Xiidra (lifitegrast) in dry eye disease: what the OPUS trials actually showed

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Lifitegrast is discussed more often than it is read about. The randomised programme behind it used co-primary sign and symptom endpoints, and the three OPUS trials did not produce the same result as each other, which is the single most useful thing to know before interpreting any of them.

This page answers the questions clinicians and patients actually ask about the drug, each under its own heading, and is explicit about where the published evidence stops.

KEY TAKEAWAYS

- Lifitegrast is an LFA-1/ICAM-1 antagonist. It blocks T-cell adhesion to the ocular surface, a step upstream of the inflammatory cascade, and does not replace tear volume.
- No single OPUS trial met both co-primary endpoints. OPUS-1 met the corneal staining endpoint and missed symptoms; OPUS-2 met symptoms and missed staining; OPUS-3 met its symptom endpoint.
- Symptom separation from placebo appeared at assessments before day 84, which is earlier than typically reported for topical ciclosporin.
- SONATA is a 1 year randomised study powered for SAFETY, not efficacy. It should not be cited as evidence of maintained effect over a year.
- Dysgeusia is the adverse effect most likely to stop treatment and the one most often omitted. Warning patients before the first dose changes how they interpret it.
- There is no adequately powered head-to-head trial against topical ciclosporin, so any numerical efficacy comparison between the two is cross-trial inference rather than evidence.

How does Xiidra work, and how is that different from the alternatives?

Lifitegrast is a small-molecule integrin antagonist. It binds lymphocyte function-associated antigen 1 (LFA-1) on the T-cell surface and prevents that molecule engaging intercellular adhesion molecule 1 (ICAM-1), which is over-expressed on conjunctival epithelium and corneal tissue in dry eye disease.

Blocking that single interaction interrupts three steps at once. T cells cannot adhere to ocular surface tissue, they cannot migrate into it, and the activation and cytokine release that would follow does not happen. It was the first LFA-1/ICAM-1 antagonist approved in this disease, and the point of attack is the adhesion step that precedes the inflammatory cascade rather than the cascade itself.

That distinction is worth holding onto because the alternatives act elsewhere. Artificial tears replace or stabilise the tear film and do nothing to inflammation. Topical ciclosporin suppresses T-cell activation through calcineurin inhibition, which is downstream of adhesion. Corticosteroids suppress inflammation broadly and effectively, and cannot be used indefinitely because of raised intraocular pressure and cataract formation. Lifitegrast occupies a position none of those do.

What it does not do matters as much for prescribing. It does not restore lacrimal secretion, so it is not a substitute for tear volume. It does not treat meibomian gland dysfunction, so in a patient whose disease is predominantly evaporative it is addressing one limb of a two-limb problem. A prescriber who expects a drop targeting T-cell adhesion to fix an obstructed meibomian gland will be disappointed, and so will the patient.

The mechanism also explains why the drug is dosed twice daily and why adherence is the quiet determinant of whether it works. Blocking an adhesion interaction requires the antagonist to be present when T cells are arriving at the surface, which is continuously. This is not a rescue drop taken when the eye feels dry, and patients who use it that way are running an intermittent blockade against a continuous process. Framing it at the point of prescribing as a scheduled medicine rather than a comfort drop is a small intervention that changes the outcome more than any titration decision available here.

Does it treat the root cause, or manage the symptoms?

The question contains a premise that will not survive contact with the disease definition, and the useful answer is to say why.

TFOS DEWS II describes dry eye disease as multifactorial, with tear film instability, hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities all aetiological rather than one of them primary. There is no single root cause to treat. A drug can address a mechanism within that picture, and no drug currently addresses all of it.

What can be stated precisely is that lifitegrast acts on the inflammatory limb, and acts on it upstream. That is a mechanistic intervention rather than symptomatic relief, which distinguishes it from a lubricant. It is not, on that basis, curative, and the vicious circle TFOS DEWS II describes has entry points that a T-cell adhesion blocker does not reach.

The practical consequence is that TFOS DEWS II sets out staged management for a reason, and an anti-inflammatory agent sits inside that staging rather than replacing it. Lid hygiene, tear supplementation and treatment of meibomian gland disease do not become unnecessary because an anti-inflammatory has been added. Where they have been abandoned in favour of a prescription drop, the drop tends to be blamed for a failure that belongs to the regimen.

There is a second reason the root cause framing misleads, and it is the neurosensory limb of the TFOS DEWS II definition. A proportion of patients with severe symptoms have minimal signs, and a proportion with heavy staining report little discomfort. Where symptoms are driven by corneal nerve dysfunction rather than by surface inflammation,

an anti-inflammatory can produce an objective improvement the patient does not feel. That mismatch is not a treatment failure and should not be managed as one by escalating the dose or switching agent.

What did the OPUS trials actually show about corneal staining and symptoms?

This is where a reference page can be more useful than a summary, because the trial programme is less uniform than it is usually presented.

Lifitegrast was studied in randomised, double-masked, placebo-controlled trials built on co-primary endpoints: a sign endpoint, inferior corneal staining score (ICSS), and a symptom endpoint. Three trials reported, and they did not agree with one another. OPUS-1 met its sign endpoint, producing significantly greater reduction in inferior corneal staining than placebo, and missed its co-primary symptom endpoint. OPUS-2 inverted that exactly: the symptom endpoint, eye dryness score, separated from placebo and the corneal staining endpoint did not. OPUS-3 was designed with a symptom primary endpoint and met it.

Read as a programme, that supports an effect on both signs and symptoms. Read as individual trials, no single study demonstrated both at once. A pooled analysis across three of the randomised trials was published precisely because the individual results needed reconciling, and it is the citation to reach for when the question is whether the drug works on both dimensions.

The reason this matters in practice is that clinicians who have read one OPUS paper hold a materially different view of the drug from those who have read three, and neither group usually knows which it is in. Anyone quoting a corneal staining result should be able to say whether it came from OPUS-1, where the endpoint was met, or OPUS-2, where it was not. The discrepancy is also a caution about sign and symptom correlation in this disease generally, which is poor, and which is why trials in dry eye disease routinely fail one of a pair of co-primary endpoints.

How quickly does it work, and what should a patient be told to expect?

Symptom improvement arrives earlier than is typical for topical anti-inflammatory therapy in this disease. In OPUS-3, separation from placebo on eye dryness score was observed at assessments before the primary day 84 timepoint, including at day 14. Against topical ciclosporin, where several weeks to months is the figure usually quoted, that is a meaningful difference in the conversation a clinician has at the point of prescribing.

Corneal staining behaves differently, and the reason is biological rather than pharmacological. Staining reflects accumulated epithelial damage. Damage takes time to accrue and takes time to re-epithelialise, so a sign endpoint of this kind is inherently slower to move than a patient's sensation of dryness. The trial programme assessed staining at 12 weeks.

What the published evidence does not support is a precise claim about the earliest point at which staining improves, because the trials were not designed to identify it. Specific figures circulate for this and they are not traceable to the randomised programme. If a patient asks when their staining will improve, the honest answer is that the trials measured

it at 12 weeks and did not establish an earlier threshold.

Onset also has a counterintuitive early phase worth warning about. The most common adverse effects, instillation site irritation and dysgeusia, appear immediately, while the benefit accrues over weeks. For the first fortnight a patient therefore experiences all of the cost of the drug and little of the return, which is precisely when discontinuation happens. The sequence is predictable, so it can be predicted out loud.

The practical framing for a patient is therefore two timelines, not one. Symptoms may begin to shift within a fortnight. The objective finding a clinician is looking at on the slit lamp is a longer proposition, and a patient told to expect both at once will conclude the drug has failed at the four-week mark.

Does the effect last, and what does the one-year evidence actually establish?

The randomised efficacy trials ran to 12 weeks, which is short relative to how long this disease is treated.

The longest dedicated study is SONATA, a one-year multicentre randomised placebo-controlled study. The distinction that gets lost is that it was designed and powered as a safety study. It supports a position on long-term tolerability, and it is regularly cited as though it demonstrates maintained efficacy across a year. It does not, and a submission or a lecture that uses it that way will not withstand a reader who has looked at the protocol.

Longer-term effectiveness evidence is observational. A retrospective study of 600 patients across the United States and Canada described patient characteristics, treatment patterns and clinical effectiveness in routine practice. That kind of data is genuinely informative about how a drug behaves outside a trial population, where adherence is worse and comorbidity is higher, and it cannot establish causal efficacy because there is no randomised comparator.

So the accurate answer to a patient asking whether it keeps working is uncomfortable but defensible: tolerability across a year has been studied in a randomised setting, sustained efficacy across a year has not. The gap between those two statements is where most of the confident claims about this drug live.

The absence of long-term randomised efficacy data is not peculiar to this drug, and saying so is fair. Chronic ocular surface disease is difficult to run placebo-controlled trials in beyond a few months, because withholding treatment from a symptomatic control group for a year is hard to justify and harder to retain patients through. That is a real constraint on the evidence rather than a failure of diligence. It means the honest position is uncertainty, not that the uncertainty should be filled in with the safety study.

What are the side effects, and how do they compare with other eye drops?

A pooled safety analysis of five randomised controlled trials gives the most reliable picture, and the profile is unusually predictable: local, early, and largely self-limiting.

Three effects characterise the drug. Instillation site irritation, which is burning or stinging on application. Dysgeusia,

an altered or metallic taste, which happens because the drop drains through the nasolacrimal duct to the pharynx and is therefore a consequence of ocular anatomy rather than of the eye. And reduced visual acuity, typically transient and immediately after instillation.

Dysgeusia deserves separating out because it is the effect most likely to stop treatment and the one most often omitted from a brief description. A patient who has not been warned experiences an unexplained metallic taste minutes after putting a drop in their eye, and reasonably concludes something is wrong. A patient who has been warned experiences a predicted nuisance. The clinical content is identical and the discontinuation rate is not, which makes the pre-prescription conversation part of the treatment.

The comparison that matters clinically is with topical corticosteroids. Steroids work in this disease and carry a class risk of raised intraocular pressure and cataract formation with sustained use, which is what rules them out as maintenance. Lifitegrast does not carry that risk, and in the one-year randomised safety study no serious ocular treatment-emergent adverse events attributable to the drug were identified. Against topical ciclosporin the differences are in the character of local intolerance rather than its severity: burning on instillation is described with both, and dysgeusia is distinctive to lifitegrast. A real-world pharmacovigilance analysis of spontaneous reports has since been published and is consistent with the trial profile, with the reporting biases that always attach to such databases.

How does it compare with topical ciclosporin?

There is no adequately powered head-to-head randomised trial, and in its absence cross-trial comparison is not evidence.

The reason is not pedantry. Trials in this disease differ in entry criteria, in baseline severity, in which corneal staining scale was used, and in which symptom instrument was administered. Those differences are large enough on their own to generate apparent efficacy gaps that have nothing to do with the drugs being compared. A percentage improvement from one trial set beside a percentage improvement from another is an artefact of study design presented as a finding.

What can be compared fairly is mechanism and onset. Lifitegrast acts on LFA-1/ICAM-1 adhesion, ciclosporin through calcineurin inhibition, and the lifitegrast programme demonstrated symptom separation at earlier assessments than is generally reported for ciclosporin. Tolerability differs in character rather than degree.

The practical test for any comparative claim about these two agents is to ask which trial it came from. If the answer is two different trials, the claim is inference. That is not a reason to refuse to choose between them in clinic, where onset, tolerability, formulation and access all legitimately inform the decision. It is a reason not to present that choice as though a trial had settled it.

One asymmetry does favour a practical distinction. Ciclosporin has been available far longer, so the accumulated observational and post-marketing experience behind it is deeper, and in some health systems that history is reflected in formulary position and in cost. A newer agent with a coherent mechanism and a shorter track record is a different

proposition from an older one with a longer track record, and that difference is legitimate to weigh even though it is not an efficacy comparison.

Which patients is it prescribed for, and does the formulation matter?

The retrospective study of 600 patients in the United States and Canada is the best published description of real prescribing as opposed to label indication. Broadly, use concentrates in patients with an inflammatory phenotype and moderate to severe disease who have not been adequately controlled by artificial tears and lid hygiene.

Phenotype is the judgement that decides whether the drug performs. Aqueous-deficient and inflammatory disease is where an anti-inflammatory belongs. Predominantly evaporative disease driven by meibomian gland dysfunction needs the gland dysfunction addressed, and adding a T-cell adhesion blocker to an untreated obstructed gland produces a disappointed patient and a prescriber who concludes the drug does not work.

On formulation, lifitegrast is supplied in single-use containers rather than a multi-dose bottle requiring a preservative, and in this disease specifically that is more than a convenience question. Benzalkonium chloride, the most common ophthalmic preservative, is itself toxic to corneal and conjunctival epithelium on repeated exposure, and patients with ocular surface disease are instilling drops several times daily onto an already compromised surface. TFOS DEWS II addresses preservative exposure directly in its management report. The trade-off is practical rather than clinical: single-use containers generate more waste and usually cost more per dose.

The cataract population is worth a separate word. Ocular surface disease is common in it, and it matters more than it once did because biometry for intraocular lens calculation depends on a stable tear film, so an unstable surface degrades refractive outcomes. Treating ocular surface inflammation before biometry is recognised surgical planning. But the randomised evidence for lifitegrast does not address the perioperative cataract setting as a studied indication, and that reasoning is drawn from ocular surface management principles rather than from a trial of this drug in these patients. The distinction should be stated rather than blurred.

What will a payer ask, and is there a generic?

Generic availability changes by jurisdiction and by date, and an answer written here would go out of date silently. The reliable sources are the relevant regulator's own approved products database and the current national formulary, which is where the question belongs rather than on a clinical reference page.

Coverage policy is similarly decided per payer and per country and is not a clinical question. What is worth knowing for anyone assembling a reimbursement argument is the actual shape of the evidence base, because a reviewer will know it.

That shape is specific. A randomised programme whose three trials produced inconsistent results across co-primary sign and symptom endpoints, reconciled in a pooled analysis. A one-year randomised study powered for safety rather than efficacy. Observational data for longer-term effectiveness. Against topical ciclosporin, no head-to-head trial.

A submission characterising the efficacy evidence as uniformly positive across signs and symptoms will not survive scrutiny by anyone who has read the three OPUS papers, and the credibility lost on that point tends to be spent on the rest of the case. Presenting the programme accurately, including the discordance, is the stronger position, because the pooled analysis exists and the mechanism is coherent.

The argument that tends to land with payers is not efficacy magnitude but position in the pathway. The alternative for sustained anti-inflammatory control is topical corticosteroid, which carries a class risk of raised intraocular pressure and cataract formation and therefore cannot be used as maintenance. A drug that occupies that role without the class risk is answering a question the payer already has, and the one-year randomised safety data speaks directly to it. That is the part of the evidence base built for this conversation.

What should a clinician take from the evidence overall?

Lifitegrast has a defined mechanism acting upstream of the inflammatory cascade, randomised evidence of effect on both signs and symptoms across a programme, randomised one-year safety data, and a distinctive but manageable local tolerability profile.

It is not a tear substitute. It does not treat meibomian gland dysfunction. Sustained efficacy across a year has not been demonstrated in a randomised setting, and no head-to-head trial against topical ciclosporin exists.

The most common error in how this drug is discussed is treating the OPUS programme as three confirmations of a single result. It is not, and the discordance between sign and symptom endpoints is itself informative about dry eye disease rather than a flaw to be explained away.

The second most common error is smaller and costs more patients. Dysgeusia is predictable, harmless and disconcerting, and whether it is mentioned before the first dose changes whether a patient reaches the point at which the drug could have helped them.

For a patient in front of you, the decision reduces to three questions. Is the disease inflammatory and aqueous-deficient rather than predominantly evaporative, because that determines whether this mechanism is the right one. Has lid hygiene and tear supplementation actually been done, because an anti-inflammatory added to an unmanaged surface will underperform and be blamed for it. And has the patient been told what the first two weeks feel like, because that is when they decide whether to continue.

Where those three are addressed, the evidence supports a reasonable expectation of symptomatic improvement within weeks and of objective improvement over a longer horizon. Where they are not, the drug will be judged on a trial it was never given.

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