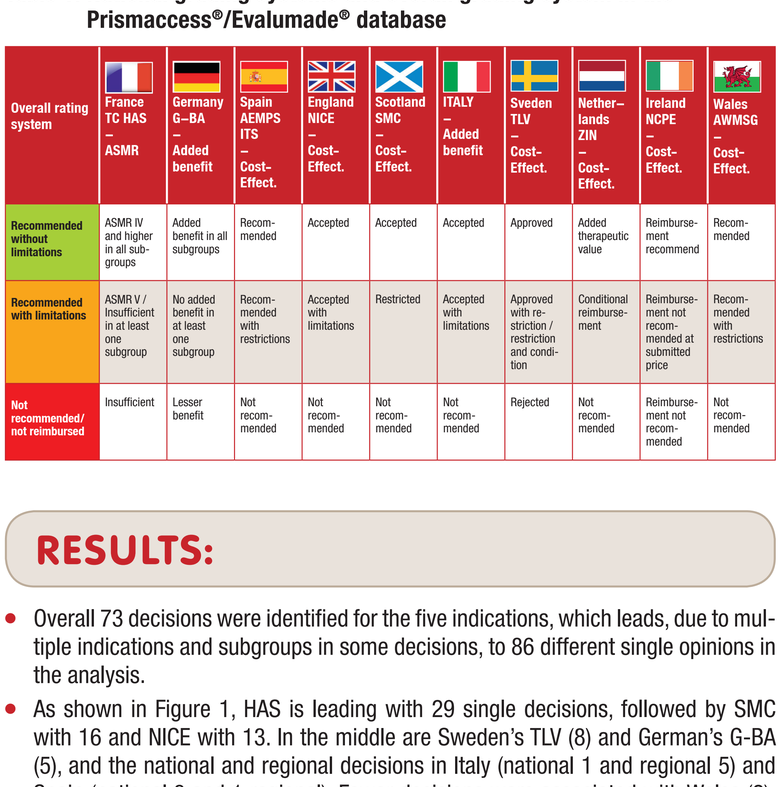
Table 1: National grading systems and overall grading system in the Prismaccess®/Evalumade® database

Overall rating system	France TC HAS – ASMR	Germany G-BA – Added benefit	Spain AEMPS ITS – Cost-Effect.	England NICE – Cost-Effect.	Scotland SMC – Cost-Effect.	ITALY – Added benefit	Sveden TLV – Cost-Effect.	Nether-lands ZIN – Cost-Effect.	Ireland NCPE – Cost-Effect.	Wales AWMSG – Cost-Effect.
Recommended without limitations	ASMR IV and higher in all sub-groups	Added benefit in all subgroups	Recom-mended	Accepted	Accepted	Accepted	Approved	Added therapeutic value	Reimburse-ment recommend	Recom-mended
Recommended with limitations	ASMR V / Insufficient in at least one subgroup	No added benefit in at least one subgroup	Recom-mended with restrictions	Accepted with limitations	Restricted	Accepted with limitations	Approved with re-striction / restriction and condi-tion	Conditional reimburse-ment	Reimburse-ment not recom-mended at submitted price	Recom-mended with restrictions
Not recommended/ not reimbursed	Insufficient	Lesser benefit	Not recom-mended	Not recom-mended	Not recom-mended	Not recom-mended	Rejected	Not recom-mended	Reimburse-ment not recom-mended	Not recom-mended

RESULTS:

- Overall 73 decisions were identified for the five indications, which leads, due to multiple indications and subgroups in some decisions, to 86 different single opinions in the analysis.
- As shown in Figure 1, HAS is leading with 29 single decisions, followed by SMC with 16 and NICE with 13. In the middle are Sweden's TLV (8) and German's G-BA (5), and the national and regional decisions in Italy (national 1 and regional 5) and Spain (national 3 and 1 regional). Fewer decisions were associated with Wales (2), the Netherlands (2) and Ireland (2).

Figure 1: Number of decisions for different visual impairment indications by different HTA agencies in Europe



Age-related macular degeneration (AMD)

- For the indication age-related macular degeneration (AMD), 16 decisions were identified for two products EYLEA (Aflibercept) and LUCENTIS (Ranibizumab).
- LUCENTIS (Ranibizumab) was partly assessed before 2009 and is therefore not part of this analysis. Decisions by HAS (4 decisions) and TLV (2 decisions) have been partly positive assessed. ZIN evaluated it in 2012 negative due to cost-effectiveness in comparison to AVASTIN (Bevacizumab).
- For EYLEA (Aflibercept), as shown in table 2, multiple assessments showed a unique picture of no additional benefit in comparison with LUCENTIS (Ranibizumab) and therefore receives recommendation with limitations.

Table 2: Decisions for age-related macular degeneration (AMD) by different HTA agencies in Europe – EYLEA (Aflibercept)

Agency	Product / Decision / Date	Rationale and commentary
NICE	**EYLEA (Aflibercept)** Accepted (July 2013)	**Recommended with limitations: Only if it is used in accordance with the recommendations for ranibizumab in NICE TA155. If the manufacturer provides aflibercept solution for injection with the discount agreed in the PAS.** Bevacizumab should be used in future also as comparator.
SMC	EYLEA (Aflibercept) Accepted (08/04/2013)	**Recommended with limitations: With the PAS, aflibercept offered similar effectiveness as ranibizumab at lower cost. This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost–effectiveness of aflibercept.**
HAS	**EYLEA (Aflibercept)** Substantial – V (03/04/2013)	**Recommended with limitations: SMR substantial – ASMR V (Requested IV): No additional benefit vs. LUCENTIS.**
G–BA	**EYLEA (Aflibercept)** No added benefit (6/06/2013)	**An additional benefit over the appropriate comparator ranibizumab has not been proved**, due to unsuitable data for the comparison with ranibizumab.
Italy	**EYLEA (Aflibercept)** Comparable (03/04/2014)	**Regione del Veneto: Comperable: Aflibercept is considered as a comparable in efficacy and safety with ranibizumab**. Cost should be the same, but are unclear due to missing data. The studies VIEW 1 and VIEW 2 have been prooved as also long term data after 96 weeks.
	EYLEA (Aflibercept) Comparable (19/05/2015)	**Commissione Regionale del Farmaco della Regione Emilia–Romagna: Comparable:** RCTs View 1 and View 2 showed not to be less than ranibizumab, but also it is not proven to be superior. Also same result with data after 96 weeks.
Spain	**EYLEA (Aflibercept)** Category C-2 – no added benefit (03/10/2013)	**Committee Upgrade Guide Pharmacotherapeutic Hospital Andalucía: Category C–2.:** Aflibercept is comparable safety and efficacy in the proposed indication.
TLV	No decision identified	
ZIN	No decision identified	
NCPE	No decision identified	
AWMSG	No decision identified	

Visual impairment due to choroidal neovascularisation (CNV)

- For the indication visual impairment due to choroidal neovascularisation (CNV) overall only 2 decisions were identified, both for LUCENTIS (Ranibizumab).
- AWMSG rated it recommended with the decisions from 12-Jun-2018.
- HAS rated it substantial with an ASMR of IV with the decisions from 21-Feb-2018.

Visual impairment to choroidal neovascularisation (CNV) secondary to pathologic myopia

- For the indication visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia 15 decisions were identified, all for the two products EYLEA (Aflibercept) and LUCENTIS (Ranibizumab). Table 3 shows a comparison of the decisions.
- For EYLEA (Aflibercept), the manufactorer presented only the placebo controlled study MYRROR (sham intravitreal injections (IVT)) and no indirect treatment comparison. The defined appropriate comparator therapy by G-BA and HAS is LUCENTIS (Ranibizumab). Due to concomitant developments, there is no comparative data available. HAS rated it positive, while G-BA did not accept the clinical data and rated it as "an added benefit is not proven".
- LUCENTIS (Ranibizumab) was compared with vPDT in the study RADIANCE. The NICE committee noted, that vPDT as a comparator is in future no longer useful, since ranibizumab and bevacizumab are more and more used as a treatment for CNV. SMC critized the length of the trial and the not formal indirect comparison. Because of the lack of clinical trials, the presented data was accepted, partly with limitations.

Table 3: Decisions for visual impairment to choroidal neovascularisation (CNV) secondary to pathologic myopia by different HTA agencies in Europe

Agency	EYLEA (Aflibercept) Product / Decision / Date	LUCENTIS (Ranibizumab) Product / Decision / Date
NICE	Recommended with limitations 01-Nov-2017	Recommended with limitations November 2013
SMC	Accepted 10-Oct-2016	Accepted 11-Nov-2013
HAS	Substantial – III 20-Jul-2016	Substantial – III 04-12-2013
		Substantial – V 01-Apr-2015 (Additional Range) Substantial – V 05-Feb-2014 (Additional Range) Substantial – IV 21-Jan-2015 (Re-assessment) Substantial – V 20-May-2015 (Additional Range)
G–BA	Added benefit not proven 19-May-2016	
Italy	Reimbursed 21-Dec-2016	
Spain		
TLV		Recommended 26-Jan-2012 Recommended 18-Jun-2014 ZIN
ZIN		
NCPE		
AWMSG	Recommended 14-Mar-2017	

Visual impairment due to to diabetic macular oedema (DMO)

- For the indication visual impairment due to to diabetic macular oedema (DMO) 26 decisions were identified for four drugs. Table 4 shows a comparison of the decisions.
- LUCENTIS (Ranibizumab) was mainly recommended with limitations compared with standard laser photocoagulation treatment. Not recommendations are caused to unbalanced costs/exceeding ICER and have been accepted later with limitations of a patient access scheme. The clinical data was mainly accepted.
- OZURDEX (Dexamethasone) was mainly recommended with limitations. Two RCT MEAD compared to Placebo showed significant results and were combined with a network meta analysis. An economic analysis compared dexamethasone with a range of other treatments for DMO. There were some limitations with the analysis but overall it was found that dexamethasone offered value for money for the treatment of DMO in this group of patients.
- ILUVIEN (Fluocinolone acetonide) was mainly recommended with limitations. Two identical dose-finding placebo controlled-studies (FAME A and B) were presented as a pooled analysis. Not recommendations are caused to unbalanced costs/exceeding ICER and have been accepted later with limitations of a patient access scheme (NICE) or with the restriction only in patients in whom the affected eye is pseudophakic (has an artificial lens after cataract surgery) and; retreatment would take place only if the patient had previously responded to treatment with fluocinolone acetonide and subsequently best corrected visual acuity had deteriorated to less than 20/32.
- EYLEA (Aflibercept) was mainly recommended with limitations. Two RCT VISTA and VIVID compared Aflibercept with laser photocoagulation. Although this showed significant results, a comparison against Dexamethasone (HAS) or Ranibizumab (HAS, G-BA) was not presented or showed not equal data for some patient group. The italien Commissione Regionale del Farmaco della Regione Emilia-Romagna evaluated the presented data positive to treatment with lasers. HAS limited EYLEA (Aflibercept) for the subgroup diabetic macular edema in case of diffuse or leak near the center of the macula with a lower visual loss or equal to 5/10, SMC restricted with PAS for use in the treatment of visual impairment due to DMO in adults with BCVA 75 ETDRS letters or less at baseline and NICE restricted it with PAS only for patients the eye has a central retinal thickness of 400 micrometres or more at the start of treatment according to the decision of LUCENTIS (Ranibizumab). For the assessment, also different patient populations have been considered, e.g. G-BA with patients with visual impairment due to DMO with and without the involvement of the fovea.

Table 4: Decisions for Visual impairment due to to diabetic macular oedema (DMO) by different HTA agencies in Europe

Agency	EYLEA (Aflibercept)	LUCENTIS (Ranibizumab)	OZURDEX (Dexamethasone)	ILUVIEN (Fluocinolone acetonide)
NICE	Recommended with limitations 22-Jul-2015	Recommended with limitations February 2013	Recommended with limitations Jul 2015	Recommended with limitations November 2013
		Not recommended - November 2011		Not recommended - January 2013
SMC	Restricted 10-Nov-2014	Restricted 10-Dec-2012	Accepted 10-Apr-2015	Restricted 10-Feb-2014
		Not recommended - 10-Jul-2011		Not recommended - 10-Jun-2013
France	Substantial – IV / Insufficient 18-Mar-2015	Not rated 02-Dec-2015 (New data) Substantial – V 01-Apr-2015 (Additional Range) Substantial – V 05-Feb-2014 (Additional Range) Important – IV Insufficient 22-Jun-2011	Moderate – V / Moderate – V / Moderate – V / Insufficent 29-Apr-2015	Moderate – IV 26-Jun-2013
G–BA	Added benefit not proven 05-Mar-2015			
Italy	Commissione Regionale del Farmaco della Regione Emilia-Romagna: Comparable 19-May-2015			
Spain				
TLV		Recommended 26-Jan-2012 Recommended 18-Jun-2014		
ZIN		Not recommended - 25-Jul-2011		
NCPE				Not recommended - 02-Mar-2016
AWMSG				

Visual impairment due to macular oedema secondary to retinal vein occlusion (branch BRVO or central CRVO)

- For the indication visual impairment due to macular oedema secondary to retinal vein occlusion (branch BRVO or central CRVO) 27 decisions were identified for four drugs. Table 5 shows a comparison of the decisions.
- For EYLEA (Aflibercept) the manufacturer presented different studies for branch BRVO and central CRVO.
  - o For BRVO the RCT VIBRANT comparing the drug with laser treatment was presented. Although this showed significant results, a comparison against Dexamethasone (HAS) or Ranibizumab (HAS, G-BA) was not presented and leaded to recommendations with limitations. Aflibercept was considered cost-effectiveness with a PAS only.
  - o For CRVO the two sham injection placebo controlled RCT COPERNICUS and GALILEO were presented. A network meta-analysis showed no difference to ranibizumab, and in comparison to dexamethasone, it was better due to the health-related quality of life data and whether it was applied to the 'worse-seeing eye' or 'better-seeing eye'. For NICE and SMC a Patient Access Scheme applied to become cost-effective.
- For LUCENTIS (Ranibizumab), the two RCT BRAVO study (BRVO) and CRUISE study (CRVO) comparing to placebo (sham injection) were presented. Due to non cost-effectiveness, NICE limited the recommendation to patients when treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage and only if the manufacturer provides a PAS with a discount granted. SMC differed between BRVO and CRVO patients, and restricted it with a PAS for CRVO patients. HAS compared LUCENTIS (Ranibizumab) with OZURDEX (Dexamethasone).
- AVASTIN (Bevacizumab) was only evaluated by Spanish Genesis. The assessment was rated as recommendation due to a network meta-analysis showing no differences and a cost comparison of about 150 times smaller than LUCENTIS (Ranibizumab).
- For OZURDEX (Dexamethasone), the manufacturer presented two placebo (sham injection) controlled studies. Although of showing some significant results, the trial design was missing long-term results (HAS/SMC). NICE splits its recommendation in an option for the treatment of macular oedema following central retinal vein occlusion (CRVO) and as an option for the treatment of macular oedema following branch retinal vein (BRVO) occlusion when treatment with laser photocoagulation has not been beneficial, or treatment with laser photocoagulation is not considered suitable because of the extent of macular haemorrhage. A missing recommendation at SMC is due to not submitting a dossier.

Table 5: Decisions for visual impairment due to macular oedema secondary to retinal vein occlusion (branch BRVO or central CRVO) by different HTA agencies in Europe

Agency	EYLEA (Aflibercept)	LUCENTIS (Ranibizumab)	OZURDEX (Dexamethasone intravit–real implant)
NICE	Recommended with limitations February 2014 Recommended with limitations 28-Sep-2016	Recommended with limitations May 2013	Recommended July 2011
SMC	Accepted 07-Mar-2014 Accepted 07-Aug-2015	Accepted (BRVO) 13-May-2013	Restricted 11-Jun-2012
		Restricted (CRVO) 07-Nov.2011	Not recommended 12-Dec-2011 13-Dec-2010
HAS	Substantial – IV 06-Jan-2016	Substantial – IV 21-Jan-2015(Re-evaluation) Substantial – V 05-Feb-2014(Additional Range) Substantial – IV 21-Nov-2012(Renewal of decision) Substantial – IV 18-Jan-2012	Substantial – IV 17-Nov-11
G–BA	Added benefit not proven 20-Mar-2014 Added benefit not proven 03-Sep-2015		
Italy			Regione del Veneto Suspended 20-Dec-2011
			Commissione Regionale del Farmaco della Regione Emilia-Romagna: Recommended 19-May-2015
Spain		C1 – comparable 18-Oct-2012	
TLV		Recommended 26-Jan-2012 Recommended 18-Jun-2014	
ZIN			
NCPE			Not recommended 16-Mar-2012
AWMSG			

CONCLUSIONS:

- The analysis shows differences in the benefit assessment of drugs for visual impairments between the different market access authorities in Europe.
- The different results can be explained with the different interpretation and acceptation of appropriate comparator therapy and the results of the clinical endpoints.
- While some countries accepted placebo or Laser controlled trials as an appropriate comparator therapy like SMC or Italian authority, some did not accept the data like the German G-BA.
- Also the different approaches of cost-effectiveness in the methodology of the market access authorities lead to different results. Especially the presented drugs LUCENTIS (Ranibizumab), EYLEA (Aflibercept) have been considered as too expensive, e.g. exceeding ICER of 25.000 GBP, especially in comparison with AVASTIN (Bevacizumab).

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[1] World Health Organization (WHO) and International Agency for the Prevention of Blindness (IAPB) (2019): GBVI – Global Cause Estimates. - https://www.iapb.org/vision-2020/who-facts/ (last access 21.10.2019)