HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

17 November 2010

OZURDEX 700 micrograms, intravitreal implant in applicator
B/1 (CIP code: 494 071-1)

Applicant: ALLERGAN FRANCE S.A.S.

Dexamethasone
ATC code: S01BA01

List I
Prescription-only medicine restricted to ophthalmologists

Date of Marketing Authorisation (centralised procedure): 27 July 2010

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Dexamethasone

1.2. Background

OZURDEX is the first dexamethasone prolonged-effect intravitreal implant. It does not contain preservative.

1.3. Indication

“OZURDEX is indicated for the treatment of adult patients with macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).”

1.4. Dosage

“OZURDEX must be administered by an ophthalmologist experienced in intravitreal injections.

Posology

The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended (see section 4.4 of the SPC).

Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician’s opinion may benefit from retreatment without being exposed to significant risk (see section 5.1 of the SPC).

Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated.

There is only very limited information on repeat dosing intervals less than 6 months (see section 5.1 of the SPC). There is currently no experience of repeat administrations beyond 2 implants in Retinal Vein Occlusion.

Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs (see section 4.4 of the SPC).

Special populations

Elderly (≥ 65 years old)

No dose adjustment is required for elderly patients.

Renal impairment

OZURDEX has not been studied in patients with renal impairment, however no special considerations are needed in this population.

Hepatic impairment
OZURDEX has not been studied in patients with hepatic impairment, however no special considerations are needed in this population.

Paediatric population
There is no relevant use of OZURDEX in the paediatric population in macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO).

Method of administration
Single-use intravitreal implant in applicator for intravitreal use only.
Each applicator can only be used once for the treatment of a single eye.

The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent).

A broad spectrum topical antimicrobial should be given prior to and on the day of the injection procedure. Adequate local anaesthesia should be administered. Remove the foil pouch from the carton and examine for damage (see section 6.6). Then, in a sterile field, open the foil pouch and gently place the applicator on a sterile tray. Carefully remove the cap from the applicator. Once the foil pouch is opened the applicator should be used immediately.

Hold the applicator in one hand and pull the tolerance tab straight off the applicator. Do not twist or flex the tab. With the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

Immediately after injecting OZURDEX, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualisation is possible in the large majority of cases. In cases in which the implant cannot be visualised, take a sterile cotton bud and lightly depress over the area around the injection site to bring the implant into view.

Following the intravitreal injection patients should continue to be treated with a broad spectrum antimicrobial."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

S: Sensory organs
S01: Ophthalmologicals
S01B: Antiinflammatory agents
S01BA: Corticosteroids, plain
S01BA01: Dexamethasone

2.2. Medicines in the same therapeutic category

OZURDEX is the first intravitreal dexamethasone implant indicated in the treatment of macular oedema following either branch retinal vein occlusion or central retinal vein occlusion.

2.3. Medicines with a similar therapeutic aim

There is no medicinal product with marketing authorisation in the indications of OZURDEX.

3. ANALYSIS OF AVAILABLE DATA

The efficacy and tolerance of OZURDEX have been evaluated in two phase III studies versus sham injections in patients with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

3.1. Efficacy

The two randomised double-blind studies, which had a similar protocol, compared three groups who received either an intravitreally implanted device containing 700 µg of dexamethasone (at the dosage of OZURDEX), an intravitreally implanted device containing 350 µg of dexamethasone, or a sham injection corresponding to the application of an injector without injection. The duration of the studies was 6 months, plus an additional, 6-month open-label extension phase to study the tolerance of the implant with the 700 µg dose. A total of 1267 patients were included, comprising 599 in study 008 and 668 in study 009.

The patients included were aged at least 18 years and an eye examination had identified macular oedema in at least one eye. Where both eyes were eligible for treatment, the one with the more recent macular oedema was studied.

The macular oedema had to:
- involve the centre of the macula (the fovea),
- be associated with a BRVO or a CRVO,
- be present at least 6 weeks to 9 months before inclusion for patients with a CRVO and 6 weeks to 12 months before inclusion for patients with a BRVO,
- have resulted in a loss of visual acuity,
- be unlikely to be stable in the opinion of the investigator, even if untreated for 6 months.

In addition, patients had to have:
- a best corrected visual acuity (BCVA) score of between 34 (approximately equivalent to 20/200 on the Snellen chart or 1/10 on the Monoyer chart) and 68 letters (approximately equivalent to 20/50 on the Snellen chart or 4/10 on the Monoyer chart) at the eye examination, measured on inclusion by the ETDRS method,
- a retinal thickness ≥ 300 µm in the central macular zone 1 mm in diameter, measured by optical coherence tomography (OCT) on inclusion, in the opinion of the investigator.

The main exclusion criteria were:
- an ocular pathology which, in the opinion of the investigator, could prevent an improvement in visual acuity of 15 letters (for example severe macular ischaemia),
- the following ocular pathologies: epiretinal membrane, aphakia (absence of the lens), presence of an anterior intraocular chamber lens, rubeosis iridis, active eye infection, ocular hypertension in the studied eye (intraocular pressure (IOP) > 23 mmHg if untreated with a glaucoma drug or > 21 mmHg if a glaucoma drug is being taken, or if at least 2 glaucoma drugs are being taken),
- history of ocular herpes infection, central serous retinopathy, pars plana vitrectomy, IOP elevation in response to steroid treatment, or glaucoma,
- the following retinal pathologies: retinal or prepapillary neovascularisation, diabetic retinopathy, choroidal neovascularisation,
- uncontrolled systemic illness.

In the first, six-month study phase, the patients were randomised to receive either:
- an intravitreally implanted device containing 700 µg of dexamethasone
- an intravitreally implanted device containing 350 µg of dexamethasone
- a sham injection corresponding to the application of an injector without injection.

In addition, all treatments that could affect the assessment of the study medications had to be taken at constant dose. Investigators were free to treat ocular hypertension, so that it could be controlled. The use of ocular hypertension drugs was allowed. Ocular antiinflammatories were not allowed in the eye to be studied. If oral NSAIDs were being taken before the study, they had to be continued during the study.
The following medicinal products were not allowed: intravitreal steroids in the studied eye, systemic corticoids, dexamethasone (any route of administration) during the first 90 days of the study, periarticular corticoids, any surgical or laser treatment for macular oedema, immunosuppressants, immunomodulators, antimetabolite agents, alkylating agents, NSAIDs or corticoids in the eye, VKAs and heparin.

The primary endpoint was different in the two studies:

- Study 008: percentage of patients showing an improvement in best corrected visual acuity (BCVA) with a gain of at least 15 letters (ETDRS scale) after 3 months.

- Study 009: percentage of patients showing an improvement in BCVA with a gain of at least 15 letters after 6 months.

Note: The Committee regrets the absence of an assessment of the primary endpoint after 3 and 6 months in the two studies.

The secondary endpoints included:

- percentage of patients showing an improvement in BCVA with a gain of 5 to 14 letters after 3 and 6 months;
- percentage of patients stabilised (variation of -5 to +5 letters) after 3 and 6 months;
- percentage of patients showing a deterioration in BCVA with a loss of 5 to 14 letters after 3 and 6 months;
- percentage of patients showing a deterioration in BCVA with a loss of at least 15 letters after 3 and 6 months.

Results:

Only the results for the dosage in the marketing authorisation, i.e. 700 µg of dexamethasone, are described below.

- **Study 008:**

A total of 599 patients were included, comprising 201 in the dexamethasone 700 µg group, 196 in the dexamethasone 350 µg group and 202 in the sham injection group.

Approximately 95% of the patients (n = 567) in each group completed the first 6 months of the study (double-blind phase).

The patients' characteristics were similar in each group (Table 1). About two-thirds of patients were suffering from branch retinal vein occlusion and about one-third from central retinal vein occlusion. In about half the patients the macular oedema had been present for 90 to 179 days. A best corrected visual acuity score of the order of 54 letters is a marked loss of visual acuity (this corresponds to vision of 2.5/10, which is the lower limit of reading).

Table 1: Demographic characteristics of patients in study 008 – ITT population

Characteristics	**Dexamethasone 700 µg N = 201**	**Dexamethasone 350 µg N = 196**	**Sham injection N = 202**
Average age (years) (range)	65.8 (36 to 90)	65.9 (37 to 88)	64.8 (32 to 91)
Sex Men Women	 106 (52.7%) 95 (47.3%)	 104 (53.1%) 92 (46.9%)	 117 (57.9%) 85 (42.1%)
Iris colour Dark Light	 109 (54.2%) 92 (45.8%)	 110 (56.1%) 86 (43.9%)	 125 (62.5%) 75 (37.5%)
Eye examination diagnosis CRVO BRVO	 61 (30.3%) 140 (69.7%)	 72 (36.7%) 124 (63.3%)	 72 (35.6%) 130 (64.4%)
MO present for < 90 days 90 to 179 days 180 to 269 days ≥ 270 days	 28 (13.9%) 111 (55.2%) 42 (20.9%) 20 (10.0%)	 40 (20.4%) 95 (48.5%) 44 (22.4%) 17 (8.7%)	 24 (11.9%) 100 (49.5%) 55 (27.2%) 23 (11.4%)
Mean retinal thickness [µm]	548.9	541.6	534.4
BCVA score at start of study Mean (range)	 54.5 (34 to 68)	 53.7 (34 to 72)	 54.4 (29 to 69)

- Primary endpoint:

In the ITT population, the percentage of patients showing an improvement in best corrected visual acuity with a gain of at least 15 letters 3 months after the start of treatment was significantly higher in the group treated with dexamethasone 700 µg (22.4%) than in the sham injection group (12.4%) (p = 0.008).

- Secondary endpoints:

After 6 months, the percentage of patients showing an improvement in best corrected visual acuity with a gain of at least 15 letters no longer differed between the dexamethasone 700 µg group (19.4%) and the sham injection group (18.3%).

After 3 months and 6 months there was no significant difference between the two groups in the percentage of patients showing a gain of 5 to 14 letters in best corrected visual acuity, patients stabilised (variation between -5 and +5 letters), patients showing a loss of 5 to 14 letters or patients showing a loss ≥ 15 letters (see Table 2).

Table 2: Results for the percentage of patients showing a mean change relative to baseline after 3 months and 6 months in the five BCVA categories – ITT population (study 008)

Category of improvement relative to baseline vision	Dexamethasone 700 µg N = 201	Sham injection N = 202
Day 90		
(1): Gain ≥ 15 letters	**45 (22.4%)***	**25 (12.4%)**
(2): Gain of 5 to 14 letters	80 (39.8%)	69 (34.2%)
(3): Stabilisation (variation between -5 and +5 letters)	55 (27.4%)	70 (34.7%)
(4): Loss of 5 to 14 letters	14 (7.0%)	27 (13.4%)
(5): Loss ≥ 15 letters	7 (3.5%)	11 (5.4%)
Day 180		
(1): Gain ≥ 15 letters	39 (19.4%)	37 (18.3%)
(2): Gain of 5 to 14 letters	70 (34.8%)	56 (27.7%)
(3): Stabilisation (variation between -5 and +5 letters)	59 (29.4%)	61 (30.2%)
(4): Loss of 5 to 14 letters	22 (10.9%)	30 (14.9%)
(5): Loss ≥ 15 letters	11 (5.5%)	18 (8.9%)

*Statistically significant superiority of the dexamethasone 700 µg group over the sham injection group (p < 0.001)

- **Study 009:**

A total of 668 patients were included, comprising 226 in the dexamethasone 700 µg group, 218 in the dexamethasone 350 µg group and 224 in the sham injection group.

Approximately 95% of the patients (n = 567) in each group completed the first 6 months of the study (double-blind phase).

The patients' characteristics were similar in each group (see Table 3) and similar to those of the patients included in study 008. About two-thirds of patients were suffering from branch retinal vein occlusion and about one-third from central retinal vein occlusion. In about half the patients the macular oedema had been present for 90 to 179 days. The best corrected visual acuity score was of the order of 54 letters.

Table 3: Demographic characteristics of patients in study 009 – ITT population

Characteristics	Dexamethasone 700 µg N = 226	Dexamethasone 350 µg N = 218	Sham injection N = 224
Average age (years) (range)	63.7 (33 to 89)	64.0 (31 to 96)	63.1 (31 to 89)
Sex Men Women	 111 (49.1%) 115 (50.9%)	 116 (53.2%) 102 (46.8%)	 123 (54.9%) 101 (45.1%)
Iris colour Dark Light	 132 (58.4%) 94 (41.6%)	 134 (61.5%) 84 (38.5%)	 140 (62.5%) 84 (37.5%)
Eye examination diagnosis CRVO BRVO	 75 (33.2%) 151 (66.8%)	 82 (37.6%) 136 (62.4%)	 75 (33.5%) 149 (66.5%)
MO present for < 90 days 90 to 179 days 180 to 269 days ≥ 270 days	 42 (18.6%) 108 (47.8%) 51 (22.6%) 25 (11.1%)	 36 (16.5%) 123 (56.4%) 44 (20.2%) 15 (6.9%)	 41 (18.3%) 120 (53.6%) 44 (19.6%) 19 (8.5%)
Mean retinal thickness [µm]	573.6	566.6	542.5
BCVA score at start of study Mean* (range)	 54.1 (34 to 68)	 54.0 (31 to 79)	 55.0 (28 to 80)

*These scores correspond to vision of 2.5/10, which is the lower limit of reading: this is a marked loss of visual acuity.

- Primary endpoint:

In the ITT population, 6 months after the start of treatment no statistically significant difference was observed between the dexamethasone 700 µg and sham injection groups in terms of the percentage of patients showing an improvement in best corrected visual acuity with a gain of at least 15 letters (23.5% versus 17.0%, p = 0.087).

Note: In this study, it would have been desirable to have had an assessment at 3 months. The absence of a significant difference at 6 months could in fact be due to exhaustion of the dexamethasone in the intravitreal implant.

- Secondary endpoints:

In the ITT population, the percentage of patients showing an improvement in best corrected visual acuity with a gain of at least 15 letters 3 months after the start of treatment was significantly higher in the group treated with dexamethasone 700 µg (21.2%) than in the sham injection group (13.8%) (p = 0.039).

After 3 months and 6 months, no significant difference was observed between the two groups in the percentage of patients showing a gain of 5 to 14 letters in best corrected visual acuity, patients stabilised (variation between -5 and + 5 letters) or patients showing a loss of 5 to 14 letters.
After 3 and 6 months, the percentage of patients showing a loss of ≥ 15 letters was smaller with dexamethasone 700 µg than with the sham injection (statistically significant difference, see Table 4).

Table 4: Results for the percentage of patients showing a mean change relative to baseline at 3 months and 6 months in the five BCVA categories – ITT population (study 009)

Category of improvement relative to baseline vision	Dexamethasone 700 µg N = 226	Sham injection N = 224
Day 90		
(1): Gain ≥ 15 letters	48 (21.2%)*	31 (13.8%)
(2): Gain of 5 to 14 letters	102 (45.1%)	83 (37.1%)
(3): Stabilisation (variation between -5 and +5 letters)	58 (25.7%)	67 (29.9%)
(4): Loss of 5 to 14 letters	10 (4.4%)	25 (11.2%)
(5): Loss ≥ 15 letters	8 (3.5%)**	18 (8.0%)
Day 180		
(1): Gain ≥ 15 letters	53 (23.5%)	38 (17.0%)
(2): Gain of 5 to 14 letters	79 (35.0%)	64 (28.6%)
(3): Stabilisation (variation between -5 and +5 letters)	61 (27.0%)	64 (28.6%)
(4): Loss of 5 to 14 letters	18 (8.0%)	31 (13.8%)
(5): Loss ≥ 15 letters	15 (6.6%)***	27 (12.1%)

*Statistically significant superiority of the treated group over the sham injection group (p = 0.039)
**Statistically significant superiority of the treated group over the sham injection group (p = 0.041)
***Statistically significant superiority of the treated group over the sham injection group (p = 0.048)

3.2. Adverse effects

Tolerance in studies 008 and 009

- Randomised 6-month phase

During the first 6 months of the phase III studies, the overall incidence of adverse events was higher in the dexamethasone 700 µg group (72.4%) than in the group that received the sham injection (57.0%), of which 47.3% and 17.5% respectively were attributable to treatment.

Ocular adverse effects, in particular oedema, were reported more frequently in the dexamethasone 700 µg group (64.1%) than in the sham injection group (45.4%). The incidence of non-ocular adverse effects was similar in the two groups.

The adverse effects most commonly observed (in > 2% of patients) during the first 6 months of the studies were in the studied eye: increased IOP, conjunctival haemorrhage, pain, conjunctival hyperaemia, maculopathies, retinal haemorrhage, ocular hypertension, cataracts (see Table 5). The majority of these adverse effects were of mild to moderate intensity.

The tolerance profile was comparable in the two groups, except for increased IOP and ocular hypertension, which were reported more frequently in the dexamethasone 700 µg group (25.2% and 4.0% versus 1.2% and 0.9%) with the sham injection. During this period, 3 patients in the dexamethasone 700 µg group needed laser treatment or surgery, compared with 1 patient who had received the sham injection. Increased IOP is a known adverse effect of corticoids. Where necessary, increased IOP was treated with a topical glaucoma drug. At the 6-month visit, the intraocular pressure was close to the baseline value on inclusion and there was no difference between the dexamethasone 700 µg group and the sham injection group.

The percentage of patients who experienced a serious adverse event was comparable in the two groups (5% in the dexamethasone 700 µg group and 5.9% in the sham injection group).

The number of patients who discontinued treatment was 7 (1.7%) in the dexamethasone 700 µg group and 8 (1.9%) in the sham injection group, mainly for severe adverse events not attributable to the treatment.

Four patients died in the course of this phase (3 in study 008 and 1 in study 009). None of the deaths was considered to be attributable to the treatment.

Table 5: Studies 008 and 009 combined – Adverse events observed during the first 6 months in > 2% of patients (safety analysis population)

Description of adverse events (according to the MedDRA classification)	Dexamethasone 700 µg N = 421	Sham injection N = 423
Investigations		
Intraocular pressure increased*	106 (25.2%)	5 (1.2%)
Eye disorders		
Conjunctival haemorrhage	85 (20.2%)	63 (14.9%)
Eye pain	31 (7.4%)	17 (4.0%)
Conjunctival hyperaemia	28 (6.7%)	20 (4.7%)
Maculopathy	19 (4.5%)	23 (5.3%)
Retinal haemorrhage	19 (4.5%)	11 (2.6%)
Ocular hypertension**	17 (4.0%)	4 (0.9%)
Cataract	15 (3.6%)	7 (1.7%)
Vitreous detachment	13 (3.1%)	10 (2.4%)
Vitreous floaters	13 (3.1%)	8 (1.9%)
Sensation of a foreign body	11 (2.6%)	11 (2.6%)
Vitreous haemorrhage	10 (2.4%)	12 (2.8%)
Retinal exsudation	10 (2.4%)	14 (3.3%)
Conjunctival oedema	9 (2.1%)	7 (1.7%)
Macular oedema	9 (2.1%)	8 (1.9%)
Decreased visual acuity	7 (1.7%)	9 (2.1%)
Cortical cataract	7 (1.7%)	9 (2.1%)
Eye irritation	5 (1.2%)	9 (2.1%)
Retinal neovascularisation	3 (0.7%)	11 (2.6%)
Infections		
Influenza	9 (2.1%)	2 (0.5%)
Nervous system disorders		
Migraine	14 (3.3%)	7 (1.7%)
Vascular disorders		
Hypertension	17 (4.0%)	15 (3.5%)

* statistically significant difference between the dexamethasone 700 µg and placebo groups ($p < 0.001$)
** statistically significant difference between the dexamethasone 700 µg and placebo groups ($p = 0.004$)

- Extension to 12 months phase

At the end of the randomised phase (6 months), 341 patients received a second injection of dexamethasone 700 µg and 327 patients from the sham injection group received an injection of dexamethasone 700 µg.

At 12 months, the overall incidence of adverse effects in the dexamethasone 700 µg group (2 injections) was similar (85.3%) to that in the group of patients who received a sham injection followed by an injection of dexamethasone 700 µg in the open-label phase (80.1%), of which 63.3% and 49.5% respectively were attributable to the treatment.

The incidence of ocular adverse events was similar irrespective of the number of dexamethasone 700 µg injections (77.7% for 2 injections versus 71.9% for 1 injection).

The adverse events reported most frequently (in > 2% of patients) were ocular disorders (including adverse events reported in the untreated eye), such as increased IOP, conjunctival haemorrhage, cataracts, macular oedema, eye pain, conjunctival hyperaemia and retinal haemorrhage. The majority of adverse events were of mild to moderate intensity.

3.3. Conclusion

The efficacy and tolerance of OZURDEX (implant containing 700 µg of dexamethasone) were compared with that of a sham injection in two randomised double-blind studies with a similar protocol, in adult patients with macular oedema secondary to BRVO or CRVO resulting in a loss of visual acuity. The duration of the studies was 6 months, plus an additional, open-label, 6-month extension phase to study the tolerance of the implant. All the patients included in the extension phase, who on day 0 had had either an injection of OZURDEX or a sham injection, were given an injection of OZURDEX on day 180. A total of 1267 patients were included, comprising 599 in study 008 and 668 in study 009.

In study 008, the percentage of patients showing an improvement in best corrected visual acuity with a gain of at least 15 letters 3 months after the start of treatment (primary endpoint of the study) was significantly higher in the group treated with dexamethasone 700 µg (22.4%) than in the sham injection group (12.4%) (p = 0.008). This difference between the groups was no longer present after 6 months (19.4% with dexamethasone 700 µg versus 18.3% with the sham injection).

In study 009, 6 months after the start of treatment (primary endpoint), the dexamethasone 700 µg and sham injection groups did not differ in the percentage of patients showing an improvement in best corrected visual acuity with a gain of at least 15 letters (23.5% versus 17.0%, p = 0.087).

The adverse effects observed most frequently (in > 2% of patients) concerned the studied eye, such as increased IOP, conjunctival haemorrhage, eye pain, conjunctival hyperaemia, maculopathies, retinal haemorrhage, ocular hypertension or cataracts. The majority of these adverse effects were of mild to moderate intensity.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Retinal vein occlusion is an eye pathology affecting the retina and, at its centre, the macula responsible for high-resolution vision. It results in slow circulation, infiltrations and macular oedema giving rise to reduced visual acuity.
The functional prognosis depends on the clinical form of retinal vein occlusion: a distinction can be made between two main forms: an ischaemic form with poor visual prognosis and a form (termed oedematous) with good perfusion and a better prognosis.

This medicinal product is a symptomatic therapy.

Public health benefit:

The public health burden represented by retinal vein occlusions is small.

The reduction of visual impairment is a public health need (GTNDO [National Technical Group for Defining Public Health Objectives] priority).

On the basis of the available data, in the short term the medicinal product OZURDEX 700 µg is expected to have a moderate impact on the morbidity associated with such pathologies, primarily in terms of maintaining visual acuity. In the medium to long term, OZURDEX 700 µg does not seem to have an impact on visual acuity and, in the absence of any data, it is not possible to quantify its impact on quality of life.

It is uncertain whether the results of these studies would be transposed to clinical practice (uncertainty about the optimal number of injections, about repeat treatment criteria and about compliance with the injection procedure).

However, in the absence of other alternatives with marketing authorisation in this indication, the medicinal product OZURDEX 700 µg may nonetheless be able to partly meet the identified public health need.

Consequently, OZURDEX 700 µg is expected to benefit public health, although this benefit is slight.

The efficacy of dexamethasone in an intravitreal implant is modest and is of limited duration. Its tolerance seems better than that of repeated intravitreal injections of triamcinolone used off-label, particularly in respect of the risk of endophthalmitis. The efficacy/adverse effects ratio is modest.

This medicinal product is a first-line therapy.

There is no validated alternative therapy.

The actual benefit of OZURDEX 700 µg intravitreal implant in applicator is substantial.

4.2. Improvement in actual benefit (IAB)

OZURDEX 700 µg intravitreal implant in applicator offers a minor improvement in actual benefit (IAB IV) in the management of the treatment of macular oedema and oedema following either branch retinal vein occlusion or central retinal vein occlusion.

4.3. Therapeutic use

4.3.1 Treatment strategy

A distinction can be made between two main forms of retinal vein occlusion: an ischaemic form with poor visual prognosis and a form (termed oedematous) with good perfusion and a better prognosis.

The objective of treatment of oedematous retinal vein occlusion is to facilitate the restoration of normal retinal vein circulation, avoid progression to an ischaemic form, and to prevent or treat macular complications, in particular cystoid macular oedema.

The objective of treatment of mixed or ischaemic venous occlusion is to prevent or treat neovascular complications.

There is currently no validated treatment. Although various medicinal products and therapies are used, none has been evaluated in clinical studies.

Medicinal products used off-label: anticoagulants, fibrinolytics, platelet aggregation inhibitors, volaemic haemodilution, rheological correction therapies, anti-VEGF.

Slow-release triamcinolone (KENACORT retard) has also been used off-label as an intravitreal injection. It should be noted that the KENACORT formulation, which is unsuitable for intravitreal administration, contains a preservative. With intravitreal injection of KENACORT, there is a risk of pseudo-endophthalmitis-type local reactions. Other complications are the development of a cataract (occurrence almost inevitable after two injections) and the risk of ocular hypertension, with about one third of patients experiencing hypertension following intravitreal injection of triamcinolone.

- Pan-retinal laser photocoagulation in ischaemic forms/macular photocoagulation in oedematous forms 3 months previously or earlier.

- Surgical treatments for the management of macular oedema: vitrectomy, radial optic neurotomy, chorioretinal venous anastomosis, arteriovenous adventitial sheathotomy. These treatments have not been evaluated in a clinical study.

4.3.2 Therapeutic use

OZURDEX is the first medicinal product with a validated indication in the treatment of adult patients with macular oedema following either branch retinal vein occlusion or central retinal vein occlusion. This medicinal product is a first-line therapy.

4.4. Target population

According to data from the Beaver Dam Eye Study[1,2], in a population aged between 43 and 84 years the annual incidence of BRVO is estimated at 0.12% and the annual incidence of CRVO at 0.03%. If these figures are related to the French population aged 43 years and older, the number of patients affected each year by BRVO is estimated at 35,000 and by CRVO at 10,000[3].
In the Beaver Dam Eye Study[2], 17 incident cases of macular oedema were identified in the 61 cases of BRVO (28%) and 7 cases in the 18 cases of CRVO (39%).
Thus, on the basis of these data, the number of patients each year who develop macular oedema following retinal vein occlusion is estimated at about 14,000.
However, these data do not allow us to estimate the number of patients for whom treatment with OZURDEX would be justified (the possibility of spontaneous regression of the macular oedema or of progression to an ischaemic form cannot be addressed, visual acuity endpoint needs to be taken into account).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use and various public services.
The Committee would like to reassess the actual benefit of this medicinal product in two years' time in the light of the results of the post-marketing study (see below).

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%

Exception drug status:

The Committee recommends granting exception drug status to OZURDEX 700 µg. A prescription guide will specify the scope of reimbursement and the relevant dosage, along with the conditions for initiating treatment, monitoring patients and discontinuing treatment with OZURDEX 700 µg.

[1] Klein R., Klein BEK., Moss SE., Meuer SM. The epidemiology of retinal vein occlusion – the Beaver Dam Eye Study. Tr Am Ophth Soc 2000; 898:133-43
[2] Klein R, Moss SE., Meuer S. The 15-year cumulative incidence of retinal vein occlusion. Arch Ophthalmol 2005; 123: 807-14
[3] Population aged 43 years and older in France on 1 January 2010: 29 453 771 (source: http://www.insee.fr)

Request for a study:

The Transparency Committee would like to be provided with additional, medium- to long-term data reassessing OZURDEX 700 µg in respect of the following points (see reasons given in the annex):

- the characteristics of the patients treated for retinal vein occlusion with or without OZURDEX 700 µg
- the characteristics of the doctors (type of practice, any training before use of the product, etc.)
- the terms of the treatment of these patients (conditions under which the procedure is performed, different treatments undertaken, number of patients undergoing repeated treatment and interval between repeat procedures)
- the adverse effects experienced by patients treated with OZURDEX 700 µg, with the frequency of discontinuation of treatment and reasons for this,
- change in visual acuity and quality of life.

The duration of patient follow-up must be justified and sufficient to answer the questions raised by the Transparency Committee.
Data must be available by the time OZURDEX 700 µg undergoes reassessment.

If scheduled or ongoing studies, in particular within the remit of the European Risk Management plan, do not answer all the questions raised by the Transparency Committee, a specific study must be conducted.

ANNEX

REASONS FOR THE REQUEST FOR POST-MARKETING DATA

OZURDEX (intravitreal dexamethasone implant)

For the medicinal product OZURDEX intravitreal dexamethasone implant, indicated in the treatment of adult patients with macular oedema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), additional data were requested by the Transparency Committee at the meeting on 03/11/2010.

This request for additional information is justified by the lack of medium- to long-term data in the dossier submitted to the Transparency Committee on the following three main points:
- the optimal number of intravitreal injections and the criteria for repeated treatment;
- the impact on the benefit when used in real-life conditions and the occurrence of serious local adverse events, particularly given the doubts about proficiency in, and compliance with, the injection technique;
- the place of OZURDEX in the current treatment strategy for the management of retinal vein occlusion.