

XIIDRA- lifitegrast solution/ drops
Shire US Manufacturing Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIIDRA safely and effectively. See full prescribing information for XIIDRA.

XIIDRA® (lifitegrast ophthalmic solution) 5%, for topical ophthalmic use
Initial U.S. Approval: 2016

----- **RECENT MAJOR CHANGES** -----

Contraindications (4)

12/2017

----- **INDICATIONS AND USAGE** -----

Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED). (1)

----- **DOSAGE AND ADMINISTRATION** -----

One drop twice daily in each eye (approximately 12 hours apart). (2)

----- **DOSAGE FORMS AND STRENGTHS** -----

Ophthalmic solution containing lifitegrast 50 mg/mL (5%). (3)

----- **CONTRAINDICATIONS** -----

Hypersensitivity. (4)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions (incidence 5-25%) following the use of Xiidra were instillation site irritation, dysgeusia and decreased visual acuity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2017

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 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.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing lifitegrast 50 mg/mL (5%).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation [see *Adverse Reactions* (6.2)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [see *Contraindications* (4)]

6.1 Clinical Studies 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. Because

these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported [*see Contraindications (4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 [*see Clinical Pharmacology (12.3)*].

Data

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.

8.2 Lactation

Risk Summary

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 [*see Clinical Pharmacology (12.3)*]. 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.

8.4 Pediatric Use

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

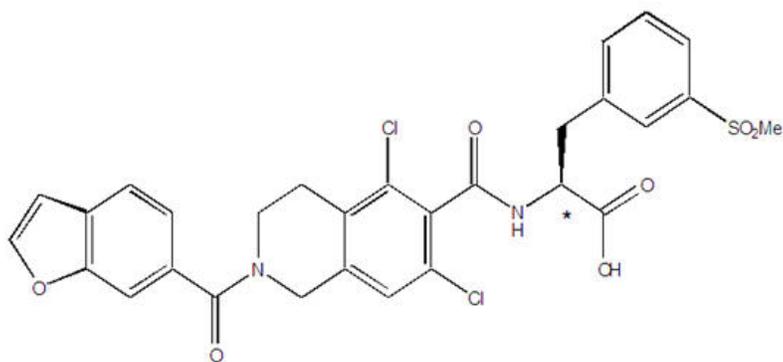
8.5 Geriatric Use

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

11 DESCRIPTION

The chemical name for lifitegrast is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-

tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. The molecular formula of lifitegrast is $C_{29}H_{24}Cl_2N_2O_7S$ and its molecular weight is 615.5. The structural formula of lifitegrast is:



* Chiral center

Lifitegrast is a white to off-white powder which is soluble in water.

Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist supplied as a sterile, clear, colorless to slightly brownish-yellow colored, isotonic solution of lifitegrast with a pH of 7.0–8.0 and an osmolality range of 200–330 mOsmol/kg.

Xiidra contains **Active:** lifitegrast 50 mg/mL; **Inactives:** sodium chloride, sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lifitegrast binds to the integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 may be overexpressed in corneal and conjunctival tissues in dry eye disease. LFA-1/ICAM-1 interaction can contribute to the formation of an immunological synapse resulting in T-cell activation and migration to target tissues. *In vitro* studies demonstrated that lifitegrast may inhibit T-cell adhesion to ICAM-1 in a human T-cell line and may inhibit secretion of inflammatory cytokines in human peripheral blood mononuclear cells. The exact mechanism of action of lifitegrast in dry eye disease is not known.

12.3 Pharmacokinetics

In a subset of dry eye disease patients (n=47) enrolled in a Phase 3 trial, the pre-dose (trough) plasma concentrations of lifitegrast were measured after 180 and 360 days of topical ocular dosing (1 drop twice daily) with Xiidra (lifitegrast ophthalmic solution) 5%. A total of nine (9) of the 47 patients (19%) had plasma lifitegrast trough concentrations above 0.5 ng/mL (the lower limit of assay quantitation). Trough plasma concentrations that could be quantitated ranged from 0.55 ng/mL to 3.74 ng/mL.

13 NONCLINICAL TOXICOLOGY

13.1 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.

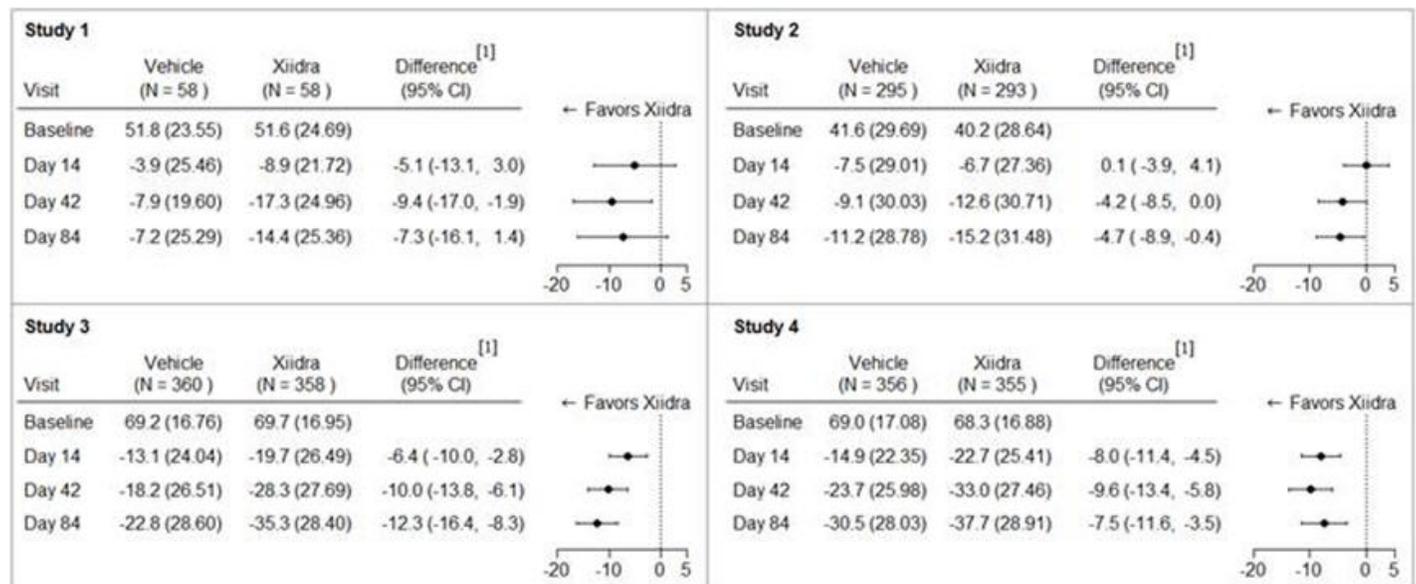
14 CLINICAL STUDIES

The safety and efficacy of lifitegrast for the treatment of dry eye disease were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multi-center, double-masked, vehicle-controlled studies. Patients were randomized to Xiidra or vehicle (placebo) in a 1:1 ratio and dosed twice a day. Use of artificial tears was not allowed during the studies. The mean age was 59 years (range, 19–97 years). The majority of patients were female (76%). Enrollment criteria included, minimal signs (i.e., Corneal Fluorescein Staining (CFS) and non-anesthetized Schirmer Tear Test (STT)) and symptoms (i.e., Eye Dryness Score (EDS) and Ocular Discomfort Score (ODS)) severity scores at baseline.

Effects on Symptoms of Dry Eye Disease

Eye dryness Score (EDS) was rated by patients using a visual analogue scale (VAS) (0 = no discomfort, 100 = maximal discomfort) at each study visit. The average baseline EDS was between 40 and 70. A larger reduction in EDS favoring Xiidra was observed in all studies at Day 42 and Day 84 (see Figure 1).

Figure 1: Mean Change (SD) from Baseline and Treatment Difference (Xiidra – Vehicle) in Eye Dryness Score in 12-Week Studies in Patients with Dry Eye Disease

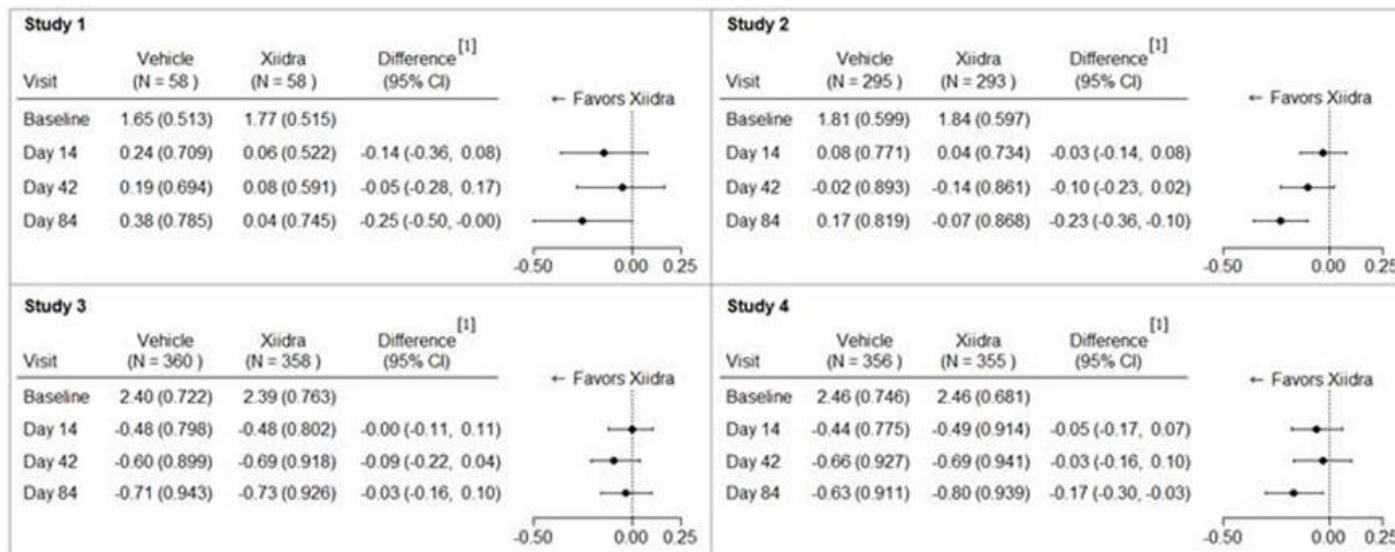


[1] Based on ANCOVA model adjusted for baseline value in Study 1, and ANCOVA model adjusted for baseline value and randomization stratification factors in Studies 2–4. All randomized and treated patients were included in the analysis and missing data were imputed using last-available data. In Study 1, one Xiidra treated subject who did not have a baseline value was excluded from analysis.

Effects on Signs of Dry Eye Disease

Inferior fluorescein corneal staining score (ICSS) (0 = no staining, 1 = few/rare punctate lesions, 2 = discrete and countable lesions, 3 = lesions too numerous to count but not coalescent, 4 = coalescent) was recorded at each study visit. The average baseline ICSS was approximately 1.8 in Studies 1 and 2, and 2.4 in Studies 3 and 4. At Day 84, a larger reduction in ICSS favoring Xiidra was observed in three of the four studies (see Figure 2).

Figure 2: Mean Change (SD) from Baseline and Treatment Difference (Xiidra – Vehicle) in Inferior Corneal Staining Score in 12-Week Studies in Patients with Dry Eye Disease.



[1] Based on ANCOVA model adjusted for baseline value in Study 1, and ANCOVA model adjusted for baseline value and randomization stratification factors in Studies 2-4. All randomized and treated patients were included in the analysis and missing data were imputed using last-available data. In Study 2, one Vehicle treated subject who did not have a study eye designated was excluded from analysis.

16 HOW SUPPLIED/STORAGE AND HANDLING

Xiidra (lifitegrast ophthalmic solution) 5% (50 mg/mL) is supplied in a foil pouch containing 5 low density polyethylene 0.2 mL single-use containers.

NDC 54092-606-01; Carton of 60 single-use containers.

Storage:

Store at 20 to 25°C (68 to 77°F). Store single-use containers in the original foil pouch.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling.

Handling the Single-use Container

Advise patients not to touch the tip of the single-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

Use with Contact Lenses

Advise patients that contact lenses, should be removed prior to administration of Xiidra and can be reinserted 15 minutes after administration [see Dosage and Administration (2)].

Administration

Advise patients that the solution from one single-use container is to be used immediately after opening. It can be used to dose both eyes. The single-use container, including any remaining contents should be

discarded immediately after administration [see *Dosage and Administration (2)*].

Storage Information

Instruct patients to store single-use containers in the original foil pouch until ready to use.

Patient Information

Xiidra® (ZYE-druh)

(lifitegrast ophthalmic solution) 5%

What is Xiidra?

Xiidra is a prescription eye drop solution used to treat the signs and symptoms of dry eye disease. It is not known if Xiidra is safe and effective in children under 17 years of age.

Do not use Xiidra:

- If you are allergic to lifitegrast or any of the other ingredients in Xiidra (see ‘What are the ingredients in Xiidra?’)

Before you use Xiidra, tell your doctor if you:

- are using any other eye drops
- wear contact lenses
- are pregnant or plan to become pregnant. It is not known if Xiidra will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Xiidra passes into your breast milk. Talk to your doctor about the best way to feed your baby if you use Xiidra.

How should I use Xiidra?

See the complete Instructions for Use at the end of this Patient Information leaflet for detailed instructions about the right way to use Xiidra.

- Use Xiidra as your doctor tells you.
- Use 1 drop of Xiidra in each eye, 2 times each day, about 12 hours apart.
- Use Xiidra right away after opening. Throw away the single-use container and any unused solution after you have applied the dose to both eyes. Do not save any unused Xiidra for later.

What are the possible side effects of Xiidra?

The most common side effects of Xiidra include eye irritation, discomfort, or blurred vision when the drops are applied to the eyes, and an unusual taste sensation (dysgeusia).

Seek medical care immediately if you get any symptoms of wheezing, difficulty breathing, or swollen tongue.

These are not all the possible side effects of Xiidra.

Tell your doctor if you have any side effects that bother you.

You may report side effects to FDA at 1-800-FDA-1088.

How should I store Xiidra?

- Store Xiidra at room temperature between 68°F to 77°F (20°C to 25°C).
- Store Xiidra in the original foil pouch to protect it from light.
- Do not open the Xiidra foil pouch until you are ready to use the eye drops.
- Return unused single-use containers to their original foil pouch to protect from excessive light exposure.

Keep Xiidra and all medicines out of the reach of children.

General information about the safe and effective use of Xiidra.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or doctor for information about Xiidra that is written for health professionals. Do not use Xiidra for a condition for which it was not prescribed. Do not give Xiidra to other people, even if they have the same symptoms you have. It may harm them.

What are the ingredients in Xiidra?

Active ingredient: lifitegrast

Inactive ingredients: sodium chloride, sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

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.

**This Patient Information has been approved by the U.S. Food and Drug Administration
Issued: December 2017**

Instructions for Use

**Xiidra® (ZYE-druh)
(lifitegrast ophthalmic solution) 5%
for topical ophthalmic use**

Read this Instructions for Use before you start using Xiidra® and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

Important:

- Xiidra is for use in the eye.
- Wash your hands before each use to make sure you do not infect your eyes while using Xiidra
- If you wear contact lenses, remove them before using Xiidra.
- Xiidra single-use containers are packaged in a foil pouch. Do not remove from the foil pouch until you are ready to use Xiidra.
- Do not let the tip of the Xiidra single-use container touch your eye or any other surfaces.
- Use 1 drop of Xiidra in each eye 2 times each day (1 drop in the morning and 1 drop in the evening, approximately 12 hours apart). Each single-use container of Xiidra will give you enough medicine to treat both of your eyes, 1 time. There is some extra Xiidra in each single-use container in case you miss getting a drop into your eye. After you have applied the drops, throw away the single-use container and any unused Xiidra. Do not save any unused Xiidra.

Follow Steps 1 to 9 each time you use Xiidra:

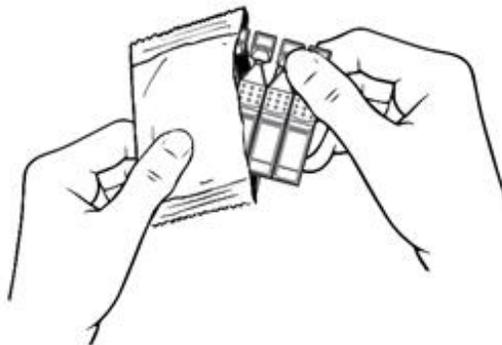
Step 1. Take a foil pouch out of the Xiidra box. Open the pouch and remove the strip of single-use containers.



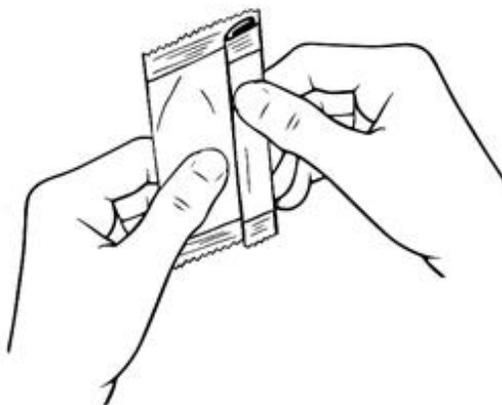
Pull off 1 single-use container from the strip.



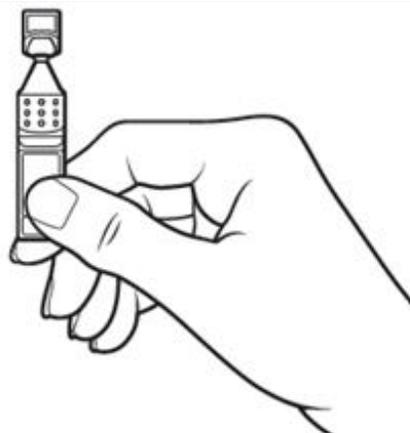
Step 2. Put the remaining strip of single-use containers back in the pouch.



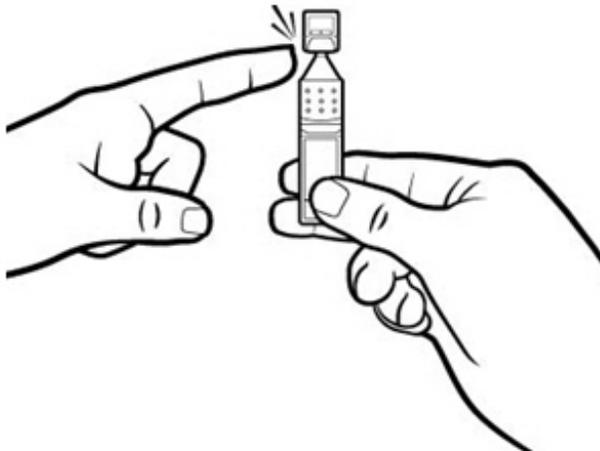
Fold the edge to close the pouch.



Step 3. Hold the Xiidra container upright.



Tap the top of the container until all of the solution is in the bottom part of the container.



Step 4. Open the Xiidra single-use container by twisting off the tab. Make sure that the tip of the single-use container does not touch anything, to avoid contamination.



Step 5. Tilt your head backwards. If you are not able to tilt your head, lie down.

Step 6. Gently pull your lower eyelid downwards and look up.

Step 7. Place the tip of the Xiidra single-use container close to your eye, but be careful not to touch your eye with it.

Step 8. Gently squeeze the single-use container and let 1 drop of Xiidra fall into the space between your lower eyelid and your eye. If a drop misses your eye, try again.



Step 9. Repeat steps 5-8 for your other eye. There is enough Xiidra in one single-use container for both eyes.

Once you have applied a drop to both eyes, throw away the opened single-use container with any remaining solution. If you use

contact lenses, wait for at least 15 minutes before placing them back in your eyes.

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

Patented: please see <https://www.shire.com/legal-notice/product-patents>

This Instructions for Use has been approved by the U.S. Food and Drug Administration

Issued: 12/2017

PRINCIPAL DISPLAY PANEL - 0.2 mL Ampule Pouch Carton

NDC-54092-606-01

60 Single-Use

Containers:

12 pouches x 5 single-use
containers (0.2 mL each)

Rx Only

xiidra™

(lifitegrast

ophthalmic solution) 5%

For Topical Application to the Eye

Manufactured for:

Shire US Inc.

300 Shire Way

Lexington, MA 02421

www.shire.com

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Shire

xiidra™
 (lifitegrast
 ophthalmic solution) 5%
 For Topical Application to the Eye

60 Single-Use Containers:
 12 pouches x 5 single-use containers (0.2 mL each)

Rx Only

Manufactured for:
 Shire US Inc.
 300 Shire Way
 Lexington, MA 02421
 www.shire.com
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36275V4

Rx Only



12 pouches x 5 single-use containers (0.2 mL each)

60 Single-Use Containers:

NDC-54092-606-01

For Topical Application to the Eye
 ophthalmic solution) 5%
xiidra™
 (lifitegrast

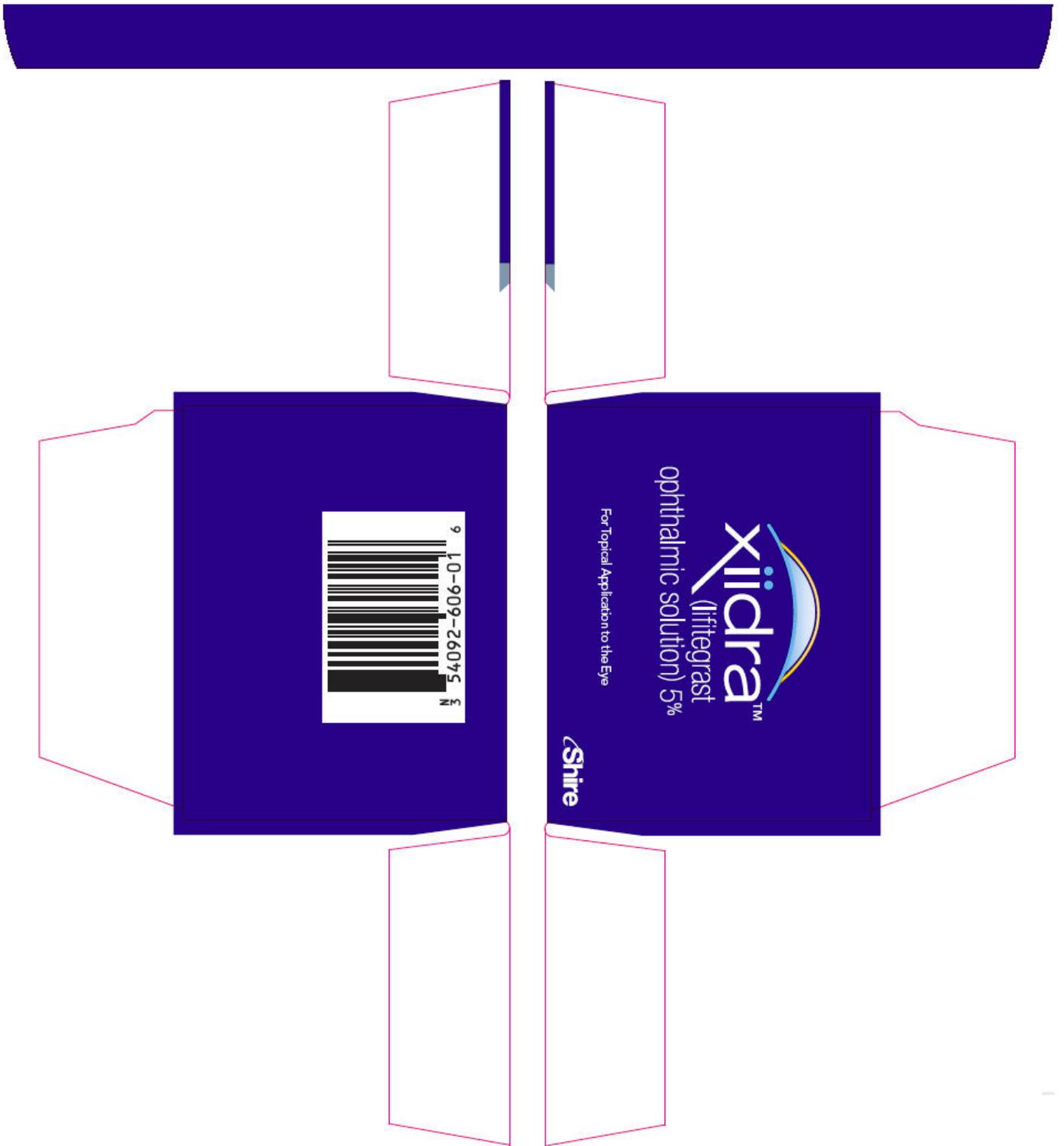
Usual dosage: Place one drop twice daily in each eye. Use one single-use container immediately after opening and then discard.
Storage: Store at 20-25°C (68-77°F). Store single-use containers in the original foil pouch.
 Preservative-Free, Sterile
Active: lifitegrast 5% (10 mg lifitegrast per single-use container)
Inactives: sodium chloride, sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection

Rx Only

60 Single-Use Containers:
 12 pouches x 5 single-use containers (0.2 mL each)

xiidra™
 (lifitegrast
 ophthalmic solution) 5%





XIIDRA

lifitegrast solution/ drops

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54092-606
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
LIFITEGRAST (UNII: 038E5L962W) (LIFITEGRAST - UNII:038E5L962W)	LIFITEGRAST	50 mg in 1 mL

Inactive Ingredients	
Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: 22ADO53M6F)	
SODIUM THIOSULFATE (UNII: HX1032V43M)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0KO0R)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54092-606-01	12 in 1 CARTON	07/11/2016	
1	NDC:54092-606-06	5 in 1 POUCH		
1		0.2 mL in 1 AMPULE; Type 0: Not a Combination Product		
2	NDC:54092-606-02	12 in 1 CARTON	07/11/2016	
2	NDC:54092-606-07	5 in 1 POUCH		
2		0.2 mL in 1 AMPULE; Type 0: Not a Combination Product		
3	NDC:54092-606-04	4 in 1 CARTON	07/11/2016	
3	NDC:54092-606-07	5 in 1 POUCH		
3		0.2 mL in 1 AMPULE; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208073	07/11/2016	

Labeler - Shire US Manufacturing Inc. (964907406)

Establishment			
Name	Address	ID/FEI	Business Operations
The Ritedose Corporation (TRC)		837769546	MANUFACTURE(54092-606) , ANALYSIS(54092-606) , PACK(54092-606) , LABEL(54092-606)

Establishment			
Name	Address	ID/FEI	Business Operations
AMRI Rensselaer, Inc.		124193793	API MANUFACTURE(54092-606) , ANALYSIS(54092-606) , PACK(54092-606)

Establishment			
Name	Address	ID/FEI	Business Operations
Sharp Corporation		143696495	LABEL(54092-606) , PACK(54092-606)

