



NATURAL HEALTH PRODUCT COUNTERIRRITANTS

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLA) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredients.

Definition of Counterirritant

An externally applied substance that causes irritation or mild inflammation of the skin for the purpose of relieving pain in muscles or joints by reducing inflammation in deeper adjacent structures (Medline 2012; MediLexicon 2012; US FDA 1983).

Notes

- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- The solidus (/) indicates that the terms and/or statements are synonymous. Either term or statement may be selected by the applicant.

Date

March 7, 2017

Proper name(s), Common name(s), Source material(s) and Dose(s)

Table 1 Medicinal ingredients

Proper name ³	Common name ³	Source information ^{1,2,3}	Dose ⁴
3-isothiocyanato-1-propene allyl isothiocyanate isothiocyanic acid allyl ester	allyl isothiocyanate	allyl isothiocyanate (CAS No. 57-06-7)	0.5 - 5.0 %
ammonium hydroxide	ammonium hydroxide/ammonia water	ammonium hydroxide (CAS No. 1336-21-6)	1.0 - 2.5 %
d-camphor (1 <i>R</i> , 4 <i>R</i>)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one	d-camphor/(+)-camphor/natural camphor/camphor	d-camphor (CAS No. 464-49-3)	3 - 11 %
dl-camphor (1 <i>RS</i> , 4 <i>RS</i>)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one	dl-camphor/(+)-camphor/racemic camphor	dl-camphor (CAS No. 76-22-2)	3 - 11 %
(<i>E</i>)-8-methyl- <i>N</i> -vanillyl-6-nonenamide	capsaicin	capsaicin (CAS No. 404-86-4)	0.025 - 0.25 %

Proper name ³	Common name ³	Source information ^{1,2,3}	Dose ⁴
(6 <i>E</i>)- <i>N</i> -[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-6-nonenamide			
eucalyptus globulus	eucalyptus essential oil/eucalyptus globulus leaf essential oil	eucalyptus globulus leaf (CAS No. 8000-48-4)	0.5 - 25.0 %
1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane 1,8-epoxy- <i>p</i> -menthane 1,8 cineole	eucalyptol/cineole	eucalyptol (CAS No. 470-82-6)	0.5 - 20.0 %
1 <i>H</i> -imidazole-4-ethanamine, dihydrochloride 2-imidazol-4-ylethylamine dihydrochloride 4-(2-aminoethyl)imidazole dihydrochloride	histamine dihydrochloride	histamine dihydrochloride (CAS No. 56-92-8)	0.025 - 0.1 %
l-menthol (1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-5-methyl-2-(propan-2-yl)cyclohexan-1-ol (1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-5-methyl-2-(1-methylethyl)-cyclohexanol	l-menthol/menthol	l-menthol (CAS No. 2216-51-5)	1.25 - 16 %
dl-menthol (1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-rel-5-methyl-2-(1-methylethyl)-cyclohexanol (1 <i>RS</i> ,2 <i>RS</i> ,5 <i>RS</i>)-(±)-5-Methyl-2-(1-methylethyl)cyclohexanol	dl-menthol/racemic menthol	dl-menthol (CAS No. 89-78-1)	1.25 - 16 %
3-pyridinecarboxylic acid methyl ester	methyl nicotinate	methyl nicotinate (CAS No.93-60-7)	0.25 - 1.0 %
methyl 2-hydroxybenzoate 2-hydroxybenzoic acid methyl ester 2-(methoxycarbonyl)phenol	methyl salicylate	methyl salicylate (CAS No.119-36-8)	10 - 30 %
turpentine essential oil	turpentine essential oil/turpentine oil	turpentine essential oil (CAS No. 8006-64-2)	6 - 50 %

¹. The CAS number may be provided as additional information on the PLA and label, but is not required.

². All ingredients, except ammonium hydroxide, must be pharmacopoeial grade (see Table 4 in the specifications below).

³. At least one of the following references was consulted per proper name, common name and source information: Ph.Eur. 2013; BP 2012; Merck 2012; NLM 2012; USP 36; ChEBI 2011; CTFA 2008; Bruneton 1999.

⁴. At least one of the following references was consulted per dosage: JC 2012; AU TGA 2007; Janjua et al. 2004; ESCOP 2003; APhA 2002; WHO 2002; Blumenthal et al. 2000; CPhA1996; Mathias et al. 1995; US FDA 1983, 1979.

Table 2 Complementary ingredients (safety only)

Proper name ³	Common name ³	Source information ^{1,2,3}	Dose ⁴
clove essential oil syzygium aromaticum	clove essential oil	syzygium aromaticum flower bud (CAS No. 8000-34-8)	0.1 - 2.0 %
5-methyl-2-(propan-2-yl)phenol 5-methyl-2-(1-methylethyl)-phenol 5-methyl-2-isopropyl-1-phenol 1-methyl-3-hydroxy-4-isopropylbenzene	thymol	thymol (CAS No.89-83-8)	0.1 - 2 %

¹. The CAS number may be provided as additional information on the PLA and label, but is not required.

². All ingredients must be pharmacopoeial grade (see Table 4 in the specifications below).

³. At least one of the following references was consulted per proper name, common name and source information: Ph.Eur. 2013; BP 2012; Merck 2012; NLM 2012; USP 36; ChEBI 2011; Bruneton 1999.

⁴. The following reference was consulted for the dosage: US FDA 1979.

Route(s) of administration

Topical

Dosage form(s)

Those that are suited to topical administration and are established, and scientifically-recognized dosage forms, including aerosols, creams, emulsions, gels, liniments, liquids, liquid sprays, lotions, oils, ointments, pump sprays, roll-ons, sprays, salves, semi-solid waxes, and tinctures.

Plaster, compress or patch

Menthol, methyl salicylate, eucalyptus oil and eucalyptol are the only medicinal ingredients allowed in these forms (Higashi et al. 2010).

Use(s) or Purpose(s) Statement(s) to the effect of

Products containing an ingredient in Table 1

Temporarily relieves aches and pains of muscles and joints associated with one or more of the following: Simple backache, lumbago, strains and sprains (involving muscles, tendons, and/or ligaments), and arthritis.

Dose(s)

Subpopulation(s)

Adults, adolescents, and children ≥ 2 years

Quantity(ies)

Refer to Tables 1 and 2 above.

Permitted combinations

- Clove essential oil and thymol must be used in combinations with other medicinal ingredients in Table 1, as they cannot support the efficacy of the product on their own (US FDA 1983; US FDA 1979).
- Except as noted above, any ingredient from Table 3 can be combined with other ingredients from the table provided that the combination contains only one ingredient from each group and that each ingredient is within the quantities given in Tables 1 and 2 (US FDA 1983).
- Group B1 ingredients may be used in combination with each other, and this may be combined with any ingredients from the table provided that combination contains only one ingredient from each of the other groups.

Table 3 Permitted combinations¹

Group ²	Ingredient
A	allyl isothiocyanate, ammonium hydroxide, methyl salicylate, turpentine essential oil
B1	camphor, menthol
B2	eucalyptus essential oil, eucalyptol
C	histamine dihydrochloride, methyl nicotinate
D	capsaicin
E	thymol, clove essential oil

¹ See Appendix 1 for grouping rationale and examples of combinations.

² Permitted combinations for all groups are supported by US FDA 1979, except for Group E which is supported by Merck 2012, Martindale 2010, and Leung and Foster 2003.

Directions for use Statement(s) to the effect of

All products

- For external use only.



- Avoid contact with the eyes and mucous membranes (US FDA 1983).
- Do not apply to wounds or damaged skin (US FDA 1983).
- Do not tightly bandage (US FDA 1983).
- Do not apply with external heat, such as an electric heating pad, as this may result in excessive skin irritation or skin burn (Pray 2006; APhA 2002).

For children (2-12 years)

Application should be supervised by an adult (Ragucci et al. 2007; Love et al. 2004).

Products in liquid or semi-solid form

Apply thinly and evenly to affected area up to 3-4 times per day. Rub and/or massage into skin until solution vanishes (US FDA 1979).

Products in compress, plaster or patch form

Do not leave on skin for more than 8 hours (Higashi et al. 2010).

Products in pump spray form

Do not inhale (APhA 2002).

Duration(s) of use Statement(s) to the effect of

Products containing capsaicin as a single medicinal ingredient

May take 1-2 weeks to produce beneficial effects. For use beyond 6 weeks, consult a health care practitioner (Martindale 2010; CPS 2008; APhA 2002; CPhA1996).

All other products (including multiple ingredient products containing capsaicin)

For use beyond 7 days, consult a health care practitioner (US FDA 1983).

Risk information Statement(s) to the effect of

Caution(s) and warning(s)

All products

- Keep out of the reach of children.
- If overdose or accidental ingestion occurs, call a Poison Control Center immediately (CPS 2008; HC 2006).



- If symptoms worsen, or re-occur within a few days, discontinue use and consult a health care practitioner (CPhA1996; US FDA 1983).

Products containing camphor, menthol, and/or methyl salicylate

If you are pregnant or breastfeeding, consult a health care practitioner prior to use (Brinker 2001).

Products containing methyl salicylate and/or methyl nicotinate

If you are taking anticoagulant medications, consult a health care practitioner prior to use (Martindale 2010; APhA 2002).

Products containing methyl nicotinate

If you are taking medication or natural health products that cause dilation of blood vessels, consult a health care practitioner prior to use (APhA 2002).

Contraindication(s)

No statement required.

Known adverse reaction(s)

All products

Hypersensitivity, rashes and/or burning discomfort have been known to occur; in which case, discontinue use (Martindale 2010; Zhang et al. 2008; Hoffman 2003; APhA 2002; McCleane 2000).

Products containing capsaicin

Headache and redness have been known to occur; in which case, discontinue use (Zhang et al. 2008; APhA 2002; McCleane 2000).

Products containing menthol

If you experience pain, swelling or blistering, stop use and get medical help right away (HC 2017).

Non-medicinal ingredients

Must be chosen from the current NNHPD *Natural Health Products Ingredients Database* (NHPID) and must meet the limitations outlined in the database.

Storage conditions

Store in airtight, light-resistant container at room temperature (Ph.Eur. 2013; BP 2012; USP 36).

Specifications

- The finished product specifications must be established in accordance with the requirements described in the NNHPD *Quality of Natural Health Products Guide*.
- The medicinal ingredient must comply with the requirements outlined in the NHPID.
- The medicinal ingredient must be of pharmacopoeial grade and may comply with the specifications outlined in the pharmacopoeial monographs listed in Table 4 below. Please note that other pharmacopoeias may also be acceptable.
- *To mitigate the potential risk to the health of children, child-resistant packaging/containers should be used for (JC 2012 sections C.01.001(2) to (4)):*
 - clove essential oil (Martindale 2010)
 - camphor (AU TGA 2008)
 - eucalyptol (AU TGA 2008)
 - eucalyptus essential oil (AU TGA 2008)
 - methyl salicylate (JC 2012 subsections C.01.031(1) (a) (i); APhA 2002).

Table 4 Monographs published in the British (BP), European (Ph.Eur.), and American (USP) Pharmacopoeias

Pharmacopoeia	Monograph
BP 2012	Natural Camphor Racemic Camphor Cineole Histamine Dihydrochloride Methyl Nicotinate Methyl Salicylate Thymol
Ph.Eur. 2013	D-Camphor Camphor, racemic Cineole Clove Oil Eucalyptus Oil Histamine dihydrochloride Menthol, Racemic Methyl Nicotinate Methyl Salicylate Thymol Turpentine Oil
USP 36 – NF 31	Allyl isothiocyanate Camphor Capsaicin

Pharmacopoeia	Monograph
	Clove Oil Eucalyptol Menthol Methyl Salicylate Thymol

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Appendix 1

Table 5 Groupings based on effects (US FDA 1983; US FDA 1979)

Group	Ingredient	Effect ¹
A	allyl isothiocyanate, ammonium hydroxide, methyl salicylate, turpentine essential oil	Redness, irritation; relatively more potent than other commonly used counterirritants
B1	camphor, menthol	Cooling/warmth/tingling sensation, organoleptic properties
B2	eucalyptus essential oil, eucalyptol	Cooling/warmth/tingling sensation, organoleptic properties
C	histamine dihydrochloride, methyl nicotinate	Vasodilation, vasoactive properties
D	capsaicin	Irritation without rubefaction, although about equal in potency to Group A do not produce redness
E	clove essential oil, thymol	

¹ These are not uses or purposes.

Table 6 Examples of combinations

Combination	Example	Concentration	Group
2 ingredients	methyl salicylate	30.0%	A
	menthol	8.0%	B1
3 ingredients	methyl salicylate	18.0%	A
	camphor	3.5%	B1
	capsaicin	0.7%	D
4 ingredients	methyl salicylate	10.0%	A
	camphor	10.0%	B1
	menthol	10.0%	B1
	capsaicin	0.1%	D