

SOYBEAN EXTRACTS AND ISOLATES

This monograph is intended to guide industry in 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. It is a referenced document to be used as a labelling standard.

Note: 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 statements are synonyms. Either term or statement may be selected by the applicant.

Date: October 29, 2009

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

Table 1: Proper name(s), common name(s) and source material(s)

| Proper name(s) | Common name(s) | Source material(s) |
|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 4',5,7-Trihydroxyisoflavone; 5,7-Dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one ¹ | Genistein ¹ | Isolated from the bean of soy/ <i>Glycine max</i> (L.) Merr. ^{2,3} |
| <i>Glycine max</i> (L.) Merr. ⁴ | Soy protein ⁵ (extract); Soy isoflavone(s) ⁶ (extract) | Soybean ^{2,3} ; Bean of soy |
| Soy protein ⁷ (isolate) | Soy protein ⁷ (isolate) | Isolated from the bean of soy/ <i>Glycine max</i> (L.) Merr. ^{2,3} |

1 Scambia et al. 2000; Upmalis et al. 2000

2 Evans et al. 2007; Newton et al. 2006; Roudsari et al. 2005; Kreijkamp-Kaspers et al. 2004; Arjamandi et al. 2003; Alekel et al. 2000; Wangen et al. 2000; Potter et al. 1998

3 Ye et al. 2006; Yamori et al. 2002

4 USDA 2006

5 Kreijkamp-Kaspers et al. 2004; Albertazzi et al. 1998

6 D'Anna et al. 2007; Nahas et al. 2007; Ye et al. 2006; Crisafulli et al. 2004; Harkness et al. 2004; Uesugi et al. 2003; Han et al. 2002; Albert et al. 2002; Faure et al. 2002; Albertazzi et al. 1998

7 Evans et al. 2007; Newton et al. 2006; Roudsari et al. 2005; Arjamandi et al. 2003; Yamori et al. 2002; Alekel et al. 2000; Wangen et al. 2000; Potter et al. 1998

Route(s) of administration: Oral

Dosage form(s): The acceptable pharmaceutical dosage forms include, but are not limited to, chewables (e.g. gummies, tablets), caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons or tablespoons. 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:
- ▶ 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 (Marini et al. 2007; Newton et al. 2006; Ye et al. 2006; Chen et al. 2004; Kreijkamp-Kaspers et al. 2004; Lydeking et al. 2004; Uesugi et al. 2003; Alekel et al. 2000; Potter et al. 1998).
 - ▶ May reduce severe and frequent menopausal symptoms (such as hot flashes and/or night sweats) (D'Anna et al. 2007; Nahas et al. 2007; Williamson-Hughes et al. 2006; Crisafulli et al. 2004; Albert et al. 2002; Han et al. 2002; Scambia et al. 2000; Upmalis et al. 2000; Albertazzi et al. 1998).

Dose(s):

Notes:

- For soy protein and soy isoflavone products:
Total isoflavones content must be expressed in aglycone isoflavone equivalents (AIE) on the product label and in the potency section of the PLA. Additionally, genistein/genistin compounds (including genistein, genistin, acetyl genistin, and malonyl genistin) content must also be expressed in AIE on the product label and in the potency section of the PLA for products with reduction of menopausal symptom claims. Refer to Appendix 1 for the definition and derivation of AIE.
- For genistein only products:
Genistein quantity must be expressed in AIE on the product label and in the quantity section of the PLA.
- Total quantities of soy protein (extract and/or isolate) must be ≤ 35 g, per day, in order not to exceed acceptable potassium levels (CNF 2007; CPS 2004).

REDUCTION OF BMD LOSS:

Subpopulation: Post-menopausal women (Marini et al. 2007; Newton et al. 2006; Ye et al. 2006; Chen et al. 2004; Kreijkamp-Kaspers et al. 2004; Lydeking et al. 2004; Uesugi et al. 2003; Alekel et al. 2000; Potter et al. 1998)

Potency: Total isoflavones:
Preparations equivalent to 75-125 mg AIE, per day (Marini et al. 2007; Newton et al. 2006; Ye et al. 2006; Chen et al. 2004;

Kreijkamp-Kaspers et al. 2004; Lydeking et al. 2004; Uesugi et al. 2003; Alekel et al. 2000; Potter et al. 1998)

REDUCTION OF MENOPAUSAL SYMPTOMS:

Subpopulation: Menopausal and post-menopausal women (D’Anna et al. 2007; Nahas et al. 2007; Crisafulli et al. 2004; Albert et al. 2002; Faure et al. 2002; Han et al. 2002; Scambia et al. 2000; Upmalis et al. 2000; Albertazzi et al. 1998)

Potency: Total isoflavones:
Preparations equivalent to 30-100 mg AIE with a minimum of 15 mg AIE from genistein/genistin compounds, per day (D’Anna et al. 2007; Nahas et al. 2007; Williamson-Hughes et al. 2006; Crisafulli et al. 2004; Albert et al. 2002; Han et al. 2002; Scambia et al. 2000; Upmalis et al. 2000; Albertazzi et al. 1998)

ALL USES:

Directions for use: Take a few hours before or after taking other medications or health care products (Sweetman 2007; ASHP 2005).

Duration(s) of use:

Reduction of BMD loss: Use for a minimum of 6 months to see beneficial effects (Ye et al. 2006; Harkness et al. 2004; Alekel et al. 2000; Potter et al. 1998).

Reduction of menopausal symptoms:
Use for a minimum of 2 weeks to see beneficial effects (D’Anna et al. 2007; Nahas et al. 2007; Crisafulli et al. 2004; Han et al. 2002; Scambia et al. 2000; Upmalis et al. 2000; Albertazzi et al. 1998).

All uses: Consult a health care practitioner for use beyond one year (Tomar and Shiao 2008; BfR 2007; Duffy et al. 2007; Palacios et al. 2007; Unfer et al. 2004; Petrakis et al. 1996).

Risk information: Statement(s) to the effect of:

Caution(s) and warning(s):

For all products:



- ▶ Ensure you are up-to-date on mammograms and gynaecological evaluations prior to use (Tomar and Shiao 2008; BfR 2007; Duffy et al. 2007; Palacios et al. 2007; Unfer et al. 2004; Petrakis et al. 1996).
- ▶ Consult a health care practitioner if symptoms worsen.
- ▶ Consult a health care practitioner prior to use if you are taking blood thinners (Rios et al. 2008; ASHP 2005; Izzo et al. 2005; Mills and Bone 2005; Franco et al. 2004; Cambria-Keily 2002; IOM 2001; Hansten et al. 1997).
- ▶ Consult a health care practitioner prior to use if you have a history of hormonal or gynaecological disease, including ovarian cancer (Cecchi et al. 2009; NIH 2009; Jefferson et al. 2007; Maskarinec et al. 2004a; Maskarinec et al. 2004b; Wu et al. 2000; Hargreaves et al. 1999; McMichael-Phillips et al. 1998; Petrakis et al. 1996), endometriosis, and/or uterine fibroids (Chandrareddy et al. 2008; Tomar and Shiao 2008; Palacios et al. 2007; Kaari et al. 2006; Noel et al. 2006; Unfer et al. 2004; Duncan et al. 1999b; Petrakis et al. 1996).
- ▶ Consult a health care practitioner prior to use if you have a liver disorder or develop liver-related symptoms (e.g. abdominal pain, jaundice, dark urine) (Gasteyger et al. 2008; Borghi-Scoazec et al. 2002).
- ▶ Consult a health care practitioner prior to use if you are taking hormone replacement therapy (HRT) (Murray et al. 2003; Petrakis et al. 1996), including thyroid hormone replacement therapy (BfR 2007; Messina and Redmond 2006; Mazer 2004; Bell and Ovalle 2001).
- ▶ Discontinue use and consult a health care practitioner if you experience breast pain, discomfort and/or tenderness (Martinez and Lewi 2008; Olawaiye et al. 2005; Albert et al. 2002; Hargreaves et al. 1999; McMichael-Phillips et al. 1998; Petrakis et al. 1996), or if you experience a recurrence of menstruation and/or uterine spotting (Chandrareddy et al. 2008; Palacios et al. 2007; Han et al. 2002).

Contraindication(s): Do not use if you currently have or previously had breast cancer and/or breast tumours or if you have a predisposition to breast cancer, as indicated by an abnormal mammogram and/or biopsy, or a family member with breast cancer (Helferich et al. 2008; Tomar and Shiao 2008; BfR 2007; Duffy et al. 2007; Kaari et al. 2006; Nikander et al. 2005; Hargreaves et al. 1999; McMichael-Phillips et al. 1998; Petrakis et al. 1996).

Known adverse reaction(s): No statement required.

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](#).
- ▶ For an accurate measure of specific isoflavones in AIE, follow the methods outlined in AOAC 2008.03 (Collison 2008).

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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, and/or glycitein) for each of the glycoside, acetyl 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)

| Isoflavone (1 mg) | Aglycone Isoflavone Equivalent (mg AIE) quantity |
|-------------------|--------------------------------------------------|
| Genistein | 1.0 |
| Genistin | 0.625 |
| Malonyl genistin | 0.521 |
| Acetyl genistin | 0.570 |
| Daidzein | 1.0 |
| Daidzin | 0.611 |
| Malonyl daidzin | 0.506 |
| Acetyl daidzin | 0.555 |
| Glycitein | 1.0 |
| Glycitin | 0.637 |
| Malonyl glycitin | 0.534 |
| Acetyl glycitin | 0.582 |

Example of using the Aglycone Isoflavone Equivalent (AIE) conversion factors:

Converting glycoside quantity into quantity of AIE (mg):

$$\begin{aligned}
 &\text{Convert 20 mg of genistin into mg AIE:} \\
 &= 20 \text{ mg} \times 0.625 \text{ mg AIE/mg genistin} \\
 &= 12.5 \text{ mg AIE genistin}
 \end{aligned}$$

Appendix 2: Calculating Total Isoflavones and Reporting Amounts on the PLA Form

1) Example of a 30 g/day soy protein extract product:

For a product with a claim for the reduction of menopausal symptoms, the amount of protein, total isoflavones, and genistein/genistin compounds must be reported on the PLA form.

a) Calculating total isoflavones (mg AIE)

Convert genistin, genistein, malonyl genistin, acetyl genistin, daidzein, and daidzin AIE quantities into quantities of total isoflavones in AIE (mg):
 =12.5 mg AIE genistin + 10 mg AIE genistein + 1 mg AIE malonyl genistin + 1 mg AIE acetyl genistin + 6.1 mg AIE daidzin + 5 mg AIE daidzein
 =35.6 mg AIE total isoflavones

b) Calculating genistein/genistin compounds (mg AIE)

Convert genistein, genistin, malonyl genistin, and acetyl genistin AIE quantities into quantities of total isoflavones in AIE (mg):
 =12.5 mg AIE genistin + 10 mg AIE genistein + 1 mg AIE malonyl genistin + 1 mg AIE acetyl genistin
 =24.5 mg AIE genistein/genistin compounds

c) Reporting on the Product Licence Application form should be as follows:

| | | |
|-----------------------------------|-------------------------------|-------------|
| Medicinal Ingredient Proper Name: | <i>Glycine max</i> (L.) Merr. | |
| Medicinal Ingredient Common Name: | Soy protein extract | |
| Medicinal Ingredient Quantity: | 30 g | |
| Source Material: | Soybean | |
| Potencies: | Total isoflavones | 35.6 mg AIE |
| | Genistein/genistin compounds | 24.5 mg AIE |

2) Example of a 30 mg/day genistein isolate product:

For a product with a claim for the reduction of menopausal symptoms, the amount of genistein must be reported on the PLA form.

Reporting on the Product Licence Application form should be as follows:

| | |
|-----------------------------------|-----------|
| Medicinal Ingredient Proper Name: | Genistein |
| Medicinal Ingredient Common Name: | Genistein |
| Medicinal Ingredient Quantity: | 30 mg AIE |



Source Material:

Isolated from the bean of soy/*Glycine max* (L.)
Merr.

Potencies:

none