

# Letter to the editor: dexamethasone intravitreal implant in the treatment of diabetic macular edema

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## Dear editor

I read "Dexamethasone intravitreal implant in the treatment of diabetic macular edema" published July 2015 by Dugel et al.<sup>1</sup> This article is very interesting in terms of providing an outline of the role of inflammation in the pathogenesis of diabetic macular edema and explaining the value of corticosteroids in the treatment of diabetic macular edema.

However, I would like to draw your attention to the data presented for ILUVIEN® (fluocinolone acetonide; FAc) in Table 2, which has been presented incorrectly and does not reflect the approved product and dose in Europe. ILUVIEN is indicated in Europe for the treatment of vision impairment associated with chronic diabetic macular edema, considered insufficiently responsive to available therapies<sup>2</sup> and is approved in Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, and the United Kingdom. ILUVIEN was launched in the United Kingdom in April 2013, Germany in May 2013, and Portugal in January 2015.<sup>3</sup>

ILUVIEN contains 190 µg of FAc and delivers 0.2 µg of FAc per day. Dugel et al<sup>1</sup> presented the data for the 0.5 µg of FAc per day, which was studied in the FAME studies but is not the approved dose in Europe. This needs to be explained to the reader as the data that are relevant to the currently marketed product are those of the 0.2 µg of FAc

Parameter	ILUVIEN
Therapeutic indication	For the treatment of vision impairment associated with chronic DME, considered insufficiently responsive to available therapies <sup>2</sup>
Active drug	Fluocinolone acetonide (FAc) <sup>2</sup>
Formulation	Non-biodegradable implant (polyimide tube) <sup>2</sup>
Dose	190 µg of FAc with a daily release rate of 0.2 µg <sup>2</sup>
Duration of action (months)	Up to 36 months. This is underpinned by a pharmacokinetic study in human eyes, which showed that following a single intravitreal injection of ILUVIEN, there was a stable delivery of 0.2 µg of FAc per day that was sustained and therefore detectable after 36 months. <sup>2,4</sup> This is complemented by efficacy data that show mean improvements in BCVA and central foveal thickness, from baseline levels, for up to 36 months <sup>2,5</sup>
License approval	Status:
a. European countries where an ILUVIEN license has been granted	a. Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, the United Kingdom <sup>3</sup>
b. European countries where ILUVIEN has been launched	b. United Kingdom, April 2013; Germany, May 2013; and Portugal, January 2015 <sup>3</sup>

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Parameter	ILUVIEN
Phase III clinical trial in DME:	FAME studies: FAME A and FAME B <sup>2,5</sup>
Trial design:	a. FAME A and B studies were performed under a single protocol as randomized, double-masked, sham injection-controlled, parallel-group, multicenter studies conducted over a 36-month period and included a pre-planned subgroup analysis to assess efficacy in chronic DME patients <sup>2,5</sup>
a. Description of the FAME studies	b. The primary endpoint for the FAME studies was 24 months but the studies show ILUVIEN was efficacious for up to 36 months, and this is the basis for the license and indication being approved in Europe. Both FAME A and B trials independently met the primary efficacy endpoint of $\geq 15$ letter improvement in BCVA over baseline
b. The primary endpoint	c. A total of 956 subjects were randomized <sup>2,5</sup>
c. The number of patients studied in the FAME studies	Chronic DME patients: 34.0% vs 13.4% (0.2 $\mu$ g FAc per day vs sham control) of subjects achieved a $\geq 15$ letter improvement from baseline BCVA after 3 years <sup>2,5</sup>
Efficacy (% patients):	Release rate of 0.2 $\mu$ g FAc per day vs sham control:
15-ETDRS-letter BCVA gain at 3 years	a. 38.4% vs 14.1% required IOP-lowering drops <sup>2,5</sup>
Ocular safety (% patients):	b. 81.7% vs 50.4% where cataract was considered an adverse event <sup>2,5</sup>
a. Elevated IOP	c. 4.8% vs 0.5% underwent IOP-lowering surgery <sup>2,5</sup>
b. Cataract-related adverse events	
c. Incisional glaucoma surgery (IOP-lowering surgery)	
<b>Abbreviations:</b> DME, diabetic macular edema; BCVA, best-corrected visual acuity; FAME, Fluocinolone Acetonide for Diabetic Macular Edema; ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure.	

per day release rate.<sup>2,4</sup> Thus, Table 2 presented in Dugel et al has been amended to reflect the data for ILUVIEN.

A number of papers have been published on the pharmacokinetic,<sup>4</sup> safety, and efficacy of ILUVIEN,<sup>5</sup> and the reader can access the summary of product characteristics for ILUVIEN online.<sup>2</sup>

## Disclosure

The author reports no conflicts of interest in this communication.

## References

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## Authors' reply

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## Dear editor

We would like to thank Dr Hall for his interest in our recently published review article,<sup>1</sup> and *Clinical Ophthalmology* for inviting us to respond to the points raised in his letter.

It should be noted that the primary aim of our article was to review the clinical efficacy and safety of dexamethasone intravitreal implant in the treatment of diabetic macular edema; for this reason only brief mention was made of other intravitreal corticosteroid delivery systems. Comparative data were limited to a short summary (Table 2) of the properties of Ozurdex<sup>®</sup> (dexamethasone intravitreal implant 0.7 mg) and ILUVIEN<sup>®</sup> (fluocinolone acetonide intravitreal implant 190 µg) – the two sustained-release intravitreal corticosteroid formulations currently approved for the treatment of diabetic macular edema. The table accurately summarizes the efficacy and safety data from the published MEAD<sup>2</sup> and FAME<sup>3</sup> studies – all doses investigated in these Phase III trials are presented and clearly annotated in the table. In the

case of the FAME study, this includes both the low-dose (0.2 µg/day) and high-dose (0.5 µg/day) formulations of fluocinolone acetonide intravitreal implant 190 µg. The data, therefore, are relevant to the product currently marketed in Europe and the United States, ILUVIEN, which releases 0.2 µg of fluocinolone acetonide per day.

The content of the amended table presented by Dr Hall, based as it is on the European Summary of Product Characteristics for ILUVIEN, goes well beyond the scope and intent of our original table. Other than referring to the date of US Food and Drug Administration approval, our article avoids all mention of product licensing and labeling in the various regional markets. We feel that these marketing details would be out of place in a review of the scientific literature.

## Disclosure

The authors report no conflicts of interest in this communication.

## References

1. Dugel PU, Bandello F, Loewenstein A. Dexamethasone intravitreal implant in the treatment of diabetic macular edema. *Clin Ophthalmol.* 2015;9:1321–1335.
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