Ophthalmics, Anti-Inflammatory/Immunomodulator Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

<table>
<thead>
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<th>Drug</th>
<th>Manufacturer</th>
<th>Indication</th>
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<tr>
<td>cyclosporine emulsion (Restasis®,</td>
<td>Allergan</td>
<td>Increase tear production in patients whose tear production is presumed to</td>
</tr>
<tr>
<td>Restasis Multidose®)1, 2</td>
<td></td>
<td>be suppressed due to ocular inflammation associated with keratoconjunctivitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sicca</td>
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<tr>
<td>cyclosporine solution* (Cequa™)3</td>
<td>Sun</td>
<td>Increase tear production in patients with keratoconjunctivitis sicca (dry</td>
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<td>lifitegrast (Xiidra®)4</td>
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<td>Short-term (up to 14 days) treatment of dry eye disease signs and symptoms</td>
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* Cequa (cyclosporine) and Eysuvis (loteprednol) were approved under the United States (US) Food and Drug Administration (FDA) 505(b)(2) pathway that allows at least some data submitted for approval to be from studies not conducted by or for the applicant.6, 7, 8

OVERVIEW

Dry eye disease (DED) is related to either decreased tear volume (aqueous tear deficiency) or rapid evaporative loss (evaporative tear deficiency) due to poor tear quality.9 The terms dry eye disease, dry eye syndrome, keratoconjunctivitis sicca (KCS), and keratitis sicca are often used interchangeably, with the term keratoconjunctivitis sicca being an older term.

DES affects approximately 10% to 30% of the United States (US) population and occurs more commonly in patients over 50 years of age, with approximately twice as many women as men affected.10, 11 However, due to increased use of soft contact lenses and frequent smartphone and computer usage, the prevalence of DES is increasing among young adults aged 18 to 34 years. Patients with DED may have the following complaints: sensations of ocular dryness, grittiness, a foreign body, or irritation; hyperemia; mucoid discharge; excessive tearing; photophobia; and blurry vision. Some findings on examination consist of conjunctival hyperemia and fine, scattered loss of corneal or conjunctival epithelium.

Sjögren’s syndrome, which can be a primary or secondary autoimmune disorder, often includes dry eye symptoms.12 Aqueous tear deficient DED associated with Sjögren’s syndrome affects approximately 1% to 2% of the US population. It also occurs more common in women. Neither agent in this review is indicated specifically for patients with Sjögren’s syndrome.

In aqueous tear deficient DED, the inadequate tear production is typically idiopathic, but may also be secondary to a damaged or malfunctioning lacrimal gland or other autoimmune conditions (e.g., rheumatoid arthritis, systemic lupus erythematosus).13 Evaporative DED is generally related to loss of the oily tear film, sometimes related to poor oil quality, such as in meibomian gland dysfunction or oil degradation (e.g., seborrheic blepharitis). Diagnosis is dependent on symptoms and clinical appearance. It may be further differentiated by the Schirmer test, which uses standardized strips of filter paper placed at the junction between the middle and lateral third of the lower lid. Five millimeters or less of wetting of the paper after 5 minutes on 2 successive occasions confirms the diagnosis of aqueous tear-deficient dry eye. The tear breakup test (TBUT) helps identify evaporative DED and uses fluorescein installation to coat the eye. The patient stares and the time to the first dry spot is determined. Accelerated tear film breakup (< 10 seconds) indicates evaporative DED.
Drying of the eye can also result from inadequate closing of the eye during sleep, as seen with facial nerve palsy, or from insufficient blinking rate, as reported with conditions such as Parkinson’s disease. In general, treatment is aimed to prevent corneal ulcers and scarring. Symptomatic treatment of DED often includes the frequent application of viscous artificial tears and ointments. Multiple artificial tear products are available over-the-counter (OTC) and contain various formulations and strengths of cellulose to preserve viscosity, an agent to prevent evaporation (e.g., polyethylene glycol or an oil emulsion), and a preservative. Since there are various formulations, a patient may respond better to 1 agent than another, particularly if the patient is sensitive to certain preservatives or excipients. These products are available as drops, ointments, and gels and are dosed as needed based on symptoms. Preservative-free options are also available. Prescription cyclosporine (Cequa, Restasis, Restasis Multidose), lifitegrast (Xiidra), and loteprednol (Eysuvis) provide treatment aimed at the cause of the dry eye symptoms rather than the symptomatic management.

According to the 2018 Preferred Practice Parameter on dry eye syndrome and the 2020 Cornea/External Disease Summary Benchmark from the American Academy of Ophthalmology (AAO), specific treatment recommendations depend on the severity and source of the dry eye. Typically, treatments are selected based on the severity level of the disease. Aqueous enhancement using artificial tear substitutes are recommended for mild DED. Preservative-free versions are preferred, when available, particularly if preservative versions are not tolerated or when used frequently. Other recommendations for mild dry eye include elimination of offending topical or systemic medications (e.g., antihistamines, diuretics), cigarette smoking and exposure to second-hand smoke avoidance, eyelid therapy (e.g., warm compresses, eyelid hygiene), increased blinking, environmental changes (e.g., increasing humidity, avoiding air drafts), treatment of contributing ocular factors such as blepharitis or meibomianitis, and correction of eyelid abnormalities. Recommended measures for moderate dry eyes include use of anti-inflammatory agents, such as topical cyclosporine (Cequa, Restasis, Restasis Multidose), lifitegrast (Xiidra), topical corticosteroids, or systemic omega-3 fatty acids supplements, along with aqueous enhancement and other methods described above for mild disease. Other potential treatments for moderate dry eye include punctal plugs (lacrimal plugs) or spectacle side shields and moisture chambers. For severe dry eye, in addition to above mentioned treatments, systemic cholineric agonists, systemic anti-inflammatoryatories, mucolytic agents, autologous serum tears, contact lenses, permanent punctal occlusion, and tarsorrhaphy are recommended. Patient education is also an important part of successful management of DED.

**PHARMACOLOGY**

While cyclosporine is known to be an immunomodulator when administered systemically, the exact mechanism in the management of DED is unknown. Immunomodulating activity of cyclosporine is thought to reduce ocular inflammation. Topical cyclosporine (Cequa, Restasis, Restasis Multidose, ) may take up to 4 to 6 weeks to demonstrate benefit. The exact mechanism of lifitegrast (Xiidra), a lymphocyte function-associated antigen-1 (LFA-1) antagonist, in DED is unknown. Lifitegrast binds to LFA-1, blocking its interaction with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 is thought to be overexpressed in DED, and its interaction with LFA-1 may lead to T-cell activation and migration. Based on available clinical trials, lifitegrast has demonstrated this benefit at 12 weeks; however, a quicker onset of efficacy cannot be ruled out.
Loteprednol (Eysuvis) is a corticosteroid that inhibits the inflammatory responses, but the mechanisms associated with glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not fully understood. However, corticosteroids are thought to play a role in inhibiting prostaglandin production.

PHARMACOKINETICS\textsuperscript{27,28,29,30,31}

Blood cyclosporine (Restasis, Restasis Multidose) concentrations in all samples collected, after topical administration of cyclosporine 0.05% twice daily for 12 months, were below the quantitation limit of 0.1 ng/mL. Blood cyclosporine concentrations, after twice daily topical ocular administration of cyclosporine 0.09% (Cequa) into each eye of healthy subjects for up to 7 days and once on day 8, were either not detectable or were marginally above quantitation limit of 0.1 ng/mL.

Systemic exposure of lifitegrast (Xiidra) is minimal. Trough plasma concentrations at steady state were detectable in 19% of patients in a subset of patients with dry eyes who were on lifitegrast (range, 0.55 ng/mL to 3.74 ng/mL).

The plasma concentrations of loteprednol (Eysuvis) were below the quantitation limit of 1 ng/mL at all timepoints after bilateral topical ocular dosing of 2 drops administered 4 times daily for 14 days in 20 adult participants.

CONTRAINDICATIONS/WARNINGS\textsuperscript{32,33,34,35,36}

Both cyclosporine 0.05% (Restasis, Restasis Multidose) and lifitegrast (Xiidra) are contraindicated in patients with known hypersensitivity to the active ingredient or any excipient ingredient; however, no contraindications are listed in the product labeling for cyclosporine 0.09% solution (Cequa).

Loteprednol (Eysuvis) is contraindicated in the presence of most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis, vaccinia, and varicella. It is also contraindicated in patients with mycobacterial infection of the eye or fungal diseases of ocular structures.

Cyclosporine ophthalmic emulsions (0.05% and 0.09%), lifitegrast, and loteprednol should not be administered while wearing contact lenses. Patients should wait 15 minutes following drug administration to insert contact lenses. In addition, care should be taken not to touch the vial tip to the eye or other surfaces to avoid eye injury and contamination.

Loteprednol may delay healing and cause corneal and scleral thinning. Use of loteprednol in the presence of thin corneal or scleral tissue may lead to perforation. Thorough examination and assessment should be made prior to the initial and each subsequent renewal of the loteprednol prescription.

Prolonged use of loteprednol may result in glaucoma with optic nerve damage, as well as defects in visual acuity and fields of vision. Loteprednol may also result in formation of posterior subcapsular cataract.

Loteprednol may increase the hazard of secondary ocular infections by suppressing the immune response. Loteprednol may mask infection or enhance existing infection during acute eye purulent eye conditions. In addition, caution should be exercised when using loteprednol in patients with a history of herpes simplex. Loteprednol may prolong the course and may exacerbate the severity of viral eye infections (including herpes simplex). Long-term loteprednol use may cause fungal infections of the cornea.
**DRUG INTERACTIONS**\(^{37,38,39,40,41}\)

No information is available in the prescribing information regarding drug interactions with cyclosporine (Cequa, Restasis, Restasis Multidose), lifitegrast (Xiidra), or loteprednol (Eysuvis).

**ADVERSE EFFECTS**\(^{42,43,44,45,46}\)

The most common adverse effect with cyclosporine 0.05% (Restasis, Restasis Multidose) is ocular burning (17%). Other reported adverse effects (incidence of 1% to 5%) include conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbances (e.g., blurring). Postmarketing adverse effects that have been reported with cyclosporine 0.05% include hypersensitivity (e.g., eye swelling, urticaria, angioedema, face and/or tongue swelling, pharyngeal edema, allergic conjunctivitis, and dyspnea) and superficial eye injury secondary to the vial tip touching the eye during administration. The most common adverse reactions (incidence of 1% to 5%) reported for cyclosporine 0.09% (Cequa) include pain on instillation of drops (22%) and conjunctival hyperemia (6%).

The most common adverse reactions occurring in 5% to 25% of patients during clinical trials with lifitegrast (Xiidra) were instillation site irritation, dysgeusia, and decreased visual acuity. Rare cases of hypersensitivity have been reported following product use with various symptoms, including anaphylaxis, bronchospasm, respiratory distress, tongue swelling, pharyngeal edema, and urticaria. Postmarketing cases of eye swelling and rash have also been reported.

The most common adverse drug reaction reported with loteprednol use was instillation site pain, which occurred in 5% of patients in clinical trials.

**SPECIAL POPULATIONS**\(^{47,48,49,50,51}\)

**Pediatrics**

Safety and efficacy of cyclosporine 0.05% (Restasis, Restasis Multidose) have not been established in children < 16 years old. Safety and efficacy of cyclosporine 0.09% (Cequa) and loteprednol (Eysuvis) have not been established in patients < 18 years of age. Safety and efficacy of lifitegrast (Xiidra) have not been established in pediatric patients < 17 years old.

**Pregnancy**

Previously, cyclosporine 0.05% (Restasis in single-use containers) was assigned Pregnancy Category C, but its labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and now includes descriptive text. Cyclosporine 0.05% (Restasis Multidose), lifitegrast (Xiidra), and loteprednol (Eysuvis) have not been assigned a Pregnancy Category based on the PLLR. Clinical administration of cyclosporine 0.05% ophthalmic emulsion is not detected systemically; maternal use is not expected to result in fetal drug exposure. No human data are available on the use of cyclosporine 0.09% (Cequa), lifitegrast (Xiidra), or loteprednol (Eysuvis) in pregnant women to provide insight into drug-associated risks.
Geriatrics

No overall differences in safety or effectiveness were observed between geriatric and younger adults in clinical trials with cyclosporine (Cequa, Restasis, Restasis Multidose), lifitegrast (Xiidra), or loteprednol (Eysuvis).

**DOSAGES**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Comment</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclosporine emulsion</td>
<td>1 drop in each eye twice daily (12 hours apart)</td>
<td>Restasis Multidose: contains unidirectional valve and air filter; prime by squeezing 2 drops onto a tissue before initial use</td>
<td>0.05% ophthalmic emulsion in 0.4 mL single-use, preservative-free containers (trays of 30 or 60) Restasis Multidose: 5.5 mL of 0.05% ophthalmic emulsion in a 10 mL bottle (preservative-free)</td>
</tr>
<tr>
<td>(Restasis, Restasis Multidose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclosporine solution</td>
<td>1 drop in each eye twice daily (12 hours apart)</td>
<td>If used concomitantly, administer artificial tear products at least 15 minutes apart from cyclosporine ophthalmic emulsion</td>
<td>0.09% ophthalmic solution in 0.25 mL single-use, preservative-free container vials (cartons of 60 vials)</td>
</tr>
<tr>
<td>(Cequa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lifitegrast</td>
<td>1 drop in each eye twice daily (12 hours apart)</td>
<td>--</td>
<td>5% ophthalmic emulsion in 0.2 mL single-use, preservative-free container vials (carton of 60 single-use containers stored in foil pouches of 5 containers/pouch)</td>
</tr>
<tr>
<td>(Xiidra)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>loteprednol</td>
<td>1 to 2 drops into each eye 4 times a day</td>
<td>Shake bottle for 2 to 3 seconds prior to each use. If other eye drops are used concurrently, wait at least 5 minutes between instillation of loteprednol. This product should only be renewed after examination under magnification such as a slit lamp and evaluation of the intraocular pressure</td>
<td>0.25% sterile suspension in a 8.3 mL multi-dose bottle</td>
</tr>
<tr>
<td>(Eysuvis)</td>
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</tbody>
</table>

The single-use containers should be discarded immediately after use.

**CLINICAL TRIALS**

**Search Strategy**

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have
results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

**cyclosporine 0.05% emulsion (Restasis) versus vehicle**

Four randomized, vehicle-controlled, multicenter, clinical trials assessed the efficacy and safety of cyclosporine in approximately 1,200 patients with moderate to severe KCS whose tear production was suppressed due to ocular inflammation.\(^58\) In these trials, cyclosporine demonstrated superiority over vehicle in Schirmer wetting of 10 mm at 6 months (approximately 15% with cyclosporine versus 5% with vehicle). Notably, increased tear production did not occur in patients using topical anti-inflammatory drugs or punctal plugs.

Cyclosporine 0.05% and 0.1% ophthalmic emulsions were compared to vehicle for efficacy and safety in 877 patients with moderate to severe DED over 6 months.\(^59\) In these 2 identical, randomized, double-blind, multicenter trials, patients were administered treatment twice daily and evaluated based on corneal dye staining, Schirmer test, tear break-up time, ocular surface disease index, patient subjective rating scale, symptoms of dry eyes, use of artificial tears, and investigator's evaluation of global response to treatment. Both cyclosporine arms provided significantly greater improvement on the corneal staining and Schirmer values than the vehicle group (p≤0.05). Subjective measures including blurred vision, need for artificial tears, and investigator's global assessment were greatly improved with cyclosporine 0.05% (p≤0.05). No dose-response relationship was observed. All therapies were well tolerated.

**cyclosporine 0.09% solution (Cequa) versus vehicle**

Two clinical trials compared cyclosporine 0.09% ophthalmic solution to vehicle for efficacy and safety in 304 patients with keratoconjunctivitis sicca.\(^60,61,62\) Patients were treated with 1 drop in both eyes twice daily. After 84 days in both studies, approximately 17% of cyclosporine-treated patients experienced increases of ≥ 10 mm from baseline in Schirmer wetting compared to about 9% of vehicle-treated patients (Study 1: treatment difference, 8.2%; 95% confidence interval [CI], 1.9 to 14.6; p<0.01; and Study 2: treatment difference, 7.3%; 95% CI, 3.3 to 11.3; p<0.01).

**lifitegrast (Xiidra) versus vehicle**

Four, 12-week, randomized, double-masked, vehicle-controlled, multicenter trials demonstrated the efficacy and safety of lifitegrast in DED (n = 1,181).\(^63,64,65,66\) Study 1, a dose-finding study, also included additional concentrations that are not commercially available; Study 1, which is a phase 2 trial, is not included in this review.\(^67\) Study 2 (OPUS-1) and Study 3 (OPUS-2), both phase 3 trials, have also been published, but Study 4 has not been published. In all trials, patients with DED were randomized 1:1 to lifitegrast or vehicle twice daily. Use of artificial tears was not allowed. The mean age in all trials was 59 years (range, 19 to 97) and 76% were female. At each visit, patients rated their Eye Dryness Score (EDS) using a visual analog scale (VAS; 0 = no discomfort, 100 = maximum discomfort). Inferior Fluorescein Corneal Staining Score (ICSS) was also recorded at each visit (range, 0 [no staining] to 4 [coalescent]). At baseline, EDS scores ranged from 40 to 70 while mean ICSS scores ranged from 1.8 to 2.4. In Study 2, the difference in EDS at day 84 between vehicle and lifitegrast was -4.7 (95% CI, -8.9 to -0.4) and the difference in ICSS at day 84 between vehicle and lifitegrast was -0.23 (95% CI, -0.36 to -0.1). In Study 3, the difference in EDS at day 84 between vehicle and lifitegrast was -12.3 (95% CI, -16.4 to -8.3) and the difference in ICSS at day 84 between vehicle and lifitegrast was -0.03 (95% CI, -0.16 to 0.1). In Study 4,
the difference in EDS at day 84 between vehicle and lifitegrast was -7.5 (95% CI, -11.6 to -3.5) and the difference in ICSS at day 84 between vehicle and lifitegrast was -0.17 (95% CI, -0.3 to -0.03). Thus, a statistically significant difference was found between vehicle and lifitegrast in EDS in all 3 trials and in ICSS in 2 of 3 trials.

**Loteprednol (Eysuvis) versus vehicle**

Safety and efficacy of loteprednol were evaluated in 4 double-masked, placebo-controlled trials that enrolled approximately 2,900 patients with dry eye disease. Patients were randomized 1:1 to loteprednol 0.25% administered 4 times daily or placebo for 2 weeks. The primary endpoint of daily ocular discomfort severity (ODS) was assessed using a patient-rated visual analog scale (0 = very mild, 100 = very severe). At day 15, patients who received loteprednol experienced a greater reduction from baseline in ocular discomfort (ODS) compared to those given placebo (ODS difference based on least square means and 2-sided confidence intervals [95% CI]: Study 1, -5.27 [-10.52 to -0.03]; Study 2, -5.43 [-7.92 to -2.95]; Study 3, -1.87 [-4.3 to +0.55]; Study 4, -4.67 (-7.08 to -2.26]). In addition, in all 4 trials, a larger reduction in conjunctival hyperemia from baseline, measured using the Cornea and Contact Lens Research Unit (CCLRU) grading scale (0=none, 4=severe) at day 15, was reported with loteprednol compared to placebo (hyperemia difference based on least square means and 2-sided confidence interval [95% CI]: Study 1, -0.26 [-0.45 to -0.07]; Study 2, -0.25 [-0.33 to -0.18]; Study 3, -0.16 [-0.23 to -0.09]; Study 4, -0.18 [-0.24 to -0.12]).

**SUMMARY**

Dry eye disease (DED), also known as dry eye syndrome and keratoconjunctivitis sicca, is related to either decreased tear volume (aqueous tear deficiency) or rapid evaporative loss (evaporative tear deficiency) due to poor tear quality. Both of these conditions may be present as well. Thus, the role in therapy, or indication, of lifitegrast (Xiidra) is highly similar to that of topical cyclosporine 0.05% emulsion (Restasis, Restasis Multidose) and cyclosporine 0.09% solution (Cequa). However, lifitegrast is approved for both the signs and symptoms of DED, while both cyclosporine formulations are approved to enhance tear production and cyclosporine 0.05% emulsion (Restasis, Restasis Multidose) is also indicated to treat inflammation associated with DED. On the other hand, the newer agent, loteprednol (Eysuvis) is an ocular corticosteroid approved specifically for the short-term (up to 2 weeks) treatment of the signs and symptoms of DED.

Significant adverse effects are similar between the 4 agents in this class and primarily include ocular burning, irritation, or pain upon instillation. No clinical trials have been published comparing any of the agents in this review, but all have demonstrated efficacy against vehicle. Topical cyclosporine may take up to 4 to 6 weeks to demonstrate benefit. Published clinical trials of lifitegrast evaluated outcomes primarily at 12 weeks; it is unknown if a clinically significant improvement may occur sooner. In clinical trials, improvement in DED with loteprednol was reported at day 15.

All 4 agents may offer relief from DED. Clinical practice guidelines recommend topical cyclosporine or lifitegrast for moderate and severe dry eye syndrome, in addition to other treatment measures. Loteprednol (Eysuvis) was not available at the time of the clinical practice guidelines publishing.
REFERENCES

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3 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
5 Eysuvis [package insert]. Watertown, MA; Kala; October 2020.
22 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
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34 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
39 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
41 Eysuvis [package insert]. Watertown, MA; Kala; October 2020.
44 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
49 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
52 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
54 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
60 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.