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 the statements are synonymous. Either term or statement may be selected by the applicant.

Date

January 20, 2015

Proper name(s)

Red clover isoflavone extract (NHPID 2014)

Common name(s)

Red clover isoflavone extract (Hidalgo et al. 2005; Jeri 2002; van der Weijer and Barentsen 2002; Nachtigall et al. 1999).

Source material(s)

- *Trifolium pratense* L. - Leaf (Tsao 2006)
- *Trifolium pratense* L. - Herb Top (Tsao 2006)
- *Trifolium pratense* L. - Flower (Tsao 2006)

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

*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*

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

**Dose(s)** Statement(s) to the effect of

**Subpopulation(s)**

Menopausal and postmenopausal women

**Quantity(ies)**

*BMD loss; Hot flashes and/or night sweats*

Preparations equivalent to 40-100 mg 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 mg 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 mg AIE on the product label and in the potency section of the PLA.
- Refer to Appendix 1 for the definition and derivation of AIE.
- Safety of preparations equivalent to up to 10 mg total AIE per day is supported in pre-menopausal women and men subpopulations (valid only for Class II and III applications). See Risk information section for additional caution and warning statement required for pre-menopausal/menopausal women.
Duration of use  

Statement(s) to the effect of

*All uses*

For use beyond one year, consult a health care practitioner (Atkinson *et al.* 2004).

*BMD loss*

Use for a minimum of 6 months to see beneficial effects (Atkinson *et al.* 2004; Clifton-Bligh *et al.* 2001).

*Hot flashes and/or night sweats*

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

Risk information  

Statement(s) to the effect of

*Caution(s) and warning(s)*

*Postmenopausal women*

≤ 10 mg AIE, per day

- If you are taking thyroid hormone replacement therapy, consult a health care practitioner prior to use (BfR 2007; Suman and Whitehead 2006).
- If you have a liver disorder or develop liver-related symptoms (e.g. abdominal pain, jaundice, dark urine), consult a health care practitioner prior to use (BfR 2007).

≥ 30 mg AIE, per day

- If you have a history of hormonal or gynecological disease including ovarian cancer, endometriosis and/or uterine fibroids, consult a health care practitioner prior to use (HC 2006; Wolff *et al.* 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).
- If you experience breast pain, discomfort, soreness and/or tenderness, abnormal uterine bleeding including spotting and/or recurrence of menstruation in postmenopausal women, discontinue use and consult a health care practitioner (BfR 2007; Wolff *et al.* 2006).
- If you are taking hormone replacement therapy, consult a health care practitioner prior to use (BfR 2007; HC 2006).

*Hot flashes and/or night sweats*

If symptoms worsen, consult a health care practitioner.
Pre-menopausal women

If you are pregnant or breastfeeding, consult a healthcare practitioner prior to use.

Men

No statement required.

Contraindication(s)

Postmenopausal women

≥ 30 mg AIE, per day

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, do not use this product (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.

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


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);419-23 (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 1  Conversion of specific isoflavone quantities into aglycone isoflavone equivalent (AIE) quantities (Collison 2008; Tsao et al. 2006)

<table>
<thead>
<tr>
<th>Isoflavone (1 mg)</th>
<th>Aglycone Isoflavone Equivalents (AIE) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochanin A</td>
<td>1.0</td>
</tr>
<tr>
<td>Biochanin A -7-O-glucoside</td>
<td>0.64</td>
</tr>
<tr>
<td>Formononetin</td>
<td>1.0</td>
</tr>
<tr>
<td>Formononetin-7-O-glucoside</td>
<td>0.62</td>
</tr>
<tr>
<td>Genistein</td>
<td>1.0</td>
</tr>
<tr>
<td>Genistin</td>
<td>0.625</td>
</tr>
<tr>
<td>Malonyl genistin</td>
<td>0.521</td>
</tr>
<tr>
<td>Daidzein</td>
<td>1.0</td>
</tr>
<tr>
<td>Daidzin</td>
<td>0.611</td>
</tr>
<tr>
<td>Malonyl daidzin</td>
<td>0.506</td>
</tr>
<tr>
<td>Glycitein</td>
<td>1.0</td>
</tr>
</tbody>
</table>