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# **GUIDANCE DOCUMENT**

## **Topical Anaesthetic/Analgesic/Antipruritic Labelling Standard**

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**Health Products and Food Branch**

Canada

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by:</p> <ul style="list-style-type: none"> <li>• minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,</li> <li>• promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.</li> </ul> <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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***Également disponible en français sous le titre :*** Ligne directrice : Norme d'étiquetage pour les analgésiques, anesthésiques et antiprurigineux topiques

## Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document *may be* acceptable provided they are supported by adequate justification. Such approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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## 1. Introduction

This labelling standard describes the requirements necessary to receive marketing authorization (a Drug Identification Number (DIN) or a Natural Product Number (NPN)) for topical anaesthetic, analgesic, and antipruritic products for the temporary relief of pain and itching. This standard does not apply to products to be used on mucous membranes or surrounding areas (i.e. gums, throat, lips, nostrils, eyelids, ears, genitals, or anus).

## 2. Medicinal Ingredients

Topical anaesthetic, analgesic, and antipruritic products are classified as natural health products (NHPs) if they contain medicinal ingredients from Table 1 or in combination with ingredients from Table 3 only. Applicants applying for a NPN should use the appropriate forms, templates, and guidance.

Topical anaesthetic, analgesic, and antipruritic products are classified as drugs if they contain at least one medicinal ingredient from Table 2 or in combination with ingredients from Table 4. Applicants applying for a DIN should use the appropriate forms, templates, and guidance.

**Table 1: NHP topical anaesthetic/analgesic/antipruritic medicinal ingredients and associated doses**

**(A) Amine and “caine”-type**

Proper name(s) <sup>1</sup>	Common name(s) <sup>2</sup>	Source material(s) <sup>1</sup>	Quantity
4-Aminobenzoic acid, ethyl ester	Benzocaine	Benzocaine para-Aminobenzoic acid	5-20%

<sup>1</sup> At least one of the following references was consulted: USP 34; Merck 2014

<sup>2</sup> At least one of the following references was consulted: USP 34; Gottschalck and McEwen 2004

**(B) Alcohols and ketones**

Proper name(s) <sup>3</sup>	Common name(s) <sup>4</sup>	Source material(s) <sup>5</sup>	Quantity
<b>alpha-Hydroxytoluene</b>	<b>Benzyl alcohol</b>	<b>Benzyl alcohol</b>	<b>10-33%</b>
<b>(1R, 4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one</b> <b>d-Camphor</b>	<b>(+)-Camphor</b> <b>d-Camphor</b> <b>Camphor</b> <b>Natural camphor</b>	<b>(+)-Camphor</b> <b>d-Camphor</b>	<b>0.1-3%</b>
<b>(1RS, 4RS)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one</b> <b>dl-Camphor</b>	<b>(+)-Camphor</b> <b>dl-Camphor</b> <b>Racemic camphor</b>	<b>(+)-Camphor</b> <b>dl-Camphor</b>	
<b>Juniperus oxycedrus</b>	<b>Juniper tar</b>	<b>Twig wood of <i>Juniperus oxycedrus</i> L.</b>	<b>1-5%</b>
<b>l-Menthol</b> <b>(1R,2S,5R)-5-methyl-2-(1-methylethyl)-cyclohexanol</b> <b>(1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexan-1-ol</b>	<b>(-)-Menthol</b> <b>l-Menthol</b> <b>Menthol</b>	<b>(-)-Menthol</b> <b>l-Menthol</b>	<b>0.1-1%</b>
<b>dl-Menthol</b> <b>(1R,2S,5R)-rel-5-methyl-2-(1-methylethyl)-cyclohexanol</b> <b>(1RS,2RS,5RS)-(±)-5-Methyl-2-(1-methylethyl)cyclohexanol</b>	<b>(+)-Menthol</b> <b>dl-Menthol</b> <b>Racemic menthol</b>	<b>(+)-Menthol</b> <b>dl-Menthol</b>	
<b>Phenol</b>	<b>Phenol</b>	<b>Phenol</b>	<b>0.5-1.5%</b>
<b>Phenolate sodium</b>	<b>Phenolate sodium</b>	<b>Phenolate sodium</b>	<b>0.5-1.5%</b>
<b>1,3-benzenediol</b> <b>m-dihydroxybenzene</b>	<b>Resorcinol</b>	<b>Resorcinol</b>	<b>0.5-3%</b>

<sup>3</sup> At least one of the following references was consulted: USP 34; Merck 2014; Gottschalck and McEwen 2004; Ph.Eur. 2011; BP 2012; NIH 2014; ChEBI 2013; Rowe *et al.* 2013

<sup>4</sup> At least one of the following references was consulted: USP 34; Merck 2014; Gottschalck and McEwen 2004; Ph.Eur. 2011; BP 2012; NIH 2014

<sup>5</sup> At least one of the following references was consulted: USP 34; Merck 2014; Gottschalck and McEwen 2004; NIH 2014; McGuffin *et al.* 2000

**Table 2: Drug topical anaesthetic/analgesic/antipruritic medicinal ingredients and associated doses**

**(A) Amine and “caine”-type**

Medicinal ingredient preferred name	Quantity
Butamben picrate	1%
Dibucaine/Dibucaine hydrochloride	0.25-1%
Dimethisoquin hydrochloride	0.3-0.5%
Dyclonine hydrochloride	0.5-1%
Lidocaine/Lidocaine hydrochloride	0.5-5%
Pramoxine hydrochloride	0.5-1%
Tetracaine/Tetracaine hydrochloride	1-2%

**(B) Alcohols and ketones**

Medicinal ingredient preferred name	Quantity
Camphorated metacresol:	
Camphor	3-10.8%
Metacresol	1-3.6%

**(C) Antihistamines**

Medicinal ingredient preferred name	Quantity
Diphenhydramine hydrochloride	1-2%
Tripelennamine hydrochloride	0.5-2%

**Table 3: NHP skin protectant ingredients and associated doses**

<b>Proper name(s)<sup>6</sup></b>	<b>Common name(s)<sup>7</sup></b>	<b>Source material(s)<sup>8</sup></b>	<b>Quantity<sup>9</sup></b>
<b>(2,5-Dioxo-4-imidazolidinyl)urea</b>	<b>Allantoin</b> <b>N-(2,5-Dioxo-4-imidazolidinyl) urea</b> <b>5-Ureidohydantoin</b> <b>Glyoxyldiureide</b>	<b>Allantoin</b>	<b>0.5-2%</b>
<b>Aluminum hydroxide</b>	<b>Aluminum hydroxide</b> <b>Aluminum hydrate</b>	<b>Aluminum hydroxide</b>	<b>0.15-5%</b>
<b>Iron oxide (Fe<sub>2</sub>O<sub>3</sub>), mixture with zinc oxide</b>	<b>Calamine</b>	<b>Calamine</b>	<b>1-25%</b>
<b><i>Theobroma cacao</i></b>	<b>Cocoa butter</b> <b>Cacao butter</b> <b>Theobroma oil</b>	<b>Seed of <i>Theobroma cacao</i> L.</b>	<b>≥ 50%</b>
<b>1,2,3-propanetriol</b>	<b>Glycerin</b> <b>Glycerine</b> <b>Glycerol</b>	<b>Glycerol</b>	<b>20-45%</b>
<b>Kaolin</b>	<b>Kaolin</b> <b>Argilla</b> <b>Bolus alba</b> <b>China clay</b> <b>Hydrated aluminum silicate</b> <b>Porcelain clay</b> <b>White bole</b>	<b>Kaolin</b>	<b>4-20%</b>

<sup>6</sup> At least one of the following references was consulted: USP 34; Merck 2014; Gottschalck and McEwen 2004; Ph.Eur. 2011; NIH 2014; McGuffin *et al.* 2000

<sup>7</sup> At least one of the following references was consulted: USP 34; Merck 2014; Gottschalck and McEwen 2004; Ph.Eur. 2011; BP 2012

<sup>8</sup> USP 34

<sup>9</sup> At least one of the following references was consulted: Berardi *et al.* 2002; US FDA 2003; US FDA 1990



<b>Proper name(s)<sup>6</sup></b>	<b>Common name(s)<sup>7</sup></b>	<b>Source material(s)<sup>8</sup></b>	<b>Quantity<sup>9</sup></b>
<b>Shark Liver Oil</b> (Gottschalck and McEwen 2004; Merck 2014)	<b>Shark Liver Oil</b>	<b>Liver from sharks</b> (organisms in the orders <i>Carcharhiniformes</i> , <i>Heterodontiformes</i> , <i>Hexanchiformes</i> , <i>Lamniformes</i> , <i>Orectolobiformes</i> , <i>Pristiophoriformes</i> , <i>Squaliformes</i> , and <i>Squatinaformes</i> ) (Gottschalck and McEwen 2004)	<b>3%</b>
<b>Acetic acid; zinc salt</b>	<b>Zinc acetate</b> <b>Acetic acid, zinc salt</b>	<b>Zinc acetate</b> <b>Acetic acid, zinc salt, dihydrate</b>	<b>0.1-2%</b>
<b>Carbonic acid, zinc salt (1:1)</b>	<b>Zinc carbonate</b>	<b>Zinc carbonate</b>	<b>0.2-2%</b>
<b>Zinc oxide<sup>10</sup></b>	<b>Zinc oxide</b>	<b>Zinc oxide</b>	<b>1-25%</b>

**Table 4: Drug skin protectant ingredients and associated doses**

<b>Medicinal ingredient preferred name</b>	<b>Quantity</b>
<b>Dimethicone</b>	<b>1-30%</b>
<b>Petrolatum</b>	<b>≥ 30%</b>
<b>White petrolatum</b>	<b>≥ 30%</b>

<sup>10</sup> Products being manufactured using USP Grade Zinc Oxide Ointment or Zinc Oxide Paste should ensure that the final quantity of zinc oxide does not exceed 25%. Manufacturers must list all non-medicinal ingredients on product licence application form and label.

## 2.1 Permitted combinations

Combinations of anaesthetic/analgesic/antipruritic medicinal ingredients:

- Any single ingredient in Table 1 (A) or Table 2 (A) with any single ingredient in Table 1 (B) or Table 2 (B).
- Any single ingredient in Table 1 (B) or Table 2 (B) with any single ingredient in Table 2 (C).
- Any one of: Benzyl alcohol, Juniper tar, Phenol, Phenolate sodium, or Resorcinol (as per Table 1 (B)) combined with Camphor and Menthol (as per Table 1 (B)).
- Camphor (3-10.8%) and Phenol (4.7 %) in a light mineral oil USP vehicle.

Combinations of anaesthetic/analgesic/antipruritic medicinal ingredients and skin protectant ingredients:

- Any single ingredient in Tables 1 or 2 or any permitted combination outlined above may be combined with a skin protectant ingredient (as listed in Tables 3 and 4) or combination of skin protectant ingredients.

Note: The declaration of a skin protectant ingredient as a medicinal ingredient is optional. However, if it is declared as medicinal, then the concentration of the ingredient must meet the required level as per Tables 3 and 4.

## 3. Route of administration

Topical

## 4. Dosage forms

Acceptable dosage forms: Lotion, solution, cream, gel, liquid, ointment, spray [including non-pressurized sprays, continuous (bag-on-valve) sprays, and aerosol {non-chlorofluorocarbons (CFC)} based sprays], and powder. Wipes are an acceptable dosage form for NHPs.

## 5. Uses or purposes

Statement(s) to the effect of:

*For products containing a topical anaesthetic/analgesic/antipruritic ingredient (Tables 1 and 2):*

- For temporary relief of pain and/or itching associated with minor burns, sunburn, minor cuts, scrapes, insect bites or minor skin irritations.

*For products containing a topical anaesthetic/analgesic/antipruritic ingredient (Tables 1 and 2) in combination with a skin protectant ingredient (Tables 3 and 4): \*\**

- For temporary relief of pain and/or itching associated with minor burns, sunburn, minor cuts, scrapes, insect bites or minor skin irritations and for temporary protection of minor skin irritations.

\*\* Note: If such a claim is made, then the skin protectant ingredient(s) must be declared as a medicinal ingredient on the label and meet the required concentration as per Tables 3 and 4.

## 6. Directions for use

Statement(s) to the effect of:

- Adults and children two (2) years of age and older: Apply (Spray) to affected area not more than 3 to 4 times daily.

## 7. Risk information

Statement(s) to the effect of:

### 7.1 Cautions and warnings

**For all products:**

- For external use only.<sup>11</sup>
- Keep out of reach of children.
- For children (2 - 12 years): Application should be supervised by an adult.
- Avoid contact with eyes; if this happens, rinse thoroughly with water.<sup>10</sup>
- If condition worsens or if symptoms persist for more than seven (7) days or clear up and occur again within a few days, discontinue use and consult a health care practitioner.<sup>10, 12</sup>

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<sup>11</sup> US FDA 1983

<sup>12</sup> Berardi *et al.* 2002

- If overdose or accidental ingestion occurs, call a Poison Control Centre immediately.<sup>13</sup>

**For butamben picrate:**

- This product stains skin and clothing yellow.<sup>10</sup>

**For glycerin, aluminum hydroxide:**

- Consult a health care practitioner prior to use on children less than six (6) months of age.<sup>14</sup>

**For zinc acetate:**

- Consult a health care practitioner prior to use on children less than two (2) years of age.<sup>13</sup>

## 7.2 Contraindications

**For all drug products:**

- Do not use if you are allergic to any of the ingredients.

**For butamben picrate, resorcinol:**

- Do not apply over large areas of the body.<sup>10</sup>

**For dibucaine, dibucaine hydrochloride:**

- Do not use in large quantities, particularly over raw surfaces or blistered areas.<sup>10</sup>

**For benzocaine, lidocaine, lidocaine hydrochloride, tetracaine, tetracaine hydrochloride:**

- Do not use under a bandage.<sup>15, 16</sup>
- Do not use in large quantities or over large areas of the body.<sup>14, 17</sup>
- Stop use and consult a health care practitioner if the following symptoms appear: weakness, confusion, headache, difficulty breathing and/or pale, grey or blue coloured skin as these may be signs of methemoglobinemia, a rare disorder, which may appear up to two (2) hours after use.<sup>16, 18</sup>

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<sup>13</sup> CPS 2014

<sup>14</sup> US FDA 2003

<sup>15</sup> US FDA 2009

<sup>16</sup> Hahn et al. 2004

<sup>17</sup> Health Canada 2012

<sup>18</sup> Health Canada 2011

- Do not use over raw surfaces or blistered areas.<sup>10, 19, 20</sup>

**For camphorated metacresol, phenol, phenolate sodium:**

- Do not apply over large areas of the body or under a bandage.<sup>10</sup>

**For diphenhydramine hydrochloride:**

- Do not use on large areas of the body or with any other product containing diphenhydramine, even one taken by mouth.<sup>21</sup>

**7.3 Known adverse reaction(s)**

**For benzocaine:**

- Hypersensitivity/allergy is known to occur; in which case, discontinue use.<sup>11, 16</sup>

**8. Non-medicinal ingredients**

Non-medicinal ingredients must be chosen from the current Natural Health Products Ingredients Database and must meet the limitations outlined in that database.

Non-medicinal ingredients must be restricted to those substances, necessary for the formulation of the dosage form. Their concentration must not exceed the minimum required to provide their intended effect. They must be harmless in the amounts used, their presence must not affect the therapeutic efficacy or safety of the medicinal ingredients and they must not interfere with assays and tests for the medicinal ingredients and, if present, antimicrobial preservatives. Sponsors should be aware that ingredients of botanical origin added as non-medicinal ingredients must comply with the Health Canada Policy *Herbs Used as Non-Medicinal Ingredients in Nonprescription Drugs for Human Use* (1995).

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<sup>19</sup> CPhA 2002

<sup>20</sup> Martindale 2014

<sup>21</sup> US FDA 2002

## 9. Specifications

### **For all products:**

This labelling standard describes those requirements that are specific to this class of drugs and to natural health products (NHPs). Any change to the manufacturing process that impacts the safety and efficacy of the ingredients, such as the use of novel technology (e.g. nanotechnology), requires supporting data and will be reviewed outside the labelling standard.

Guidance Document Labelling of Pharmaceutical Drugs for Human Use: This guidance document should be consulted for applicable labelling requirements.

### **For products containing ingredients from Table 1 NHP medicinal ingredients:**

Products must comply with the minimum specifications in the current Natural and Non-prescription Health Products Directorate (NNHPD) Compendium of Monographs.

The finished product must comply with the minimum specifications outlined in the NNHPD Quality of Natural Health Products Guide (Health Canada 2013).

### **For products containing ingredients from Table 2 drug medicinal ingredients:**

Products must comply with the requirements in the *Food and Drugs Act* and associated Regulations. It is also noted that all products are subject to Part C, Division 2 of the *Food and Drug Regulations*.

When applicable, the medicinal ingredient(s) should comply with the specifications outlined in the associated monograph from the standards listed on Schedule B to the *Food and Drugs Act*.

Where no Schedule B monograph exists for the finished product's dosage form, specifications should be similar to those of a comparable compendial dosage form demonstrating the product's identity, potency, purity and quality.

Products that contain medicinal ingredients not included in Table 2 may be considered New Drugs as per section C.08.001 of the *Food and Drug Regulations*.

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## **Appendix 1: Dosage forms that fall outside the scope of this labelling standard**

The following dosage forms for topical anaesthetic/analgesic/antipruritic products are associated with indications of use that fall outside the scope of this labelling standard:

- Patch
- Wipe (for drug products)

These, as well as all other dosage forms not identified as acceptable in the ‘Dosage form(s)’ section of this document, require assessment outside of the labelling standard stream.

## **Appendix 2: Uses or purposes that fall outside the scope of this labelling standard**

The following indications for topical anaesthetic/analgesic/antipruritic products would require a review outside of the labelling standard and applicants/sponsors may request a pre-submission meeting to discuss appropriate supporting data. These include, but are not limited to:

- Male genital desensitizer
- Numbing of skin prior to cosmetic procedures (e.g. laser hair removal)
- Numbing of skin prior to medical procedures (e.g. mammograms; vaccinations; minor skin surgery)
- Any indication suggesting an oral, buccal, otic, rectal, nasal, or oromucosal route of administration
- Use on poison ivy, eczema, or rashes
- Treatment of moles, cold sores, or warts