SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
CAPCIDERM 0.075% cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 g cream contains,

Active substance(s):
Capsaicin 0.75 mg

Excipient(s):
Cetyl alcohol 100.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Cream
Almost white cream

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
CAPCIDERM cream is indicated for;

- Symptomatic relief of neuralgia (postherpetic neuralgia) accompanying herpes zoster infections or following infection after healing of open skin lesions,
- Symptomatic treatment of painful diabetic peripheral polyneuropathy,
- Symptomatic treatment of arthritis, osteoarthritis, muscle and joint pain.

4.2. Posology and method of administration
Posology/frequency of administration and duration of the treatment
CAPCIDERM is for topical administration to unbroken skin.

Posology:
It is applied in adults 3 or 4 times a day.

Frequency of administration and duration of the treatment:
It is applied only a small amount of cream (pea size), 3 or 4 times a day to the affected area. These applications should be evenly spaced throughout the waking hours and not more often than every 4 hours.

The recommended duration of use in the first instance is 8 weeks, since there is no clinical trial evidence of efficacy for treatment of more than 8 weeks duration for the treatment of painful diabetic peripheral polyneuropathy. After this time, it is recommended that the patient's condition should be fully clinically assessed prior to continuation of treatment, and regularly re-evaluated thereafter, by the supervising consultant.

Method of Application:
It is applied only a small amount of cream (pea size) to the affected area. The cream should be applied slowly until it disappears completely on the skin surface. CAPCIDERM may cause a transient burning sensation. When applied more than 4 times a day, the burning sensation is

observed more. Hands should be washed immediately after application of CAPCIDERM. When needed, it is recommended to be used with a massage head. It should not be applied near the eyes.

Patients using CAPCIDERM for the treatment of painful diabetic peripheral polyneuropathy should only do so under the direct supervision of a hospital consultant who has access to specialist resources.

Additional information for special populations
Renal/Hepatic Failure:
The use of CAPCIDERM cream in patients with renal and hepatic failure has not been studied.

Pediatric population:
It should not be used in children under 12 years of age.

Geriatric population:
There is no feature in using CAPCIDERM cream in elderly patients.

4.3. Contraindications

CAPCIDERM cream is contra-indicated in patients with known hypersensitivity to capsaicin or any of the excipients used in this product and for use on broken or irritated skin.

4.4. Special warnings and precautions for use
It should not be used under tight bandages.

It should be kept away from the eyes.

Skin irritation has been reported following application of CAPCIDERM. The hands should be washed immediately after application of the cream, unless the hands are the treated areas, in which case, they should be washed 30 minutes after application.

Contact with eyes and mucous membranes should be avoided.

Patients should avoid taking a hot bath or shower just before or after applying CAPCIDERM, as it can enhance the burning sensation.

Patients and carers should avoid inhalation of vapors from the cream, as transient irritation of the mucous membranes of the eyes and respiratory tract (including exacerbation of asthma) has been reported.

If the condition worsens, seek medical advice.

Since CAPCIDERM contains cetyl alcohol, it can cause local skin reactions (eg contact dermatitis).

4.5. Interactions with other medicinal products and other forms of interaction
No interaction studies have been conducted.

Additional information for special populations:
There is no additional information on special populations.

Pediatric population:
There is no additional information on pediatric population.

4.6. Pregnancy and lactation
General advice:
Pregnancy category: C

Women of childbearing potential/Birth control (contraception)
There are insufficient data on its use in women of childbearing potential.

Pregnancy period
Animal studies are insufficient with respect to pregnancy / and-or / embryonal / fetal growth / and-or /natal / and-or / postnatal development. Potential risk is not known for human.

The safety of capsaicin during pregnancy or lactation has not been established in either humans or animals. However, in the small amounts absorbed transdermally from CAPCIDERM Cream, it is considered unlikely that capsaicin will cause any adverse effects in humans.

Lactation period
It should be used under the supervision of a doctor.

Reproductive ability/Fertility
The effect of CAPCIDERM on reproductive ability has not been established.

4.7. Effects on ability to drive and use machines
CAPCIDERM cream has no effect on the ability to drive and use machines.

4.8. Undesirable effects
The specified adverse effects can be grouped by frequencies as:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100), rare (≥1/10.000 to <1/1.000); very rare (<1/10.000); not known (cannot be estimated from the available data).

Respiratory, thoracic and mediastinal disorders:
Rare: Irritation of the mucous membranes of the eyes and respiratory tract, resulting in symptoms such as coughing, sneezing and runny eyes, irritation in the nose and throat, dyspnea, wheezing and exacerbation of asthma

Skin and subcutaneous tissue disorders:
Very common: Itching, papule, dry skin at the application site.
Common: Temporary increase in pain (decreases in continuous use), erythema, burning, irritation at the application site

CAPCIDERM may cause a transient burning sensation. When applied more than 4 times a day, the burning sensation is observed more. This burning sensation may increase if too much cream is used and if the cream is applied just before or after a bath or shower.

Irritation in the mucous membranes of the eyes and respiratory tract (such as irritation in the nose and throat), which is rare with CAPCIDERM cream application and causes symptoms such as coughing, sneezing and runny eyes, is usually mild and resolves spontaneous.
There are a few reports available related with dyspnea, wheezing and exacerbation of asthma.

4.9. Overdose and treatment
As a result of topical application of CAPCIDERM cream, overdose is not expected.

Systemic effect is not expected after topical application due to its low systemic exposure and rapid elimination of capsaicin.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Topical products used for joint and muscle pain, capsaicin and similar agents
ATC Code: M02AB01
Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin renders skin insensitive to pain by depleting and preventing re-accumulation of substance P in peripheral sensory neurons. Substance P is thought to be the principal chemo-mediator of pain impulses from the periphery to the Central Nervous System.

5.2. Pharmacokinetic properties

General properties
In studies conducted, the size of the site applied in topical use and the residence time of the drug on the skin when applied with a patch are variables that significantly affect the pharmacokinetics of capsaicin. Treatment on the feet produced far lower systemic exposure than treatment on the trunk.

The average consumption of dietary spice obtained from Capsicum fruit has been estimated as 2.5 g / person / day in India and 5.0 g / person / day in Thailand. Capsaicin content in capsicum fruit is approximately 1%, and therefore, the daily dietary intake of capsaicin may range from 0.5 to 1 mg / kg / day for a 50 kg person. Application of two tubes of capsaicin containing cream 0.075% (90 g) each week results in 9.6 mg / day topical exposure. Assuming 100% absorption in a 50kg person, the daily exposure would be 0.192 mg / kg which is approximately one third to one quarter of the above-mentioned dietary intake.

Absorption:
It has been observed in *in vivo* and *in situ* studies in rats that oral capsaicin is rapidly absorbed from the stomach and small intestines. It was found that approximately 85% of the dose given in *in vivo* studies was absorbed from the gastrointestinal tract within 3 hours. In the same study, after a 60-minute capsaicin application in situ, it was shown to be absorbed from the stomach, jejunum and ileum at a rate of 50, 80 and 70%, respectively.

In 173 patients, patches containing 640 mcg / cm2 capsaicin were applied on the skin for 60 and 90 minutes. After that, the percentages of patients with quantifiable levels of capsaicin at any time point were 31% (30/96 patients) in postherpetic neuralgia patients, 7% (3/44) in painful neuropathy patients accompanying the human immunodeficiency virus, and 3% (1/33) in painful diabetic neuropathy patients.

Distribution:
After patches containing 640 mcg / cm2 capsaicin were applied on the skin for 60 and 90 minutes, the maximum plasma concentration observed in any patient was 17.8 ng/mL. Mean area under the curve and C max values after a 60-minute application were 7.42 ng x h/mL and 1.86 ng/mL, respectively. Ninety-minute applications of CAPCIDERM resulted in capsaicin area under the curve and Cmax values approximately 1.78- and 2.15-fold higher than those observed in patients treated for 60 minutes.

Biotransformation:
Capsaicin is metabolized in the liver before reaching the general circulation and extrahepatic organs. *In vitro* and *in vivo* studies have shown that capsaicinoids are metabolized by P450 enzymes with different pathways:

- Hydrolysis of the acid-amide bond and oxidative deamination of the vanillylamine formed,
- Hydroxylation of the vanilyl ring, possibly through epoxidation,
- Formation of phenoxy radicals and capsaicinoid dimers by an electron oxidation of the hydroxyl ring,
- Oxidation of the terminal carbon of the side chain.

Elimination:
Elimination half-life of capsaicin is 1.64 hours. It was found that 8.7% of the dose applied 48 hours after the application of dihydrocapsaicin to male rats was excreted unchanged in the urine and 10% in feces. Metabolites as free forms or glucuronide form in urine are vanillylamine (4.7%), vanillin (4.6%), vanillylalcohol (37.6%) and vanicic acid (19.2%)

Linearity/non-linearity:
Elimination kinetics of capsaicin is linear.

5.3. Preclinical safety data
The available animal toxicity data relating to capsicum, capsicum extracts and capsaicin do not suggest that, in usual doses, they pose any significant toxicity hazard to man. Thus, in both single and repeat dosing studies which have been reported, capsicum extracts and capsicum are generally well tolerated at many times even the highest estimated human intakes. The safety of capsaicin for use in human pregnancy has not been established since no formal reproduction studies have been performed on either animals or man. However, there is no reason to suspect from human or animal studies currently available that any adverse effects in humans are likely.

Studies reported in the published literature, which relate to potential genotoxic and carcinogenic action of capsaicin have produced inconclusive and conflicting data. However, it is unlikely that capsaicin, in the quantities absorbed transdermally from CAPCIDERM Cream, will pose any significant hazard to humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Benzyl alcohol
Cetyl alcohol
Sorbitol (70%) (E420)
White paraffin
Isopropyl myristate
Glyceryl stearate
PEG-100 stearate
Deionized water

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
24 months

6.4. Special precautions for storage
Store at room temperature below 25°C.

6.5. Nature and contents of container
It is marketed in epoxyphenolic aluminum tubes covered with high density polyethylene (HDPE) massage cap closures containing 45 g cream.

6.6. Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with "Directive on Control of Medical Waste" and "Directive on the Control of Packaging and Packaging Waste".

7. MARKETING AUTHORIZATION HOLDER
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8. MARKETING AUTHORIZATION NUMBER(S)
246/22

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION
Date of the first authorization: 22.11.2012
Date of the renewal of the authorization: 05.11.2018

10. DATE OF REVISION OF THE TEXT
18.03.2022