Health Canada Santé Canada

COD LIVER OIL

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 or the statements are synonymous. Either term or statement may be selected by the applicant.
- The use(s) or purpose(s) statements in this monograph are based on the efficacy of vitamin A, vitamin D, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that are present in cod liver oil. The references used to support these statements refer to the efficacy of these individual constituents and are not specific to cod liver oil.
- Consult Appendix 1 for Adequate Intake (AI), Recommended Dietary Allowance (RDA) and Tolerable Upper Intake Level (UL) definitions for nutrient intake. Refer also to Table 8 in Appendix 2 for RDA and AI values for vitamin A, and to Table 9 in Appendix 3 for RDA and AI values for vitamin D.

Date July 4, 2012

Proper name(s)

Cod liver oil (Ph.Eur. 2012; USP 35)

Common name(s)

Cod liver oil (Ph.Eur. 2012; USP 35)

Source material(s)

Oil from one or more of the following sources in its natural triglyceride/triacylglycerol form and/or its concentrated esterified form:

- Liver of Atlantic cod, *Gadus morhua* L. (Gadidae) (Ph.Eur. 2012; USP 35; ITIS 2004)
- Liver of Greenland cod, *Gadus ogac* Richardson (Gadidae) (Ph.Eur. 2012; USP 35; ITIS 2004)
- Liver of Pacific cod, *Gadus macrocephalus* Tilesius (Gadidae) (Ph.Eur. 2012; USP 35; ITIS 2004)
- Liver from Arctic cod, *Arctogadus glacialis* Peters (1872) (Gadidae) (Ph.Eur. 2012; USP 35; ITIS 2004)

- Liver from all species of Gadidae (Cod family) (BP 2012; Ph.Eur. 2012; USP 35)

Note
- "Atlantic cod, *Gadus morhua*", "Greenland cod, *Gadus ogac*", "Pacific cod, *Gadus macrocephalus*", "Arctic cod, *Arctogadus glacialis*" or any other species of Gadidae must be indicated on the PLA and label as source material information.
- Refer to Appendix 4 for a complete listing of species in the Family Gadidae (Cod).

Route(s) of administration

Oral

Dosage form(s)

- The acceptable pharmaceutical dosage forms include, but are not limited to capsules, chewables (e.g. gummies, tablets), liquids, powders, strips or tablets.
- This monograph is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.

Use(s) or Purpose(s)

Statement(s) to the effect of:

For products providing daily doses of vitamin A at or above the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) (adjusted for the life stage groups):
Helps to prevent vitamin A deficiency (IOM 2006; Shils et al. 2006; Groff and Gropper 2000).

For products providing daily doses of vitamin D at or above the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) (adjusted for the life stage groups):
Helps to prevent vitamin D deficiency (IOM 2011, 2006, 1997; Shils et al. 2006; Groff and Gropper 2000).

For products providing 138-3,000 µg retinol activity equivalents (RAE) (µg vitamin A/all-*trans* retinol (palmitate)), per day:
- Helps to maintain eyesight, skin membranes and immune function (IOM 2006; Shils et al. 2006; Groff and Gropper 2000).
- Helps in the development and maintenance of night vision (IOM 2006; Shils et al. 2006; Groff and Gropper 2000).
- Source of vitamin A, a factor in the maintenance of good health (IOM 2006)

For products providing 1.15-25 µg vitamin D_3/cholecalciferol, per day:

- Helps in the development and maintenance of bones and teeth (IOM 2011; Shils et al. 2006).
- Helps in the absorption and use of calcium and phosphorus (IOM 2011; Shils et al. 2006; Groff and Gropper 2000).
- Source of vitamin D, a factor in the maintenance of good health (IOM 2011).

For products providing 100-1,360 mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA), per day:

- Source of omega-3 fatty acids for the maintenance of good health (Simopoulos 2007; Oh 2005; IOM 2002; Simopoulos 1999)
- Source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for the maintenance of good health (Simopoulos 2007; Oh 2005; IOM 2002; Simopoulos 1999)

For products providing 100-1,360 mg EPA + DHA including at least 100 mg DHA, per day:
Helps support cognitive health and/or brain function (van de Rest et al. 2008; Freund-Levi et al. 2006; Fontani et al. 2005a,b; Haag 2003; Morris et al. 2003; IOM 2002).

For products providing 150-1,360 mg EPA + DHA including at least 150 mg DHA, per day (maximum doses of EPA + DHA in Table 4 below will apply):
Helps support the development of the brain, eyes and nerves in children up to 12 years of age (Agostini 2008; Helland et al. 2008; Ryan and Nelson 2008; Marszalek and Lodish 2005; Haag 2003; IOM 2002; Giedd et al. 1999; Mills 1999).

Dose(s)

Note
The potencies of vitamin A, vitamin D_3 and EPA + DHA must be indicated on the PLA and label, in addition to the dose of Cod liver oil.

Quantities

Table 1 Daily dose for cod liver oil[1]

Life stage group		Cod liver oil			
		Minimum[2]		Maximum[4]	
		(ml/day)[5]	(g/day)	(ml/day)	(g/day)
Infants	0-12 mo	0.83	0.77	0.87	0.80
Children	1-3 y	0.83	0.77	0.87	0.80
	4-8 y	0.83	0.77	1.3	1.2
Adolescents	9-13 y	0.83	0.77	2.4	2.2
	14-18 y	0.83	0.77	4.0	3.7
Adults[3]	≥ 19 y	0.83	0.77	4.3	4.0

[1] BP 2012, Ph.Eur. 2012 or USP 35 grade Cod liver oil must be used to ensure that potencies of vitamin A, vitamin D_3, and EPA + DHA listed in Tables 2, 3 and 4 are met.
[2] The minimum dose of Cod liver oil is based on the minimum quantities of EPA + DHA required for efficacy.
[3] Includes pregnant and breastfeeding women.

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[4] For all subpopulations, the maximum dose is based on the quantity of Cod liver oil providing the maximum daily amount of vitamin A, in µg RAE, according to the UL (IOM 2006).
[5] Based on the specific gravity of Cod liver oil (USP 35)

Potencies

Table 2 Potency[1] for vitamin A palmitate/all-*trans* retinol palmitate in cod liver oil

Life stage group		Vitamin A (µg RAE/day)	
		Minimum[1]Minimum[2]	Maximum[3]
Infants	0-12 mo	138	600
Children	1-3 y	138	600
	4-8 y	138	900
Adolescents	9-13 y	138	1,700
	14-18 y	138	2,800
Adults[4]	≥ 19 y	138	3,000

[1] References for the potency of vitamin A are: BP 2012, Ph.Eur. 2012, and Tischer 1938.
[2] Calculated as the minimum amount of vitamin A available in 0.77 g Cod liver oil, which is the based on the minimum quantities of EPA + DHA required for efficacy.
[3] Maximum potency based on the UL (IOM 2006).
[4] Includes pregnant and breastfeeding women.

Table 3 Potency[1] for vitamin D_3/cholecalciferol in cod liver oil

Life stage group		Vitamin D_3 (µg/day)	
		Minimum[2]	Maximum[3]
Infants	0-12 mo	1.15	5.00
Children	1-3 y	1.15	5.00
	4-8 y	1.15	7.50
Adolescents	9-13 y	1.15	14.06
	14-18 y	1.15	23.12
Adults[4]	≥ 19 y	1.15	25.00

[1] References for the potency of Vitamin D_3 are: BP 2012, Ph.Eur. 2012, and Green 1951.
[2] Based on the minimum amount of vitamin D_3 available in 0.77 g Cod liver oil, and supported by the RDA and AI for.vitamin D_3 (IOM 2011, 2006). See Appendix 1 for definitions and Table 9 in Appendix 3 for RDA and AI values.
[3] For all subpopulations, the maximum potencies are based on the amount of vitamin D_3 available in the quantity of Cod liver oil which provides the maximum daily amount of vitamin A, in µg RAE, according to the UL (IOM 2006).
[4] Includes pregnant and breastfeeding women.

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Table 4 Potency[1] for EPA + DHA in cod liver oil

Life stage group		EPA + DHA (mg/day)	
		Minimum[2]	Maximum[3]
Infants[4]	0-12 mo	100	272
Children	1-3 y	100	272
	4-8 y	100	408
Adolescents	9-13 y	100	765
	14-18 y	100	1,258
Adults[5]	≥ 19 y	100	1,360

[1] References for the potency of EPA + DHA are: BP 2012 and Ph.Eur. 2012.
[2] Restrictions to minimum potency may apply according to Use(s) or Purpose(s) section above.
[3] For all subpopulations, the maximum potencies are based on the amount of EPA + DHA available in the quantity of Cod liver oil which provides the maximum daily amount of vitamin A, in µg RAE, according to the UL (IOM 2006).
[4] USP 35; Rajakumar and Thomas 2005; Stene et al 2003; Linday et al. 2002.
[5] Includes pregnant and breastfeeding women.

Duration(s) of use

No statement required.

Risk information

Caution(s) and warning(s)

No statement required.

Contraindication(s)

No statement required.

Known adverse reaction(s)

No statement required.

Storage condition(s)

Statement(s) to the effect of:

For all products:
Store in airtight container, protected from light (Ph.Eur. 2012; USP 35).

For all products, except those encapsulated:
Refrigerate after opening (Wille and Gonus 1989).

Non-medicinal ingredients

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

Specifications

- The finished product must comply with the minimum specifications outlined in the current NHPD *Compendium of Monographs*.
- The medicinal ingredient may comply with the specifications outlined in the pharmacopoeial monographs listed in Table 5 below.
- Peroxide, anisidine, and totox values of cod liver oil and omega-3 fatty acids derived from cod liver oil must be in accordance with the methods set out by the Association of Analytical Communities (AOAC) and/or Pharmacopoeial analytical methods. These specifications are necessary to ensure the oxidative stability of the cod liver oil and the omega-3 fatty acids from cod liver oil (HC 2007). Refer to Table 6 below.
- The dioxins, polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs); the dioxin-like polychlorinated biphenyls (DL PCBs); and the polychlorinated biphenyls (PCBs) are contaminants in marine oils. Testing for these contaminants are required and must be performed using either the analytical method of the European Commission Regulation EU 252/2012 (EU 2012) or the U.S. Environmental Protection Agency's method 1613B for PCDDs and PCDFs and method 1668A for PCBs (USP 35; US EPA 2010, 2008,1994). Applicants are advised to consult the Council of the European Union document on these contaminants for further information (EU 2011). Refer to Table 7 below.

Table 5 Cod Liver Oil Monographs published in the American (USP), British (BP) and European (Ph.Eur.) Pharmacopoeias

Pharmacopoeia	Monograph
BP	Cod-Liver Oil (Type A) Cod-Liver Oil (Type B)
Ph.Eur.	Cod-Liver Oil, Farmed Cod-Liver Oil (Type A) Cod-Liver Oil (Type B)
USP	Cod Liver Oil

Table 6 Maximum values of oxidative stability parameters for oils from cod liver (HC 2007)

Oxidative stability parameter	Maximum value
Peroxide value (PV)	5 mEq/kg
p-Anisidine value (AV)	20
Totox value	26 (calculated as (2 x PV) + AV)

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Table 7 Maximum levels of dioxins, dioxin-like polychlorinated biphenyls (DL PCB) and polychlorinated biphenyls (PCB) in oils from marine sources

Dioxin, DL PCB, and PCB contaminants	Maximum level	
	EU 1259/2011	USP 35
Dioxins (sum of PCDDs + PCDFs)[1,2]	1.75 pg/g	1.0 pg/g
Sum of dioxins and DL PCBs[1,3]	6 pg/g	
PCBs[4]	200 ng/g	0.5 ppm[5]

1. Expressed in World Health Organization (WHO) toxic equivalents using WHO-toxic equivalent factors (TEFs). Analytical results relating to 17 individual dioxin congeners of toxicological concern are expressed in a single quantifiable unit: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxic equivalent concentration (TEQ) (USP 35; EU 2011).
2. Sum of dioxins: WHO-PCDD/F-TEQ (USP 35; EU 2011)
3. Sum of dioxins and dioxin-like PCBs: WHO-PCDD/F-PCB-TEQ (EU 2011)
4. Sum of PCB congeners 28, 52, 101, 118, 138, 153 and 180 (USP 35; EU 2011)
5. Equivalence: 0.5 ppm = 500 ng/g

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Appendix 1 Definitions

Adequate Intake (AI): The recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate. An AI is used when a Recommended Dietary Allowance (RDA) cannot be determined (IOM 2006).

Recommended Dietary Allowance (RDA): The average daily dietary nutrient intake level sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a particular life stage and gender group (IOM 2006).

Tolerable Upper Intake Level (UL): The highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase (IOM 2006).

Appendix 2 Recommended Dietary Allowance (RDA) and Adequate Intake (AI) for vitamin A

Table 8 RDA and AI* values for vitamin A based on life stage group (IOM 2006)

Life stage group		Vitamin A (µg RAE/day)
Infants	0-6 mo	400*
	7-12 mo	500*
Children	1-3 y	300
	4-8 y	400
Adolescent males	9-13 y	600
	14-18 y	900
Adult males	≥ 19 y	900
Adolescent females	9-13 y	600
	14-18 y	700
Adult females	≥ 19 y	700
Pregnancy	14-18 y	750
	19-50 y	770
Breastfeeding	14-18 y	1,200
	19-50 y	1,300

Appendix 3 Recommended Dietary Allowance (RDA) and Adequate Intake (AI) for vitamin D

Table 9 RDA and AI* values for vitamin D based on life stage group (IOM 2011)

Life stage group		Vitamin D (µg/day)
Infants	0-6 mo	10*
	7-12 mo	10*
Children	1-3 y	15
	4-8 y	15
Adolescent Males	9-13 y	15
	14-18 y	15
Adult Males	19-30 y	15
	31-50 y	15
	51-70 y	15
	>70 y	20
Adolescent Females	9-13 y	15
	14-18 y	15
Adult Females	19-30 y	15
	31-50 y	15
	51-70 y	15
	>70 y	20
Pregnancy	14-18 y	15
	19-50 y	15
Breastfeeding	14-18 y	15
	19-50 y	15

Appendix 4 Species of the Family Gadidae (Nelson 2006)

Subfamily Gadinae

- Genus *Arctogadus* (Dryagin, 1932)
  - East Siberian cod *(Arctogadus borisovi)* (Dryagin, 1932)
  - Arctic cod *(Arctogadus glacialis)* (Peters, 1872)
- Genus *Boreogadus* (Günther, 1862)
  - Polar cod *(Boreogadus saida)* (Lepechin, 1774)
- Genus *Eleginus* (Fischer, 1813)
  - Saffron cod *(Eleginus gracilis)* (Tilesius, 1810)
  - Navaga *(Eleginus nawaga)* (Koelreuter, 1770)
- Genus *Gadiculus* (Guichenot, 1850)
  - Silvery cod *(Gadiculus argenteus argentus)* (Guichenot, 1850)
  - *Gadiculus argenteus thori* (Schmidt, 1914)
- Genus *Gadus* (Linné, 1758)
  - Pacific cod *(Gadus macrocephalus)* (Tilesius, 1810)
  - Atlantic cod *(Gadus morhua)* (Linnaeus, 1758)
  - Greenland cod *(Gadus ogac)* (Richardson, 1836)

Canada

- Genus *Melanogrammus* (Gill, 1862)
  - Haddock *(Melanogrammus aeglefinus)* (Linnaeus, 1758)
- Genus *Merlangius* (Garsault, 1764)
  - Whiting *(Merlangius merlangus)* (Linnaeus, 1758)
- Genus *Microgadus* (Gill, 1865)
  - Pacific tomcod *(Microgadus proximus)* (Girard, 1854)
  - Atlantic tomcod *(Microgadus tomcod)* (Walbaum, 1792)
- Genus *Micromesistius* (Gill, 1863)
  - Southern blue whiting *(Micromesistius australis)* (Norman, 1937)
  - Blue whiting *(Micromesistius poutassou)* (Risso, 1827)
- Genus *Pollachius* (Nilsson, 1832)
  - Atlantic pollock *(Pollachius pollachius)* (Linnaeus, 1758)
  - Saithe *(Pollachius virens)* (Linnaeus, 1758)
- Genus *Theragra* (Lucas in Jordan & Evermann, 1898)
  - Alaska pollock *(Theragra chalcogramma)* (Pallas, 1814)
  - Norwegian pollock *(Theragra finnmarchica)* (Koefoed, 1956)
- Genus *Trisopterus* (Rafinesque, 1814)
  - Norway pout *(Trisopterus esmarkii)* (Nilsson, 1855)
  - Pouting *(Trisopterus luscus)* (Linnaeus, 1758)
  - Poor cod *(Trisopterus minutus)* (Linnaeus, 1758)

Subfamily Ranicipitinae

- Genus *Raniceps* (Oken, 1817)
  - Tadpole fish or tadpole cod *(Raniceps raninus)* (Linnaeus, 1758)

Subfamily Lotinae (cuskfishes**)**

- Genus *Lota* (Oken, 1817)
  - Burbot *(Lota lota)* (Linnaeus, 1758)
- Genus *Brosme* (Oken, 1817)
  - Brosme (cusk) *(Brosme brosme)* (Ascanius, 1772)
- Genus *Molva* (three species) (Lesueur, 1819)
  - Blue ling *(Molva dypterygia)* (Pennant, 1784)
  - Mediterranean ling (*Molva macrophthalma* (Rafinesque, 1810)
  - European ling/drizzie (*Molva molva* (Linnaeus, 1758)