Incorporating the ASCRS Preoperative OSD Algorithm into practice

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This supplement about the ASCRS Cornea Clinical Committee’s algorithm for the preoperative diagnosis and treatment of ocular surface disorders is based off of discussion from a corporate-sponsored roundtable that took place at the 2019 ASCRS Annual Meeting. The supplement takes the discussion a step further with co-moderators of the roundtable, Christopher Starr, MD, and Francis Mah, MD, and the faculty, Kenneth Beckman, MD, Marjan Farid, MD, Terry Kim, MD, and Preeya Gupta, MD, giving new insights and practical applications for today’s dry eye practice.

Introduction to the ASCRS Preoperative OSD Algorithm

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Preeya Gupta, MD, is an Associate Professor of Ophthalmology at Duke University School of Medicine in Durham, North Carolina. She has no relevant financial interests.

Co-moderators

The last 15 years has been a new era for ocular surface disease, but advances in diagnostics and treatment options have, according to recent ASCRS Clinical Surveys, left many ophthalmologists confused and overwhelmed, said Christopher Starr, MD.

“The ASCRS Cornea Clinical Committee … decided to take this on as a very important educational initiative, but first, why does ASCRS care so much about OSD?” Dr. Starr asked.

There are several reasons:

• Ocular surface disease (OSD) is present in the majority of cataract patients, many of whom are asymptomatic.
• OSD reduces the accuracy of preop and postop refractive measurements.
• OSD reduces visual quality, quantity, and performance.
• Anterior blepharitis may increase the risk of endophthalmitis.
• Any eye surgery will worsen dry eye disease (DED)/OSD symptoms.

In 2017, the ASCRS Clinical Survey found that 73% of respondents thought a practical, efficient preop diagnostic algorithm would be helpful. So that’s what the Cornea Clinical Committee set out to create and provide to members. The goals were for the algorithm to be consensus- and evidence-based, integrated into the preoperative surgery visit, reliant on techniques and objective testing to reduce chair time, and able to identify all visually significant subtypes of OSD, Dr. Starr said.

The important steps of the algorithm created by the committee are as follows:

**Step 1.** Noninvasive refractive preop measurements (keratometry, topography, optical biometry, aberrometry, etc.)

**Step 2.** OSD screening battery (assessing for signs with tests—osmolarity and inflammatory marker testing—and symptoms with the ASCRS SPEED II Preop Questionnaire). If there is a positive screen, further OSD testing can be used if you’ve got it, Dr. Starr said.

**Step 3.** Directed, quick exam to assess for visually significant OSD (look, lift, push, pull, then stain)

**Step 4.** OSD ruled in or out (if ruled in, determine visual significance)

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For more information on the algorithm, go to: https://ascrs.org/clinical-education/cornea/ascrs-preoperative-osd-algorithm
Discover

Xiidra

Check it out at

Xiidra-ECP.com
Step 5. Visually significant OSD aggressively treated based on subtypes and severity

In the last several years, a number of new algorithms, suggestions, and guidelines have come out, said Francis Mah, MD. Is the ASCRS Preoperative OSD Algorithm different?

“There have been a lot of initiatives in terms of dry eye guidelines over the past several years. ... I think the main difference with our algorithm is that it’s a very practical, evidence-based approach in addressing dry eye in the presurgical patient,” said Terry Kim, MD. “All the other initiatives have focused on dry eye in the general population; this focuses on the preoperative cataract and refractive patient.”

Dr. Kim noted the unique features of the algorithm, such as the customized patient questionnaire, its pearls for the clinical exam, and its multifaceted treatment recommendations to optimize the ocular surface quickly to proceed to the surgical procedure.

If ophthalmologists use this algorithm in their preoperative practice, Dr. Kim said he thinks “we’ll see a better and more improved identification of these patients so that we can get better IOL calculations and surgical results.”

It’s been more than a year since the algorithm was introduced and Dr. Starr said its reception has been amazing.

“It thrills me to see it referenced by others and hear other speakers lecture about it,” Dr. Starr said, adding that he’s heard it called among the most influential and widely cited ophthalmic manuscripts in recent history. “For all those reasons I’m extremely proud of what we did, and I’m glad we spent the extra time to get it just right and break new ground.”

Dr. Mah said the ASCRS Cornea Clinical Committee’s ultimate goal was to make more ophthalmologists aware of the impact of OSD and encourage them to use some sort of screening and treatment algorithm.

“I think people think OSD is an important issue surrounding cataract surgery, and the next steps are how do we diagnose it and treat it. The algorithm is a great way to do that.”

—Francis Mah, MD

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“... [The algorithm is] meant to highlight that OSD is important; start with whatever testing and treatment options you’ve got.”

A point that Dr. Starr clarified is what to do (or not do) when the algorithm diagnoses neuropathic corneal pain (i.e., pain without stain). This contraindicates elective incisional surgery like laser vision correction or astigmatic limbal or corneal incisions, Dr. Starr said. “While it is technically non-visually significant OSD (NVS-OSD) due to an absence of corneal staining, when cataract surgery is needed, it is safe to proceed without delay. But patients should be counseled in advance and told that it might worsen or become visually significant after surgery and may require more advanced treatment afterward,” Dr. Starr said.

“As new diagnostic tools and treatments get approved, they will all have a place in the algorithm, and hopefully we will update it periodically as new things enter the market,” Dr. Starr added.

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*This list may not include all OSD diagnostic tools.
Indications for Use: TearCare® is a tool indicated for the application of localized heat when the current medical community recommends the application of warm compress to the eyelids. Such applications would include Meibomian Gland Dysfunction (MGD), Dry Eye, or Blepharitis. TearCare® may not be right for everyone. Please see Instructions for Use or visit TearCare.com for Contraindications, Warnings, Precautions and Adverse Events.

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Personalized open-eye MGD experience.

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The dry eye screening battery in the ASCRS Preoperative OSD Algorithm guides physicians in assessing signs and symptoms of dry eye.

For signs, it starts with osmolarity testing (TearLab Osmolarity System, TearLab) and looking for inflammatory biomarkers, like MMP-9 (InflammaDry, Quidel). For symptoms, the ASCRS Cornea Clinical Committee developed the ASCRS SPEED II Preop Questionnaire, which includes elements of other validated dry eye questionnaires as well as additional questions specific to the preoperative patient.

In the 2018 ASCRS Clinical Survey, more than 50% of respondents said osmolarity, MMP-9, and a dry eye questionnaire were not included in their practice. These three elements are an integral part of starting the ASCRS Preoperative OSD Algorithm, said Francis Mah, MD. So what if a practice doesn’t have osmolarity or MMP-9 testing? What if a practice has its own dry eye questionnaire or OSD patient feedback process already in place?

“I think screening is very important, and point-of-care testing, while it’s new, it’s not that new, and we’ve had time to realize that it adds so much value to diagnosing our patients who are at risk for ocular surface disease or who have ocular surface disease and are asymptomatic,” said Preeya Gupta, MD. “I would say if you’re not using point-of-care testing, now is the time. … We have a lot of data showing that if you’re utilizing point-of-care testing, you’re going to be able to identify dry eye and ocular surface disease in the asymptomatic state, and I would even say earlier in the disease state. If we take that out to how we manage and treat these patients, the earlier we catch this, the easier it is to treat, the happier the patients are in terms of their comfort. That would be my one request to everyone who isn’t using point-of-care testing.”

Dr. Gupta said that if you don’t have point-of-care testing, that doesn’t mean you can’t use the algorithm. Integrating vital dyes like lissamine green or fluorescein and topography can help identify ocular surface disease, she said.

“Everyone can participate, there are a lot of tests and tools, and if you have access to any of the tools in the algorithm, even starting with one of them is better than not participating at all. This algorithm highlights an opportunity for us to become better diagnosticians, better clinicians, and get to that next point-of-care testing.”

Dr. Mah gets a topography on everyone. “Topography clues me in on the fact that there is something wrong with the ocular surface and that will throw up the yellow flag to look at keratometry and I look at biometry,” he said. “It gets me to talk to the patient about the ocular surface and the fact that we need to get this normal.”

The topographic picture helps in this patient discussion. Dr. Mah described a patient with irregular topography who was originally indicated to receive a toric IOL. He spoke with the patient preoperatively about needing to get her ocular surface managed (it turned out she had meibomian gland disease). Eight weeks of warm compresses, lid scrubs, TearCare (Sight Sciences), steroids, and lifitegrast (Xiidra, Novartis) changed her repeat measurements dramatically.

“Not only did she not need a toric IOL, but it changed the amount of sphere correction 18 D to 19 D, from a T4 to a spherical IOL,” Dr. Mah said. “I think people are motivated to get the right lens to get their vision improved.”

Visually significant corneal staining is common prior to cataract surgery, but patients are often asymptomatic.

Source: Christopher Starr, MD
level vision quality when we’re talking about our refractive and cataract patients,” Dr. Gupta said.

If a practice were to consider integrating MMP-9 or osmolarity testing as a new feature, Dr. Gupta said to get staff and administrators involved to streamline how it fits into your specific practice. She said it’s certainly feasible to integrate one of these at a time into a practice in a financially stable way.

“From a clinician standpoint, it’s not taking more time for me to assess for OSD. My staff is gathering the data and I’m doing the data analysis,” Dr. Gupta said. “I think this is a small change that makes a big impact.”

Terry Kim, MD, noted peer-reviewed studies that have identified a significant number of patients with OSD in the preoperative population, many of whom are asymptomatic.1,2

“I think it’s that asymptomatic population that’s surprising and strengthens the reasons to look at and use the algorithm,” Dr. Mah said. “Along with the literature on the asymptomatic patients, it’s also the peer-reviewed literature that has grown in terms of the instruments that we now have available.”

If a practice already has its own dry eye questionnaire, should they switch to the ASCRS SPEED II Preop Questionnaire?

“I think there are many excellent questionnaires out there,” Dr. Gupta said, adding later that she doesn’t think any questionnaire is wrong. It’s a mistake, however, to not use a questionnaire.

The ASCRS SPEED II boils two questionnaires into one—the validated, easy-to-use SPEED questionnaire, along with questions important to understand a cataract and refractive patient’s expectations and goals, Dr. Gupta said.

“I would recommend physicians look at the questionnaires available, see which ones resonate with you. You can participate with the algorithm using a different questionnaire,” she said.

For the direct slit lamp exam, the ASCRS Cornea Clinical Committee developed the LLPP mnemonic for look, lift, pull, push. Christopher Starr, MD, said the steps of the LLPP exam are nothing new, but he hopes giving it a catchy name reminds physicians to do it on every preoperative patient. Lifting the upper lid to examine the superior cornea and conjunctiva, pulling to assess lid laxity and floppiness, and pushing to assess meibum quality are all valuable but sometimes overlooked, Dr. Starr said. In fact, Dr. Mah pointed out that 20% of respondents to the 2018 ASCRS Clinical Survey said they were not doing this diagnostic expression at the initial point of care. Not assessing for MGD is one of the main reasons dry eye patients might not be successfully managed, Dr. Starr said.

The final step of the diagnostic portion of the algorithm is for the surgeon to use the basket of data and the exam to make a judgment on visual significance and any potential adverse impact on the upcoming surgery, Dr. Starr said.

Marjan Farid, MD, said in the preoperative setting that signs outweigh symptoms. Most patients who come in for cataract surgery are not complaining about dry eyes, and you won’t identify it unless you look for it in their exam and diagnostic testing.

“Relying on symptoms is not enough. We need to look at these signs in detail to be able to identify these patients,” she said.

### References

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**OSD treatment tools**

**FDA-approved medications**
- Cequa (cyclosporine ophthalmic solution, Sun Pharma)
- Restasis (cyclosporine ophthalmic emulsion, Allergan)
- Xiidra (lifitegrast ophthalmic solution, Novartis)

**OTC topical lubricants**
- Artificial tears
- Gels
- Ointments

**Devices**
- BlephEx (RySurg)
- iLux (Alcon)
- Intense pulsed light therapy

**Other tools**
- Anti-inflammatories, such as Flarex (fluorometholone acetate ophthalmic suspension, Eyevance)
- Bruder masks
- Omega-3s
- Punctal plugs
- Scrubs and cleaners
- Warm compresses

*This list may not include all OSD treatment tools.*
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How the protocol impacts surgical decisions

It can be hard to convince busy ophthalmologists to treat OSD, often a chronic condition, said Kenneth Beckman, MD. But with unhappy patients postop, the PHACO study finding under-reporting of dry eye signs and symptoms among cataract patients,1 and the release of the ASCRS Preoperative OSD Algorithm, more and more ophthalmologists are coming on board with preoperative identification and treatment of OSD.

While the algorithm itself can seem overwhelming, it’s a critical part of the cataract evaluation. “It’s easy to use if someone wants to pay attention to it,” Dr. Beckman said. “I think the confusion people get with all these algorithms is it’s not that these are competitive algorithms—they build on each other,” he said.

Christopher Starr, MD, said the ASCRS Preoperative OSD Algorithm was not created in a vacuum, and all the seminal papers—CEDARS DTS, TFOS DEWS II, TFOS MGDW, and others—were all highly influential.

The value of the ASCRS Preoperative OSD Algorithm is it tells the surgeon 1) don’t forget to look for OSD, 2) how to look for it, 3) how to deal with it after you’ve discovered it, Dr. Beckman said.

While some might talk about treating visually significant OSD as delaying surgery, Dr. Beckman said that’s not usually the case in his practice. He said patients often come in for their annual exam and at that time say they’re ready to have their worsening cataracts addressed. Dr. Beckman conducts screening for OSD at that time, ahead of the initial cataract consult. If dry eye is mild, patients are started on an artificial tear and asked to come back in a week for cataract preop testing. If their dry eye is more severe, he’ll start them on a more aggressive treatment, such as a steroid, and have them come back 2 weeks later. Sometimes he’ll test and find that the patient needs further intervention, but it’s rare to do it more than twice. Patients are usually on board with the regimen and repeat testing because he explains the value to them.

“If you give them the proper message, they know how vulnerable they are,” he said.

Dr. Beckman’s message is that surgery is being “delayed” to 1) prevent infection, 2) ensure accurate measurements for correct lens calculations, and 3) to prevent postop aberrations.

To the point of patient conversations, Francis Mah, MD, said non-visually significant, asymptomatic OSD should still be discussed with the patient preoperatively because it could become symptomatic after surgery.

Dr. Starr shared similar advice, saying that he thinks the algorithm is “most useful in those mild, non-obvious cases that could easily be missed in a busy clinic during a lengthy preop exam. Similarly, in those patients with mild or non-visually significant OSD, if you don’t inform the patient of its presence and the possibility of postoperative worsening it could be perceived later as a complication rather than a pre-existing condition.”

“For the obvious visually significant OSD cases, like central corneal staining, you don’t necessarily need an algorithm to arrive at the diagnosis, but having our guidelines and recommendations, as well as objective data, makes the conversation with the patient easier and clearer. … It is great for facilitating patient education and buy-in to our treatment plans.”

Dr. Beckman thinks more ophthalmologists are aware of testing for OSD preoperatively now.

“I used to get a lot of patients from doctors who put in premium lenses that ended up being unhappy, and I was cleaning them up afterward,” Dr. Beckman said. “Now those same doctors are sending patients to me before cataract surgery. … A lot of times I’ll tell them not to put in a premium lens but at least get them cleaned up for regular cataract surgery. That’s a change I’ve seen, so they’re paying attention to it.”

Reference
Reversing a toric decision

One patient Dr. Beckman saw for a toric evaluation had 3 D of irregular astigmatism. Looking at the location of the astigmatism and the mires on Placido imaging, Dr. Beckman knew something else was afoot. “When I did my dry eye workup, I noted he had a rapid tear breakup time, staining, lid margins were a mess,” he said. After 2 weeks treating the dry eye, the patient’s vision was so much better that he didn’t need a toric IOL. His astigmatism was actually 0.5 D. Though this was before the algorithm was developed, Dr. Beckman said it highlights the importance of knowing what you’re treating and eliminating other factors before you jump into cataract surgery.

Keratoconus?

Though not a cataract surgery evaluation, Dr. Beckman also described a patient he saw for keratoconus and crosslinking consultation. He observed irregular cones on topography and determined it was due to the tear film. After treating the dry eye, the topography normalized and the patient didn’t even have keratoconus. “This is a great example of how the tear film may affect corneal measurements for any surgery and needs to be optimized before moving forward,” he said.
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Developing an OSD treatment plan based on subtype and severity

There are a range of OSD subtypes and severity levels for which the ASCRS Preoperative OSD Algorithm helps identify and guide a treatment plan.

When it comes to this plan, Marjan Farid, MD, said physicians want to take a more aggressive multifaceted treatment approach.

“Where do we start? Where do we go from here? There is not as much time in the preoperative setting to take the stepwise approach that we sometimes do with non-surgical patients. With these patients, we want to clear up the ocular surface as quickly as possible so that we can get them in for their surgery.

“What we want to do in this setting is take a multifaceted, aggressive approach, optimize the tear film, really clear up the surface of the eye, and get these patients back in for biometry measurement and get them into surgery,” Dr. Farid said.

So where should you start? Dr. Farid has three big areas to work on. The first is to treat ocular surface inflammation. The second is to improve the lipid layer of the tear film by lid disease management. The third is to clean tear film by lid disease management.

“Addressing bacterial dry eye disease is important as well. For this Dr. Farid turns to microblepharoexfoliation (BlephEx, RySurg). She couples this with thermal pulsation because the microblepharoexfoliation can clear debris, epithelial hyperproliferation, and anything that might be plugging the meibomian gland.

“It debrides the bacteria, which also decreases your risk of endophthalmitis,” she said.

Oral macrolides are a "great adjunct" to when there is concurrent rosacea. Physicians may want to do a low-dose doxycycline for a month to 6 weeks before biometry and surgical planning to clean up the lid margin inflammation, Dr. Farid said. Oral omega-3 supplementation is also a great addition for treatment of inflammation and lipid layer normalization.

When there is central corneal staining, which is agreed to be visually significant OSD, Dr. Farid said she’ll adjust her approach depending on severity. There are a lot of therapies that can be used in this subset of patients, including autologous serum, self-retaining amniotic membrane, and bandage contact lenses. Dr. Farid said “steroids are fantastic,” and she reaches for them early on with these patients to also help clear significant punctate keratitis.

Francis Mah, MD, said he thinks the range of procedural, in-office treatments can be attractive to patients to address OSD every 3–6 months, rather than more regular, patient-directed home therapies. Overall, he thinks there has been a shift in that devices are being used first with medications and at-home warm compresses, for example, being used as the adjunct.

“I’m surprised when I offer [procedural therapies] to patients in that we’d expect because it’s a cash-pay procedure that they would be turned off, but more patients would rather pay a small amount up front to get their lids taken care of than have to be regimented to do a warm compress every day,” Dr. Farid said.

Preeya Gupta, MD, said OSD is also being diagnosed more frequently at younger ages, and these younger patients seem more receptive to the out-of-pocket procedures that get the situation taken care of and are easier than having to do something every day at home.

“One caveat I have with that, though, is as we keep the bar lower with the expectation for our implants, we have to do that with these treatments because most of these treatments are lifetime treatments; while it’s nice to think you can still get it fixed, I don’t encourage them to think ‘Get this and you’re done and you don’t have to take drops anymore,’” said Kenneth Beckman, MD.

“They have to understand this is a chronic condition,” Dr. Gupta said.

OSD tools in the pipeline

*This list may not include all OSD tools in the pipeline.

- EYSUVIS (Kala Pharmaceuticals)
- Lacripep (Tear Solutions)
- OC-1 (Oyster Point Pharmaceuticals)
- Reproxalap (Aldeyra Therapeutics)
- TOP1630 (TopiVert)
- TP-03 (Tarsus Pharmaceuticals)
- Voclosporin ophthalmic solution (Aurinia Pharmaceuticals)
RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05% and RESTASIS MULTIDOSE® (Cyclosporine Ophthalmic Emulsion) 0.05%

BRIEF SUMMARY—PLEASE SEE THE RESTASIS® AND RESTASIS MULTIDOSE® PACKAGE INSERTS FOR FULL PRESCRIBING INFORMATION.

INDICATION AND USAGE

RESTASIS® and RESTASIS MULTIDOSE® ophthalmic emulsion are indicated to decrease tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

CONTRAINDICATIONS

RESTASIS® and RESTASIS MULTIDOSE® are contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation. [see Adverse Reactions]

WARNINGS AND PRECAUTIONS

Use with Contact Lenses

RESTASIS® and RESTASIS MULTIDOSE® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of RESTASIS® and RESTASIS MULTIDOSE® ophthalmic emulsion.

ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling: Potential for Eye Injury and Contamination [see Warnings and Precautions]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials 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 clinical trials, the most common adverse reaction following the use of cyclosporine ophthalmic emulsion 0.05% was ocular burning (17%). Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Post-marketing Experience

The following adverse reactions have been identified during post approval use of cyclosporine ophthalmic emulsion 0.05%. 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.

Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the container tip touching the eye during administration).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: Clinical administration of cyclosporine ophthalmic emulsion 0.05% is not detected systemically following topical ocular administration [see Clinical Pharmacology (12.3)], and maternal use is not expected to result in fetal exposure to the drug. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses [see Data].

Data

Animal Data: At maternally toxic doses (30 mg/kg/day in rats and 100 mg/kg/day in rabbits), cyclosporine oral solution (USP) was teratogenic as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body surface area) are 5,000 and 32,000 times greater, respectively, than the daily recommended human dose of one drop (approximately 28 mcL) of cyclosporine ophthalmic emulsion 0.05% twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater, respectively, than the daily recommended human dose. An oral dose of 45 mg/kg/day cyclosporine administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. This dose is 7,000 times greater than the daily recommended human dose. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily recommended human dose).

Lactation

Risk Summary

Cyclosporine is known to appear in human milk following systemic administration, but its presence in human milk following topical treatment has not been investigated. Although blood concentrations are undetectable following topical administration of cyclosporine ophthalmic emulsion 0.05% [see Clinical Pharmacology (12.3)], caution should be exercised when RESTASIS® and RESTASIS MULTIDOSE® are administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for RESTASIS® and RESTASIS MULTIDOSE® and any potential adverse effects on the breast-fed child from cyclosporine.

Pediatric Use

Safety and efficacy have not been established in pediatric patients below the age of 16.

Geriatric Use

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 80 times greater (normalized to body surface area) than the daily human dose of one drop (approximately 28 mcL) of cyclosporine ophthalmic emulsion 0.05% twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis: Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes in vitro gave indication of a positive effect (i.e., induction of SCE).

Impairment of Fertility: No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

PATIENT COUNSELING INFORMATION

Handling the Container

Advise patients to not allow the tip of the container to touch the eye or any surface, as this may contaminate the emulsion. Advise patients to not touch the container to their eye to avoid the potential for injury to the eye. [see Warnings and Precautions]

Use with Contact Lenses

RESTASIS® and RESTASIS MULTIDOSE® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of RESTASIS® and RESTASIS MULTIDOSE® ophthalmic emulsion.

Administration

Advise patients that the emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Advise patients to read the Instructions for Use for detailed first-time use instructions for the multidose bottle.

Rx Only
INDICATIONS AND USAGE:
RESTASIS® and RESTASIS MultiDose® ophthalmic emulsion are indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS: RESTASIS® and RESTASIS MultiDose® are contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNINGS AND PRECAUTIONS
POTENTIAL FOR EYE INJURY AND CONTAMINATION: Be careful not to touch the container tip to your eye or other surfaces to avoid potential for eye injury and contamination.

USE WITH CONTACT LENSES: RESTASIS® and RESTASIS MultiDose® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of RESTASIS® and RESTASIS MultiDose® ophthalmic emulsion.

ADVERSE REACTIONS: In clinical trials, the most common adverse reaction following the use of cyclosporine ophthalmic emulsion 0.05% was ocular burning (upon instillation)—17%. Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

PLEASE SEE NEXT PAGE FOR A BRIEF SUMMARY OF THE FULL PRODUCT INFORMATION.

REFERENCES: 1. RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% [prescribing information]. Irvine, CA: Allergan, Inc; 2017. 2. RESTASIS Multidose® (cyclosporine ophthalmic emulsion) 0.05% [prescribing information]. Irvine, CA: Allergan, Inc; 2016. 3. Symphony Health, PHAST Prescription Monthly, data through October 2019. 4. IQVIA, Xponent PlanTrak, January 2019-October 2019. 5. Managed Markets Insight & Technology, LLC. Yardley, PA: Managed Markets Insight & Technology, LLC; March 2020.

*Increased tear production was seen at 6 months when used as directed. 1,2
†Source: Managed Markets Insight & Technology, LLC™, a trademark of MMIT Database, as of March 2020. Data are subject to change. Data are not guarantee of coverage, or partial or full payment, by any payers. Actual benefits determined by respective plan administrators, insurer plans, coverage criteria, and formularies are subject to change without notice. Check each patient’s coverage with applicable insurer. Allergan does not endorse any individual plan. Formulary coverage does not imply efficacy or safety.

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IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS: RESTASIS® and RESTASIS MultiDose® are contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNINGS AND PRECAUTIONS
POTENTIAL FOR EYE INJURY AND CONTAMINATION: Be careful not to touch the container tip to your eye or other surfaces to avoid potential for eye injury and contamination.

USE WITH CONTACT LENSES: RESTASIS® and RESTASIS MultiDose® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of RESTASIS® and RESTASIS MultiDose® ophthalmic emulsion.

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