

NATURAL HEALTH PRODUCT

RED CLOVER ISOFLAVONE EXTRACT

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.

Date

August 28, 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)	
		Proper name(s)	Part(s)
Red clover isoflavone extract	Red clover isoflavone extract	<i>Trifolium pratense</i>	<ul style="list-style-type: none"> ▶ Flower ▶ Herb top ▶ Leaf

References: Proper name: NHPID 2018; Common name: Hidalgo et al. 2005, Jeri 2002, van der Weijer and Barentsen 2002, Nachtigall et al. 1999; Source materials: Tsao 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 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)

Menopausal and postmenopausal women

May reduce severe and frequent menopausal symptoms (such as hot flashes/flushes and/or night sweats) (Hidalgo et al. 2005; Jeri 2002; van der Weijer and Barentsen 2002; Nachtigall et al. 1999).

Postmenopausal women

When used with adequate amounts of calcium and vitamin D, helps to attenuate/reduce bone mineral density (BMD) loss in post-menopausal women (Atkinson et al. 2004; Clifton-Bligh et al. 2001).

Dose(s)

Subpopulation(s)

Menopausal and postmenopausal women

Quantity(ies)

Methods of preparation: Standardized extracts (Dry extract, Tincture, Fluid extract, Decoction, Infusion)

40 - 100 milligrams total Aglycone Isoflavone Equivalents (AIE), per day (Hidalgo et al. 2005; Atkinson et al. 2004; Jeri 2002; van der 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 products



Consult a health care practitioner/health care provider/health care professional/doctor/physician for use beyond one year (Atkinson et al. 2004).

BMD loss

Use for at least 6 months to see beneficial effects (Atkinson et al. 2004; Clifton-Bligh et al. 2001).

Hot flashes and/or night sweats

Use for at least several weeks to see beneficial effects (van der Weijer and Barentsen 2002; Nachtigall et al. 1999).

Risk information

Caution(s) and warning(s)

- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have a history of hormonal or gynecological disease (e.g. ovarian cancer, endometriosis and/or fibroids) (HC 2006; Wolff et al. 2006).
- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking hormone replacement therapy (BfR 2007; HC 2006).
- ▶ Ensure that you are up-to-date on appointed clinical tests such as mammograms and endometrial ultrasounds or biopsies before using this product (BfR 2007; Suman and Whitehead 2006; Wolff et al. 2006).
- ▶ Stop use and consult a health care practitioner/health care provider/health care professional/doctor/physician if you experience breast pain, discomfort, soreness and/or tenderness, abnormal uterine bleeding including spotting and/or recurrence of menstruation in postmenopausal women (BfR 2007; Wolff et al. 2006).

Hot flashes and/or night sweats

Consult a health care practitioner/health care provider/health care professional/doctor/physician if symptoms worsen.

Contraindication(s)

Do not use this product if you currently have or previously had breast cancer or if you have a predisposition to breast cancer, as indicated by an abnormal mammogram and/or biopsy, or if you have a family member with breast cancer (BfR 2007; Suman and Whitehead 2006).

Known adverse reaction(s)

No statement required.



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

No statement required.

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.

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.

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HC 2006: Health Canada. Product Monographs of Non-Contraceptive Estrogen/Progestin Containing Products [Internet]. Ottawa (ON): Therapeutic Products Directorate, Health Canada. [Accessed 2018 June 18]. Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/pm_mp_nonconce- eng.pdf

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Jeri AR. The use of an isoflavone supplement to relieve hot flushes. *The Female Patient* 2002; 27:35-7. [Accessed 2018 June 18]. Available from: <https://search.proquest.com/openview/d9f403b164c346cf6ffe2d09f26ba625/1?pq-origsite=gscholar&cbl=47705>

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Suman R, Whitehead SA. Phytoestrogens and breast cancer – promotes or protectors. *EndocrineRelated 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 Equivalent (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.



Conversion of specific isoflavone quantities into aglycone isoflavone equivalent (AIE) quantities (Collison 2008; Tsao *et al.* 2006)

Isoflavone(s) (1 mg)	Aglycone Isoflavone Equivalents (AIE) (mg)
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