xiidra® (lifitegrast) ophthalmic solution 5%

Treating Signs and Symptoms of Dry Eye Disease: Practical Experience with Xiidra®

ALAN KABAT, OD, FAAO

PAUL KARPECKI, OD, FAAO

LESLIE O'DELL, OD, FAAO

INDICATION

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

IMPORTANT SAFETY INFORMATION

- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity.

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A major reason for visits to eye care practitioners, dry eye disease (DED) is a common yet undertreated condition. Recent data suggests that about 30 million American adults experience dry eye symptoms (Figure 1).[1,2] However, the number of people who are actually diagnosed and treated is estimated to be much lower.[3] Within our practices, the proportion of patients presenting with dry eye symptoms may fall anywhere between about 20% to nearly 100% of daily clinical encounters.

The management of DED has improved significantly over the past decade as a result of an increased understanding of the disease. The time when diagnosis of DED relied only on tear breakup time (TBUT) and corneal fluorescein staining, and when treatment regimens focused primarily on tear supplementation, is long gone. Today, a multitude of technologies are available to thoroughly assess DED, as are prescription drugs and treatment procedures. One of these, Xiidra® (lifitegrast ophthalmic solution) 5% is the first prescription agent approved to treat both the signs and symptoms of DED.[4] Here, three ocular surface disease experts share their insights on the diagnosis and treatment of DED and their experience incorporating Xiidra® into clinical practice.

Why is DED Important to Treat?

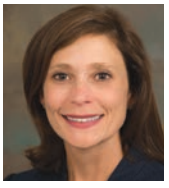
From our perspective, DED is first and foremost a disease of vision. As eye care professionals, we strive to provide patients with the best vision, corrected or not. This goal cannot be achieved without a properly functioning tear film. For patients with DED, blurry, fluctuating vision is often one of the first noticeable symptoms and what motivates them to seek professional care. Unlike other ocular pathologies that impair vision, such as cataract or diabetic retinopathy, the visual impact of DED is variable and intermittent. It is, in part, the sporadic nature of the visual symptoms that makes DED so disruptive for patients.

Indeed, DED can impact all aspects of a patient's vision-related life, including work productivity and leisure activities such as reading, driving, computer use, or watching TV.[5-7] DED is also an important cause of contact lens intolerance and patient dissatisfaction following corneal or lens refractive surgeries.[8-10]

DED may be a chronic, often progressive condition, for which we believe early intervention is important.[11] Individuals with DED may self-treat in the early stages, using over-the-counter options such as artificial tears. If these methods are not enough to address their symptoms, they may be quite discour-

Alan Kabat, OD, FAAO, is professor at Southern College of Optometry in Memphis, TN. He is a consultant to Bio-Tissue and Vmax Vision, and serves on advisory boards for Bruder, OCuSoft, and Shire.

Paul Karpecki, OD, FAAO, is Director of Cornea Services at Kentucky Eye Institute in Lexington, KY. He is a consultant to Akorn, AMO, Alcon, Allergan, Avellino, Bausch + Lomb, Blephex, BVI, Bio-Tissue, Bruder, eyeBrain, Eyegate, Essilor, Eyes4Lives, Focus Labs, Glaukos, iCare, Imprimis, Katena, Konan, Ocular Therapeutix, Oasis, Oculus, OCuSoft, Paragon, Bioteck, Reichert, Shire, Rendia, Science Based Health, TearLab, TearScience, Topcon, and Zeiss.



Leslie O'Dell, OD, FAAO, is director of the Dry Eye Center at Wheatlyn Eye Care Center in Manchester, PA. She is a consultant for Shire, Allergan, Aerie Pharmaceuticals, and Eye Eco.

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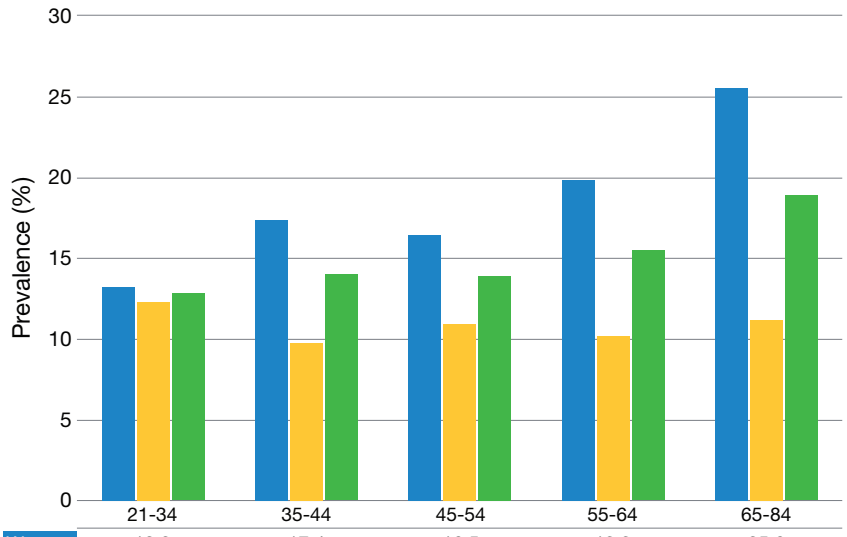

	21-34	35-44	45-54	55-64	65-84
Women	13.2	17.4	16.5	19.9	25.6
Men	12.3	9.7	10.9	10.2	11.2
Overall	12.8	14	13.9	15.5	18.9

FIGURE 1 Dry eye symptoms by age group and sex, the Beaver Dam Offspring Study 2005 to 2008. *(Adapted from reference 1.)*

aged by the time they seek professional care. With these issues in mind, it is important for practitioners to communicate to patients that DED may be a chronic condition that tends to worsen over time, that various options exist depending upon the etiology and severity of the disease, and that very likely, the sooner they start treatment, the better.

The Diagnostic Approach

Accurate diagnosis of early DED begins with a mindful inquiry into the patient's symptoms. Questions to help screen for dry eye symptoms upon initial patient encounter are useful, and should be as specific as possible. An eye with DED does not necessarily feel "dry"—instead, patients may have gritty, burning, watering, or simply tired eyes. Specific questions tend to yield specific responses, and open-ended questions such as "How do your eyes feel after work?" are helpful in opening the doors of communication. At present, routine use of a validated dry eye survey is commonplace in dry eye clinics but less so in general optometric practice. The most common choices include the Ocular Surface Disease Index© (OSDI©), Standard Patient Evaluation of Eye Dryness (SPEED™), and the Dry Eye Questionnaire 5 (DEQ-5). Corneal fluorescein staining is also widely incorporated into routine exams as a screening tool, but it is important to keep in mind that fluorescein staining is often a late sign of DED, and may not be present in mild to moderate cases.

There is still no single magic-bullet diagnostic test for DED. However, the introduction of sensitive and accurate point-of-care diagnostics (eg, for tear osmolarity and inflammatory biomarkers) enable us to identify patients across severity levels. By employing a combination of diagnostic tests that focus on distinct aspects of DED, practitioners can better isolate individual etiologies and select therapeutic measures accordingly (Table I). Diagnostic testing is particularly useful in ruling out DED in patients with classic dry eye

TABLE I Characteristic findings for diagnostic tests in DED

	TEST	FINDINGS
Primarily aqueous-deficient DED	Staining	Pattern of exposure zone; corneal and bulbar conjunctiva typical
	Tear break-up time	Less than 10 seconds considered abnormal
	Schirmer test (with anesthesia)	10 mm or less considered abnormal
	Tear osmolarity	Above 300 mOsm/L and/or a large (greater than 8 mOsm/L) difference between eyes
Primarily evaporative DED	Staining	Staining of inferior cornea and bulbar conjunctiva typical
	Tear break-up time	Less than 10 seconds considered abnormal
	Tear osmolarity	Above 300 mOsm/L and/or a large (greater than 8 mOsm/L) difference between eyes

(Adapted from reference 3.)

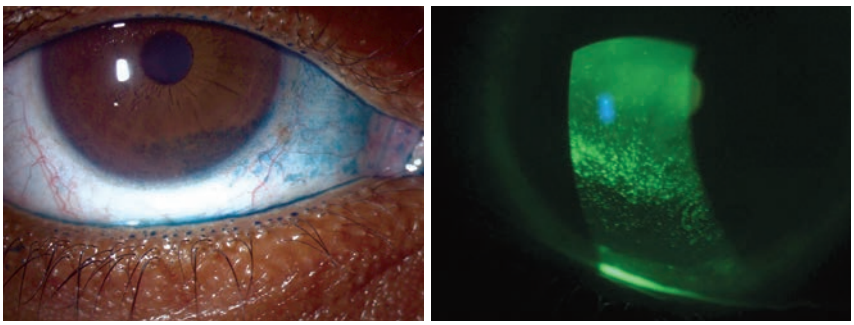

FIGURE 2 Ocular surface staining in DED: at left, lissamine green staining of the conjunctiva, and at right, fluorescein staining of the cornea. *(Images courtesy of Dr. Kabat.)*

symptoms but minimal signs. A range of ocular surface disorders can produce symptoms that can overlap with those of DED, including allergic conjunctivitis, blepharitis, conjunctivochalasis, and even corneal dystrophies.[12,13]

One major reason why the diagnosis of DED remains challenging is the long-recognized poor correlation between patient-reported symptoms and clinical signs.[14,15] Many patients with early or mild DED are more symptomatic than the signs show, whereas the scales often tilt in favor of signs over symptoms in advanced cases. Recent studies suggest that use of symptoms alone could result in missing as many as 40% of patients with DED, particularly with early or mild disease.[14,16] A commonly used approach is to rely on patients' symptom severity to form a diagnostic impression and then look for signs to verify the suspicion (Figure 2).

This disconnect between symptoms and signs of DED, if present, should be communicated to patients to help them understand their condition. Showing patients images of their eyes or test results is an effective way to help them appreciate the severity of the disease. Advanced cases are more challenging, because patients often "look" worse than they "feel," which may limit their motivation to adhere to a treatment regimen. It can be worthwhile to explain that severe DED has been shown to correlate with decreased corneal sensitivity,[17,18] similar to the way advanced diabetes impairs sensation in the extremities.[19]

Main Aspects of Treatment

Depending on disease subtype and severity, the appropriate initial therapy for one patient with DED may be quite different from that of another. The newly published TFOS DEWS II report defines DED as a multifactorial ocular surface disease "…accompanied by ocular symptoms in which tear film instability and hyperosmolarity, ocular surface inflammation, and damage and neurosensory abnormalities play etiological roles."[11] Key to success in managing this often-complex disease is addressing all of its components, with choice of treatment based on the severity measured. For a patient with evaporative DED, elements to manage may include obstruction of the meibomian glands, microbial infection and biofilm formation, tear film abnormalities, and ocular surface inflammation; in aqueous-deficient DED, more emphasis may be placed on increasing tear production, as well as managing inflammation. Differentiating aqueous-deficient from evaporative DED lays the groundwork for making an effective treatment plan; however, mixed cases are very common, and more than 80% of all DED patients have an evaporative component.[20]

"Visual disturbance is probably the first casualty of dry eye disease." – DR. KABAT

It is now recognized that ocular surface inflammation occurs ubiquitously in DED irrespective of its etiopathogenesis, and that addressing this underlying inflammation is a crucial aspect of treatment (Figure 3).[3,21-23] Mediated by activated T lymphocytes, the ocular surface inflammation induced by DED is self-perpetuating and gives rise to symptoms of discomfort.[21-24] Left to persist, it can result in clinically evident tissue damage and neuropathic changes.[17,18]

Signs of inflammation associated with DED may not always be clinically overt, but several diagnostic tests (eg, InflammaDry®, Quidel) can be used to help reveal inflammatory elements in the tear film and monitor treatment response. Inflammation is triggered early on in DED, and can arise from various avenues. The inciting stress could be hyperosmolarity resulting from evaporative tear loss, microbial biofilm formation on the eyelids, or perhaps an increase in the shear force applied to the ocular surface during blinking, due to impairment of the tear film's lubricating ability—or all of these.[21] In a small percentage of patients, the inflammation is associated with systemic autoimmune disorder (eg, Sjogren syndrome, rheumatoid arthritis) and involves the lacrimal glands as well as the ocular surface.

Closing the Therapeutic Gap

Due to the chronicity of DED, we prioritize a treatment's safety profile as well as its efficacy. In the short-term, improvement of symptoms is crucial—most patients with DED seek care because they are symptomatic. If symptoms do not improve within a reasonable amount of time, patients may lose the motivation to continue with care. In our experience, most patients are prepared to try a therapy for no more than three or four months before noting symptomatic relief,

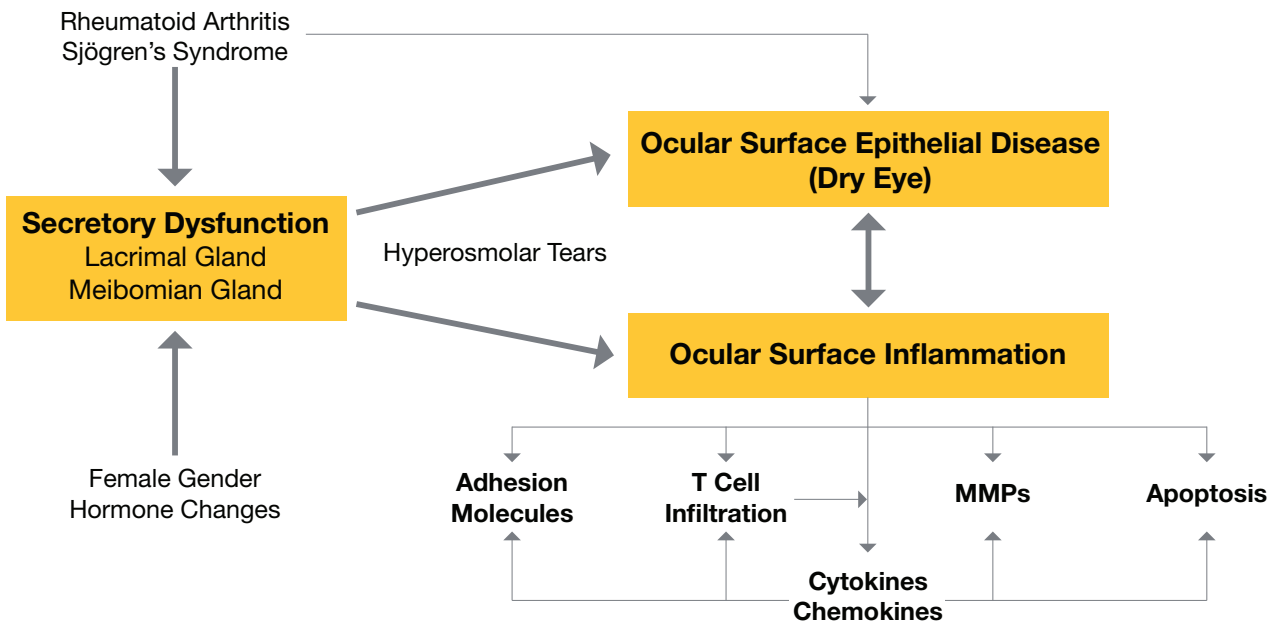

FIGURE 3 The inflammatory cycle in DED. Desiccating and other types of environmental or inherent stress trigger an inflammatory response on the ocular surface that involves the infiltration of T cells and various inflammatory mediators. This inflammation plays a central role in the pathogenesis of DED. *(Figure adapted from reference 3.)*

though this may vary case by case.

Some of the current therapies (eg, omega fatty acid supplements) are innocuous enough to use long-term, but some store brands lack potency; others (eg, topical corticosteroids) can quickly achieve substantial effect but may not be suitable for chronic use because of a high risk of long-term side effects.

"The more insults to the ocular surface, the higher the osmolarity, the more inflammation you get, and the more damage occurs."

– DR. KARPECKI

Xiidra® (lifitegrast ophthalmic solution) 5% is a small-molecule inhibitor designed to interfere with the T cell-mediated inflammation behind DED (Figure 4).[4,25] Xiidra® has demonstrated efficacy and proven safety according to four 12-week randomized clinical trials (N=2133 patients), and one 12-month randomized safety study.[4,26] Patients treated with Xiidra® experienced a measurable reduction in eye dryness in all four studies at 6 and 12 weeks, and in two of the four studies, in as few as 2 weeks.[4] Inferior corneal fluorescein staining was improved in Xiidra®-treated patients at 12 weeks in three of the four trials.[4]

Xiidra® in Practice

Because inflammation plays a pivotal role in all forms of DED, Xiidra® can be used for a wide range of patients with DED, including those with more advanced disease. Notably, the enrollment criteria of the Xiidra® clinical trials would capture many of the patients we often see in daily practice: moderate symptoms of eye dryness (self-assessed to be at least 40 on a scale from 0 to 100), moderate inferior corneal staining with fluorescein (around 2 on a scale of 0 to 4), and a

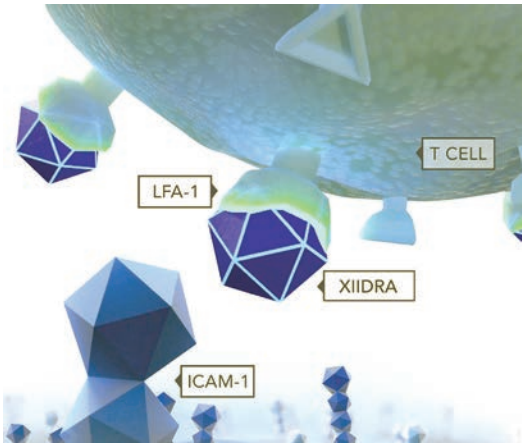

FIGURE 4 The interaction of intercellular adhesion molecule-1 (ICAM-1), a protein expressed on ocular surface epithelial cells, and lymphocyte function-associated antigen-1 (LFA-1) on the T cell surface, is critical to the inflammation behind DED. Xiidra® is designed to specifically block the ICAM-1/LFA-1 interaction, although its exact mechanism of action in DED is not known.

recent history of artificial tear use.[27,28] Based on clinical trial results, and our own clinical experience, we find Xiidra® (lifitegrast ophthalmic solution) 5% to be a favorable option in these patient types.

Overall, our experience with Xiidra® has been overwhelmingly positive. Indeed, Xiidra® has become a first-line treatment for most of our patients with DED. Given the data from the clinical trials and our growing experience, we may also consider trying Xiidra® for patients who have not achieved adequate improvement with previous therapies.

According to clinical trials, 5% to 25% of patients treated with Xiidra® experienced side effects such as: dysgeusia (altered taste sensation), blurred vision, and burning upon instillation.[4] Our clinical experience has been consistent with the trials, and overall, these adverse reactions have been mild to moderate (Figure 5).[4]

When prescribing Xiidra®, patients should first be made aware of these possible adverse reactions to set reasonable expectations. We also want to let them know that there may be ways to help manage such side effects, should they occur. One simple step some of us take to let patients experience the medication for themselves is to have them instill a first dose of Xiidra® in the office.

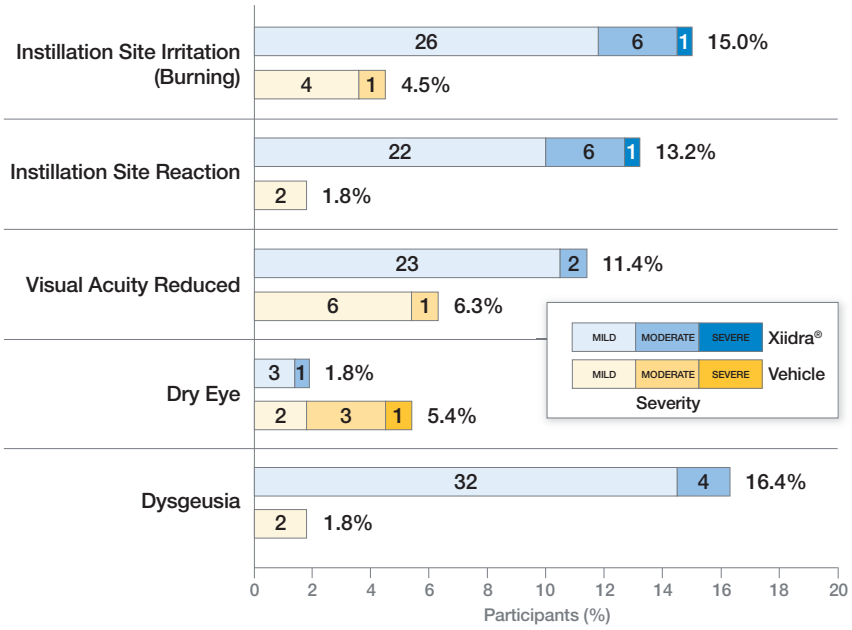

FIGURE 5 Incidence and severity of most frequent adverse events (> 5%) in a 12-month, randomized, double-masked, placebo-controlled safety study of Xiidra®. *(Figure adapted from reference 26.)*

> *"If I diagnose a patient with DED, I know that inflammation is at play. My first priority is to initiate a treatment that's designed to help address inflammation. Having Xiidra® as a first-line therapy is really changing my approach."* – DR. O'DELL

For patients who experience reduced visual acuity or irritation upon instillation, timing the doses (eg, before taking a shower in the morning or before going to bed in the evening) can help minimize the impact. For many of our patients who have noticed dysgeusia, brushing teeth, taking a breath mint, or having some food after administering the drop may be helpful in alleviating the unpleasant taste.

Access to Xiidra®

Since the approval of Xiidra®, Shire has gone to great lengths to ensure its accessibility for the majority of patients who are diagnosed with DED. Access to Xiidra® has improved steadily over time, and within a year of its approval, coverage was in place for well over 80% of commercially insured patients.*[29]

With Shire's prescription cost-savings program, eligible commercially insured patients can get a one-month supply at no cost. This is a strong motivating factor, because it provides us ample time to assess how patients respond to Xiidra® and to find out about their insurance coverage. Additionally, a variety of resources are available to help meet patients' access needs. For patients whose insurances require prior authorization, Xiidra® is available on PARx Solutions. There is **ask iiris** (1-844-694-4747), a live-person phone service launched by Shire to provide coverage information and verify patients' benefits, which can be especially useful for those beginning the treatment. Shire also offers a Xiidra iinsider® card which can help reduce the cost of Xiidra® for eligible commercial patients.

Closing Thoughts

Xiidra® is the first in a new class of medications, approved specifically for the treatment of the signs and symptoms of DED. While not all

*Covered at any tier; additional restrictions may apply for certain plans.

patients with DED are appropriate for treatment with Xiidra® (lifitegrast ophthalmic solution) 5%, it is a viable option for many. Its record of efficacy and safety in our practices supports our use as a first-line therapy. If patients are made aware of the potential for adverse events and armed with the appropriate resources to access the medication, the outlook is positive. According to the robust clinical trial data and our collective experience, Xiidra® has the potential to help a great many patients with DED.

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For additional safety information, see Brief Summary on page 8.
For Full Prescribing Information, please visit Xiidra-ECP.com

Shire

xiidra® (lifitegrast ophthalmic solution)5%

Rx Only

BRIEF SUMMARY:
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single use container. Discard the single use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg /day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast. *Mutagenesis:* Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation. *Impairment of fertility:* Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

Shire

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.

For more information, go to www.Xiidra.com or call 1-800-828-2088.

US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553; 8927574; 9447077; 9353088 and pending patent applications.
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