Cequa®
(cyclosporine ophthalmic solution) 0.09%

AUTHORIZATION AND APPEALS KIT

To Support Patients' Access To Prescribed Therapy

Sun Pharma cannot guarantee insurance coverage or reimbursement. Coverage or reimbursement may vary significantly by payer, plan, patient, and setting of care. It is the sole responsibility of the health care provider to ensure the accuracy of all statements made in seeking coverage and reimbursement for an individual patient.

SUN OPHTHALMICS

Please see Important Safety Information on page 15.
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HOW TO USE THIS KIT

This kit provides you with information and sample letters that can help your communications with health plans regarding a prior authorization (PA) or appeal be as complete as possible. These samples are intended to provide you with the type of information that will usually be required. You can refer to the checklist on the first page of each section as you develop your own letters. The more complete your submission, the more quickly you will be able to meet a plan's requirements for prescribing CEQUA® (cyclosporine ophthalmic solution) 0.09% and help your patients receive their prescribed therapy.

Physician Letters

Patient Letters

If an initial appeal is rejected: There can be multiple levels of appeal. Each of the appeal letters can be adapted for higher-level appeals. After a second-level appeal, additional adjudication may include review by an independent noninsurance-affiliated external review board or hearing. Please refer to the plan's specific appeal guidelines, which are often available on their website.

SUGGESTIONS FOR WRITING A PRIOR AUTHORIZATION REQUEST LETTER

All CEQUA PA forms should be completed and submitted to the plan by your office.

This letter comes from the patient and the physician. Fax the PA request to the health plan or submit it electronically to help streamline the process.

Many payers will allow up to 3 levels of appeal of PA denials. The third level of appeal may include review by an independent noninsurance-affiliated external review board or hearing. Refer to page 5, the Prior Authorization Appeals letter.

Checklist

- ☐ **Refer to the health plan's website to locate their PA form**
- ☐ **Include the patient's name, policy number, and date of birth**
- ☐ **List previous therapies, including any over-the-counter** (OTC) **medications, if applicable**
  - Explain why each therapy was discontinued and give the duration of therapy for each agent
- ☐ **Confirm and document that all PA requirements of the plan have been met**
- ☐ **Confirm and document that the patient has satisfied any step therapy requirements**
- ☐ **Provide rationale and clinical support for your recommendation, such as:**
  - Efficacy and safety data for CEQUA
  - Adverse events or contraindications with other treatment options
- ☐ **Review sample letter format on the next page for additional information**

SAMPLE PA REQUEST LETTER FOR CEQUA

[Physician letterhead]

[Date]
[Health plan name]
ATTN: [Name of prior authorization department]
[Contact name (if available)]
[Health plan address]
[City, State ZIP]

Re: Prior Authorization Request for CEQUA®

[Patient name]
[Date of birth]
[Insurance ID number]
[Insurance group number]
[Case ID number]
[Date(s) of service]

Dear [Medical Director]:
This letter is being submitted for the prior authorization of CEQUA® (cyclosporine ophthalmic solution) 0.09%, on behalf of [Patient name, ID, and group number] for the treatment of dry eye disease (keratoconjunctivitis sicca) [diagnosis code]. The authorization requested is for the current date of [insert date] through the date of [insert future date].

Listed below are the patient's relevant diagnosis, medical history, previous therapies, and further reasoning as to why I recommend CEQUA as an appropriate treatment for [Patient name].

Patient's diagnosis and medical history
[Patient name] is [a/an] [age]-year-old [male/female] patient who has been diagnosed with dry eye disease as of [date]. [He/She] has been in my care since [date].

[Give a brief summary of rationale for treatment with CEQUA. This includes a brief description of the patient's diagnosis, including the ICD-10-CM code, the severity of the patient's condition and symptoms, as well as other factors (eg, underlying health issues, age) that have affected your treatment selection.]

Previous therapies (including any OTC artificial tear products), reasons for discontinuation, and duration of therapy
[List here]

Clinical support for the prior authorization
[Provide evidence for your recommendation, such as clinical guidelines or trial data from the CEQUA Prescribing Information.]

Summary
As [a/an] [specialty], I believe CEQUA is appropriate and medically necessary for this patient. If you have any further questions about this matter, please contact me at [Physician phone number] or via email at [Physician email]. Thank you for your time and consideration.

Sincerely,
[Physician and patient signatures]

Enclosures
[List additional documents, which may include: Letter of Medical Necessity, CEQUA Prescribing Information, clinical notes/medical records, or clinical practice guidelines.]

Download this letter at CequaPro.com

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SUGGESTIONS FOR WRITING A PRIOR AUTHORIZATION APPEALS LETTER

This type of letter can be used when a PA request has been denied. There can be multiple levels of appeal. Please refer to the plan's specific appeal guidelines. This letter should be submitted along with a copy of the patient's relevant medical records and a Letter of Medical Necessity (see page 7). Many payers will allow up to 3 levels of appeals for PA denials.

Checklist

- ☐ **Include the patient's name, policy number, date of birth, PA denial reference number, and date of denial**
- ☐ **Acknowledge that you are familiar with the company's policy and state the reason for the denial**
- ☐ **Patient's medical records:**
  - Patient history, diagnosis, current condition, and symptoms
  - Include copies of relevant medical records (payers may want to see if any drug allergies or comorbidities are present)
- ☐ **Document severity of condition** (familiarize yourself with the severity scoring system preferred by the health plan)
- ☐ **List previous therapies, including any OTC medications, if applicable**
  - Explain why each therapy was discontinued, and give the duration of therapy for each agent
- ☐ **Explain why formulary-preferred agents are not appropriate** (if they have not already been listed as previous therapies)
- ☐ **Provide clinical support for your recommendation**
  - This can be clinical trial data from the CEQUA package insert
- ☐ **Attach a Letter of Medical Necessity** (see page 7)

For second- and third-level appeals, it may be helpful to include:

- ☐ **The original letter of denial**
- ☐ **Specific medical notes in response to the denial**
  - A third level of appeal may include review by an independent noninsurance-affiliated external review board or hearing

SAMPLE PA APPEALS LETTER FOR CEQUA

[Physician letterhead]

[Date]
[Health plan name]
ATTN: [Name of prior authorization department]
[Contact name (if available)]
[Health plan address]
[City, State ZIP]

Re: Appeal for Denial of CEQUA®

[Patient name]
[Date of birth]
[Insurance ID number]
[Insurance group number]
[Case ID number]
[Date(s) of service]

To the health plan administrator:
I am writing to request that you reconsider your denial of coverage for CEQUA® (cyclosporine ophthalmic solution) 0.09%, which I have prescribed for my patient, [Patient name].

Your reason(s) for the denial [is/are] [list reason(s) for the denial]. Listed below are the patient's relevant diagnosis, medical history, previous therapies, and further reasoning as to why I recommend CEQUA as an appropriate treatment for [Patient name].

Patient's diagnosis and medical history
[Patient name] is [a/an] [age]-year-old [male/female] patient who has been diagnosed with dry eye disease (keratoconjunctivitis sicca) as of [date]. [He/She] has been in my care since [date].

[Give a brief summary of rationale for treatment with CEQUA. This includes a brief description of the patient's diagnosis, including the ICD-10-CM code, the severity of the patient's condition and symptoms, as well as other factors (eg, underlying health issues, age) that have affected your treatment selection.]

Previous therapies (including any OTC artificial tear products), reasons for discontinuation, duration of therapy
[List here]

Clinical support for the appeal
[Provide evidence for your recommendation, such as clinical guidelines or trial data from the CEQUA Prescribing Information.]

Summary
As [a/an] [specialty], I believe CEQUA is appropriate and medically necessary for this patient. This is my [insert level of request] prior authorization appeal. A copy of the most recent denial letter is included along with medical notes in response to the denial. If you have any further questions about this matter, please contact me at [Physician phone number] or via email at [Physician email]. Thank you for your time and consideration.

Sincerely,
[Physician signature]

Enclosures
[List additional documents, which may include: denial letter, Letter of Medical Necessity, CEQUA Prescribing Information, clinical notes/medical records, or clinical practice guidelines.]

Download this letter at CequaPro.com

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SUGGESTIONS FOR WRITING A LETTER OF MEDICAL NECESSITY

Some plans require that a Letter of Medical Necessity be submitted along with a PA Appeals Letter (see page 5) to support the choice of CEQUA over agents that are on formulary. You may find that this checklist and the sample letters that follow are a helpful guide to preparing that letter. A Letter of Medical Necessity should also accompany a Formulary Exception Request Letter (see page 9) as well as a Tiering Exception Request Letter (see page 11).

Checklist

- ☐ **Include the patient's name, policy number, date of birth, and, if appropriate, PA denial reference number, and date of denial**
- ☐ **Include specific diagnosis codes where appropriate**
- ☐ **Clearly state the rationale for treatment with CEQUA and why it is appropriate for your patient**
- ☐ **Support your recommendations with the following:**
  - Patient history, diagnosis, current condition, and symptoms
  - Include copies of relevant medical records (payers may want to see if any drug allergies or comorbidities are present)
- ☐ **Be sure to include all the listed documents with the letter when you send it to your patient's insurance provider**
- ☐ **Document severity of condition (familiarize yourself with the severity scoring system preferred by the health plan)**
- ☐ **List previous therapies, including any OTC medications, if applicable**
  - Explain why each therapy was discontinued, and give the duration of therapy for each agent
- ☐ **Explain why formulary-preferred agents are not appropriate (if they have not already been listed as previous therapies)**
- ☐ **Provide clinical support for your recommendation**
  - This can be clinical trial data from the CEQUA package insert
- ☐ **To close the letter, summarize your recommendation, and provide a phone number should any additional information be required**

SAMPLE LETTER OF MEDICAL NECESSITY FOR CEQUA

[Physician letterhead]

[Date]
[Health plan name]
ATTN: [Name of prior authorization department]
[Contact name (if available)]
[Health plan address]
[City, State ZIP]

Re: Letter of Medical Necessity for CEQUA®

[Patient name]
[Date of birth]
[Insurance ID number]
[Insurance group number]
[Case ID number]
[Date(s) of service]

Dear [Contact Name/Medical Director]:
I am writing this letter on behalf of [Patient's name] to request coverage for CEQUA® (cyclosporine ophthalmic solution) 0.09% for the treatment of dry eye disease (keratoconjunctivitis sicca). This letter documents the medical necessity for CEQUA and provides information about the patient's medical history and treatment.

Patient's diagnosis and medical history
[Patient name] is [a/an] [age]-year-old [male/female] patient who has been diagnosed with dry eye disease as of [date]. [He/She] has been in my care since [date].

[Give a brief summary of rationale for treatment with CEQUA. This includes a brief description of the patient's diagnosis, including the ICD-10-CM code, the severity of the patient's condition, symptoms, prior treatments/therapies to date, the duration of each, responses to those treatments, the rationale for discontinuation of prior treatments, as well as other factors (eg, underlying health issues, age) that have affected your treatment selection.]

Treatment plan
On [date], the FDA approved CEQUA for the treatment of dry eye disease. [Include plan of treatment (dosage, length of treatment) and clinical practice guidelines that support the use of CEQUA.]

[Include a summary of reasons why preferred drugs on formulary are not appropriate for this patient.]

Summary
As [a/an] [specialty], I believe CEQUA is appropriate and medically necessary for this patient. If you have any further questions about this matter, please contact me at [Physician phone number] or via email at [Physician email]. Thank you for your time and consideration.

Sincerely,
[Physician signature]

Enclosures
[List additional documents, which may include: CEQUA Prescribing Information, clinical notes/medical records, diagnostic test results, relevant peer-reviewed articles, clinical practice guidelines, FDA approval letter, scans showing progressive disease, pathology reports.]

Download this letter at CequaPro.com

SUGGESTIONS FOR WRITING A FORMULARY EXCEPTION REQUEST LETTER

This type of letter can be used when CEQUA is not listed on a formulary or if it has an NDC block. While the plan may provide a form on its website that can be used to apply for an exception, you can refer to the sample provided in this kit to see the type of information that is typically required.

This letter comes from the patient and is also signed by the physician. It should be submitted along with a copy of the patient's relevant medical records and a Letter of Medical Necessity (see page 7).

Checklist

- ☐ **The patient's name, policy number, date of birth, and, if appropriate, the denial reference number from a previous appeal and the date of denial**
- ☐ **The patient's diagnosis**
- ☐ **List of previous therapies, including any OTC medications, if applicable**
- ☐ **The main reasons in support of a formulary exception for CEQUA for this patient**
- ☐ **The patient's relevant medical records**
- ☐ **If this is a second- or third-level appeal, include level of appeal, letter of denial, and medical notes in response to denial**
- ☐ **Letter of Medical Necessity** (see page 7)

SAMPLE FORMULARY EXCEPTION REQUEST LETTER FOR CEQUA

[Physician letterhead]

[Date]
[Health plan name]
ATTN: [Name of prior authorization department]
[Contact name (if available)]
[Health plan address]
[City, State ZIP]

Re: Formulary Exception Request for CEQUA®

[Patient name]
[Date of birth]
[Insurance ID number]
[Insurance group number]
[Case ID number]
[Date(s) of service]

Dear [Contact Name/Medical Director]:
I am a member of [enter name of health plan]. Currently, CEQUA® (cyclosporine ophthalmic solution) 0.09% is not listed in my formulary and, according to my doctor, [insert why, according to your doctor, your medical condition necessitates the use of CEQUA].

I am requesting an exception to your formulary so that I am able to fill my prescription for CEQUA. I request that it be available to me as a preferred drug and that any applicable NDC blocks be removed.

Diagnosis and medical history
I have been diagnosed with dry eye disease [diagnosis code] and my doctor has prescribed CEQUA. Dr. [insert physician name] practices in the medical specialty of [insert medical specialty] at the address [insert physician address]. My past treatments have included [list previous treatments and drugs]. I have enclosed my medical records and a Letter of Medical Necessity from my physician supporting my request for the formulary exception approval of CEQUA.

The main reasons that I am requesting this exception are:
[Insert main medical necessity points]

Summary
These reasons are supported by the information that I have included. My physician can be contacted at [Physician phone number] to answer any additional questions or to participate in a peer-to-peer review discussing the necessity of providing a formulary exception for the use of CEQUA in the treatment of my condition. Thank you for your time and consideration.

Sincerely,
[Patient and Physician signature]

Enclosures
[List additional documents, which may include: denial letter, Letter of Medical Necessity, CEQUA Prescribing Information, medical records, or test results, if available.]

Download this letter at CequaPro.com

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SUGGESTIONS FOR WRITING A TIERING EXCEPTION REQUEST LETTER

This type of letter can be used when CEQUA is on formulary but is on a tier with a high co-pay. Based on medical necessity, a patient can appeal to the plan to consider the drug as if it were a preferred branded agent for that patient in order to reduce the co-pay and help alleviate the financial burden. This may be most useful for patients on plans that require coinsurance.

This letter comes from the patient and is also signed by the physician.

Checklist

- ☐ **Include the patient's name, policy number, date of birth, and, if appropriate, the denial reference number from a previous appeal and the date of denial**
- ☐ **Include the patient's diagnosis**
- ☐ **Include a statement of financial hardship**
- ☐ **List previous therapies, including any OTC medications, if applicable**
- ☐ **Include relevant medical records**
- ☐ **If this is a second- or third-level appeal, include level of appeal, letter of denial, and medical notes in response to denial**
- ☐ **Attach a Letter of Medical Necessity** (see page 7)

SAMPLE TIERING EXCEPTION REQUEST LETTER FOR CEQUA

[Physician letterhead]

[Date]
[Health plan name]
ATTN: [Name of prior authorization department]
[Contact name (if available)]
[Health plan address]
[City, State ZIP]

Re: Tiering Exception Request for CEQUA®

[Patient name]
[Date of birth]
[Insurance ID number]
[Insurance group number]
[Case ID number]
[Date(s) of service]

Dear [Contact Name/Medical Director]:
I am requesting a tier exception for the drug CEQUA® (cyclosporine ophthalmic solution) 0.09% prescribed to me by [insert physician name and specialty] for the diagnosis of dry eye disease [diagnosis code].

[If prior insurance covered CEQUA on a preferred tier, describe this previous coverage.] The initial requested length of tier exception approval is for [insert requested length of initial approval].

Diagnosis and medical history
I have attached the following to support the need for CEQUA over other drugs listed as preferred in my formulary:

- Medical records dating to the initial prescription of CEQUA
- Letter of Medical Necessity from physician
- Test results showing improvement on CEQUA since starting treatment (if available)

I am requesting a tier exception because I am not able to afford the [select co-pay or coinsurance] for CEQUA without financial relief.

Summary
In summary, my physician believes that CEQUA is the best choice for my health and for the treatment of my dry eye disease. My physician may be reached at [Physician phone number] to answer any additional questions or to participate in a peer-to-peer review. Thank you for your time and consideration.

Sincerely,
[Patient and Physician signature]

Enclosures
[List additional documents, which may include: denial letter, Letter of Medical Necessity, CEQUA Prescribing Information, medical records, or test results, if available.]

Download this letter at CequaPro.com

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PA Determinations, Faster.

PA support is available for CEQUA through CoverMyMeds.

Through an online platform and integrations with 75% of electronic health records, more than 750,000 providers use CoverMyMeds to electronically submit PA requests to every health plan.

- Submit requests for any medication and all plans
- Receive faster PA determinations, often in real time
- Automatically renew previously submitted PA requests
- Use the solution at no cost

How to initiate a PA request at the provider office:

01 **Create an account with CoverMyMeds**, or log into your existing account at covermymeds.com.

02 **Shorten time to therapy by creating a PA request** required for treatment.

03 Fill in medical details and then **click one button to electronically submit the request** to any plan for determination.

How to complete a pharmacy initiated request:

01 **Create an account with CoverMyMeds**, or log into your existing account at covermymeds.com.

02 On your CoverMyMeds dashboard, click **"Enter Key."**

03 Enter the access key, as well as **your patient's last name and DOB**, as indicated on the fax. You'll see that most of the request is already completed.

04 Fill in any remaining fields and click **"Send to Plan."**

05 **Mark determinations directly** in your CoverMyMeds account. Once it's determined by the plan, the pharmacy will be notified of the outcome.

Questions? CoverMyMeds can help.
Live support: call 1-866-452-5017 or chat at covermymeds.com
FAQ and webinar registration: go.covermymeds.com/help

ALL OF YOUR COMMERCIAL AND MEDICARE-INSURED PATIENTS CAN GET THE LOWEST PRICE OPTION FOR CEQUA[a,b,c]

PhilRx makes it easy for your practice, too.

How it works

1

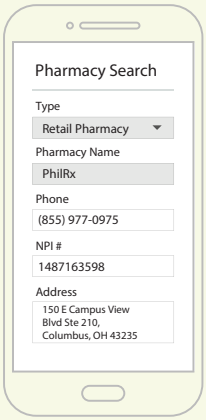
Select "PhilRx" in the EHR's retail pharmacy finder, and let your patient know to expect a text within minutes

If you are having trouble locating PhilRx in the EHR, you can search by the phone number, NPI, or address shown here.

You can also send an Rx via phone (1-855-977-0975, option 1) or fax (1-888-975-0603).

To minimize callbacks, include:

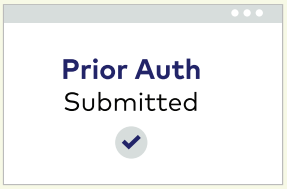
- Patient's phone number, chart notes, prior tried/failed, and ICD-10 in the Rx note to pharmacist
- PhilRx will contact you if patient cannot be reached



2

Submit prior authorization when required

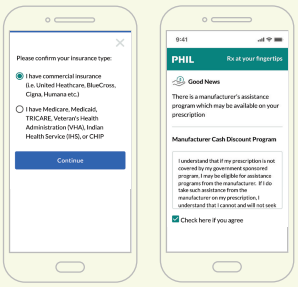
PhilRx will prepopulate the PA form and fax you the CoverMyMeds® key to submit.



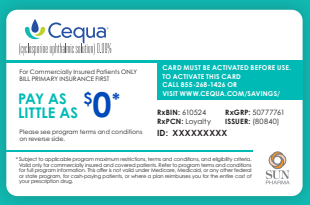
3

Patient's PA status determines savings

Patients must confirm their coverage type to get the lowest possible price based on their insurance and co-pay offer—as little as **$0 co-pay or $89 per month** for each box of CEQUA (60 vials).



For more information, please go to phil.us/healthcare-providers/#faqs or contact PhilRx support team at:
1-855-977-0975 | mdsupport@phil.us | 150 E Campus View Blvd Ste 210, Columbus, OH 43235 | NPI #1487163598



Commercially insured patients can also use a CEQUA Co-pay Card at their favorite pharmacy[a]

Patients with good access and an approved PA may use the CEQUA Co-pay Card in person to receive their lowest cost option (as little as $0 per month) based on their commercial insurance coverage.

[a] Eligibility rules apply. Co-pay cards are only available with commercial insurance. Maximum benefit is $250 per prescription. Not valid for patients paying cash or with government insurance including, but not limited to, Medicare or Medicaid. Patients must reside in the United States, Puerto Rico, Guam or the Virgin Islands. Please read full Terms and Conditions at cequapro.com/savingsterms.

[b] PhilRx is a third-party vendor. By participating in the program, patients acknowledge that they currently meet the eligibility criteria. This program is only available for eligible commercially or Medicare Part D insured patients who are prescribed CEQUA through PhilRx.

[c] Medicare patients may be eligible for manufacturer cash discount pricing in case their plan does not cover CEQUA as a benefit and there is a confirmed PA denial. Subject to patient agreeing to program terms and conditions for opt out.

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Cequa® (cyclosporine ophthalmic solution) 0.09%

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

CEQUA® (cyclosporine ophthalmic solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

Use with Contact Lenses: CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

ADVERSE REACTIONS

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

PM-US-CQA-1059 07/2023

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CEQUA® (cyclosporine ophthalmic solution) 0.09%, for topical ophthalmic use
Initial U.S. Approval: 1983

INDICATIONS AND USAGE

CEQUA ophthalmic solution is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye) (1).

DOSAGE AND ADMINISTRATION

Instill one drop of CEQUA twice daily (approximately 12 hours apart) into each eye. Discard the vial immediately after using in both eyes (2).

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing cyclosporine 0.9 mg/mL (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces (5.1).

ADVERSE REACTIONS

The most common adverse reactions following the use of CEQUA (cyclosporine ophthalmic solution) 0.09% was instillation site pain (22%) and conjunctival hyperemia (6%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-406-7984 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CEQUA ophthalmic solution is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye). (1)

2 DOSAGE AND ADMINISTRATION

Instill one drop of CEQUA twice daily (approximately 12 hours apart) into each eye. CEQUA can be used concomitantly with artificial tears, allowing a 15-minute interval between products. Discard the vial immediately after using in both eyes. (2)

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing cyclosporine 0.9 mg/mL (3)

4 CONTRAINDICATIONS

None. (4)

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Eye Injury and Contamination

To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

5.2 Use with Contact Lenses

CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

6 ADVERSE REACTIONS

6.1 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, 769 subjects received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated subjects were female (83%). The most common adverse reactions reported in greater than 5% of subjects were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of the patients were blepharitis, eye irritation, headache, and urinary tract infection.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of CEQUA administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses [see Data].

Data

Animal Data

Oral administration of cyclosporine oral solution (USP) to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body weight) were approximately 3200 and 21000 times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5 mcg/kg/day, respectively. No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 1800 and 6400 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 4800 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (approximately 1600 times greater than the MRHOD).

8.2 Lactation

Risk Summary

Cyclosporine blood concentrations are low following topical ocular administration of CEQUA *[see Clinical Pharmacology (12.3)]*. There is no information regarding the presence of cyclosporine in human milk following topical administration or on the effects of CEQUA on the breastfed infants and milk production. Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses *[see Pregnancy (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CEQUA and any potential adverse effects on the breast-fed child from cyclosporine.

8.4 Pediatric Use

The safety and efficacy of CEQUA ophthalmic solution have not been established in pediatric patients below the age of 18.

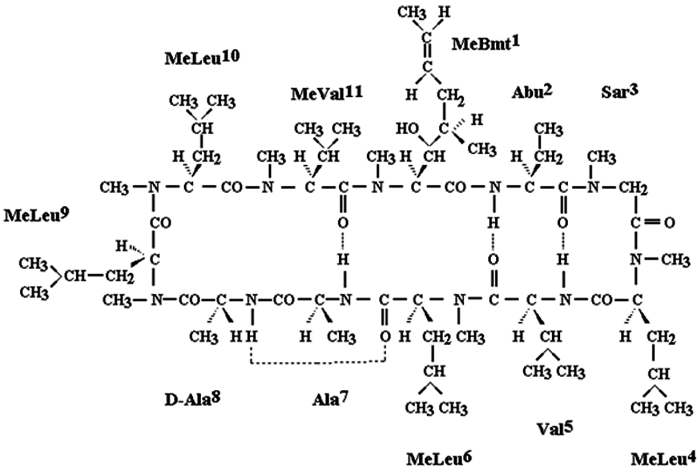
8.5 Geriatric Use

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

11 DESCRIPTION

CEQUA (cyclosporine ophthalmic solution) 0.09% contains a topical calcineurin inhibitor immunosuppressant. Cyclosporine's chemical name is Cyclo[[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl] and it has the following structure:

Structural Formula



Formula: $C_{62}H_{111}N_{11}O_{12}$ Mol. Wt.: 1202.6

Cyclosporine is a white powder that is insoluble in water. CEQUA is supplied as a sterile, clear, colorless ophthalmic solution for topical ophthalmic use. It has an osmolality of 160 to 190 mOsmol/kg and a pH of 6.5-7.2. Each mL of CEQUA contains:

- Active: cyclosporine 0.09%
- Inactives: Polyoxyl 40 Hydrogenated Castor Oil, Octoxynol-40, polyvinylpyrrolidone, sodium phosphate monobasic dihydrate, sodium phosphate dibasic anhydrous, sodium chloride, water for injection, and sodium hydroxide or hydrochloric acid to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cyclosporine is a calcineurin inhibitor immunosuppressant agent when administered systemically. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, topical administration of cyclosporine is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

12.3 Pharmacokinetics

Blood concentrations of cyclosporine after twice daily topical ocular administration of 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 the lower limit of assay quantitation of 0.100 ng/mL (range 0.101 to 0.195 ng/mL) for up to 2 hours after a single dose, and up to 4 hours after multiple doses.

13 NONCLINICAL TOXICOLOGY

13.1 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 55 times higher than the maximum recommended human ophthalmic dose (1.5 mcg/kg/day), normalized to body surface area.

Mutagenesis

In genetic toxicity tests, 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. Cyclosporine was positive in an in vitro sister chromatid exchange (SCE) assay using human lymphocytes.

Impairment of Fertility

Oral administration of cyclosporine to rats for 12 weeks (male) and 2 weeks (female) prior to mating produced no adverse effects on fertility at doses up to 15 mg/kg/day (1620 times higher than the maximum recommended human ophthalmic dose).

14 CLINICAL STUDIES

Two multicenter, randomized, adequate and well-controlled clinical studies treated 1,048 patients with keratoconjunctivitis sicca (NCT # 02254265 and NCT # 02688556). In both studies, compared to vehicle at Day 84, there was a statistically significant ($p<0.01$) higher percentage of eyes with increases of 2 10 mm from baseline in Schirmer wetting. This effect was seen in approximately 17% of CEQUA-treated patients versus approximately 9% of vehicle-treated patients.

Tear Production				
	OTX-101-2014-001		**OTX-101-2016-001**	
	CEQUA N = 152	**Vehicle N = 152**	**CEQUA N = 371**	**Vehicle N = 373**
≥10-mm increase in tear production (% of eyes) at Day 84	16.8%	8.6%	16.6%	9.2%
Difference (95% CI)	8.2% (1.9%, 14.6%)		7.3% (3.3%, 11.3%)	
p-value versus vehicle	<0.01		<0.01	

16 HOW SUPPLIED/STORAGE AND HANDLING

CEQUA ophthalmic solution is packaged in sterile, preservative-free, single-use vials. Each vial contains 0.25 mL fill in a 0.9 mL LDPE vial; 10 vials (2 cards of 5 vials) are packaged in a polyfoil aluminum pouch; 6 pouches are packaged in a box. The entire contents of each box of 60 vials must be dispensed intact.

60 Single-Use Vials 0.25 mL each - NDC 47335-506-96

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

17 PATIENT COUNSELING INFORMATION

Handling the Vial

Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the solution. Advise patients also not to touch the vial tip to their eye to avoid the potential for injury to the eye *[see Warnings and Precautions (5.1)]*.

Use with Contact Lenses

CEQUA 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 solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution *[see Warnings and Precautions (5.2)]*.

Administration

Advise patients that the solution 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.

Rx Only

Manufactured for: Sun Pharmaceutical Industries Limited
By: Laboratoire Unither
1 rue de l'Arquerie
50200 Coutances
France

Cyclosporine (active ingred.) Product of Czech Republic.

Product of France
Distributed by:
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