European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

COMMITTEE OF EXPERTS ON THE CLASSIFICATION OF MEDICINES AS REGARDS THEIR SUPPLY (CD-P-PH/PHO)

Evidence-based classification review for Capsicum annuum L. var. minimum (Miller) Heiser and Capsicum frutescens L.

(ATC code M02AB)

2025

Table of Contents

Introduction

The availability of medicines with or without a medical prescription has implications for patient safety, accessibility of medicines to patients and responsible management of healthcare expenditure.

The decision on prescription status and related supply conditions is a core competency of national health authorities. The conditions of the supply of medicines vary considerably in Council of Europe Member States due to different interpretation and implementation of the provisions and since important additional classification criteria are not harmonised.

The Committee of Experts on the Classification of Medicines as Regards their Supply (CD-P-PH/PHO) is co-ordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM, Council of Europe) and its work programme is based on Committee of Ministers Resolution CMRes(2018)1 on the classification of medicines as regards their supply. The CD-P-PH/PHO reviews the national legal supply status of medicinal products for human use, performs assessment according to Guidelines on key considerations in issuing recommendations on the classification of active substances as regards their supply (prescription and non-prescription status) and issues recommendations on the classification of medicines and their supply conditions to health authorities of the Council of Europe Member States parties to the European Pharmacopoeia Convention. It is important to note that the CD-P-PH/PHO does not issue recommendations on the classification of particular medicinal products, but on active substances with their respective Anatomical Therapeutic Chemical (ATC) codes.

The approach to the classification of herbal medicines described below was endorsed by the CD-P-PH/PHO in November 2025, and has no legal status.

Classification of herbal medicines

This section outlines the rationale behind the CD-P-PH/PHO's recommendations related to herbal medicines with a complete ATC code (consideration of a herbal medicine with an incomplete ATC code may be justified only in very rare cases).

The term "Herbal medicines" can be understood in different ways. In the context of the CD-P-PH/PHO recommendations, herbal medicines are medicines with a complete ATC code containing an active substance based on "herbals" – plants or parts of plants with a marketing authorisation based on well-established use application. "Non-herbal" medicines and food supplements are out of the scope of this document. The approach to traditional use herbal medicines is outlined in the document; however, these medicines are not assessed by the CD-P-PH/PHO.

The CD-P-PH/PHO assessment can contribute to the harmonisation of the classification and conditions of supply of herbal medicines across the Member States.

The European Union (EU) legislation sets out various regulatory pathways to obtain a marketing authorisation of a herbal medicine; however, information on the authorisation type is not included in the labelling of medicines. Consequently, the regulatory pathway behind these medicines, which partly determines their classification and supply conditions, is not clear to patients and sometimes even to healthcare professionals.

The regulatory pathway for herbal medicines in the EU is illustrated below (European Medicines Agency (EMA) website; "Member State" refers here to EU Member States):

Regulatory pathway	Main requirements on safety and efficacy	Where to apply
Traditional use registration (Article 16a(1) of Directive 2001/83/EC)	• No clinical tests and trials on safety and efficacy are required as long as sufficient safety data and plausible efficacy are demonstrated • Involves assessment of mostly bibliographic safety and efficacy data • Must have been used for at least 30 years, including at least 15 years within the EU • Are intended to be used without the supervision of a medical practitioner and are not administered by injection	• National competent authority of a Member State for national, mutual recognition and decentralised procedures
Well-established use marketing authorisation (Article 10a of Directive 2001/83/EC)	• Scientific literature establishing that the active substances of the medicinal products have been in well-established medicinal use within the EU for at least ten years, with recognised efficacy and an acceptable level of safety • Involves assessment of mostly bibliographic safety and efficacy data	• National competent authority of a Member State for national, mutual recognition and decentralised procedures • EMA if centralised procedure applies
Stand-alone or mixed application (Article 8(3) of Directive 2001/83/EC)	• Safety and efficacy data from the company's own development or a combination of own studies and bibliographic data	• National competent authority of a Member State for national, mutual recognition and decentralised procedures • EMA if centralised procedure applies

Medicines authorised via a traditional use authorisation are intended to be used without the supervision of a medical practitioner, i.e. have a non-prescription status. The CD-P-PH/PHO will identify herbal medicines with a complete ATC code authorised as traditional herbal medicines only, and for which a monograph has been issued by the Committee on Herbal Medicinal Products (HMPC) of the EMA. As traditional herbal medicines are out of scope of the evaluation by the CD-P-PH/PHO, the conditions of the monograph are followed and non-prescription status is recommended without any evaluation. These medicines are shown in Table 1.

Table 1 - Herbal medicines with a complete ATC code with traditional use authorisation only and an HMPC monograph

INN (ATC code)	Monograph available on
Crataegi folium cum flore (C01EB04)	https://www.ema.europa.eu/en/medicines/herbal/crataegi-folium-cum-flore
Centellae asiatica herba, incl. combinations (D03AX14)	https://www.ema.europa.eu/en/medicines/herbal/centellae-asiaticae-herba
Lavandulae aetheroleum (N05BX05)	https://www.ema.europa.eu/en/medicines/herbal/lavandulae-aetheroleum
Althaeae radix (R05CA05)	https://www.ema.europa.eu/en/medicines/herbal/althaeae-radix
Pruni africanae cortex (G04CX01)	https://www.ema.europa.eu/en/medicines/herbal/pruni-africanae-cortex

These medicines have monographs available, based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC, as amended (traditional use). Therefore, these medicines should be non-prescription according to the conditions of the monographs. The EMA list of HMPC monographs with traditional use authorisation only is very long; however, most of the medicines do not have an ATC code or have an incomplete ATC code, and therefore they are not included in Table 1.

For the other regulatory pathways, the classification outcome can be different, and it is important to establish conditions of supply and a recommendation on the classification.

For well-established use herbal medicines with a complete ATC code, regardless of whether there is a monograph issued by the HMPC (see Table 2), the CD-P-PH/PHO will assess the conditions of supply and issue a recommendation on the classification.

Table 2 - Herbal medicines with a complete ATC code with well-established use authorisation, with or without an HPMC monograph, on the EMA herbal medicines list

Agni casti fructus (G02CX03)	Menthae piperitae aetheroleum (A03AX15)
Capsici fructus (M02AB01)	Planataginis ovatae semen or Plantaginis ovatae seminis tegumentum or Psylli semen (A06AC01)
Cimifugae rhizoma (G02CX04)	Rhamni purshianae cortex (A06AB07)
Gingko folium (N06DX02)	Ricini oleum (A06AB05)
Hederae helicis folium (R05CA12)	Sabalis serrulatae fructus (G04CX02)
Hippocastani semen (C05CX03)	Sennae folium and/or Sennae fructus (A06AB06)
Hyperici herba (N06AX25)	Valerianae radix (N05CM09)
Lini semen (A06AC05)	

The Evidence-based classification review (EBR) for capsicum (Capsicum annuum L. var. minimum (Miller) Heiser and Capsicum frutescens L.), one of these medicines, is provided below.

Well-established use herbal medicines with an incomplete ATC code are listed in Table 3 for information only.

Table 3 - Herbal medicines with an incomplete ATC code with well-established use authorisation, with or without an HPMC monograph, on the EMA herbal medicines list

Aloes folii succus siccatus (A06AB)	Rhei radix (A06AB)
Echinaceae purpurae herba (R05X)	Salicis cortex (N02BG)
Frangulae cortex (A06AB)	Valerianae radix/Lupuli flos (N05CM)
Menthae piperitae folium (A03AX)	Vitis viniferae folium (C05CX)
Plantaginis ovatae seminis tegumentum (C10AX)	Zingiberis rhizome (A04AD)

Regulatory pathways are not applicable to non-EU countries; however, the rationale related to the classification of herbal medicines provided by the CD-P-PH/PHO could be considered in any setting.

Evidence-based classification review

Note: The document Guidelines on key considerations in issuing recommendations on the classification of active substances as regards their supply (prescription and non-prescription status) should be consulted.

1. Active substance

Capsicum annuum L. var. minimum (Miller) Heiser and Capsicum frutescens L.

2. ATC code

M02AB - Capsaicin and similar agents

3. First level assessment

3.1 Characteristics of the active substance

Capsicum is the common name for the fruits of the plants Capsicum annuum L. var. minimum (Miller) Heiser and Capsicum frutescens L. These are types of peppers that are cultivated or gathered to obtain the plant parts for medicinal use.

Capsicum preparations are obtained by ethanol or propanol extraction.

Herbal substance(s)

Definition in the European Pharmacopoeia (Ph. Eur.) monograph 1859 [1]:

Dried ripe fruits of Capsicum annuum L. var. minimum (Miller) Heiser and small-fruited varieties of Capsicum frutescens L. (Capsici fructus).

Content: minimum 0.4% of total capsaicinoids, expressed as capsaicin ($C_{18}H_{27}NO_3$; Mr 305.4) (dried drug).

Constituents [2]:

Capsaicinoids: 0.3 - more than 1% of total capsaicinoids, consisting of 63-77% capsaicin, 20 - 32% dihydrocapsaicin, 1 - 8% nordihydrocapsaicin and undefined amounts of homodi-hydrocapsaicin I and II, vanillylamides of caprylic acid and nonylic acid.

Other constituents: fatty oil, carotenoids, ascorbic acid, volatile compounds.

Herbal preparation(s)

Herbal preparations in the European Pharmacopoeia:

Capsicum oleoresin, refined and standardised (Capsici oleoresina raffinata et normata), monograph *2336* [3].

Extraction solvent - ethanol (minimum 90% V/V), extract standardised to a content of 12 - 18% m/m of total capsaicinoids, expressed as capsaicin ($C_{18}H_{27}NO_3$; M_r 305.4).

An overview of herbal preparations based on Article 10a of Directive 2001/83/EC as amended (well-established use) is provided in Table 4.

Table 4 - Capsicum herbal preparations, well-established use [2,4]

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Capsicum annuum L. var. minimum (Miller) Heiser and small fruited varieties of Capsicum frutescens L., fructus
Herbal preparation(s)	a) Soft extract (DER 4-7:1), standardised to 2 – 2.78% total capsaicinoids, extraction solvent ethanol 80% (V/V) b) Soft extract (DER 1.5–2.5:1), extraction solvent ethanol 96% (V/V) c) Soft extract (DER 11-30:1), extraction solvent propan-2-ol
Pharmaceutical form(s)	Herbal preparation in a medicated plaster or in semi-solid dosage forms for cutaneous use

Mechanism of action

Capsaicin, the primary pungent principle in the fruit of capsicum plants, is a selective agonist of transient receptor potential vanilloid 1 (TRPV1), which is found in the nociceptors (pain receptors) in the skin. Capsaicin is used to overstimulate TRPV1, which ‘desensitises’ the receptors and they are no longer able to respond to the stimuli that normally cause pain.

Topically applied capsaicin triggers local irritation, which manifests symptomatically as erythema and a burning, sometimes itchy sensation. This may be attributed to a neurogenic inflammatory process and explained by the release of the neurotransmitter substance P. The second stage of the capsaicin action is associated with antinociceptive effects, the duration of which ranges from hours to weeks. Substance P depletion following repeated application leads to a long-term desensitisation to burning and pain [2,4].

3.2 Pharmaceutical form/Route of administration

Herbal preparations containing capsicum are available only for topical use – in a medicated plaster or in semi-solid forms for cutaneous use.

3.3 Intended therapeutic indication

On the basis of available clinical data and its well-established use, capsicum can be used for the relief of muscle pain, such as low back pain.

Capsicum should only be used in adults over the age of 18 years and should not be used continuously for more than 3 weeks. After 3 weeks, a break of at least 2 weeks is required.

Use in children and adolescents is not considered in the HMPC monograph, as safety and efficacy in this age group are not supported by published data from clinical trials.

Medicated plasters or semi-solid dosage forms should only be used during pregnancy and lactation after a careful risk-benefit assessment, as safety during pregnancy and lactation has not been fully established.

The reported side effects are related to hypersensitivity reactions. In such cases the treatment should be discontinued [2,4].

Conclusion of First level assessment

Capsicum with the indication “for the relief of muscle pain, such as low back pain”, with the pharmaceutical form “medicated plasters and semi-solid dosage forms for topical use” could be considered for non-prescription or prescription status.

It is not definitely concluded that the active substance should have prescription status applied. Second level assessment is required to further evaluate the appropriate supply status.

4. Second level assessment

4.1 Assessment of use

The indication – muscle pain – is a very common condition that can be easily identified by patients. Patients are accustomed to going to a pharmacy to obtain medicine for this issue.

Identified risk(s): the prolonged use of these medicines without medical supervision can pose a risk (masking the effects of other rheumatological diseases, delayed diagnosis and tolerance); however, this is common to capsaicin medicines.

Capsaicinoids are known to be very aggressive compounds, particularly when applied to mucous membranes. From preclinical tests it is also evident that prolonged contact of sensitive neurons to capsaicin may lead to possibly irreversible damage of the neuronal membranes [2]. Therefore, restrictions should apply for the medicinal use of herbal preparations containing capsaicin.

In order to limit the risk for irreversible neuronal damage, the duration of continuous use should be restricted to a maximum of 3 weeks. Administration on broken skin, wounds and eczemas is contraindicated. Contact with mucous membranes should be avoided. As capsaicinoids act via a thermosensitive receptor, the application of additional sources of heat should be avoided [2,4].

The approach followed is to restrict the duration of use without medical supervision in the package leaflet.

4.2 Safety profile

4.2.1 Direct risks

Toxicity

No carcinogenicity data are available.

Contraindications, special warnings and precautions for use

Capsicum is contraindicated for use on broken skin, wounds and eczema.

The medicinal product should not be applied near the eyes or to mucous membranes.

It is recommended not to scratch the application site to avoid damage to the skin.

Application of additional sources of heat during treatment should be avoided (e.g. solar or infrared radiation, heating pad or warm water). The effect of warmth can also be intensified by physical activity (sweating).

Treatment should be discontinued if the heat effect is experienced as excessive. In this case the plaster or excess semi-solid dosage form should be removed [2,4].

Interactions

The plaster/semi-solid dosage form is not intended to be applied at the same time as other topical products, e.g. other rubefacients (which increase perfusion and cause a reddening of the skin) or pain relieving gels, at the same application site. Interactions with other products applied at the same application site may occur up to 12 hours after the plaster has been removed [2,4].

Adverse reactions

The reported side effects are related to hypersensitivity reactions. In such cases the treatment should be discontinued [2,4].

4.2.2 Indirect risks

Masking effect and delayed diagnosis

The prolonged use of capsicum can delay the diagnosis or mask effects of other issues; however, restriction of the duration of use can mitigate this risk.

Misunderstanding of posology

The posology should be clear in the package leaflet to avoid misunderstanding.

Tolerance

Capsaicinoids are known to be very aggressive compounds, particularly when applied to mucous membranes. From preclinical tests it is also evident that prolonged contact of sensitive neurons to capsaicin may lead to possibly irreversible damage of the neuronal membranes [2]. Therefore, restrictions should apply for the medicinal use of herbal preparations containing capsaicins.

In order to limit the risk for irreversible neuronal damage the duration of continuous use should be restricted to a maximum of 3 weeks. The administration is contraindicated on broken skin, wounds and eczemas. Contact with mucous membranes should be avoided. As capsaicinoids act via a thermosensitive receptor the application of additional sources of heat should be avoided.

Antimicrobial resistance

Not applicable.

4.3 Strength, posology and treatment duration

Medicated plaster

Strength: one medicated plaster (22 × 14 cm) containing soft extract of Capsici fructus, corresponding to 11 mg capsaicinoids expressed as capsaicin (= 35 µg/cm^2) or one medicated plaster (12 × 18 cm) containing soft extract of Capsici fructus, corresponding to 4.8 mg capsaicinoids expressed as capsaicin (= 22 µg/cm^2).

Posology (adults and the elderly): a maximum of 1 plaster per day. There should be an interval of at least 12 hours before a new plaster is applied at the same application area.
Use in children and adolescents under 18 years of age is not recommended.

Semi-solid dosage forms

Strength: 40 - 53 mg capsaicinoids/100 g.

Posology (adults and the elderly): to be applied in a thin layer on the affected area two to four times daily.

Treatment duration: the recommended treatment duration is 2 weeks, maximum 3 weeks. After 3 weeks, a break of at least 2 weeks is required [2,4].

4.4 Special populations (paediatric, elderly, hepatic and renal impairment, pregnancy and breast-feeding, others)

Use in children and adolescents is not considered in the monograph as safety and efficacy in this age group is not supported by published data from clinical trials.

There are no data from use in pregnant women.

Animal studies have shown reproductive toxicity after high subcutaneous doses of capsaicin. Capsaicin crosses the placenta and may pass into breast milk. Although prenatal and neonatal effects of capsaicin occurred at doses in excess of the maximum clinical dose of plaster/semi-solid dosage forms, the plaster/semi-solid dosage form should only be used during pregnancy and lactation after a careful risk-benefit assessment.

No fertility data are available [2,4].

4.5 Risk mitigation measures

Table 5 - Identified risk and mitigation measures

Identified risk(s)	Mitigation measures
Masking effect, delayed diagnosis and tolerance	Package size for 10-14 days. Duration of treatment: 10-14 days. Prolonged contact of sensitive neurons to capsaicin may lead to possibly irreversible damage of the neuronal membranes.
Pregnancy and lactation	Contraindication in pregnancy and lactation should be in the package leaflet.
Children	The use of capsicum in children is not recommended, therefore this information should be in the package leaflet.

4.6 Post-marketing data

Nil.

4.7 Public health/Socioeconomic impact

The classification as non-prescription is in line with the classification of other medicines and no specific risks regarding capsicum use impacting public health have been identified.

Conclusion of Second level assessment

The assessment of this level allows the decision that the active substance, under described conditions, could have **non-prescription status.**

RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Non-prescription status.

Under the conditions described in this document, the active substance has non-prescription status.

REFERENCES

[1] European Pharmacopoeia, Monograph 1859 Capsicum (accessed in May 2025 from https://pheur-online.edqm.eu/home).

[2] European Medicines Agency, Committee on Herbal Medicinal Products: EMA/HMPC/ 674138/2013 - Assessment report on Capsicum annuum L. var. minimum (Miller) Heiser and small fruited varieties of Capsicum frutescens L., fructus, 2015 (accessed in May 2025 from https://www.ema.europa.eu/en/documents/herbal-report/final-assessment-report-capsicum-annuum-l-var-minimum-miller-heiser-and-small-fruited-varieties-capsicum-frutescens-l-fructus_en.pdf).

[3] European Pharmacopoeia, Monograph 2336 Capsicum oleoresin, refined and standardised (accessed in May 2025 from https://pheur-online.edqm.eu/home/).

[4] European Medicines Agency, Committee on Herbal Medicinal Products: EMA/HMPC/ 674139/2013 - European Union herbal monograph on Capsicum annuum L. var. minimum (Miller) Heiser and small fruited varieties of Capsicum frutescens L., fructus, 2015 (accessed in May 2025 from https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-capsicum-annuum-l-var-minimum-miller-heiser-and-small-fruited-varieties-capsicum-frutescens-l-fructus_en.pdf).

List of authors

Overall EBR author: Denisse Mazilu (National Medicines Agency, Romania)

Introduction and Classification of herbal medicines sections (sections common to all EBRs for herbals) - drafted within the Herbals Working Group by Sandra Monteiro (Infarmed - National Authority of Medicines and Health Products, Portugal) in collaboration with (in alphabetical order): Elona Cilku (MALMED - Agency for Medicines and Medical Devices, North Macedonia), Denisse Mazilu (National Medicines Agency, Romania), Guoda Radavičiūtė (State Medicines Control Agency of Lithuania), Katarzyna Żywiec (Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Poland), and the EDQM Secretariat (Daniela Mayerová).