VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

There are approximately 415 million adults with diabetes. By 2040, global prevalence is projected to increase to 642 million people. Diabetic eye disease is the leading cause of new cases of blindness among adults 20 to 74 years of age. With the increase in people who have diabetes and an aging population, more people are developing diabetic macular oedema (DMO) and it has become one of the principle causes of vision impairment in many countries. Studies have shown that approximately a quarter of people with Type 2 diabetes can develop DMO and

it is even higher in people who use insulin. Factors contributing to an increasing number of people with DMO include aging populations, movement of economies from low-income to middle-income, increasing urbanization, less physical activity, higher sugar consumption and low fruit and vegetable intake.

VI.2.2 Summary of treatment benefits

FAME A and B: These studies were designed to look at the safety and effectiveness of fluocinolone acetonide (FA) intravitreal implants (0.2 µg/day and 0.5 µg/day) in patients with diabetic macular oedema (DMO). The primary purpose of the studies was to determine if either dose level of FA intravitreal implant is superior to the control group with respect to the proportion of patients who had a ≥15-letter improvement in best corrected visual acuity (BCVA) at Month 24 compared to the beginning of the study. There were 768 patients in the FAME studies and 120 in the FAME extension study who received FA, which also assessed the drug's safety as well as the utility of the applicator used to insert the drug. The results of these studies demonstrated the long-term safety and effectiveness of FA implants in patients with DMO. FA implants were effective in reducing retinal thickness and improving vision. This was shown by the proportion of patients with a ≥15-letter improvement from the beginning of the study as measured at Month 24. The treatment effect was particularly notable in subjects with chronic DMO.

VI.2.3 Unknowns relating to treatment benefits

The studies performed so far have not included paediatric patients as DMO is rarely seen in children. No changes in the dosage are necessary in elderly patients or those with kidney or liver impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Cataract formation or progression	In the majority of patients who have not yet had an operation for cataracts, a clouding of the eye's natural lens (a cataract) may occur after treatment. If this occurs vision will decrease and an operation to remove the cataract is likely.	Monitor incidence rate of cataract formation or progression as compared to clinical studies. This adverse effect and its management are well known to clinicians. The incidence rate may be updated in the SmPC as needed.
Increased intraocular pressure / development of glaucoma	In some patients, the eye pressure may increase with the possible development of glaucoma. Patients	Monitor incidence rate of increased intraocular pressure / glaucoma as compared to clinical studies. This adverse effect and its management

Risk	What is known	Preventability
	should be monitored by their doctor with visits to the clinic.	are well known to clinicians. The incidence rate may be updated in the SmPC as needed.
Endophthalmitis	Occasionally the injection may cause an infection inside the eye, pain or redness in the eye. Patients should tell their doctor immediately if they develop increased eye pain or discomfort and worsening redness of the eye.	Monitor adverse events related to procedural complications as compared to clinical studies. If an increase in endophthalmitis is observed, batches will be tested for sterility.
Retinal complications (i.e. retinal tear or detachment)	Occasionally the injection may cause a detachment or tear of the retina. Patients should tell their doctor immediately if they develop increased eye pain or discomfort, worsening redness of the eye, flashing lights and sudden increase in floaters, partially blocked vision, decreased vision or increased sensitivity to light.	Monitor incidence rate of retinal tear/detachment as compared to clinical studies. This adverse effect and its management are well known to clinicians. The incidence rate may be updated in the SmPC as needed.
Vitreous complications (i.e. vitreous haemorrhage or detachment)	Following the procedure, patients should be monitored for potential complications such as vitreous haemorrhages or detachments between two and seven days after the implant insertion.	Monitor incidence rate of vitreous haemorrhage/detachment as compared to clinical studies. This adverse effect and its management are well known to clinicians. The incidence rate may be updated in the SmPC as needed.
Haemorrhagic events occurring with the concurrent use of anti-coagulant and anti-platelet agents	Concurrent use of anticoagulant and anti-platelet therapies with ILUVIEN has not been studied	Monitor incidence of side effects associated with concurrent use of anticoagulant and anti-platelet agents. Incidence rates will be updated in the SmPC as needed.
Device dislocation	There is a potential risk for the implant to migrate from the original site of injection. Patients in whom the posterior capsule of the lens is absent or has a tear, are at risk of implant migration into the anterior chamber	Incidence rates will be updated in the SmPC as needed.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Systemic corticosteroid effects	Systemic side effects are not expected due to the dose and administration route of ILUVIEN, however, since corticosteroids are known to have systemic side effects when administered in other forms, systemic effects will be monitored.
Procedural complications	This safety concern is well known to clinicians who already routinely check for procedural complications when intravitreal injections are used.
Retinitis secondary to reactivation of latent viral or other ophthalmic infections	Corticosteroids are known to reactivate latent infections.

Missing information

Risk	What is known
Use in paediatric population	Studies with ILUVIEN have not been conducted in paediatric populations. The studies performed to date have not included pediatric subjects as there is no relevant use of intravitreally administered fluocinolone acetonide in the paediatric population in diabetic macular oedema.
Use in pregnant women	Studies with ILUVIEN have not been conducted in pregnant women and follow pregnancy and health of newborn. There is no expectation that pregnancy will impact efficacy; however, because corticosteroids are known teratogens, no studies are anticipated.
Use in lactating women	Studies with ILUVIEN have not been conducted in lactating women. The systemic concentration of fluocinolone acetonide following intravitreal treatment with ILUVIEN is low. It is not known whether intravitreal treatment with ILUVIEN could result in sufficient systemic absorption to produce detectable quantities in human milk.
Long-term safety data	Long-term use of ILUVIEN has not been studied
Repeat use	Repeat use of ILUVIEN has not been studied adequately
Implant removal	Implant removal has not been studied adequately
Off-label use	ILUVIEN has only been studied for patients with Diabetic Macular Oedema
Significant retinal ischaemia	Incidence of significant retinal ischaemia due to use of ILUVIEN has not been studied

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine and the risks and recommendations for minimising them. An abbreviated version of this in lay language

is provided in the form of the patient information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

Risk minimisation and the safe and effective use of the product are detailed in the SmPC and PIL. Additional risk minimisation measures have occurred with training of company Clincial Account Specialists (CASs) regarding the use of the applicator. Educational materials in the form of an instructional video and Administration Guide are available for physicians and additional requests for these materials are tracked electronically.

These additional risk minimisation measures are for the following risks:

Device Dislocation (migration of the implant to the anterior chamber)

Risk minimisation measure(s) Physician and patient educational materials
Objective and rationale
• Summary description of main additional risk minimisation measures – Physician video and Administration Guide, Targeted follow up questionnaire
Healthcare Professional and patient education Objective and rationale: • HCPs to understand that there is a potential risk for the implant to migrate from the original site of injection. Patients in whom the posterior capsule of the lens is absent or has a tear, are at risk of implant migration into the anterior chamber. Proposed action: HCP educational materials to be provided to prescribing physicians and pharmacists including advice on: • Use of the applicator prior to treatment • Importance of adherence to administration instructions Patient information leaflet will inform patients of the potential for the implant to move from the back to the front of the eye and that the risk is increased if they have had previous cataract surgery. A sign that the implant may have moved to the front of the eye could be distorted vision or other visual disturbance or they may notice a change in the appearance of the eye at the front.

VI.2.6 Planned post authorisation development plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**

IRISS M-01-12-001, An Open Label, Registry Study of the Safety of ILUVIEN® 190 Micrograms Intravitreal Implant In Applicator Category: 1	This study will assess the safety of ILUVIEN in patients diagnosed with vision impairment associated with chronic diabetic macular oedema considered insufficiently responsive to available therapies.	The safety of ILUVIEN in real world clinical practice.	started	EU submission – planned interim analysis: 27 May 2016
PALADIN M-01-15-004, A Phase 4 Safety Study Of IOP Signals In Patients Treated With ILUVIEN® (Fluocinolone Acetonide Intravitreal Implant) 0.19MG Category: 4	This study will assess the safety in patients treated with ILUVIEN, with primary focus on IOP. The specific objectives include the study of intraocular pressure IOP-related data, (e.g., IOP measurements, use of IOP-lowering medications, IOP-lowering procedures), in patients who have received ILUVIEN and how it relates to the patient's experiences following prior treatment with a course of corticosteroid which did not result in a clinically significant IOP elevation.	Determine incidence of interventional, incisional surgery for ocular hypertension in patients treated with ILUVIEN. Determine incidence of other IOP-related signals (e.g. IOP > 30mmHg) Determine if IOP-related signals observed following the administration of ILUVIEN are correlated to any IOP-related signals noted after exposure to a course of corticosteroid received prior to administration of ILUVIEN. Determine incidence of other safety signals not related to IOP.	started	US submission: planned final report Jul 2019

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time:

Version	Date	Safety Concerns	Comment
1.0	At time of authorisation	Important Identified Risks: Increased intraocular pressure/glaucoma development, Formation or progression of cataract, endophthalmitis, retinal complications, vitreous compliactions, haemorrhagic events occurring with the concurrent use of anti-	

Version	Date	Safety Concerns	Comment
		coagulant and anti-platelet agents Important potential Risks: Systemic corticosteroid effects, procedural complications, retinitis secondary to reactivation of latent viral or other ophthalmic infections Important Missing Information: Use in paediatric population, use in pregnant women, use in lactating women, long-term safety data, repeat use, implant removal, off-label use, significant retinal ischaemia	
1.1	26-Oct-2012	No changes made to safety concerns	Section 2.1 Routine pharmacovigilance practices updated to include details regarding the protocol for the IRISS study. Section 2.4 updated to include 'Draft' for Protocol version and status. Approved SmPC added. Ongoing and Completed Clinical Trial Programme table updated with study completion dates. Study M-01-12-0015 added to Pharmacoepidemiological programme table.
1.2	26-Feb-2013	No changes made to safety concerns	Section 2.1 updated to indicate that the final draft protocol for IRISS was included in Annex 4. Section 2.5 table updated in column 'Summary of newly available results'. Updated SmPC added to Annex 1 with MAH changed to Alimera

Version	Date	Safety Concerns	Comment
			Sciences Limited from CAMPHARM Ltd.
1.3	25-Mar-2016	Device dislocation added as an important identified risk. Medication Error added as a potential risk. Updated document to new template	