SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Qutenza 179 mg cutaneous patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 280 cm^2 cutaneous patch contains a total of 179 mg of capsaicin or 640 micrograms of capsaicin
per cm^2 of patch.

Excipient with known effect
Each 50 g tube of cleansing gel for Qutenza contains 0.2 mg/g butylhydroxyanisole (E320).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cutaneous patch.

Each patch is 14 cm x 20 cm (280 cm^2) and consists of an adhesive side containing the active substance and an outer surface backing layer. The adhesive side is covered with a removable, clear, unprinted, diagonally cut, release liner. The outer surface of the backing layer is imprinted with ‘capsaicin 8%’.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Qutenza is indicated for the treatment of peripheral neuropathic pain in adults either alone or in combination with other medicinal products for the treatment of pain.

4.2 Posology and method of administration

The Qutenza cutaneous patch should be applied by a physician or by a health care professional under the supervision of a physician.

Posology

The cutaneous patch should be applied to the most affected skin areas (using up to a maximum of 4 patches). This area should be determined by the physician or by a healthcare professional and marked on the skin. Qutenza must be applied to intact, non-irritated, dry skin, and allowed to remain in place for 30 minutes for the feet (e.g. HIV-associated neuropathy, painful diabetic peripheral neuropathy) and 60 minutes for other locations (e.g. postherpetic neuralgia). Qutenza treatments may be repeated every 90 days, as warranted by the persistence or return of peripheral neuropathic pain. Re-treatment after less than 90 days can be considered for individual patients only after a careful assessment by the physician (see also section 5.1). A minimum interval of 60 days between treatments is to be observed.

It is recommended to treat sufficiently long and to reassess effectiveness on a case-by-case basis after 3 treatments.

The treatment area may be pre-treated with a topical anaesthetic or the patient may be administered an oral analgesic prior to application of Qutenza to reduce potential application related discomfort. The topical anaesthetic should be applied to cover the entire Qutenza treatment area and surrounding 1 to 2 cm. Topical anaesthetics should be removed prior to applying Qutenza and the skin washed and dried thoroughly.

Renal and/or hepatic impairment

No dose adjustment is required for patients with renal or hepatic impairment.

Paediatric population

The safety and efficacy of Qutenza in children from birth to 18 years has not been established. No data are available.

Method of administration

Cutaneous use only.

Precautions to be taken before handling or administering the medicinal product
It is advisable to administer Qutenza in a well ventilated treatment area.

Nitrile gloves should be worn at all times while handling Qutenza and cleaning treatment areas. Latex gloves should NOT be worn as they do not provide adequate

protection. Use of a mask and protective glasses is recommended , particularly during application and removal of the patch.

These precautions should be taken to avoid unintentional contact with the patches or other materials that have come in contact with the treated areas. This may result in transient erythema and burning sensation (with mucous membranes being particularly susceptible), eye pain, eye and throat irritation and cough.

Patches should not be held near eyes or mucous membranes.

If necessary, hairs in the affected area should be clipped to promote patch adherence (do not shave). The treatment area(s) should be gently washed with soap and water. Following hair removal and washing, the skin should be thoroughly dried.

Instructions for use

Qutenza is a single use patch and can be cut to match the size and shape of the treatment area. Qutenza should be cut prior to removal of the release liner. The release liner should NOT be removed until just prior to application. There is a diagonal cut in the release liner to aid in its removal. A section of the release liner should be peeled and folded and the adhesive side of the printed patch placed on the treatment area. The patch should be held in place. The release liner should slowly and carefully be peeled from underneath with one hand while the patch should simultaneously be smoothed onto the skin with the other to ensure that there is complete contact between the patch and the skin, with no air bubbles and no moisture.

When treating feet, Qutenza patches can be wrapped around the dorsal, lateral and plantar surfaces of each foot to completely cover the treatment area.

To ensure Qutenza maintains contact to the treatment area, stretchable socks or rolled gauze may be used.

The Qutenza patches should be removed gently and slowly by rolling them inward to minimize the risk of aerosolisation of capsaicin. After removal of Qutenza, cleansing gel should be applied liberally to the treatment area and left on for at least one minute. Cleansing gel should be wiped off with dry gauze to remove any remaining capsaicin from the skin. After the cleansing gel has been wiped off, the area should be gently washed with soap and water.

Patients experiencing pain during and after patch application should be provided with supportive treatment (see section 4.4)

For instructions on handling and disposal of the treatment materials see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Dermal assessment

Qutenza must be used only on dry, intact (unbroken) skin and not on the face, above the hairline of the scalp, and/or in proximity to mucous membranes. In patients with painful diabetic peripheral neuropathy, a careful visual examination of the feet should be undertaken prior to each application of Qutenza and at subsequent clinic visits to detect skin lesions related to underlying neuropathy and vascular insufficiency.

Sensory function

Reductions in sensory function have been reported following administration of Qutenza. Decreases in sensory functions are generally minor and temporary (including to thermal and sharp stimuli), however, a single case of persistent hypoesthesia has been reported in clinical studies in painful diabetic neuropathy. For this case a relationship with Qutenza could not be excluded. Caution should be exercised in patients with reduced sensation in the feet and in those at increased risk for such changes in sensory function. All patients with pre-existing sensory deficits should be clinically assessed for signs of sensory loss to prior to each application of Qutenza. If sensory loss is detected or worsens, Qutenza treatment should be reconsidered.

Monitoring and management of application site reactions

Application site reactions, such as transient local applications site burning, pain, erythema and pruritus are common or very common. In addition, there have been reported cases of burns, including second-and third-degree burns, in patients treated with capsaicin patches. (see section 4.8). In patients reporting severe pain, the patch should be removed and the skin examined for chemical burn.

Unintended exposure

Unintended exposure to capsaicin may cause irritation of eyes, mucous membranes, respiratory tract, and skin in patients and healthcare professionals. Healthcare professionals should ensure that the recommended protective measures as outlined in Section 4.2 are applied appropriately.
If Qutenza comes in contact with skin not intended to be treated, cleansing gel should be applied for one minute and wiped off with dry gauze to remove any remaining capsaicin from the skin surface. After the cleansing gel has been wiped off, the area should be gently washed with soap and water. If capsaicin comes in contact with eyes or mucous membranes, these should be flushed or rinsed with cold water. If irritation of airways, eyes or mucous membranes occurs, the affected individual should leave the Qutenza treatment area. Appropriate medical care should be provided if shortness of breath develops. If respiratory irritation (see also Section 4.8) worsens or does not resolve, the affected individual should carefully consider being re-exposed to Qutenza.

Increase in blood pressure

As a result of treatment-related increases in pain, transient increases in blood pressure (on average < 8.0 mm Hg) may occur during and shortly after the Qutenza treatment. Blood pressure should be monitored during the treatment procedure. For patients with unstable or poorly controlled hypertension or a history of cardiovascular disease, the risk of adverse cardiovascular events due to the potential stress of the procedure should be considered prior to initiating Qutenza treatment. Particular attention should be given to diabetic patients with comorbidities of coronary artery disease, hypertension and cardiovascular autonomic neuropathy.

Treatment-related discomfort

Patients experiencing pain during and after patch application should be provided with supportive treatment such as local cooling (such as a cool compress) or oral analgesics.

Cleansing gel

The cleansing gel for Qutenza contains butylhydroxyanisole, which may cause local skin reactions (e.g. contact dermatitis) or irritation of the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with other medicinal products have been performed as only transient low levels of systemic absorption have been shown to occur with Qutenza.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of capsaicin in pregnant women.
Based on human pharmacokinetics, which show transient, low systemic exposure to capsaicin, the likelihood that Qutenza increases the risk of developmental abnormalities when given to pregnant women is very low. However, caution should be exercised when prescribing to pregnant women.

Breast-feeding

It is unknown whether capsaicin/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of capsaicin/metabolites in milk (for details see 5.3).

A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with Qutenza.

Fertility

There is no data in humans available on fertility. A reproductive toxicology study in rats showed a reduction in the number and percent of motile sperm and the number of pregnancies (see section 5.3).

4.7 Effects on ability to drive and use machines

Qutenza has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were transient local application site burning, pain, erythema and pruritus.

Tabulated list of adverse reactions

In Table 1 below all adverse reactions, which occurred at an incidence greater than control and in more than one patient in controlled clinical trials in patients with postherpetic neuralgia (PHN), painful Human Imunodeficiency Virus – Associated Neuropathy (HIV-AN) and painful diabetic peripheral neuropathy, are listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Tabulated list of adverse reactions

System organ class and frequency	**Adverse reaction**
Infections and infestations	
Uncommon	Herpes zoster
Nervous system disorders	

Common	Burning sensation
Uncommon	Dysgeusia, hypoaesthesia
Eye disorders	
Uncommon	Eye irritation
Cardiac disorders	
Uncommon	First degree atrio-ventricular (AV) block, tachycardia, palpitations
Vascular disorders	
Common	Hypertension
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Uncommon	Throat irritation
Gastrointestinal disorders	
Common	Nausea
Skin and subcutaneous tissue disorders	
Common	Pruritus
Musculoskeletal and connective tissue disorders	
Common	Pain in extremity, muscle spasms
General disorders and administration site conditions	
Very common	Application site pain, application site erythema
Common	Application site pruritus, application site papules, application site vesicles, application site oedema, application site swelling, application site dryness, peripheral oedema
Uncommon	Application site urticaria, application site paraesthesia, application site dermatitis, application site hyperaesthesia, application site inflammation, application site reaction, application site irritation, application site bruising
Investigations	
Common	Increased blood pressure
Injury, poisoning and procedural complications	
Not known	Application site burns (including second-and third-degree burns), accidental exposure (including eye pain, eye and throat irritation and cough)

Description of selected adverse reactions

Adverse reactions were transient, self limiting and usually mild to moderate in intensity. In controlled trials, the discontinuation rate due to adverse reactions was 2.0% for patients receiving Qutenza and 0.9% for patients receiving control.

Temporary, minor changes in heat detection (1°C to 2°C) and sharp sensations were detected at the Qutenza application site in clinical trials with healthy volunteers.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow

Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No case of overdose has been reported. Qutenza is required to be administered by a physician or under the supervision of a physician. Therefore, overdosing is unlikely to occur. Overdose may be associated with severe application site reactions, e.g. application site pain, application site erythema, application site pruritus. In case of suspected overdose, the patches should be removed gently, cleansing gel should be applied for one minute and then wiped off with dry gauze and the area should be gently washed with soap and water. Supportive measures should be taken as clinically needed. There is no antidote to capsaicin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, other local anaesthetics, ATC code: N01BX04

Mechanism of action

Capsaicin, or 6-nonenamide, N-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methyl, (6E), is a highly selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1). The initial effect of capsaicin is the activation of TRPV1-expressing cutaneous nociceptors, which results in pungency and erythema due to the release of vasoactive neuropeptides.

Pharmacodynamic effects

Following capsaicin exposure, cutaneous nociceptors become less sensitive to a variety of stimuli. These later-stage effects of capsaicin are frequently referred to as “desensitization” and are thought to underlie the pain relief. Sensations from non TRPV1-expressing cutaneous nerves are expected to remain unaltered, including the ability to detect mechanical and vibratory stimuli. Capsaicin-induced alterations in cutaneous nociceptors are reversible and it has been reported and observed that normal function (the detection of noxious sensations) returns within weeks in healthy volunteers. The neurolytic effect of capsaicin leading to a decrease in epidermal nerve density following topical administration, has also been shown to be reversible in patients with peripheral neuropathic pain.

Clinical efficacy and safety

Efficacy of a single 30-minute application of Qutenza to the feet has been shown in controlled clinical trials of 12 weeks duration conducted in patients with painful Human Imunodeficiency Virus – Associated Neuropathy (HIV-AN) and painful diabetic peripheral neuropathy (pDPN). Efficacy of a single 60-minute application of Qutenza to locations other than the feet has been shown in controlled clinical trials of 12 weeks duration conducted in patients with postherpetic neuralgia (PHN). The average pain reduction after single application of Qutenza compared to baseline at week 2 to 12 across the pivotal trials ranged between -22.8% and -32.3%, compared to a range of -10.7% to -25.0% for the control patches. Responder rates (response defined as a 30% decrease in average pain score from baseline) ranged between 34% and 47%, compared to a range of 18% to 36% for the control patches. These results were statistically significant versus low dose capsaicin (PHN and HIV-AN) or placebo (pDPN). Pain reduction was observed at week 1 in PHN, week 2 in HIV-AN and week 3 in pDPN. For all three aetiologies efficacy was maintained throughout the 12-week study period.

Consistent and reproducible efficacy and tolerability was demonstrated with repeated treatments during a 52-week period in two clinical trials (STRIDE and PACE). In these two trials, one in pDPN patients (PACE) and one in patients with HIV-AN, Post Traumatic Nerve Injury (PNI) and PHN (STRIDE), the mean time (Standard Deviation) to retreatment was 68.4 (23.31) and 107 (43.58) days respectively. Repeated treatment with Qutenza in PACE and STRIDE was associated with progressively decreasing 24-hour average pain intensity and increasing responder rates, improvement in sleep and improvement in QoL. Likewise, in real world data, repeated treatments with Qutenza could be correlated with a decrease in neuropathic pain symptoms, improvement in quality of life and sleep. In these trials 25% of patients had a retreatment time shorter than 61.5 and 78.8 days respectively and 25% of patients had a retreatment time longer than 64.6 and 118.7 days respectively. A frequency increase of up to approximately 5% of known application site reactions, such as pain and burning sensation, was reported in patients retreated with Qutenza earlier than 90 days.

The safety profile of Qutenza in diabetic patients was consistent with that seen in the non-diabetic population.

Qutenza has been shown to be effective when used alone or when used in combination with systemic medicinal products for neuropathic pain.

5.2 Pharmacokinetic properties

The capsaicin contained in Qutenza is intended for delivery into the skin. *In vitro* data (active substance dissolution and skin permeation assays) demonstrate that the rate of release of capsaicin from Qutenza is linear during the application time. Based on *in vitro* studies, approximately 1% of capsaicin is estimated to be absorbed into the epidermal and dermal layers of skin during one-hour applications. As the amount of capsaicin released from the patch per hour is proportional to the surface area of application, this amounts to an estimated total maximum possible dose for a 1000 cm^2 area of application of approximately 7 mg. Assuming 1000 cm^2 of patch area delivers approximately 1% of capsaicin from the patch to a 60 kg person, the maximum potential exposure to capsaicin is approximately 0.12 mg/kg, once every 3 months.

According to the EC Scientific Committee on Food, the average European oral intake of capsaicin is 1.5 mg/day (0.025 mg/kg/day for a 60 kg person) and the highest dietary exposure is 25 to 200 mg/day (up to 3.3 mg/kg/day for a 60 kg person).

Pharmacokinetic data in humans showed transient, low (< 5 ng/ml) systemic exposure to capsaicin in about one third of PHN patients, in 3% of patients with painful diabetic peripheral neuropathyand in no HIV-AN patients following 60-minute applications of Qutenza. No data are available following 30-minute treatments. In general, the proportions of PHN patients with systemic exposure to capsaicin increased with larger treatment areas and with longer treatment durations. The highest concentration of capsaicin detected in patients treated for 60 minutes was 4.6 ng/mL, which occurred immediately after Qutenza removal. Most quantifiable levels were observed at the time of Qutenza removal, with a clear trend towards disappearance by 3 to 6 hours after Qutenza removal. No detectable levels of metabolites were observed in any subject.

A population pharmacokinetic analysis of patients treated for 60 and 90 minutes indicated that capsaicin levels in plasma peaked around 20 minutes after Qutenza removal and declined very rapidly, with a mean elimination half-life of about 130 minutes.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single-dose toxicity, and repeated-dose toxicity.

Genotoxicity studies performed with capsaicin show a weak mutagenic response in the mouse lymphoma assay and negative responses in the Ames, mouse micronucleus and chromosomal aberrationin human peripheral blood lymphocytes assays.

A carcinogenicity study performed in mice indicates that capsaicin is not carcinogenic.

A reproductive toxicology study conducted in rats showed a statistically significant reduction in the number and percent of motile sperms in rats treated 3 hours/day beginning 28 days before cohabitation, through cohabitation and continuing through the day before sacrifice. Although neither statistically significant nor dose dependent, the Fertility Index and the number of pregnancies per number of rats in cohabitation were reduced in all capsaicin-treated groups.

A teratology study conducted in rabbits did not show any potential for embryofetal toxicity. Delays in skeletal ossification (reductions in ossified metatarsals) were observed in a rat teratology study at dose levels higher than human therapeutic levels; the significance of this finding for humans is unknown. Peri- and post-natal toxicology studies, conducted in rats do not show potential for reproductive toxicity. Lactating rats exposed to Qutenza daily for 3 hours showed measurable levels of capsaicin in the mothers' milk.

A mild sensitization was seen in a cutaneous sensitization study with guinea pigs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Patch

Matrix
silicone adhesives
diethylene glycol monoethyl ether
silicone oil
ethylcellulose N50 (E462)

Backing layer
Polyethylene Terephthalate (PET) Film, inner side siliconizedprinting ink containing Pigment White 6

Removable protective layer (release liner)
polyester film, fluoropolymer-coated

Cleansing gel

macrogol 300
carbomer
purified water
sodium hydroxide (E524)
disodium edetate
butylhydroxyanisole (E320)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

After opening sachet: apply Qutenza within 2 hours.

6.4 Special precautions for storage

Qutenza cutaneous patch: Store flat in the original sachet and carton. Store below 25°C.

Cleansing gel: Store below 25°C.

6.5 Nature and contents of container

The cutaneous patch is stored in a paper coated aluminium foil sachet with polyacrylnitril layer.

The cleansing gel is supplied in a high density polyethylene tube with a polypropylene cap.

Qutenza is available in packs containing one or two sachets of individually sealed cutaneous patches and a 50 g tube of cleansing gel.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Health care professionals should wear nitrile gloves when handling patches and cleansing treatment areas. The use of a mask and protective glasses is recommended, see section 4.2.

Used and unused patches and all other materials that have been in contact with the treated area should be disposed of immediately after use by sealing them in a polyethylene medical waste bag and placing in an appropriate medical waste container.

7 MARKETING AUTHORISATION HOLDER

Grünenthal GmbH
Zieglerstraße 6
52078 Aachen
Germany

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