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Addressing Questions Regarding Long-Term Treatment with a TPRV1 Agonist for Painful DPN of the Feet

Announcer:
Welcome to ReachMD.

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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 Simpson. Joining me to talk about long-term safety and tolerability data regarding the high-concentration capsaicin 8% topical system for the treatment of painful diabetic peripheral neuropathy of the feet is Professor Serge Perrot. Professor Perrot is an expert in the clinical development and research advancements surrounding Qutenza. He has been an investigator for multiple Qutenza studies and is here to provide an in-depth overview of the study design, the safety of repeat applications, and patient tolerability of Qutenza for treating painful diabetic peripheral neuropathy of the feet. Welcome, Serge.

Professor Perrot:
Hello, Dr. Simpson. Thank you for having me, today. It's a pleasure to participate with this interview and to discuss together the safety of

repeated application of capsaicin high-concentration in diabetic painful neuropathy.

Dr. Simpson:
Serge, can you tell me a little bit about your diabetic patient population? What options have you found to be most successful in treating painful diabetic neuropathy of the feet?

Professor Perrot:
My clinic, in fact, is in paris, in a pain center and most of my diabetic patients are referred by their endocrinologists and GPs. All patients report discomfort in their feet that is not adequately managed by systemic medication, mainly antidepressants and anticonvulsants. Patients are mainly patients with type 2 diabetes and there are around 50 to 60-year-old, frequently obese with lots of comorbidities. All these patients have tried several lines of analgesics, some specific for neuropathy pain without significant improvement and many of them have experienced important side effects and many of them also have poor compliance with these treatments. In fact, diabetes is a complex disease where patients have to take care of many organs: eyes, feet, heart, kidneys and pain in many cases is a symptom that is not taken into account by the physicians and other healthcare professionals. In fact, it takes around four to six years for the physicians to ask for specific management at our pain center.

Dr. Simpson:
Well thank you, Serge. In the pain management field, we recognize that there's both art and science in caring for patients. Of course, the goal is to reduce pain, but even more importantly to improve quality of life. And it's not just a single approach, but often multi-modal approach to therapy. We live in an era of 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 therapy. I generally use Qutenza as the first add-on therapy in patients who have taken other pain medications, often first-line agents like anticonvulsants or antidepressants.

In another episode, we reviewed the STEP study, which demonstrated that a single treatment with the high-concentration capsaicin 8% topical system can provide significant improvements in pain relief, versus a placebo patch in patients with painful diabetic peripheral neuropathy of the feet, over a period of twelve weeks and was well-tolerated with no sensory deterioration. The PACE trial was designed to evaluate the long-term safety and tolerability of Qutenza over 52 weeks. Since pain can sometimes return a few months after the first Qutenza application, we want to determine the safety of repeated use of Qutenza for diabetic patients.

Serge, would you mind walking the audience through some of the main study design details of the PACE trial?

Professor Perrot:
Of course, David. The PACE study was the first open-label evaluation of the long-term safety and durability of Qutenza compared with the treatment of Qutenza plus the standard of care to standard of care alone over fifty-two weeks. Patients were randomized to a thirty-minute application of Qutenza plus standard of care, a sixty-minute application of Qutenza plus standard of care, or standard of care alone. Qutenza retreatment could occur at both scheduled and unscheduled clinic visits at the instigator's discretion, but only after at least eight weeks have elapsed since the last treatment. Patients could not receive more than seven applications of Qutenza during the study or a maximum of once every other month. Although patients and investigators were un-blinded throughout the study, physicians assessing neurological function were blinded to treatment and not involved in the study in any other manner.

Dr. Simpson:
Well, thanks, Serge, for highlighting those details. I'd like to mention to our ReachMD audience that in the U.S. the FDA-approved and label-specified application time for Qutenza in the management of painful diabetic neuropathy is thirty-minutes. Thus, only information from the thirty-minute applications of Qutenza plus standard of care study arm and the standard of care study arm will be presented. Also note that in the U.S. the approved label-specified repeat application interval is twelve weeks, while in the study, reapplication could, at the patient and provider's discretion, be done as frequently as every eight weeks for a maximum of seven applications.

As many of us know, diabetic peripheral neuropathy is characterized by damage to large, myelinated fibers and small, thinly-myelinated fibers. Small fiber damage may occur first in the lower limb and precede large fiber damage, making it an early indicator of diabetic neuropathy. For this reason, the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy was chosen as the primary endpoint, since it's validated and comprehensive patient-reported outcome that captures the entire impact of nerve dysfunction on quality of life in diabetic neuropathy. It was used to assess any functional consequences associated with potentially deleterious effects of capsaicin treatment on peripheral nerve endings in patients with painful diabetic neuropathy. From baseline to end of study, the primary endpoint revealed no deterioration in the QOL score in the Qutenza group, plus standard of care compared with standard of care alone. Patients who received the maximum number of seven capsaicin treatments also had no deterioration in the QOL score when compared with the overall population.

Serge, prior to the PACE trial, did you have any concerns administering repeat applications of Qutenza to patients with painful diabetic neuropathy?

Professor Perrot:
Of course, David. In fact, capsaicin is a highly selective agonist for the TRPV1 receptor and it causes an initial desensitization and defunctionalization of hyperactive nociceptors in the skin. Over the course of several months, there may be a gradual re-emergence of the painful neuropathy thought to be due to the reactivation of TRPV1 expressing neurofibers in the treatment area. There were previously some concerns regarding the use of capsaicin for diabetic patients where the severity of neuropathy and reduction of intraepidermal nerve fiber density progressed with the duration of disease. Initially, diabetic neuropathy was excluded for safety reasons. Furthermore, local application of Qutenza provides minimal systemic absorption without drug/drug interactions or those adjustments in elderly patients or patients with renal or hepatic impairment. Only some diabetic patients with feet skin alterations are not candidates for high-concentration capsaicin due to the risk of induced pain when one applied capsaicin high-concentration on disruptive skin.

Dr. Simpson:
Well, I agree with you, Serge. There was theoretical concern with this agent, but the safety and tolerability profile of Qutenza has been extremely favorable and certainly in comparison to oral systemic agents with a wide variety of generalized side effects.

Diabetic peripheral neuropathy often progresses from initial functional changes to late, poorly-reversible structural changes. Therefore, it was important to determine that high-concentration capsaicin had no negative impact on peripheral nerve endings in patients with painful diabetic peripheral neuropathy of the feet.

Serge, can you go into more detail regarding the sensory and reflex data from the pace trial and provide insight as to why this is so important for patients with diabetic neuropathy.

Professor Perrot:
Yes, David. In fact, the PACE study demonstrated that Qutenza had no negative impact on sensory perception and reflex testing and the majority of patients had no change from baseline to the end of the study. In patients who received maximum of seven treatments, there was also no negative impact from baseline to the end of the study. I'd like to, also to mention that the patient tolerated the application very well. The difference in patient-reported adverse events between the capsaicin plus standard of care groups and standard of care alone was primarily due to the reporting of application site pain or erythema in the capsaicin groups, which were predominantly mild or moderate. From my experience, the best way to alleviate application site discomfort, is to use a cold pack and place it over the application site and give explanation to the patients. This helps counteract the burning sensation and patient's adverse reactions.

Dr. Simpson:
Well thank you, Serge. I think you addressed some great points regarding the safety of the Qutenza topical system for diabetic patients. To summarize for our audience, in patients with painful diabetic peripheral neuropathy, the long-term PACE study showed Qutenza repeat treatment plus standard of care over fifty-two weeks was well-tolerated, had no negative functional or neurological effects, and raised no new safety concerns compared with standard of care therapy, alone.

For those who are just joining us, this is ReachMD, I'm your host, Dr. David Simpson. Professor Serge Perrot and I are speaking about long-term safety and patient preference data regarding the high-concentration capsaicin 8% topical system for the treatment of painful diabetic peripheral neuropathy of the feet.

It's now widely recognized that neuropathy can be associated with diminished physical an emotional functioning and affective symptoms. This can have a direct effect on the perception and interpretation of pain and quality of life. The neuropathic pain associated with diabetes represents and ever-present and increasingly challenging problem. About a quarter of patients with diabetes report chronic nerve pain, while several oral medications have been used and approved for the indication of diabetic neuropathy, the control of pain is often insufficient, and tolerability of these medications is frequent limited by systemic or central affects.

Serge, can you provide some insight into the reported changes in concomitant mediations throughout the study?

Professor Perrot:
Of course, David. The most commonly prescribed categories of pain medications at baseline and during the study were analgesics and antiepileptics, mostly gabapentin and pregabalin. Overall, there was no decrease in the use of concomitant medications in the Qutenza group throughout the study. However, the proportion of patients using antiepileptic drugs had increased by greater than 10% in the standard of care group alone, at the end of the study. Small increases were also observed in antidepressant and opioid use in the standard of care group alone, from baseline to the end of the study. Therefore, it appears that Qutenza reduced the likelihood of needing other medications to reduce their pain along the study.

Dr. Simpson:
Thank you, Serge. You bring up a very important observation from the PACE trial that is very similar in most pain studies. I think it's important for clinicians and patients to understand that virtually none of the treatments were providing obliterate pain to zero but finding better suited and effective options can allow patients to reduce other medications that are causing deleterious side effects.

Patient preference is very important when evaluating treatment options and it is also important to educate patients on these options beforehand. Patient satisfaction has been shown to affect patient's health-related decisions and treatment-related behaviors, which in turn can substantially impact the success of treatment and outcome. In addition, patient satisfactions with their treatments also predicts the continuance of this therapy, correct medication use, and compliance with their regimens.

Serge, can you speak a little bit about patient satisfaction and treatment preference from the PACE trial, as well as your own clinic experience surrounding the use of Qutenza?

Professor Perrot:
Of course, David. Patient preference and patient satisfaction are very important to consider in clinical practice but also in this study. A second paper from the PACE trial was published in 2019 that presents the result for the secondary endpoint. By the end of the study, greater improvement in the patients' Global Impression of Change since starting the treatment were observed in the capsaicin plus standard of care group versus standard of care alone. A greater proportion of patients preferred Qutenza over the previous treatment and indicated their willingness to undergo treatment with Qutenza again. Furthermore, a greater proportion of patients in the Qutenza versus standard of care group reported improvement in their quality of life compared with standard of care alone.

Dr. Simpson:
Well, thank you for those insights, Serge. I'd like to conclude by speaking about your experience with Qutenza for painful diabetic neuropathy of the feet. Have you experienced any similarities or differences between the data presented from the PACE trial and real world applications?

Professor Perrot:
In fact, David, PACE trial is really similar to clinical practice. We have in our practice increasing number of elderly patients with diabetes with poor tolerability of systemic treatment and this kind of local treatment represents an important improvement in the quality of life of the patients but also in the safety of care. It's very important to explain the mode of action of such topical treatment, really different from other topical therapies. This should be explained, not only to the patients but also to our colleagues. Since it's not easy to understand this specific mode of action on the TRPV1 receptors. Qutenza is now my second-line of treatment in many cases, just after lidocaine patches and in growing cases, before systemic approaches and medications. It seems that treatment is more effective when it is proposed in patient with recent history of pain. To my knowledge, there are no predictors of response in terms of quality of pain, demographic, characteristics or types of diabetes.

Dr. Simpson:
Well, thanks for those wonderful insights, Serge. With that, I want to thank Professor Serge Perrot for joining me, today, to discuss long-term safety, tolerability, and patient preference data surrounding the use of the high-concentration capsaicin 8% topical system for the treatment of painful diabetic peripheral neuropathy of the feet with our ReachMD audience. Thank you.

Professor Perrot:
Thanks a lot, Dr. Simpson, for this very interesting discussion and exchanges. I hope that with this study, we will convince our colleagues that this treatment is safe, and it can be applied in patients with painful diabetic neuropathy and that will improve the quality of care and also the quality of life of our patients.

Dr. Simpson:
Thank you, Serge.

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

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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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