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Capsaicin 8% Topical System: An Advancement in the Treatment of Painful Diabetic Peripheral Neuropathy of the Feet

Announcer:
Welcome to ReachMD.

This medical industry feature titled, "Capsaicin 8% Topical System: An Advancement in the Treatment of Painful Diabetic Peripheral Neuropathy of the Feet", is sponsored by Averitas Pharma.

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QUTENZA® (capsaicin) 8% topical system is indicated in adults for the treatment of neuropathic pain associated with postherpetic neuralgia (PHN) and for neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet.

Do not dispense QUTENZA to patients for self-administration or handling. Only physicians or healthcare professionals under the close supervision of a physician are to administer and handle QUTENZA.

Aerosolization of capsaicin can occur upon rapid removal of QUTENZA. Therefore, remove QUTENZA gently and slowly by rolling the adhesive side inward. Inhalation of airborne capsaicin can result in coughing or sneezing. Administer QUTENZA in a well-ventilated treatment area. Provide supportive medical care if shortness of breath develops. If irritation of airways occurs, remove the affected individual from the vicinity of QUTENZA. If respiratory irritation worsens or does not resolve, do not re-expose the affected healthcare professional or patient to QUTENZA.

If skin not intended to be treated is exposed to QUTENZA, apply Cleansing Gel for one minute and wipe off with dry gauze. After the Cleansing Gel has been wiped off, wash the area with soap and water.

Patients may experience substantial procedural pain and burning upon application and following removal of QUTENZA. Prepare to treat acute pain during and following the application procedure with local cooling (such as a cold pack) and/or appropriate analgesic medication.

When administering QUTENZA, it is important to follow the procedures in the Important Dosage and Administration Instructions in the US Prescribing Information.

Please listen to Select Safety Information at the end of this podcast and for full Important Safety Information visit Qutenza.com.

Here's your host Dr. David M. Simpson.

Dr. Simpson:
Well, hello and welcome. I'm Dr. David M. Simpson, principal investigator of the STEP trial evaluating the efficacy of Qutenza for painful diabetic neuropathy of the feet. Joining me to talk about an advancement in the treatment of painful diabetic peripheral neuropathy of the feet is Rory Abrams, an expert neurologist and author of a recent high-concentration capsaicin 8% topical system review paper. Dr. Abrams, was one of my trainees and now we work together at Mt. Sinai. Dr. Abrams and I will provide an in-depth overview of the STEP study design and data supporting the use of Qutenza for treating painful diabetic peripheral neuropathy, or PDPN of the feet. Welcome, Rory.

Dr. Abrams:

Hello, Dr. Simpson, thank you for having me, today. I'm really looking forward to speaking about the data supporting the use of Qutenza for painful diabetic peripheral neuropathy. The STEP study was designed to investigate the efficacy and safety of a single application of Qutenza for patients with diabetic peripheral neuropathy of the feet. I was hoping, Dr. Simpson, if you could provide some of the STEP study design details for our audience?

Dr. Simpson:
Sure. My pleasure. Of course, the STEP study was a phase 3, randomized, double-blind, placebo-controlled, multi-centered trial. The patients that were randomized included type 1 and type 2 diabetics. Hemoglobin A1C was required to be 11 or less. Concomitant pain medications were permitted at stable doses and the primary efficacy endpoint was the so-called numeric pain rating scale, the so-called NPRS, which required a mean of greater or equal to 4 for entry into the study. Now, patients were randomized to receive a single treatment with the capsaicin 8% topical system or an identical placebo patch that contained no capsaicin to the painful areas of the feet. As I've mentioned, the primary efficacy endpoint, the NPRS average daily pain score was assessed over the previous 24 hours and that is, in fact, a commonly used and validated outcome measure in many of these types of pain studies. As we know from other clinical trials and several authors, a pain reduction of 30 to 50% is considered clinically meaningful.

Rory, can you please discuss how that would be determined in the STEP study and provide some insights as to what this 30% reduction in the NPRS means for your patients with painful diabetic neuropathy?

Dr. Abrams:
For some of the patients that I'm currently treating, a 30% reduction in their pain has a big impact on their overall quality of life. Sometimes the pain in their feet is so severe that patients will limit the amount of water that they drink just to avoid having to walk frequently to the bathroom. A 30% reduction in pain, for example, could mean that these patients have more freedom and more independence in their everyday lives and get a better night's sleep, as well.

So, Dr. Simpson, I was curious about how does one actively go about blinding a study with a patch that has discernable side effects?

Dr. Simpson:
Well, that is a real challenge and,in this trial, a different approach was taken and that is using a true inactive placebo. Now, in order to do all possible to maintain the blinding, measures were taken and specifically, physicians or nurses who conducted the clinical assessments and had responsibility for recording efficacy and safety data were independent from those carrying out the patch application and perhaps having access to the dermal assessments.

I'd also like to take a closer look at the primary endpoint results showing the mean percentage change from baseline in average daily pain scores throughout the study. There was a modest and statistically significant reduction in average daily pain from baseline to between weeks 2 through 8 in the capsaicin group. The results were about a 30% improvement compared to placebo, which had only a 22% improvement. Analysis of change in average daily pain score from baseline became apparent at week 2 and was maintained throughout the end of the study, week 12. These findings were of similar magnitude to the effects of other treatments with known efficacy in neuropathic pain; agents such as anti-convulsants and anti-depressants, for example.

The median time to onset of pain or relief for Qutenza, 19 days is faster than for treatments commonly prescribed in painful diabetic neuropathy. For example, pregabalin has a 36 day onset of pain relief. This observation helped support the use and recommendation of topical therapies for the treatment of peripheral neuropathic pain, particularly with the absence in systemic adverse effects.

An interesting finding in this study was the duration of response after treatment in the placebo group. Rory, were you surprised by the magnitude of the placebo response?

Dr. Abrams:
I think that the observed placebo response was not unexpected because in this study, patients in the capsaicin and the placebo groups both underwent a physical patch application. I think that experience of seeing the treatment application can induce a very large placebo response. Although a placebo patch without capsaicin was used in this study, the placebo response was also maintained for the full 12 weeks. This was an interesting finding in this study and is actually in line with recent analyses of placebo response in peripheral neuropathic pain studies, as you mentioned. However, the relative difference in pain reduction between the capsaicin group and the placebo group was 36% and well within the boundary of statistical significance in the primary analysis. I think it should also be noted that the efficacy was demonstrated regardless of concomitant use of other medications in both treatment groups.

Dr. Simpson:
Well, thanks, Rory. And, in fact, you, you highlight the challenge of pain studies in general. And that is the very variable and, frankly, unpredictable magnitude of placebo response. That's one of the reason that so many pain studies fail, um, because of an excess placebo response and, as one might imagine, when one is doing this physical application of the patch to the patient, that certainly may

engender a significant placebo response. But in spite of that, the study was successful in separating efficacy of capsaicin from the placebo.

And it's important, I think, for clinicians and patients to understand that virtually none of the treatments we're providing obliterate pain to 0. And so, whereas 30 to 50% may, on its face, seem modest, in fact, as you indicate, it can make major clinical differences for patients' quality of life.

In the STEP study, efficacy was demonstrated regardless of concomitant use of other medications. About half of the patients in this study were taking concomitant medications, including, anti-convulsants, non-selective serotonin reuptake inhibitors, anti-depressants, or opioids at baseline and were required to keep dosing stably throughout the duration of the study. Now, as I previously mentioned, the median time to treatment response with the capsaicin topical system was 19 days compared with 72 days with the placebo group. Now, in comparison to previously-published postherpetic neuralgia data, the time to treatment response occurred approximately 1 week later in the painful diabetic neuropathy patients.

Now, Rory, from your capsaicin research, how would you explain the difference in time to treatment response between postherpetic neuralgia and painful diabetic neuropathy patient populations?

Dr. Abrams:
I think that's a really great question. I think, although further research is needed to determine the exact reason for this difference, there were several factors that may help explain this observation. For one, patients with painful diabetic neuropathy may have a relatively reduced number of the transient vanilloid subtype 1 receptors.

Ultimately, capsaicin is understood to lead to defunctionalization of surviving sensory neurofibers, including activation of voltage-gated sodium channels and temporary reduction of epidermal and dermal nerve-fiber terminals, which leads to decreased pain transmission. And so, while this receptor, also known as TRPV1 is a prerequisite for the efficacy of capsaicin, the latter is mainly driven by an over-expression and distribution of voltage-gated sodium channels and therefore a reduction of TRPV1 expressing nociceptors and/or a reduction of expression of the TRPV1 receptors on these nerve fibers do not preclude a therapeutic effect of capsaicin.

And I think one additional point is that patients with painful diabetic neuropathy are often treated with more than one oral medication. And while we consider many of these conventional medications used to be effective, often times, patients don't report a satisfactory pain response for weeks, months, or maybe ever.

And I think the bigger issue is that it's often challenging to ever titrate the dosage of these systemic medications to a clearly-effective level and I frequently find my patients use of these medications limited by tolerability or other medical factors. And I'm just curious is that something that you've seen, as well?

Dr. Simpson:
Absolutely, we recognize that there's as much art to science in caring for patients. Of course, the goal is to reduce pain but perhaps even more importantly to improve quality of life. And we use not just a single approach but often a multi-modal approach. We live in an era of what some call rational poly-pharmacy, using combinations of agents, different mechanisms of action, different administration techniques to ultimately result in the best possible outcome, often combining pharmacologic and non-pharmacologic therapies.

Now, historically, there were concerns about using capsaicin in patients with diabetic neuropathy, partly based on the concern of a reduced rate of nerve regeneration in patients with diabetes with or without evidence of neuropathy, which may indicate abnormalities in peripheral nerve function, even before symptoms develop.

Rory, do you have any concerns about the use of an agent like capsaicin with its known effect on epidermal nerve fibers in individuals who already have potential nerve fiber pathology?

Dr. Abrams:
So, what we have seen in terms of both safety and tolerability has actually been fairly consistent across multiple clinical trials, including the STEP study. Since this is a topical application system, there are few systemic adverse effects. In the STEP study, the skin application sites were pre-treated with local anesthetics to limit this discomfort and the patients were allowed to use additional oral pain medications, if needed. I think my biggest concern, however, is ensuring that there are no apparent diabetic skin ulcerations or other lesions to the skin. And I think one other point one might consider is that the capsaicin patch may lead to a further loss of sensory function in these patients. This is based on conceptually the concern had been that if capsaicin leads to nociceptor defunctionalization, might it be expected that patients with diabetes develop worsening sensory responses after treatment.

In the STEP trial, the majority of patients had no changes in sensory perception and reflex testing following patch application. And in fact, a small proportion of patients experienced improvement in their sensory responses. since this was only a 12 week study, there

was also a separate open label study that assessed the long-term safety and tolerability with repeat patch applications, along with the standard of care oral medications versus those standard of care medications alone over a period of 52 weeks in patients who had painful diabetic neuropathy.

Dr. Simpson:
Well, Rory, I think you've highlighted the very reassuring data that have emerged both from the double-blind and the long-term open label studies concerning safety. Certainly a theoretical concern with this agent but one that has not born out in terms of any concerns of worsening sensory function in this vulnerable population

The types of side effects one generally encounters with the capsaicin include application site reaction. The most frequent side effect being application site pain. There's a sense of burning pain in the extremity at the application site but these are generally managed with local measures, including cooling and they fairly rapidly resolve. Importantly, there were no drug-related serious treatment emergent adverse effects.

Now, in my own clinic, as I mentioned earlier, we generally use an agent like Qutenza as add-on therapy in patients who've usually taken other pain medications; often first line agents, like anti-convulsants or anti-depressants. And then we bring in Qutenza as yet another agent in our armamentarium to improve benefit.

So, Rory, to conclude, where do you see Qutenza fitting into your treatment algorithm for patients with confirmed painful diabetic peripheral neuropathy?

Dr. Abrams:
Before being referred to a specialist, many patients with painful diabetic neuropathy will have already been prescribed one or more of these conventional medications. So, at that point, I think it would be reasonable to discuss Qutenza within their treatment plan. And I actually believe most patients would be excited to try an additional therapy because unfortunately, the current outlook on treatment options for painful diabetic neuropathy is less than optimistic. The therapies are limited, the current options are not always effective and the addition of something topical may be encouraging for patients.

I think that all these patients should be counseled that the capsaicin 8% topical system can provide improvement for pain relief. It's generally well-tolerated. It may improve their sleep quality. And it has no drug/drug interactions and it does not contribute to worsening sensory function in the lower extremities. And while the expected efficacy may be similar to some of these more conventionally-prescribed oral medication options, there's actually a lack of chronic systemic adverse effects seen compared with those agents where that's often a challenge that we have to deal with.

Dr. Simpson:
Well, thank you, Rory for that very nice perspective. With that, I'd like to thank my colleague, Dr. Rory Abrams for joining me, today in discussing an exciting advancement in the treatment of painful diabetic peripheral neuropathy with our ReachMD audience.

Announcer:
INDICATION

QUTENZA® (capsaicin) 8% topical system is indicated in adults for the treatment of neuropathic pain associated with postherpetic neuralgia (PHN) and for neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet.

IMPORTANT SAFETY INFORMATION

Do not dispense QUTENZA to patients for self-administration or handling. Only physicians or healthcare professionals under the close supervision of a physician are to administer and handle QUTENZA.

When administering QUTENZA, it is important to follow the procedures in the Important Dosage and Administration Instructions in the US Prescribing Information.

In patients treated for neuropathic pain associated with diabetic peripheral neuropathy of the feet, a careful examination of the feet should be undertaken prior to each application of QUTENZA to detect skin lesions related to underlying neuropathy or vascular insufficiency.

Contraindications

None

Warnings and Precautions

- Unintended exposure to capsaicin can cause severe irritation of eyes, mucous membranes, respiratory tract, and skin in healthcare professionals, patients, and others. Healthcare professionals should ensure that the recommended procedures and protective measures are used when administering QUTENZA.
- For healthcare professionals, wear nitrile gloves when administering QUTENZA and avoid unnecessary contact with items in the room, including items that the patient may later have contact with, such as horizontal surfaces and bedsheets.
- Do not apply QUTENZA to the patient's face, eyes, mouth, nose, or scalp to avoid risk of exposure to eyes or mucous membranes. Accidental exposure to the eyes and mucous membranes can occur from touching QUTENZA, or items exposed to capsaicin, and then touching the eyes and mucous membranes. If irritation of eyes or mucous membranes occurs, flush eyes and mucous membranes with cool water. Remove the affected individual (healthcare professional or patient) from the vicinity of QUTENZA.
- Aerosolization of capsaicin can occur upon rapid removal of QUTENZA. Therefore, remove QUTENZA gently and slowly by rolling the adhesive side inward. Inhalation of airborne capsaicin can result in coughing or sneezing. Administer QUTENZA in a well-ventilated treatment area. Provide supportive medical care if shortness of breath develops. If irritation of airways occurs, remove the affected individual from the vicinity of QUTENZA. If respiratory irritation worsens or does not resolve, do not re-expose the affected healthcare professional or patient to QUTENZA.
- If skin not intended to be treated is exposed to QUTENZA, apply Cleansing Gel for one minute and wipe off with dry gauze. After the Cleansing Gel has been wiped off, wash the area with soap and water.
- Patients may experience substantial procedural pain and burning upon application and following removal of QUTENZA. Prepare to treat acute pain during and following the application procedure with local cooling (such as a cold pack) and/or appropriate analgesic medication.
- Transient increases in blood pressure may occur during and shortly after QUTENZA treatment. Blood pressure changes were associated with treatment-related increases in pain. Monitor blood pressure and provide adequate support for treatment-related pain. Patients with unstable or poorly controlled hypertension, or a recent history of cardiovascular or cerebrovascular events, may be at an increased risk of adverse cardiovascular effects. Consider these factors prior to initiating QUTENZA treatment.
- Reductions in sensory function have been reported following administration of QUTENZA. Decreases in sensory function are generally minor and temporary. All patients with pre-existing sensory deficits should be clinically assessed for signs of sensory deterioration or loss prior to each application of QUTENZA. If sensory deterioration or loss is detected, or pre-existing sensory deficit worsens, continued use of QUTENZA treatment should be reconsidered.

Adverse Reactions

In all controlled clinical trials, adverse reactions occurring in ≥5% of patients in the QUTENZA group, and at an incidence at least 1% greater than in the control group, were application site erythema, application site pain, and application site pruritus.

Adverse Event Reporting

Physicians, other healthcare professionals, and patients are encouraged to voluntarily report adverse events involving drugs or medical devices. To make a report you can:

- In the US, visit www.fda.gov/medwatch or call 1-800-FDA-1088; or
- For QUTENZA, you may also call 1-877-900-6479 and select option 1, or press zero on your keypad to talk to an operator to direct your call.

Please visit Qutenza.com to view the full Prescribing Information, including Patient Information.

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