Health Canada Santé Canada

NATURAL HEALTH PRODUCT

PSEUDOEPHEDRINE
Children 6-11 years

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

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.

Compliance with Precursor Control Regulations:

The *Precursor Control Regulations* (PCR) (JC 2018a) allows Canada to fulfill its international obligations with respect to the *United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988,* and provides a framework for the regulation of activities involving precursor chemicals which can be used in the production of illicit drugs and substances. Under the PCR, regulated chemicals are grouped into two classes: Class A and Class B. For Class A precursors such as pseudoephedrine and/or products containing them, persons wishing to be involved in activities such as importation, exportation, production, packaging, selling, and/or providing must first obtain a licence.

Further information regarding compliance with the PCR, including application forms and guidance documents pertaining to the application for a Class A precursor licence, is available at: http://www.healthcanada.gc.ca/precursors.

Date September 25, 2018

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

Table 1. Proper name(s), Common name(s), Source material(s)

Proper name(s)	Common name(s)	Source material(s)
		Common name(s)
▸ (1S,2S)-2-Methylamino-1-phenylpropan-1-ol ▸ (alphaS)-alpha-[(1S)-1-(Methylamino)ethyl]benzenemethanol ▸ d-psi-Ephedrine	Pseudoephedrine	▸ Pseudoephedrine ▸ Pseudoephedrine hydrochloride ▸ Pseudoephedrine sulfate

References: Proper names: NLM 2018, O'Neil et al. 2018; Common name: NLM 2018, O'Neil et al. 2018; Source materials: NLM 2018, O'Neil et al. 2018.

Route of administration

Oral

Dosage form(s)

This monograph excludes foods or food-like dosage forms as indicated in the Compendium of Monographs Guidance Document.

Acceptable dosage forms for the age category listed in this monograph and specified route of administration are indicated in the Compendium of Monographs Guidance Document.

Use(s) or Purpose(s)

- Used as a decongestant (for common cold) (O'Neil et al. 2018; HC 2009; Williamson 2003; Mills and Bone 2000; Bright et al. 1981; Bye et al. 1980).
- Used to relieve nasal congestion (due to the common cold) (O'Neil et al. 2018; HC 2009; Williamson 2003; Mills and Bone 2000; Bright et al. 1981; Bye et al. 1980).
- Nasal decongestant (O'Neil et al. 2018; HC 2009; Williamson 2003; Mills and Bone 2000; Bright et al. 1981; Bye et al. 1980).

Dose(s)

Subpopulation(s)

Children 6 to 11 years

Quantity(ies)

30-120 milligrams pseudoephedrine per day; Not to exceed 30 milligrams per single dose (Simons et al. 1996; Dickerson et al. 1978).

Direction(s) for use

- Take a single dose every 4-6 hours up to 4 times a day (HC 2009).
- Do not give with any other cough and cold medications since harm may occur (HC 2009).

Duration(s) of use

Consult a health care practitioner/health care provider/health care professional/doctor/physician for use beyond 7 days (HC 2009; US FDA 2004).

Risk information

Caution(s) and warning(s)

- Keep out of reach of children (HC 2009).
- Consult a health care practitioner/health care provider/health care professional/doctor/ physician if symptoms persist or worsen.
- Consult a health care practitioner/health care provider/health care professional/doctor/ physician prior to combining this product with other medications, including natural health products, prescription drugs or non-prescription drugs (HC 2009).
- Consult a health care practitioner/health care provider/health care professional/doctor/ physician prior to use if the child has cardiovascular disease, diabetes, glaucoma, pre-existing psychiatric/behavioural conditions, renal dysfunction, seizure/central nervous system disorders or thyroid problems (Brinker 2010; HC 2009; Eccles 2006; Bensky et al. 2004; Williamson 2003; Blumenthal et al. 2000; Mills and Bone 2000; Simons et al. 1996; Lambert 1987).
- Consult a healthcare practitioner/health care provider/health care professional/doctor/ physician prior to use if the child is taking other products which contain caffeine, ephedrine, phenylpropanolamine or pseudoephedrine (Brinker 2010; Mills and Bone 2005; Greenway et al. 2004; Naik and Freudenberger 2004).
- Call a Poison Control Centre or health care practitioner/health care provider/health care professional/doctor/physician immediately in case of overdose, even if you do not notice any signs or symptoms (HC 2009).
- To mitigate the potential risk to the health of children, it is recommended that child resistant packaging/containers be used as described in Sections C.01.001(2) to (4), and subsection C.01.031(1) (a) (i) of the *Food and Drug Regulations* (JC 2018b).

Contraindication(s)

No statement required.

Known adverse reaction(s)

Stop use if allergic reactions, breathing difficulties, convulsions, drowsiness, hallucinations or rapid heart rate occur (Blumenthal et al. 2000; Dickerson et al. 1978).

Non-medicinal ingredients

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

Storage Conditions

Store protected from light and moisture (BP 2009; USP 32 2009; Ph. Eur. 2007).

Specifications

- The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Product Directorate (NNHPD) Quality of Natural Health Products Guide.
- The medicinal ingredient must comply with the requirements outlined in the NHPID.

References cited

Bensky D, Clavey S, Stoger E. Gamble A. 2004. Chinese Herbal Medicine: Materia Medica, 3RD Edition. Seattle (WA): Eastland Press.

Blumenthal M, Goldberg A, Brinkmann J, editors. 2000. Herbal Medicine: Expanded Commission E Monographs. Boston (MA): Integrative Medicine Communications.

BP 2009: British Pharmacopoeia Commission. 2009. British Pharmacopoeia, 2009, Volume 1. London (GB): The Stationary Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA).

Bright TP, Sandage Jr BW, Fletcher HP. 1981. Selected cardiac and metabolic responses to pseudoephedrine with exercise. The Journal of Clinical Pharmacology 21:488-492.

Brinker F. Herb Contraindications and Drug Interactions, 4th edition. Sandy (OR): Eclectic Medical Publications; 2010.

Bye CE, Cooper J, Empey DW, Fowle ASE, Hughes DTD, Letley E, O'Grady J. 1980. Effects of pseudoephedrine and tripolidine, alone and in combination, on symptoms of the common cold. British Medical Journal 281(6234):189-190.

Dickerson J, Perrier D, Mayersohn M, Bressler R. 1978. Dose tolerance and pharmacokinetic studies of L (+) pseudoephedrine capsules in man. European Journal of Clinical Pharmacology 14:253-259.

Eccles R. 2006. Substitution of phenylephrine for pseudoephedrine as a nasal decongestant. An illogical way to control methamphetamine abuse. British Journal of Clinical Pharmacology 63(1):10-14.

Greenway FJ, de Jonge L, Blanchard D, Frisard M, Smith, SR. 2004. Effect of a dietary herbal supplement containing caffeine and ephedra on weight, metabolic rate, and body composition. Obesity Research 12(7):1152-1157.

HC 2009: Health Canada Guidance Document: Nonprescription oral paediatric cough and cold labelling standard. Health Products and Food Branch (HPFB). Minister of Public Works and Government Services Canada.

JC 2018a: Justice Canada. 2018. Precursor Control Regulations. Part 1 – Class A Precursors [online]. Ottawa (ON) Department of Justice Canada. [Accessed 2018 July 13]. Available from: http://laws-lois.justice.gc.ca/eng/regulations/SOR-2002-359/index.html

JC 2018b: Justice Canada. 2018. Food and Drug Regulations. Sections C.01.029, C.01.031 and C.01.031.2 (1). Cautionary Statements and Child Resistant Packages. [online]. Ottawa (ON): Department of Justice Canada. [Accessed 2018 July 13]. Available from: http://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/page-97.html
Lambert MT. 1987. Paranoid psychoses after abuse of proprietary cold remedies. British Journal of Psychiatry 151:548-550.

Mills S, Bone K. 2000. Principles and Practice of Phytotherapy. Toronto (ON): Churchill Livingstone.

Mills S, Bone K. 2005. The Essential Guide to Herbal Safety. St. Louis (MO): Elsevier Churchill Livingstone.

Naik SJ, Freudenberger RS. 2004. Ephedra–associated cardiomyopathy. The Annals of Pharmacotherapy 38:400-403.

NLM 2018: United States National Library of Medicine. ChemIDplus Advanced [online]. 2018. Search terms: Pseudoephedrine, Pseudoephedrine Hydrochloride, Pseudoephedrine Sulfate. Bethseda (MD): Specialized Information Services, United States National Library of Medicine, National Institutes of Health, United States Department of Health & Human Services. [Accessed 2018 July 13]. Available from: https://chem.nlm.nih.gov/chemidplus/

O'Neil MJ, Smith A, Heckelman PE, Budavari S, editors. 2018. The Merck Index [Online]: An Encyclopedia of Chemicals, Drugs, and Biologicals, 14th edition. Whitehouse Station (NJ): Merck & Co., Inc. [Accessed 2018 July 13]. Available from: http://www.medicinescomplete.com/mc/merck/current/03608.htm?q=ephedrine&t=search&ss=text&p=1#_hit

Ph. Eur. 2007: European Pharmacopoeia Commission. 2007. European Pharmacopoeia, 6th edition. Strasbourg (FR): Directorate for the Quality of Medicines and HealthCare of the Council of Europe (EDQM).

Simons FE, Gu X, Watson WT, Simons KJ. 1996. Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. Journal of Pediatrics 129(5):729-734.

US FDA 2004: United States Food and Drug Administration. Final Rules Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk; Final Rule [online]. Federal Register, Volume 69, Number 28, February 11, 2004, Rules and Regulations, Docket Number 1995N-0304. Rockville (MD): United States Department of Health and Human Services, U.S. Food and Drug Administration. [Accessed 2018 July 13]. Available from: https://www.gpo.gov/fdsys/pkg/FR-2004-02-11/pdf/04-2912.pdf

USP 32 2009: United States Pharmacopeial Convention. 2009. United States Pharmacopeia and the National Formulary (USP 32 - NF 27). Rockville (MD): The United States Pharmacopeial Convention.

Williamson EM. 2003. Potter's Herbal Cyclopaedia: The Authoritative Reference work on Plants with a Known Medical Use. Saffron Walden (GB): The C.W. Daniel Company Limited.

References reviewed

Aaronson AL, Ehrlich NJ, Frankel DB, Gutman AA, Aaronson DW. 1968. Effective oral nasal decongestion. A double-blind crossover analysis. Annals of Allergy 26(3):145-150.

Burke LM. 2000. Positive drug tests from supplements. Sportscience 4(3):1-5.

CRN 2000: Council for Responsible Nutrition. Safety Assessment and Determination of a Tolerable Upper Limit for Ephedra. [online] Mississauga (ON): Cantox Health Sciences International. [Accessed 2009 November 23]. Available from: http://www.crnusa.org/pdfs/Cantoxreport.doc

Dawson JK, Earnshaw SM, Graham CS. 1995. Dangerous monoamine oxidase inhibitor interactions are still occurring in the 1990s. Journal of Accident and Emergency Medicine 12:4951.

Dingemanse J, Guentert T, Gieschke R, Stabl M. 1996. Modification of the cardiovascular effects of ephedrine by the reversible monoamine oxidase A-inhibitor moclobemide. Journal of Cardiovascular Pharmacology 28(6):856-861.

Drew CD, Knight GT, Hughes DT, Bush M. 1978. Comparison of the effects of D-(-)-ephedrine and L-(+)-pseudoephedrine on the cardiovascular and respiratory systems in man. British Journal of Clinical Pharmacology 6(3):221-225.

Elis J, Laurence DR, Mattie H, Prichard BNC. 1967. Modification by monoamine oxidase inhibitors of the effect of some sympathomimetics on blood pressure. British Medical Journal 2:75-78.

Empey DW, Young GA, Letley E, John GC, Smith P, McDonnell KA, Bagg LR, Hughes DTD. 1980. Dose-response study of the nasal decongestant and cardiovascular effects of pseudoephedrine. British Journal of Clinical Pharmacology 9:351-358.

Farel RM, Fanta CH. 2009. Drug therapy for asthma. New England Journal of Medicine 360(24):2578-2579.

Gurley BJ, Gardner SF, White LM, Wang PL. 1998. Ephedrine pharmacokinetics after the ingestion of nutritional supplements containing Ephedra sinica (ma huang). Therapeutic Drug Monitoring 20(4):439-445.

Haller CA, Jacob P 3rd, Benowitz NL. 2004. Enhanced stimulant and metabolic effects of combined ephedrine and caffeine. Clinical Pharmacology and Therapeutics 75(4):259-273.

HC 1996: 1996 TPD Labelling Standard Ephedrine/Pseudoephedrine. Ottawa (ON): Therapeutic Products Directorate, Health Canada.

HC 2006: A Summary of NHP/DRUG Classification of TPD Category IV Monographs and Labelling Standards Ingredients. Natural Health Products Directorate, Health Canada [Accessed 2009 December 23]. Available from: http://www.hc-sc.gc.ca/dhpmps/prodnatur/applications/licen-prod/monograph/list_mono4-eng.php

HC 2009: First Nations, Inuit & Aboriginal Health. Drug Benefit List 04:00 Anthistamine Drugs. [Accessed 2009 December 23]. Available from: http://www.hc-sc.gc.ca/fniah-spnia/nihbssna/provide-fournir/pharma-prod/med-list/04-00-eng.php

HC 2009: Natural Health Products Ingredients Database. Ingredient Search: ephed [online]. Ottawa (ON): Natural Health Products Directorate, Health Canada. [Accessed 2009 November 27]. Available from: http://webprod.hc-sc.gc.ca/nhpid-bdipsn/ingredsReq.do?srchRchTxt=ephed&srchRchRole=-1&lang=eng

Herridge CF, A'Brook MF. 1968. Ephedrine psychosis. British Medical Journal 2:160.

Hoffman D. 2003. Medical Herbalism: The Science and Practice of Herbal Medicine. Rochester (VT): Healing Arts Press.

IOM 2002: Institute of Medicine. 2002. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington (DC): The National Academy of Sciences.

Jacobs KM, Hirsch KA. 2000. Psychiatric complications of ma-huang. Psychosomatics 41(1):5862.

JC 2009. Justice Canada. Food and Drug Regulations C.R.C., c. 870. Minister of Justice. Available from http://laws.justice.gc.ca/en/showtdm/cr/C.R.C.-c.870.

Laitinen LA, Empey DW, Bye C, Britton MG, McDonnell K, Hughes DTD. 1982. A comparison of the bronchodilator action of pseudoephedrine and ephedrine in patients with reversible airway obstruction. European Journal of Clinical Pharmacology 23:107-109.

HC 2006: A Summary of NHP/DRUG Classification of TPD Category IV Monographs and Labelling Standards Ingredients. Natural Health Products Directorate, Health Canada [Accessed 2009 December 23]. Available from: http://www.hc-sc.gc.ca/dhpmps/prodnatur/applications/licen-prod/monograph/list_mono4-eng.php

MHRA 2009: MHRA Public Assessment Report - Controlling the risk of misuse of medicines containing pseudoephedrine and ephedrine. 2009. London (GB): Medicines and Healthcare products Regulatory Agency.

Mizoguchi H, Wilson A, Jerdack GR, Hull JD, Goodale M, Grender JM, Tyler BA. 2007. Efficacy of a single evening dose of syrup containing paracetamol, dextromethorphan hydrobromide, doxylamine succinate and ephedrine sulfate in subjects with multiple common cold symptoms. International Journal of Clinical Pharmacology and Therapeutics 45(4):230-236.

Mortimer EA. 1977. Drug toxicity from breast milk? Pediatrics 60(5):780-781.

NAPRA 2009: Outline of National Drug Schedules. Search: ephedr [online]. Ottawa (ON). National Association of Pharmacy Regulatory Authorities. [Accessed 2009 December 17]. Available from: http://napra.ca/pages/Schedules/Search.aspx

Salem CB, Slim R, Denguezli M, Sriha B, Hmouda H, Bouraoui K. 2008. Pseudoephedrineinduced acute generalized exanthematous pustulosis. The International Society of Dermatology 47:418-419.

Slodki SJ, Montgomery CA. 1965. Clinical comparison of oxymetazoline and ephedrine in nasal congestion. Current Therapeutic Research, Clinical and Experimental 7:19-22.

TGA 2008: Australian Therapeutic Goods Administration. Personal Import Scheme for

Unapproved Medicines [online]. Symonston (AU): Australian Government Department of Health and Ageing, Therapeutic Goods Administration. [Accessed 2009 November 23]. Available from: http://www.tga.gov.au/import/persimp.htm

Theoharides TC. 1997. Sudden death of a healthy college student related to ephedrine toxicity from a ma huang-containing drink. Journal of Clinical Psychopharmacology 17(5)437-439.

US FDA 1993: United States Food and Drug Administration. Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for Over-the-Counter Human Use; Amendment of Final Monograph for OTC Bronchodilator Drug Products [online]. Federal Register, Volume 58, Number 201, October 20,1993, Final Rule. Docket Number 91N–0323. Rockville (MD): Department of Health and Human Services, U.S. Food and Drug Administration. [Accessed 2009 November 23]. Available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm116064.pdf

US FDA 1997: United States Food and Drug Administration. Dietary Supplements Containing Ephedrine Alkaloids [online]. Federal Register, Volume 62, Number 107, June 4,1997, Proposed Rule. Docket Number 95N–0304. Rockville (MD): Department of Health and Human Services, U.S. Food and Drug Administration. [Accessed 2009 November 23]. Available from: http://frwebgate1.access.gpo.gov/cgi-bin/TEXTgate.cgi?WAISdocID=999886443355+0+1+0&WAISaction=retrieve

White LM, Gardner SF, Gurley BJ, Marx MA, Wang PL, Estes M. 1997. Pharmacokinetics and cardiovascular effects of ma huang (Ephedra sinica) in normotensive adults. The Journal of Clinical Pharmacology 37:116-122.

Whitehouse AM, Duncan JM. 1987. Ephedrine psychosis rediscovered. British Journal of Psychiatry 150:258-261.

Wingert WE, Mundy LA, Collins GL, Chmara ES. 2007. Possible role of pseudoephedrine and other over-the-counter cold medications in the deaths of very young children. Journal of Forensic Science 52(2):487-490.