

Red Clover Isoflavone Extract

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RED CLOVER ISOFLAVONE EXTRACT Help on accessing alternative formats, such as Portable Document Format (PDF), Microsoft Word and PowerPoint (PPT) files, can be obtained in the alternate format help section. (PDF Version - 54 KB) 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 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 on the label. Restrictions when this monograph is combined with other monographs (Class II and III applications): Red clover isoflavone extract cannot be combined with other monographed ingredients with estrogenic or anti-estrogenic effects as a Class II application (e.g., Indole-3-carbinol, Soybean Extracts and Isolates, DIM, Tribulus terrestris , Brassica oleracea varieties (cruciferous vegetables), Dong quai - Angelica sinensis). These products may be submitted as a Class III application. Date June 27, 2025 Proper name(s), Common name(s), Source information Table 1. Proper name(s), Common name(s), Source information Proper name(s) Common name(s) Source information Source material(s) Part(s) Red clover isoflavone extract Red clover isoflavone extract Trifolium pratense Flower Herb top Leaf References: Proper name: NHPID 2025; Common name: Hidalgo et al. 2005, Jeri 2002, van de Weijer and Barentsen 2002, Nachtigall et al. 1999; Source information: Tsao et al. 2006. 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 oral use are indicated in the dosage form drop-down list of the web-based Product Licence Application form for Compendial applications. Use(s) or Purpose(s) Helps to attenuate/reduce/decrease bone (mineral density (BMD)) loss in postmenopausal women when used in conjunction with adequate amounts of calcium and vitamin D (Atkinson et al. 2004; Clifton-Bligh et al. 2001). May reduce severe and frequent menopausal symptoms (such as hot flashes and/or night sweats) (Hidalgo et al. 2005; Jeri 2002; van de Weijer and Barentsen 2002; Nachtigall et al. 1999). Dose(s) Subpopulation(s) Perimenopausal women; Postmenopausal women Quantity(ies) Methods of preparation: Standardized extracts 40 - 100 milligrams of total Aglycone Isoflavone Equivalents (AIE), per day (Hidalgo et al. 2005; Atkinson et al. 2004; Jeri 2002; van de Weijer and Barentsen 2002; Clifton-Bligh et al. 2001; Nachtigall et al. 1999). Notes The total isoflavones content must be expressed in milligrams total AIE on the product label and in the potency section of the PLA. Optional: Potencies may be indicated for specific isoflavones (biochanin A, genistein, formononetin, daidzein). Their content must also be expressed in milligrams AIE on the product label and in the potency section of the PLA. Refer to Appendix 1 for the definition and derivation of AIE. Direction(s) for use No statement required. Duration(s) of Use All uses Ask a health care practitioner/health care provider/health care professional/doctor/physician for use beyond 1 year (Atkinson et al. 2004). Reduction of BMD loss (For BMD loss:)* Use for at least 6 months to see beneficial effects (Atkinson et al. 2004; Clifton-Bligh et al. 2001). Reduction of menopausal symptoms (For menopausal symptoms:)* Use for at least 8 weeks to see beneficial effects (van de Weijer and Barentsen 2002; Nachtigall et al. 1999). *Note: Information in brackets is required on the label when both uses for BMD loss and menopausal symptoms are listed on the label. Risk Information Caution(s) and warning(s) Ask a health care practitioner/health care provider/health care professional/doctor/physician before use if you are not up-to-date on mammograms and gynaecological evaluations (BfR 2007; Suman and Whitehead 2006; Wolff et al. 2006). Ask a health care practitioner/health care provider/health care professional/doctor/physician if symptoms worsen. Ask a health care practitioner/health care provider/health care professional/doctor/physician before use if you have a history of hormonal or gynecological disease (HC 2006; Wolff et al. 2006). Ask a health care practitioner/health care provider/health care professional/doctor/physician before use if you are taking any hormone replacement therapy (BfR 2007; HC 2006). Contraindication(s) Do not use if you have or had breast cancer or tumours or a predisposition to breast cancer, as indicated by an abnormal mammogram or biopsy, or a family member with breast cancer (BfR 2007; Suman and Whitehead 2006). Known adverse reaction(s) Stop use and ask a health care practitioner/health care provider/health care professional/doctor/physician if new symptoms develops such

as breast pain, a recurrence of menstruation or uterine spotting (BfR 2007; Wolff et al. 2006). 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 Must be established in accordance with the requirements described in the Natural Health Products Regulations . Specifications The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) Quality of Natural Health Products Guide. The medicinal ingredient must comply with the requirements outlined in the NHPID. EXAMPLE OF PRODUCT FACTS: Consult the Guidance Document, Labelling of Natural Health Products for more details. References cited Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. *American Journal of Clinical Nutrition*; 2004;79:326-333. BfR 2007: Risiken erkennen - Gesundheit schützen. Isolated Isoflavones are not without risk. Expert Opinion - Federal Institute for Risk Assessment. Germany, October 2007. Collison MW. Determination of total soy isoflavones in dietary supplements, supplement ingredients, and soy foods by high-performance liquid chromatography with ultraviolet detection: Collaborative Study. *Journal of AOAC International* 2008;91(3):489-500. Clifton-Bligh PB, Baber RJ, Fulcher GR, Nery M-L, Moreton T. The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism. *Menopause* 2001;8(4):259-265. HC 2006: Health Canada. Product Monographs of Non-Contraceptive Estrogen/Progestin Containing Products. Ottawa (ON): Therapeutic Products Directorate, Health Canada. [Accessed 2025 January 17]. Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/p_m_mp_noncontracept-eng.pdf Hidalgo LA, Chedraui PA, Morocho N, Ross S, San Miguel G. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: a randomized, double-blind, placebo-controlled study. *Gynecological Endocrinology* 2005;21:257-264. Jeri AR. The use of an isoflavone supplement to relieve hot flushes. *The Female Patient* 2002; 27:35-7. [Accessed 2025 January 17]. Available from: <https://search.proquest.com/openview/d9f403b164c346cf6ffe2d09f26ba625/1?pq-origsite=gscholar&cbl=4770> Nachtigall LB, La Grega L, Lee WW, Fenichel R, Nactigall L. The effects of isoflavones derived from red clover on vasomotor symptoms and endometrial thickness. 9th International Menopause Society World Congress on the Menopause 1999;331-336. NHPID 2025: Natural Health Products Ingredients Database. Natural and Non-Prescription Health Products Directorate. [Accessed 2025 January 17]. Available from: <https://webprod.hc-sc.gc.ca/nhp-id-bdipsn/?lang=eng> Suman R, Whitehead SA. Phytoestrogens and breast cancer - promotes or protectors. *Endocrine Related Cancer* 2006;(13):995-1015. Tsao R, Papadopoulos Y, Yang R, Young JC, McRae K. Isoflavone profiles of Red clovers and their distribution in different parts harvested at different growing stages. *Journal of Agricultural and Food Chemistry* 2006;54:5797-5805. Van de Weijer PHM, Barentsen R. Isoflavones from red clover (Promensil®) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas* 2002;42:187-193. Wolff LP, Martins MR, Bedone AJ, Monteiro IM. Endometrial evaluation in menopausal women after six months of isoflavones. *Revista da Associação Médica Brasileira* 2006;Nov-Dec; 52(6):419-423 (Article in Portuguese). Appendix 1: Definitions and Conversion Factors Definitions: Aglycone Isoflavone Equivalents (AIE): The maximum amount of bioavailable isoflavone upon ingestion. The glycoside forms of the isoflavones must first be cleaved to the aglycone form before they can be absorbed. As such, simple addition of aglycone and glycoside forms of isoflavone quantities, without taking into consideration the biochemical transformation of the isoflavones, will overestimate bioavailable quantities by almost a factor of two (Wang and Murphy 1996). Conversion factors: The quantity of isoflavones must always be determined in terms of AIE quantities (i.e. in terms of genistein, daidzein, biochanin A and formononetin) for each of the glycoside, malonyl glycoside and/or aglycone forms present in the product. Table 2. Conversion of specific isoflavone quantities into aglycone isoflavone equivalent (AIE) quantities (Collison 2008; Tsao et al. 2006) Isoflavone (1 mg) Aglycone Isoflavone Equivalents (mg AIE) Biochanin A 1.0 Biochanin A -7-O-glucoside 0.64 Formononetin 1.0 Formononetin-7-O-glucoside 0.62 Genistein 1.0 Genistin 0.625 Malonyl genistin 0.521 Daidzein 1.0 Daidzin 0.611 Malonyl daidzin 0.506 Glycitein 1.0 Report a problem on this page Date modified: 2019-03-01

MEDICINAL INGREDIENT(S)

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database. Storage conditions Must be established in accordance with the requirements described in the Natural Health Products Regulations.

DOSAGE FORM(S)

Acceptable dosage forms for oral use are indicated in the dosage form drop-down list of the web-based Product Licence Application form for Compendial applications.

RISK INFORMATION

Caution(s) and warning(s) Ask a health care practitioner/health care provider/health care professional/doctor/physician before use if you are not up-to-date on mammograms and gynaecological evaluations (BfR 2007; Suman and Whitehead 2006; Wolff et al. 2006).Ask a health care practitioner/health care provider/health care professional/doctor/physician if symptoms worsen.Ask a health care practitioner/health care provider/health care professional/doctor/physician before use if you have a history of hormonal or gynecological disease (HC 2006; Wolff et al. 2006).Ask a health care practitioner/health care provider/health care professional/doctor/physician before use if you are taking any hormone replacement therapy (BfR 2007; HC 2006). Contraindication(s) Do not use if you have or had breast cancer or tumours or a predisposition to breast cancer, as indicated by an abnormal mammogram or biopsy, or a family member with breast cancer (BfR 2007; Suman and Whitehead 2006). Known adverse reaction(s) Stop use and ask a health care practitioner/health care provider/health care professional/doctor/physician if new symptoms develops such as breast pain, a recurrence of menstruation or uterine spotting (BfR 2007; Wolff et al. 2006).

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 Must be established in accordance with the requirements described in theNatural Health Products Regulations.

STORAGE CONDITION(S)

Must be established in accordance with the requirements described in theNatural Health Products Regulations.

SPECIFICATIONS

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

REFERENCES

Route of Administration Oral

Proper name(s)	Common name(s)	Source information	
Source material(s)	Part(s)		
Red clover isoflavone extract	Red clover isoflavone extract	Trifolium pratense	FlowerHerb topLeaf

Isoflavone (1 mg)	Aglycone Isoflavone Equivalents (mg AIE)
Biochanin A	1.0
Biochanin A -7-O-glucoside	0.64
Formononetin	1.0
Formononetin-7-O-glucoside	0.62
Genistein	1.0
Genistin	0.625
Malonyl genistin	0.521
Daidzein	1.0
Daidzin	0.611
Malonyl daidzin	0.506
Glycitein	1.0