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## Preventing Leg Cramps

### What drugs are used for leg cramps?

Quinine is the most widely known drug used to treat leg cramps, even though it's not approved for this use by the FDA. Many patients have used quinine and swear by it, but there are downsides. For a small number of people, quinine causes serious side effects like severe bleeding and heart problems. Unfortunately, no one can predict who will have a problem with quinine. You and your healthcare professional should discuss the benefits and risks of quinine before you decide to try it. During this discussion, your doctor may mention other possible serious side effects such as kidney failure, hypersensitivity/skin reactions, vision and hearing problems, muscle pain or weakness, and difficulty breathing.

There are other drugs that are sometimes tried for leg cramps, but there is no good proof that they are helpful. Some people drink tonic water because it contains quinine. But tonic water doesn't have enough quinine in it to help with leg cramps. Pain relievers like acetaminophen (e.g., Tylenol) or ibuprofen (e.g., Advil) can help make you more comfortable, but they don't prevent leg cramps.

### What should I know if I'm already taking quinine?

For starters, if you already take quinine, you may begin to pay more for your medicine very soon. Because of some new FDA requirements, most quinine products will no longer be available by June 2007. Qualaquin, the product that will remain on the market, will cost much more than those quinine products which are being removed from market.

Quinine can cause stomach upset. To lessen the risk of this, take quinine with some food. If you are taking quinine at bedtime, drink a glass of water or milk with it. In some patients, quinine may cause vision changes. Make sure you know how you'll react to this medicine before you drive.

Tell your healthcare professional immediately if you have any of the following problems:

- \* severe stomach cramps or diarrhea
- \* blurry vision
- \* unusual bleeding or bruising
- \* lightheadedness, dizziness, confusion, sweating, or other symptoms of low blood sugar
- \* chest pain or abnormal heart beats
- \* rash, hives, severe itching, trouble breathing
- \* other effects that are concerning to you.

### What can I do to prevent leg cramps from happening?

Often, leg cramps can be prevented with some simple lifestyle changes. By following the suggestions below, the need for medications may be avoided.

\* Stretch your muscles. Stretching your calf muscles at least a couple times a day may work the best. Stand about two to three feet from a wall and put your hands on the wall. Lean towards the wall while keeping your heels on the ground. Try to hold this for ten to thirty seconds and repeat two to four times.

\* Avoid dehydration. Make sure you drink plenty of water to keep from getting dehydrated.

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\* Apply cold or heat. You may want to try taking a warm shower or bath, or try using a heating pad before going to bed.

## **FDA Approves First Quinine Product, Qalaaquin**

### **Qalaaquin**

Mutual Pharmaceutical Company has received Food and Drug Administration (FDA) approval for their quinine product, Qalaaquin. Qalaaquin is available in 324 mg capsules and is approved to treat malaria. It's the first quinine to be evaluated and approved by the FDA, and is priced at an AWP of \$131.25 for 30 tablets. Qalaaquin was approved in August 2005 and was granted seven years of exclusivity as an orphan drug.<sup>1,2</sup>

### **Unapproved Drugs in the U.S.**

Most drugs on the U.S. market have been approved by the FDA. However, some medications, mostly older ones, have not been formally evaluated. Therefore, these are unapproved and technically illegal.<sup>3</sup> There are probably around 200 unapproved prescription ingredients, including phenobarbital, chloral hydrate, oxycodone, and single-ingredient codeine.<sup>4</sup> Before the approval of Qalaaquin, no quinine product had gone through the FDA approval process.

Many healthcare providers are not aware that unapproved prescription products exist in the U.S. market. In fact, 89% of surveyed pharmacists thought all quinine sulfate products dispensed were approved by the FDA.<sup>2</sup>

The FDA has begun to focus on reducing the number of unapproved prescription products. Recently, the FDA required that manufacturers stop production of unapproved products with the antihistamine, carbinoxamine. This decision occurred due to questions of carbinoxamine safety in children under age two.<sup>5</sup> Mikart's carbinoxamine products, which have received FDA approval, are the only products that can still be manufactured.

With the approval of Qalaaquin, the FDA is now pulling unapproved quinine products from the market. In fact, Mutual delayed the launch of Qalaaquin for a year in the hope that the FDA would take this action.<sup>2</sup> Although some unapproved quinine will remain on the shelves for a while, manufacturing must stop by February 13, 2007. Manufacturers have until June 13, 2007 to cease shipping any available supply.<sup>6</sup>

### **Quinine for Leg Cramps**

Although Qalaaquin is approved only for the treatment of malaria, quinine is commonly used off-label to treat leg cramps. Quinine has been used for leg cramps since the 1940s when a small case series showed beneficial results.<sup>7</sup>

Today, many clinicians prescribe quinine for leg cramps because it has the most evidence supporting its use. A meta-analysis showed that quinine reduced the average number of cramps by 3.6 over a four week period (95% CI 2.15-5.05).<sup>8-10</sup> However, it did not affect the duration of the cramps that occurred. In a trial not included in the meta-analysis, quinine led to an average of two fewer cramps over a two-week time frame, compared to placebo.<sup>11</sup>

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Some patients drink tonic water due to its quinine content. But tonic water only contains up to 83 mg of quinine per liter.<sup>12</sup> Therefore, it is probably not beneficial, or harmful, unless a patient drinks several liters a day.

Other medicines such as calcium channel blockers, muscle relaxants, gabapentin, magnesium, and B complex vitamins have been tried for leg cramps with some success.<sup>9</sup> However, studies with these agents are usually small and uncontrolled. Vitamin E is not effective in reducing the frequency of leg cramps. Given the lack of conclusive evidence with alternatives, it's not surprising that quinine is commonly used.

However, quinine is not without its problems. In 1994, the FDA banned OTC quinine. And in 1995, the FDA discouraged using quinine for leg cramps due to its unfavorable risk-to-benefit ratio.<sup>13</sup> Most commonly, quinine can cause GI toxicity. But it's the rare cases of thrombocytopenia that are of greater concern. It's estimated that quinine can dramatically drop platelet counts in one out every of 1,000 to 3,500 patients.<sup>14</sup> Based on published reports, quinine is second only to quinidine in being implicated in the development of thrombocytopenia.<sup>15</sup> While most of quinine's adverse effects are dose-dependent, thrombocytopenia can occur at any dose, and at any time during treatment. Additionally, quinine can cause symptoms of cinchonism including ringing in the ears, visual changes, GI disturbances, CV abnormalities, and deafness. It is these effects that led to the FDA's decision and recommendation.

## **Conclusion**

Qalaaquin is the only FDA-approved quinine product on the market. Manufacturers of other quinine products, will have to quit making their products by February 13, 2007 and stop shipping by June 13, 2007. Therefore it will be difficult for you to restock the less expensive, unapproved products. Start telling your patients now about this change in availability, and prepare them for possible increases in cost.

If patients are using Qalaaquin or other quinine products for leg cramps, make sure they understand the risks and benefits of therapy. Recommend nonpharmacologic therapies, such as stretching the calf muscles or using a heating pad before bed as safe alternatives.

Project Leader in preparation of this Detail-Document: Melissa M. Blair, PharmD, FCCP, BCPS, CDE, Assistant Editor

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## **Legal Issues Surrounding Use of Quinine**

### **Unapproved Quinine**

The recent launch of Qualaquin (quinine sulfate) is bringing up questions about unapproved drugs. For a variety of historical reasons, some drugs, mostly older products, continue to be marketed in the United States without required FDA approval.

The FDA will eventually require all of these drugs to prove their safety and efficacy. This will take years. Meanwhile, most of the drugs have been allowed to remain on the market if there are no immediate concerns of safety or efficacy problems. This has been the case for quinine.

But now that there's an FDA-approved formulation of quinine on the market, the FDA has given all other quinine manufacturers until February 13, 2007 to cease production of new product. Manufacturers have until June 13, 2007 before they are required to ship any remaining quinine products.

Meanwhile, here are answers to some questions that might come up regarding unapproved quinine products remaining on shelves.

#### **Is it illegal to dispense unapproved quinine?**

Any FDA enforcement on unapproved drugs targets the manufacturers...not pharmacists or physicians. It is not the FDA's intention to interfere with medical or pharmacy practice. The pharmacist or physician should use their professional judgment on what is in the best interest of the patient.

In the case of quinine, legal experts contend that since given a choice, it's best to go with an approved product over an unapproved product. However, if an unapproved quinine product is selected, the patient should be notified of any potential risk with taking an unapproved drug.

#### **Is unapproved quinine unsafe?**

At this time, there is no indication that any of the marketed prescription quinine products are less safe or effective than Qualaquin. However, you should keep in mind that the product labeling of these unapproved products is not as complete as Qualaquin's, especially in regards to warnings, contraindications, or drug interactions.

#### **Can you substitute Qualaquin with a non-FDA-approved quinine sulfate?**

There is no AB-rated equivalent for Qualaquin. Therefore, it would be a violation of some state's substitution laws to use a different quinine product in place of Qualaquin without the prescriber's approval.

Is it considered health fraud for a pharmacy to submit a claim to a third party payer for reimbursement of an unapproved quinine sulfate?

A claim for reimbursement that properly discloses the NDC of the product actually used should not give rise to a fraud claim. It could possibly result in refusal by the third party to pay for the claim. If the pharmacist uses the Qualaquin NDC but dispenses something else, then that would be fraud.

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## **Quinine for Leg Cramps**

Quinine sulfate is commonly used off-label to treat leg cramps. But quinine products are only approved for malaria. The package insert for Qualaquin specifically says NOT to use quinine for leg cramps. The FDA discourages use of quinine for leg cramps due to its unfavorable risk-to-benefit ratio. Quinine can cause severe thrombocytopenia, cinchonism, visual disturbances, cardiac arrhythmias, and death. Most of quinine's adverse effects are dose-dependent, but thrombocytopenia can occur at any dose, and at any time during treatment.

### **What is my legal liability if I prescribe quinine for leg cramps?**

It is not illegal to prescribe a drug for off-label use. However, since package labeling specifically says not to use quinine for leg cramps, this could possibly increase your legal liability if a patient were to experience an adverse event as a result of receiving quinine for this use.

Before prescribing quinine for treating leg cramps, the patient should be notified of all risks associated with its use and be informed of other alternatives for treating leg cramps. If a patient chooses to take quinine for leg cramps, legal experts recommend documenting, preferably with the patient's signature, that the patient agreed to treatment despite known risks associated with quinine.

### **What is my legal liability if I dispense quinine for leg cramps?**

It is not illegal for a physician to prescribe a drug for off-label use. It is up to the prescriber's discretion as to whether a patient may benefit from the off-label use of a drug. Pharmacists should not be liable for any adverse events that occur as the result of a drug being used off-label.

However, since package labeling specifically says not to use quinine for leg cramps, pharmacists should make sure patients are aware of this fact and are counseled on risks associated with quinine therapy.

**Note to Prescribers:** Off-label use of quinine now presents some unique challenges. Currently, the only quinine drug approved by the FDA is not indicated for leg cramps. The FDA cites an unfavorable risk/benefit analysis and specifically warns against the use of quinine for leg cramps. It is legal to prescribe quinine for off-label uses, but precautions should be taken to ensure patient awareness of possible risks or complications and prescribers should consider obtaining and documenting patient consent.

Prescribing quinine off-label poses serious medical and legal concerns. This sample form is intended for informational use only and does not constitute or attempt to provide legal advice. As individual state laws vary greatly, each practitioner is encouraged to seek advice of counsel as to the applicability of this sample form and specific issues contained within.

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**Sample Informed Consent Form For Off-Label Quinine Use**

Once a medication is approved by the Food and Drug Administration (FDA) for marketing, the drug manufacturer produces a label to describe its purpose and use. A practitioner may prescribe FDA-approved medications for use or in a treatment regimen or a particular patient that is not included in approved labeling. This is called "off-label" use. Practitioners may use their professional judgment by prescribing "off-label" uses for medications in any way they believe will best serve the patient. All medications including those considered to be "off-label," involve medical risks. Patients must be informed of these medical risks.

Insert PROPOSED USE/PURPOSE for off-label use of quinine (For example, quinine is prescribed to treat leg cramps. The use of quinine to treat leg cramps is not within the indications approved for the medication by the FDA.)

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Insert any ALTERNATIVES to off-label use of quinine (List, if any, available and appropriate medical alternatives or if no appropriate alternative exists, that should be noted. Include the reason the practitioner believes quinine is an appropriate medication in this case.)

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Insert known RISK/COMPLICATIONS/SIDE EFFECTS of off-label use of quinine

Note: The FDA has issued a warning against using quinine for leg cramps.

(For example) This medication is contraindicated in patients with prolonged QT interval, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, myasthenia gravis, optic neuritis, or in patients with hypersensitivity to quinine, quinidine, or mefloquine. Quinine may lead to serious hypersensitivity reactions affecting the skin, blood, liver, kidneys, and respiratory systems. Other rare, but life threatening effects may include cardiac arrhythmias or thrombocytopenia. Quinine can cause adverse effects including but not limited to: Fever, chills, sweating, flushing, headache, altered mental status, tremors, seizures, nausea, vomiting, diarrhea, abdominal pain, chest pain, hypotension, cardiac rate and rhythm disturbances, rash, dermatitis, drug reactions, vasculitis, thrombocytopenia, neutropenia, asthma, dyspnea, pulmonary edema, hypoglycemia, hemoglobinuria, various stages of renal failure, myalgias, weakness, jaundice, abnormal LFTs, tinnitus, vertigo, various vision abnormalities including blindness, and deafness. (Include any other relevant risks/side effects/complications.)

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I have been informed of and understand that the drug quinine was approved by the FDA only for malaria treatment and that it has not been approved for leg cramps. My provider has discussed with me and I understand the known potential risks, complications and side effects associated with off-label use of quinine, and the fact that the FDA has warned against the use of quinine for leg cramps. I acknowledge that there may be other risks unknown at this time and that the complete long-term effects, complications, and risks of this medication may not be known. I am willing to accept these risks associated with the "off-label" use of this medication. I have been advised and understand that I am free to withhold or withdraw consent at any time to the prescribing, administering or furnishing of the medication.

\_\_\_\_\_  
Patient Signature

\_\_\_\_\_  
Date



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Provider Signature

Date

## **Informed Consent for Off-Label Drug Use: Things to Consider**

### **What is an Informed Consent Form?**

An informed consent form documents discussions between practitioners and patients regarding off-label quinine use, the medical risks and benefits involved, and the alternate modes of treatment available. Practitioners should never use an informed consent form in place of an actual patient discussion.

### **Here are some guidelines to follow when an informed consent form is used:**

1. Discuss the information contained in the informed consent form with the patient prior to obtaining the patient's signature.
2. A patient education handout on the drug or treatment may also be provided to the patient further explaining the purpose of the treatment, medical risks and benefits.
3. Once the patient has acknowledged that he or she understands the information and signs the informed consent form, keep the original signed copy in the patient's chart and provide patients with a copy of the signed form to take with them.
4. Notate the patient's chart that he or she was provided with a copy of the form, as well as provided a copy of the patient education handout if relevant.
5. Invite patients to contact you if they have any further questions at a later date or time.

When discussing the possible medical risks, complications and side effects of quinine with patients, it is not always necessary to inform patients of every single known risk; however slight or immaterial.<sup>1</sup> It is a good idea to inform each patient that quinine is unapproved for nocturnal leg cramps and explain probability of side effects and the serious and significant risks each individual patient faces.<sup>2</sup>

### **Are Informed Consent Forms required when prescribing quinine for leg cramps?**

Currently, the answer is no. Federal law does not presently require physicians to obtain a signed informed consent form merely because they are prescribing an off-label drug or treatment.<sup>3</sup> However, physicians who prescribe medications for off-label uses MAY subject themselves to potentially increased legal exposure.<sup>4</sup> One way practitioners may be able to reduce their liability and malpractice exposure is to emphasize to the patient that the proposed treatment involves unapproved, off-label, use of the medication and to consistently document patient informed consent to the treatment.<sup>5</sup>

Some states are moving closer to requiring the use of informed consent forms for any off-label use of a drug or treatment. Legislation was introduced in California in early 2006 that could, if passed, eventually require practitioners to obtain informed consent from a patient before prescribing, administering, or furnishing a prescription medication for an off-label use.<sup>6</sup>

### **Benefits and Limitations of Informed Consent Forms**

An informed consent form should not be considered a complete shield from legal exposure. Every practitioner still faces medical and legal risks when prescribing an off-label medical treatment. This risk is greater when the particular drug or treatment is expressly unapproved of by the FDA. A struggle of power exists as the FDA remains unable



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to regulate the practice of medicine, yet retains control over the labeling of approved drugs, including approved and unapproved uses. Such a dilemma exists now with quinine.

Properly signed informed consent forms can help practitioners prove that material information relevant to the patient's decision was discussed and provided to the patient.<sup>7</sup> This includes information you believe would be significant to a reasonable person in the patient's position.<sup>8</sup> Signed informed consent forms become part of the patient's medical record and may provide evidence in legal proceedings that the patient was notified of the status of the drug, informed of the risks, and consented to acceptance of the risks involved with the treatment.<sup>9</sup>

However, information contained in package inserts also carries legal weight and may be used to argue the standard of care regarding a drug's proper use.<sup>10</sup> Legal experts acknowledge that if a particular drug use is contraindicated, the risk associated with legal liability is greater.<sup>11</sup> On the other hand, off-label prescribing practices, if based on reasonable medical evidence, done in good faith and in the best interests of the patient, conform to accepted professional standards so long as practitioners demonstrate the same judgment and prudence as exercised in medical practice in general.<sup>12</sup>

Another limitation to keep in mind with informed consent forms is that the informed consent doctrine varies from state to state. It is best to discuss the issues present in your practice and the use of an informed consent form with counsel familiar with your state laws in order to adapt any informed consent form or procedure to your particular issues and needs.

Project Leader in preparation of this Detail-Document: Jessica Tomlinson, JD, Medical Malpractice Defense Attorney and member Prescriber's Letter editorial team.

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