ILUVIEN 190 micrograms, intravitreal implant in applicator
B/1 (CIP: 34009 222 858 1 8)
Applicant: NOVEX PHARMA

<table>
<thead>
<tr>
<th>INN</th>
<th>Fluocinolone acetonide</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (year)</td>
<td>S01BA15 (ophthalmological preparation containing corticosteroid)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
</tr>
<tr>
<td>List(s) concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17)</td>
</tr>
<tr>
<td></td>
<td>Hospital Use (French Public Health Code L.5123-2)</td>
</tr>
<tr>
<td>Indication(s) concerned</td>
<td>“Treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies”</td>
</tr>
</tbody>
</table>

**Actual Benefit**

- moderate AB

**Improvement in Actual Benefit**

- ILUVIEN provides a minor improvement in actual benefit (IAB IV) in the treatment strategy for vision impairment caused by chronic diabetic macular oedema in adults, insufficiently responsive to available therapies (laser photocoagulation, ranibizumab).

**Therapeutic use**

- End of line treatment in patients with vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies (laser photocoagulation, ranibizumab), despite optimum management of diabetes.
01 ADMINISTRATIVE AND REGULATORY INFORMATION

<table>
<thead>
<tr>
<th>Marketing Authorisation (procedure)</th>
<th>16 July 2012 (decentralised procedure)</th>
</tr>
</thead>
</table>
| Prescribing and dispensing conditions/ special status | List I  
Prescription-only medicine restricted to ophthalmologists |

<table>
<thead>
<tr>
<th>ATC Classification</th>
</tr>
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<tbody>
<tr>
<td>2012 S</td>
</tr>
<tr>
<td>S01 S01B S01BA S01BA15</td>
</tr>
<tr>
<td>Sensory organs Ophthalmologicals Anti-inflammatory agents Corticosteroids, plain Fluocinolone acetonide</td>
</tr>
</tbody>
</table>

02 BACKGROUND

ILUVIEN is an intravitreal implant containing the acetate of fluocinolone, a corticosteroid. It is the only medicine that currently has a Marketing Authorisation for use in vision impairment associated with chronic diabetic macular oedema (DMO) considered insufficiently responsive to available therapies (LUCENTIS which has a Marketing Authorisation for the treatment of vision impairment associated with DMO, and the corticosteroids used off-label up until now).

03 THERAPEUTIC INDICATIONS

"Treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies."

04 DOSAGE

"The recommended dose is one ILUVIEN implant in the affected eye. Administration in both eyes concurrently is not recommended. An additional implant may be administered after 12 months if the patient experiences decreased vision or an increase in retinal thickness secondary to recurrent or worsening diabetic macular oedema. Retreatments should not be administered unless the potential benefits outweigh the risks. Only patients who have been insufficiently responsive to prior treatment with laser photocoagulation or other available therapies for diabetic macular oedema should be treated with ILUVIEN."
Paediatric population
There is no relevant use of ILUVIEN in the paediatric population in diabetic macular oedema (DMO).

Special populations
No dosage adjustments are necessary in elderly patients, or those with renal or hepatic impairment.

05 THERAPEUTIC NEED

Diabetic macular oedema is a complication of diabetic retinopathy. The risk of onset of macular oedema may be reduced by control of blood glucose and blood pressure.

Laser photocoagulation is the reference therapy for alleviating vision impairment secondary to diabetic macular oedema. It does not improve visual acuity.

There are two laser photocoagulation methods for treating diabetic macular oedema:
- focal photocoagulation targeting the focal lesions causing the oedema (microaneurysm and/or specific blood vessels)
- grid laser photocoagulation of the perifoveal area to treat diffuse macular oedema.

Laser treatment is effective in the focal forms.

When the lesions are close to the centre of the macula, the anticipated benefits of this therapy need to be balanced against the possible complications, such as paracentric scotoma, accidental treatment of the fovea, neovascularisation developing from a photocoagulation scar. In view of these side effects, the number of retreatments should be limited.

According to the ETDRS guidelines, all patients with clinically significant macular oedema should receive laser therapy, irrespective of their visual acuity, to reduce progression of macular oedema. Clinically significant oedema is defined as one of the following three criteria:
- retinal thickening and/or exudate involving the centre of the macula,
- retinal thickening and/or exudate situated less than 500 µm from the centre of the macula but not touching it,
- retinal thickening with an area of 1 papillary diameter (PD) or more, situated at least partly less than 1 PD from the centre of the macula.

In 2011, ranibizumab obtained an extension of indication for the treatment of visual impairment due to diabetic macular oedema. In the absence of long-term data on the use of ranibizumab monotherapy and because the treatment regimen is demanding, requiring monthly injections until stable visual acuity is reached at three consecutive monthly assessments under treatment, treatment by laser photocoagulation remains the reference treatment (Transparency Committee Opinion of 22 June 2011).

Ranibizumab should be reserved for patients who cannot benefit from laser treatment, i.e. in cases of diffuse macular oedema or leakage close to the centre of the macula. This treatment should be started when visual acuity falls to 5/10 or lower, as is the case for laser photocoagulation and only if the best possible diabetes control has been obtained.

In the absence of specific data, ranibizumab is not recommended in diabetic macular oedema with focal or diffuse components.

ILUVIEN is the first medicine with a Marketing Authorisation in chronic forms considered insufficiently responsive to laser photocoagulation or to ranibizumab.

Surgical treatment by vitrectomy is indicated for the rare cases of tractional macular oedema induced by contraction of the thickened and condensed premacular hyaloid membrane.

## 06 CLINICALLY RELEVANT COMPARATORS

### 06.1 Medicinal products

ILUVIEN is the only medicine indicated in vision impairment associated with chronic forms of DMO after failure of available therapies.

### 06.2 Other health technologies

None.

> Conclusion

There are no relevant comparators to ILUVIEN.

## 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

<table>
<thead>
<tr>
<th>Country</th>
<th>REIMBURSEMENT</th>
<th>Population(s) That of the Marketing Authorisation or restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES/NO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If no, why not</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>NO</td>
<td>Treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies.</td>
</tr>
<tr>
<td>(not on the market)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>YES</td>
<td>Treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies.</td>
</tr>
<tr>
<td>Portugal</td>
<td>NO</td>
<td>Treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies.</td>
</tr>
<tr>
<td>(not on the market)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>YES</td>
<td>Treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies.</td>
</tr>
</tbody>
</table>
ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The evidence for the effectiveness of fluocinolone acetonide in chronic DMO after failure of other available therapies is derived from two placebo-controlled (sham injection) phase III trials using the same protocol, i.e. the FAME A and FAME B (Fluocinolone Acetonide for diabetic Macular Edema) trials in patients with vision impairment associated with DMO previously treated by at least one laser photoocoagulation session. The population of these trials was stratified according to whether or not the DMO was chronic.

<table>
<thead>
<tr>
<th>Primary objective of the study</th>
<th>To demonstrate the superiority of 0.2 and 0.5 μg/day of fluocinolone acetonide compared with sham injection of an implant, in terms of ≥ 15 letter increase in best corrected visual acuity (BCVA) at 24 months compared with baseline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Placebo-controlled comparative randomised double-blind trial.</td>
</tr>
</tbody>
</table>

### Inclusion criteria

- Age ≥ 18 years
- BCVA of ≥ 19 and ≤ 68 letters (20/50 or worse but at least 20/400) in the study eye by an ETDRS chart. BCVA of the non-study eye must be no worse than 20/400.
- Diagnosis of diabetes mellitus (type 1 or type 2). Any one of the following was considered to be sufficient evidence that diabetes is present:
  - Use of insulin for the treatment of diabetes for at least the 3 months prior to screening
  - Use of oral antihyperglycaemic agents for the treatment of diabetes for at least the 3 months prior to screening
- At least one macular laser treatment more than 12 weeks prior to the screening visit
- DMO based on investigator’s clinical evaluation and demonstrated on fundus photographs, fluorescein angiograms, and optical coherence tomography (OCT)
- Mean foveal thickness of at least 250 μm by OCT in the study eye

### Exclusion criteria

- Any ocular surgery in the study eye within 12 weeks prior to screening
- Yag capsulotomy in the study eye within 15 days prior to screening
- Prior intravitreal, subtenon, or periocular steroid therapy within 3 months prior to enrolment (e.g. triamcinolone) or prior treatment with intravitreal anti-VEGF treatment during the 2 months preceding enrolment (Lucentis™, Avastin®, Macugen®). Systemic treatment with Avastin was also not allowed within 3 months prior to screening
- Any change in systemic steroidal therapy during the 3 months preceding screening
- Glaucoma, ocular hypertension, intraocular pressure (IOP) > 21 mmHg or concurrent therapy at screening with IOP-lowering agents in the study eye
- Retinal or choroidal neovascularisation due to ocular conditions other than diabetic retinopathy (e.g. presumed ocular histoplasmosis, high myopia (spherical equivalent > 8 dioptres), macular degeneration)
- Peripheral retinal detachment in prospective area of insertion

### Treatment groups

- Fluocinolone acetonide implant (FAc) 0.2 μg/day (dose approved by the Marketing Authorisation)
Fluocinolone acetonide implant (FAc) 0.5 µg/day
- Sham injection
Randomisation 2:2:1

Course of the study
- Treatment on D0 in the affected eye or the most affected of the two eyes.
- Retreatment was allowed at the same dose, after the first 12 months and not later than month 33, in the case of visual loss ≥ 5 letters on the ETDRS eye chart or retinal thickening ≥ 50 µm visible on OCT in the centre of the fovea compared with patient's best status during the previous 12 months.
- Patients were followed-up to 36 months

Concomitant therapy
- Additional laser treatment permitted for the study eye during the 6-week visit if considered necessary by a masked assessing investigator and if the eye was not showing improvement in oedema compared with inclusion. During subsequent visits, further laser therapy was permitted based on the investigator's judgement, provided that the subject had not been retreated with the study medicine during the previous 6 weeks. In addition, laser treatments had to be spaced at least 6 weeks away from a visit that included optical coherence tomography (OCT).
- Intravitreal corticosteroids used off-label and/or vascular endothelial growth factor (VEGF) antagonists were prohibited by the protocol, but used at the masked investigator's discretion, in accordance with current reference therapy used by retinal specialists for treating DMO during the trial. In accordance with the principle of intent-to-treat population, all subjects, including those who had received therapies not allowed in the protocol at the investigator's decision, were included in the full analysis.

Primary efficacy endpoint
- Percentage of patients with ≥ 15 letter increase in BCVA (ETDRS) at 24 months compared with baseline value.

The secondary endpoints included:
- Mean change from baseline BCVA at 24, 30 and 36 months compared with baseline value.
- Analyses of results for all patients randomised (full analysis set, FAS) with use of last known value for missing values at measurement time (last observation carried forward, LOCF)

Statistical analysis
- Subgroup analyses planned according to:
  - BCVA at inclusion: ≤ 49 letters and > 49 letters
  - chronic or non-chronic disease; chronic DMO was defined as DMO duration ≥ median duration, non-chronic DMO was defined as DMO duration < median duration.

Apart from the demographic characteristics of the trials, only the results concerning the dosage approved in the Marketing Authorisation (0.2 µg/day) will be described below.

- **Results of the FAME A trial:**
  A total of 481 patients were randomised, 190 in the FAc 0.2 µg/day group, 196 in the FAc 0.5 µg/day group and 95 in the sham injection group. A large number of patients (30% from all groups taken together) dropped out of the trial prematurely, mainly for withdrawal of consent, loss to follow-up and death (see Table 1). At least one protocol violation was recorded in 87.5% of patients, mainly because of the use of prohibited medicines or treatments (34.7% in the sham injection group, 18.9% in the FAc 0.2 µg/day group and 21.4% in the FAc 0.5 µg/day group).

Patient characteristics were comparable between the groups. Mean patient age was 63 years, and the majority (57.4%) were men. The study eye was phakic in 64% of cases and pseudophakic in 33.9% of cases. No eyes were aphakic and the data item was missing for 2.1% of cases.

DMO had been diagnosed a mean of 4 and a median of 3 years previously.
Table 1: Populations of the FAME A trial:

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sham treatment N=95</th>
<th>FAc 0.2 µg/day N=190</th>
<th>FAc 0.5 µg/day N=196</th>
<th>Total N=481</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Randomised</td>
<td>95 (100)</td>
<td>190 (100)</td>
<td>196 (100)</td>
<td>481 (100)</td>
</tr>
<tr>
<td>Randomised and treated</td>
<td>95 (100)</td>
<td>190 (100)</td>
<td>195 (99.5)</td>
<td>480 (99.8)</td>
</tr>
<tr>
<td>Dropped out prematurely for:</td>
<td>28 (29.5)</td>
<td>49 (25.8)</td>
<td>64 (32.7)</td>
<td>141 (29.3)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>3 (3.2)</td>
<td>2 (1.1)</td>
<td>14 (7.1)</td>
<td>19 (4.0)</td>
</tr>
<tr>
<td>Unsatisfactory therapeutic effect</td>
<td>2 (2.1)</td>
<td>0</td>
<td>1 (0.5)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>2 (2.1)</td>
<td>2 (1.1)</td>
<td>3 (1.5)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>6 (6.3)</td>
<td>19 (10.0)</td>
<td>13 (6.6)</td>
<td>38 (7.9)</td>
</tr>
<tr>
<td>Subject lost to follow-up</td>
<td>9 (9.5)</td>
<td>14 (7.4)</td>
<td>14 (7.1)</td>
<td>37 (7.7)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (6.3)</td>
<td>11 (5.8)</td>
<td>19 (9.7)</td>
<td>36 (7.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1 (0.5)</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Patients had previously received corticosteroid therapy in 20.3% of cases, 77.6% had not received any corticosteroid therapy and the data item was missing in 2.1% of cases.

Patients had previously received VEGF antagonist therapy in 5.2% of cases, 42.4% had not received any VEGF antagonist therapy and the data item was missing in 52.4% of cases.

Diabetes had been diagnosed a mean of 16.9 and a median of 16.0 years previously. In most cases (90.6%), diabetes was type 2. HbA1c value at inclusion was 4.8-14.2% with a mean value of 7.6%.

At inclusion, mean best corrected visual acuity (BCVA) was 57.0 letters (ETDRS) in the 0.2 µg/day group, 55.0 letters in the 0.5 µg/day group and 58.0 letters in the sham injection group.

Increased central retinal thickness was 286.6 µm in the FAc 0.2 µg/day group, 312.1 µm in the 0.5 µg/day group and 264.1 µm in the sham injection group.

The mean number of retreatments in the study eye during the trial was 1.2 in the FAc 0.2 µg/day group and the sham injection group, mainly after 12 months. Globally, 70.4% of patients received one treatment with the study medicine, 24.0% had one retreatment, 4.8% had two retreatments and 0.8% had three retreatments.

The mean number of laser treatments was 1.0 in the FAc 0.2 µg/day group and 1.6 in the sham injection group.

Results for the primary efficacy endpoint:

After 24 months, the percentage of patients with ≥ 15 letter increase in BCVA was higher in the FAc 0.2 µg/day group than in the sham injection group (26.8% versus 14.7%, p = 0.029) (see Table 2).
Results for secondary endpoints:
The significant difference in favour of fluocinolone acetonide in terms of percentage of patients with \( \geq 15 \) letter increase in BCVA was maintained after 30 months but not at 36 months (see Table 2).

Mean change in BCVA from baseline was 3.7 letters at 24 months, 4.8 letters at 30 months and 4.9 letters at 36 months in the FAc 0.2 µg/day group and 3.2 letters at 24 months, 2.9 letters at 30 months and 3.3 letters at 36 months in the sham injection group.

None of the differences observed between the groups was statistically significant.

Table 2: results for percentage of patients with \( \geq 15 \) letter increase in BCVA (ETDRS) – FAME A trial, FAS-LOCF population

<table>
<thead>
<tr>
<th>% of patients with ( \geq 15 ) letter increase in BCVA</th>
<th>FAc 0.2 µg/day</th>
<th>Sham injection</th>
<th>Difference, 95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 months</td>
<td>26.8</td>
<td>14.7</td>
<td>12.6 [2.6; 21.6]</td>
<td>0.029</td>
</tr>
<tr>
<td>30 months</td>
<td>28.9</td>
<td>14.7</td>
<td>14.2 [4.6; 23.8]</td>
<td>0.011</td>
</tr>
<tr>
<td>36 months</td>
<td>28.4</td>
<td>18.9</td>
<td>9.5 [0.7; 19.6]</td>
<td>0.106</td>
</tr>
</tbody>
</table>

These results should be interpreted with caution as a large proportion of the patients dropped out of the trial prematurely (28.6%) and used treatments not allowed in the protocol which could have an effect on DMO (mainly corticosteroids and VEGF antagonists), i.e. 23.1% for the whole population, 34.7% in the sham injection group, 18.9% in the FAc 0.2 µg/day group and 21.5% in the FAc 0.5 µg/day group.

➢ Results of the FAME B trial:

A total of 475 patients were randomised, 186 in the FAc 0.2 µg/day group, 199 in the FAc 0.5 µg/day group and 90 in the sham injection group.

A large number of patients (28.6% from all groups taken together) dropped out of the trial prematurely, mainly for withdrawal of consent, loss to follow-up and death (see Table 3).

Table 3: Populations of the FAME B trial

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sham treatment N=90</th>
<th>FAc 0.2 µg/day N=186</th>
<th>FAc 0.5 µg/day N=199</th>
<th>Total N=475</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomised</td>
<td>90 (100)</td>
<td>186 (100)</td>
<td>199 (100)</td>
<td>475 (100)</td>
</tr>
<tr>
<td>Randomised and not treated</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Randomised and treated</td>
<td>90 (100)</td>
<td>185 (99.5)</td>
<td>198 (99.5)</td>
<td>473 (99.6)</td>
</tr>
<tr>
<td>Completed the trial</td>
<td>59 (65.6)</td>
<td>133 (71.5)</td>
<td>147 (73.9)</td>
<td>339 (71.4)</td>
</tr>
<tr>
<td>Dropped out of the trial prematurely</td>
<td>31 (34.4)</td>
<td>53 (28.5)</td>
<td>52 (26.1)</td>
<td>136 (28.6)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>2 (2.2)</td>
<td>2 (1.1)</td>
<td>1 (0.5)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Unsatisfactory therapeutic effect</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>0</td>
<td>0</td>
<td>2 (1.0)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>8 (8.9)</td>
<td>12 (6.5)</td>
<td>14 (7.0)</td>
<td>34 (7.2)</td>
</tr>
<tr>
<td>Subject lost to follow-up</td>
<td>15 (16.7)</td>
<td>23 (12.4)</td>
<td>23 (11.6)</td>
<td>61 (12.8)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (5.6)</td>
<td>16 (8.6)</td>
<td>12 (6.0)</td>
<td>33 (6.9)</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>8 (8.9)</td>
<td>12 (6.5)</td>
<td>14 (7.0)</td>
<td>34 (7.2)</td>
</tr>
</tbody>
</table>

At least one deviation from the protocol was recorded in 88.6% of patients, mainly because of the use of prohibited treatments (31.1% in the sham injection group, 11.3% in the FAc 0.2 µg/day group and 11.1% in the FAc 0.5 µg/day group).
Patient characteristics were comparable between the groups.

Mean patient age was 61.8 years, and the majority (61.5%) were men. The study eye was phakic in 63.2% of cases and pseudophakic in 34.7% of cases. No eyes were aphakic and the data item was missing for 2.1% of cases.

DMO had been diagnosed a mean of 3.3 and a median of 3 years previously.

Patients had previously received corticosteroid therapy in 18.1% of cases, 79.8% had not received any corticosteroid therapy and the data item was missing in 2.1% of cases. Patients had previously received VEGF antagonist therapy in 7.2% of cases, 37.7% had not received any VEGF antagonist therapy and the data item was missing in 55.1% of cases.

Diabetes had been diagnosed a mean of 16.3 and a median of 16.0 years previously. In most cases (93.5%), diabetes was type 2. HbA1c value at inclusion was 4.7-15.3% with a mean value of 7.9%.

At inclusion, mean best corrected visual acuity (BCVA) was 53.3 letters (ETDRS) in the 0.2 µg/day and 0.5 µg/day groups and 54.7 letters in the sham injection group. Increased central retinal thickness was 276.9 µm in the FAc 0.2 µg/day group, 298.9 µm in the 0.5 µg/day group and 280.1 µm in the sham injection group.

The mean number of retreatments in the study eye during the trial was 1.1 in the FAc 0.2 µg/day group and 1.3 in the sham injection group, mainly after 12 months. Globally, 74.2% of patients received one treatment with the study medicine, 21.4% had one retreatment, 3.8% had two retreatments and 0.6% had three retreatments.

The mean number of laser treatments was 0.9 in the FAc 0.2 µg/day group and 1.4 in the sham injection group.

Results for the primary efficacy endpoint:

After 24 months, the percentage of patients with ≥15 letter increase in BCVA was higher in the FAc 0.2 µg/day group than in the sham injection group (30.6% versus 17.8%, p = 0.030) (see Table 2).

Results for secondary endpoints:

The significant difference in favour of fluocinolone acetonide in terms of percentage of patients with ≥15 letter increase in BCVA was maintained after 30 months but not at 36 months (see Table 4). Mean change in BCVA compared with baseline was greater in the FAc 0.2 µg/day group than in the sham injection group at 24 months (5.1 letters compared with 0.0 letters), at 30 months (6.7 letters compared with -0.3 letters) and at 36 months (5.7 letters compared with 0.7 letters). The differences observed (≥5 letters) were clinically relevant.

Table 4: results for percentage of patients with ≥15 letter increase in BCVA (ETDRS) – FAME B trial, FAS-LOCF population

<table>
<thead>
<tr>
<th>% of patients with ≥15 letter increase in BCVA:</th>
<th>FAc 0.2 µg/day N = 190</th>
<th>Sham injection N = 95</th>
<th>Difference, 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 months</td>
<td>30.6</td>
<td>17.8</td>
<td>12.9 [2.6; 23.2]</td>
<td>0.030</td>
</tr>
<tr>
<td>30 months</td>
<td>33.9</td>
<td>15.6</td>
<td>18.3 [8.2; 28.4]</td>
<td>0.002</td>
</tr>
<tr>
<td>36 months</td>
<td>28.4</td>
<td>18.9</td>
<td>18.9 [0.2; 20.5]</td>
<td>0.086</td>
</tr>
</tbody>
</table>
As in the FAME A trial, these results should be interpreted with caution as a large proportion of the patients dropped out of the trial prematurely (28.6%) and used treatments not allowed in the protocol which could have an effect on DMO (mainly corticosteroids and VEGF antagonists), i.e. 15.0% from the whole population, 31.1% in the sham injection group, 11.4% in the FAc 0.2 µg/day group and 11.1% in the FAc 0.5 µg/day group.

Results in the subgroup of patients with chronic DMO (Marketing Authorisation indication):

A subgroup analysis was performed to evaluate the effectiveness of fluocinolone acetonide in patients with chronic or non-chronic DMO. DMO was considered to be chronic if it had lasted ≥ 3 years (i.e. longer than or equal to the median duration of DMO in the patients enrolled in the trials). Patients with chronic DMO accounted for 60% of the total population of the FAME A trial and 53% of the total population of the FAME B trial.

In the subgroup of patients with DMO ≥ 3 years in the FAME A and B trials, the percentage of patients with ≥ 15 letter increase in BCVA after 24 months was greater in the FAc 0.2 µg/day group than in the sham injection group:
- FAME A: 31.8% versus 11.9%, i.e. difference of 20.0% (p = 0.004)
- FAME B: 37.4% versus 15.1%, i.e. difference of 22.3% (p = 0.006).

In the subgroup of patients with DMO < 3 years in the FAME A and B trials, there was no significant difference between FAc 0.2 µg/day and sham injection in terms of percentage of patients with ≥ 15 letter increase in BCVA after 24 months.

There was no significant difference in terms of mean change in BCVA at 24 months compared with baseline between the groups in patients with DMO < 3 years.

In patients with chronic DMO, there was a significant difference in favour of fluocinolone acetonide 0.2 µg/day for mean change in BCVA at 24 months, in the FAME B trial only, i.e. 6.4 letters versus 0.4 (p = 0.042).

Similar results were obtained at 30 and 36 months.

At 36 months, the percentage of patients with ≥ 15 letter increase in BCVA was:
- FAME A: 31.8% in the FAc 0.2 µg/day group compared with 13.6% with sham injection, i.e. a difference of 18.3% (p = 0.010)
- FAME B: 36.4% versus 13.2%, i.e. a difference of 23.2% (p = 0.004).

08.2 Adverse effects

Data from the FAME A and FAME B clinical trials

- **FAME A**
  
  There were 71.6% treatment-related adverse events in the FAc 0.2 µg/day group, 77.9% in the FAc 0.5 µg/day group, and 31.6% in the sham injection group. These adverse events occurred only in the study eye apart from one systemic adverse event (headache) reported in a patient in the FAc 0.5 µg/day group, and one case of increased intraocular pressure (IOP) in the non-study eye in a patient in the FAc 0.2 µg/day group.

  Adverse events were mainly cataract (35.8 and 46.2% in the FAc 0.2 µg/day and 0.5 µg/day groups versus 18.9% in the sham injection group), increased IOP in the study eye (33.2 and 40.5% in the FAc 0.2 and 0.5 µg/day groups versus 3.2% in the sham injection group) and myodesopsia (12.1 and 14.9% in the FAc 0.2 and 0.5 µg/day groups versus 0.0% in the sham injection group).

  In addition, cataract surgery was required during the trial for 44.2 and 49.2% of patients on FAc 0.2 µg/day and 0.5 µg/day compared with 5.3% of patients in the sham injection group.
Two cases of eye infection were reported in the FAc 0.2 µg/day group, one of endophthalmitis and one fungal infection.

There were 47.4 and 55.9% treatment-related serious adverse events in the 0.2 µg/day and 0.5 µg/day groups compared with 5.3% in the sham injection group. These consisted mainly of cataract surgery (44.2 and 49.2% in the FAc 0.2 µg/day and 0.5 µg/day groups compared with 5.3% in the sham injection group) and at lower levels, surgery for glaucoma (1.6 and 1.0% versus 0.0%), trabeculectomy (2.6 and 5.1% versus 0.0%) and trabecuoplasty (1.6 and 2.6% versus 0.0%).

The serious adverse events included two cases of eye infection (one endophthalmitis and one fungal infection) in the FAc 0.2 µg/day group.

- **FAME B**
There were 66.5% treatment-related adverse events in the FAc 0.2 µg/day group, 78.8% in the FAc 0.5 µg/day group and 32.2% in the sham injection group. The most common were cataract surgery (35.1 and 46.0% in the 0.2 µg/day and 0.5 µg/day groups versus 20.0% in the sham injection group), increased IOP (20.5 and 32.8% versus 5.6%), subcapsular cataract (8.1% versus 3.3%) and myodesopsia (7.0 and 4.5% versus 0.0%).
In addition, 41.1 and 54.0% of the patients on FAc 0.2 and 0.5 µg/day had cataract surgery compared with 14.4% in the sham injection group.

The most common treatment-related serious adverse events were cataract surgery (41.1 and 54.0% versus 14.4%), trabeculectomy (2.7 and 5.6% versus 0.0%), surgery for glaucoma (1.1 and 2.0% versus 1.1%) and increased IOP (2.2 and 4.0% versus 0.0%).

**Special warnings in the SPC**

The analysis of the adverse events reported during the FAME A and B trials was the subject of special precautions for use in the SPC, in particular:

"Intravitreal injections have been associated with endophthalmitis, elevation in intraocular pressure, retinal detachments and vitreous haemorrhages or detachments. Patients should be instructed to report without delay any symptoms suggestive of endophthalmitis. Patient monitoring within 2 to 7 days following the injection may permit early identification and treatment of ocular infection, increase in intraocular pressure or other complication. It is recommended that intraocular pressure be monitored at least quarterly thereafter.

Use of intravitreal corticosteroids may cause cataracts, increased intraocular pressure, glaucoma and may increase the risk of secondary infections.

The safety and efficacy of ILUVIEN administered to both eyes concurrently have not been studied. Concurrent treatment of both eyes is not recommended until the patient's systemic and ocular response to the first implant is known.

In the FAME studies, the incidence of cataract surgery among all phakic subjects was approximately 3 fold higher in the ILUVIEN treated group (80.0%) than the sham treated group (27.3%). The median time to cataract reported as an adverse event was approximately 14 months. After implant insertion, phakic subjects experienced vision impairment from the development of cataract from approximately month 9 through to month 18 after implantation, prior to cataract extraction (see section 4.8).

In the overall clinical trials population, which excluded subjects with baseline IOP > 21 mmHg, the proportion of ILUVIEN treated subjects requiring treatment with IOP lowering medication was 38% compared to 14% in the sham treated group. This proportion increased to 47% in those subjects with greater than median IOP at baseline (≥ 15 mmHg). Surgical interventions for the treatment of ocular hypertension were required in 4.8% of subjects treated with ILUVIEN compared to 0.5% of subjects treated with sham (see Section 4.8). Therefore, ILUVIEN should be used with caution in patients with high baseline IOP, and IOP must be monitored closely.

In the event of IOP increases that do not respond to IOP-lowering medications or IOP-lowering procedures, the ILUVIEN implant can be removed by vitrectomy."
The SPC also states that "While the majority of subjects in the FAME clinical trials received only one implant, the long-term safety implications of retention of the non-bioerodable implant inside the eye are not known. In the FAME clinical trials, 3-year data show that events such as cataract, increased intraocular pressure and floaters occurred only slightly more frequently in subjects receiving 2 or more implants. This is considered a function of the increased exposure to the drug rather than an effect of the implant itself. In non-clinical studies, there were no indications of an increase in safety issues other than lens changes in the rabbit eyes with 24 implants over 24 months. The implant is made of polyimide and is essentially similar to an intraocular lens haptic; it is therefore expected to remain inert inside the eye."

**08.3 Summary and discussion**

The efficacy of fluocinolone acetonide (FAc) 0.2 µg/day (Marketing Authorisation dosage) and 0.5 µg/day in an intravitreal implant was evaluated in two double-blind placebo-controlled (sham injection) randomised trials using the same protocol (FAME A and FAME B trials). The population consisted of patients with vision impairment associated with DMO previously treated by at least one laser photocoagulation session. A subgroup analysis was performed in patients with chronic (Marketing Authorisation indication) or non-chronic DMO. DMO was considered to be chronic if it had lasted ≥ 3 years (i.e. longer than or equal to the median duration of DMO in the patients enrolled in the trials). The affected eye or the most affected of the two eyes was treated and if necessary, retreated at the same dose, between months 12 and 33, in the event of decreased vision ≥ 5 letters ETDRS or retinal thickening ≥ 50 µm visible on OCT in the centre of the fovea compared with patient's best status during the previous 12 months. If there was no improvement, patients could also receive laser therapy, depending on the investigator's assessment and not sooner than 6 weeks after treatment. Intravitreal corticosteroids (off-label) and VEGF antagonists were prohibited by the protocol.

**Total population:**
The percentage of patients who received intravitreal corticosteroids (off-label) or a VEGF antagonist was greater in the placebo group than in the fluocinolone acetonide group, i.e. 34.7% with placebo, 18.9% with FAc 0.2 µg/day and 21.4% with FAc 0.5 µg/day in the FAME A trial and 34.7% with placebo, 18.9% with FAc 0.2 µg/day and 21.4% with FAc 0.5 µg/day in the FAME B trial.

The percentage of patients with ≥ 15 letter increase in BCVA after 24 months (primary efficacy endpoint) was higher with FAc 0.2 µg/day (Marketing Authorisation dosage) than with placebo, i.e. 26.8% versus 14.7% (p = 0.029) in the FAME A trial and 30.6% versus 17.8% (p = 0.030) in the FAME B trial. This superiority was maintained after 30 months but not after 36 months. Mean change in BCVA:
- was the same for FAc 0.2 µg/day and placebo in the FAME A trial at 24, 30 and 36 months
- was higher with FAc 0.2 µg/day than with placebo in the FAME B trial at 24 months (5.1 vs 0.0 letters), at 30 months (6.7 vs -0.3 letters) and at 36 months (5.7 vs 0.7 letters).

**Subgroup of patients with chronic DMO (≥ 3 years):**
The percentage of patients with ≥ 15 letter increase in BCVA after 24 months was higher with FAc 0.2 µg/day than with placebo in the FAME A trial and in the FAME B trial.
- FAME A: 31.8% versus 11.9%, i.e. a difference of 20.0% (p = 0.004)
- FAME B: 37.4% versus 15.1%, i.e. a difference of 22.3% (p = 0.006)

**Subgroup of patients with non-chronic DMO (< 3 years):** there was no difference between FAc 0.2 µg/day and placebo for the percentage of patients with ≥ 15 letter increase in BCVA after 24 months.
The safety profile of fluocinolone acetonide was similar in both the trials. The percentage of treatment-related adverse events was higher with FAc 0.2 µg/day than with placebo, i.e. 70% vs 30%.

These were mainly the adverse events usually reported with intravitreal corticosteroids such as:
- cataract: 35.8 and 35.1% with FAc 0.2 µg/day respectively in these two trials vs 18.9 and 20.0% with placebo; cataract surgery was necessary for 44.2 and 41.1% of patients with FAc 0.2 µg/day vs 5.3 and 14.4% with placebo;
- increased intraocular pressure in the study eye: 33.2 and 20.5% with FAc 0.2 µg/day vs 3.2 and 5.6% with placebo;
- myodesopsia: 12.1 and 7.0% with FAc 0.2 µg/day vs 0.0% with placebo;
- two cases of eye infection, one of endophthalmitis and one fungal infection were reported in the FAc 0.2 µg/day group.

Overall, the efficacy of fluocinolone acetonide 0.2 µg/day compared with placebo was moderate, with no clear relationship between the results in terms of percentage of patients with ≥15 letter increase in BCVA and mean change in BCVA from baseline.

A subgroup analysis showed that fluocinolone acetonide was more effective in patients with chronic DMO of more than 3 years' duration, i.e. the Marketing Authorisation population. The clinical benefit of fluocinolone acetonide has to be weighed against a poor safety profile (risk of cataract and increased intraocular pressure).

These results should be interpreted with caution as in both these trials, a sizeable proportion of patients left the trial prematurely (30%) or used prohibited treatments that may be effective against DMO (approximately 10-20% in the fluocinolone acetonide groups and 30-35% in the placebo groups). Furthermore, as these trials were not carried out in patients who had failed ranibizumab, the Committee has not been able to assess its benefit in this population, even though it is included within the Marketing Authorisation indication for ILUVIEN.

08.4 Programme of studies

The company confirmed to the EMA that it would establish a post marketing registry for open monitoring of the safety of ILUVIEN over 5 years in patients with chronic DMO. An intermediate report is scheduled at 3 years.

09 THERAPEUTIC USE

ILUVIEN is an end of line treatment in patients with vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies (laser photocoagulation, ranibizumab), despite optimum management of diabetes.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

Diabetic macular oedema (DMO) is a complication of diabetic retinopathy. It is asymptomatic but progresses to vision impairment and blindness, which is a disability and leads to considerable deterioration in quality of life.

The medicinal product is a curative therapy for vision impairment caused by chronic DMO.

In view of:
- the inclusion in these trials of patients who had not previously been treated with ranibizumab,
- the sizeable proportion of patients who dropped out of the trial (around 30%),
- the proportion of patients who received prohibited therapies during the trial (approximately 30% in the sham injection groups, 10 and 19% in the fluocinolone acetonide 0.2 µg/day group),
- the poor safety profile of intraocular corticosteroids (glaucoma, cataract),
the efficacy/adverse effects ratio is modest.

This medicinal product is an end of line therapy for vision impairment associated with chronic DMO, considered insufficiently responsive to available therapies (laser photocoagulation, ranibizumab), despite optimum management of diabetes.

There are no treatment alternatives at this stage of the disease.

Public health benefit:
Diabetic retinopathy is a major cause of poor vision and the main cause of blindness in subjects aged under 60 years, in the general population, in all industrialised countries. DMO is the primary cause of visual acuity loss in diabetics. An approximate estimate of 5% of diabetics are likely to develop macular oedema. Few epidemiological data are available on the prevalence of DMO in France.

The burden of macular oedema is related to the visual acuity loss and to the disabilities and deterioration of quality it leads to. It may also have marked psychosocial and professional repercussions, particularly in younger patients. The public health burden of DMO may be regarded as moderate. The public health burden of the target population of ILUVIEN, i.e. patients with chronic DMO (≥ 3 years) who do not respond to laser photocoagulation and ranibizumab (LUCENTIS) therapy may be regarded as low.

Reducing the frequency and severity of the complications of diabetes, improving screening for and treatment of systemic disorders leading to ophthalmological complications and improving the quality of life of people with chronic diseases are public health needs which are established priorities (objectives 55 and 66 of the Public Health Law of 09 August 2004 concerning public health policy, and the plan for improving the quality of life of patients with chronic diseases 2007-2011).

In view of the available data, these trials have demonstrated that the proprietary medicinal product ILUVIEN has a low impact compared with placebo in terms of improving visual acuity at 24 months (primary efficacy endpoint), maintained up to 36 months, in patients with chronic

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DMO (≥ 3 years). In addition, patients treated with ILUVIEN were found to need more cataract surgery and surgery related to increased intraocular pressure. ILUVIEN has not demonstrated any impact on the quality of life of treated patients compared with placebo.

In addition, it is not certain that it will be possible to transpose the results of the trials into clinical practice, for the following reasons:
- the trial populations were not representative of the target population of ILUVIEN as they consisted mainly of patients who had not previously been treated with a VEGF antagonist;
- it is doubtful whether its efficacy will be maintained in the long term (retreatment after the first 3 years) in a population with a chronic disease such as diabetes;
- the product has a poor safety profile and there is little data on patients receiving more than one implant.

Furthermore, the proprietary medicinal product ILUVIEN could have a negative impact on the health care system because of the increased number of surgical procedures for cataract and intraocular pressure in patients treated with ILUVIEN.

Consequently, it is not expected that the proprietary medicinal product ILUVIEN will benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of ILUVIEN, intravitreal implant, is moderate in vision impairment due to chronic diabetic macular oedema in adult patients considered insufficiently responsive to available therapies (laser photocoagulation, ranibizumab), despite optimum management of diabetes.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

Proposed reimbursement rate: 30%

010.2 Improvement in actual benefit (IAB)

ILUVIEN, intravitreal implant, provides a minor improvement in actual benefit (IAB IV) in the treatment strategy for vision impairment caused by chronic diabetic macular oedema in adults considered insufficiently responsive to available therapies (laser photocoagulation, ranibizumab).
**010.3 Target population**

The target population of ILUVIEN is defined as the population of adult patients with vision impairment following chronic (≥ 3 years) diabetic macular oedema who have failed the usual therapies (laser photocoagulation and ranibizumab) and whose diabetes is well-controlled.

The prevalence of diabetes in France is 4.4% (ENTRED study\(^7\)) i.e. related to the general French population (INED data, 2012), a population of 2 875 400 patients.

The estimated prevalence of diabetic macular oedema is 6.8% (Yau, 2012\(^8\)) i.e. 195 500 patients. Approximately two-thirds of patients are likely to experience vision impairment as a result (expert opinion), i.e. 130 350 patients.

About half are likely to have good blood glucose control (ENTRED) i.e. 65 175 patients.

In a market study carried out in Europe\(^9\) in 2012 among 180 ophthalmologists in seven European countries, the estimated percentage of chronic patients considered insufficiently responsive to available therapies was 44.3% in France. The population of patients with chronic DMO, concomitant vision impairment and good diabetes control, who have failed available therapies, is likely to be 28 873 patients.

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**011 TRANSPARENCY COMMITTEE RECOMMENDATIONS**

- **Packaging**
  Appropriate for the prescription conditions.

- **Specific requests inherent to reimbursement**
  Exception drug status

- **Other requests**
  The Committee would like to re assess ILUVIEN in one year.

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\(^7\) InVS ENTRED study results 2007-2010: [http://www.invs.sante.fr/entred/](http://www.invs.sante.fr/entred/)


\(^9\) John EG, Harris J. Comparison of US and EU physicians perception of diabetic macular edema treatments and outcomes (submitted for publication).