Black Cohosh 40 mg Softgels

Product Summary:

Black Cohosh, known as either *Actaea racemosa or Cimicifuga racemosa*, is an indigenous herb in the United States and Canada with a long history in folk medicine, especially among Native Americans who used it as a tea for a variety of complaints, including dysmenorrhea, and it has been used in a much more formal clinical way in Germany since the 1940's. Black Cohosh root and rhizomes [see definition below this paragraph] are the plant parts approved by the German government as a non-prescription drug. An extract of the root and rhizomes is described in the Commission E Report as a treatment for premenstrual discomfort, dysmenorrhea, neurovegetative [pertaining to autonomic nervous system] menopausal symptoms such as hot flashes, heart palpitations, nervousness, irritability, vertigo, sleep disturbances, perspiration, and depression.[2,3] The collective clinical and observational experience suggests that Black Cohosh may be approximately 11 to 40 percent more effective than placebo, including its use for hot flashes.[4-7] Because Black Cohosh has been observed to provide help for many women, it is hoped that it will be tried, at least in an initial personal trial for a non-estrogenic and non-prescription solution for menopausal complaints, especially for hot flashes.

[rhizome – ri-zom – a creeping stem lying, usually horizontally, at or under the surface of the soil and differing from a root in having scale leaves, bearing leaves or aerial shoots near its tips, and producing roots from its under surface: Webster's New World Dictionary, Simon & Schuster, Third College Edition, 1988]

Properties/Uses:

The claim as approved by *Natural Health Products Directorate* (NHPD): Clinically proven to help relieve menopausal symptoms.

GENERAL HEALTH & WELLNESS

Pharmacology:

Most commercial Black Cohosh is a standardized alcoholic/aqueous extract that delivers 1 mg of *triterpene glycosides* per tablet, calculated as 26-*deoxyactein* (not as 27-deoxyactein as originally and commonly reported8), and most clinical studies on the effectiveness of Black Cohosh have used this standardization.[9] A common tablet size is 40 mg, yet still delivering only 1 mg triterpene glycosides, and standardized to 2.5% triterpene glycosides, calculated as 26-deoxyactein. Caution must be used in evaluating the triterpene glycoside content in different tablet sizes.

Studies in the past have evaluated the effects of using as much as 4-8 mg of triterpene glycosides per day, over various ranges of time from 12 to 24 weeks.[9] However, in a comparative evaluation of two dose strengths comparing 39 mg (~ 2 mg triterpene glycosides) and 127.3 (~ 6.6 mg triterpene glycosides), Liske *et al.* reported no statistical difference in the global assessment of efficacy between the two doses.[10] Similarly, there was no statistically significant difference in treatment tolerability between the two dose strengths or in the rates of adverse side effects (1.8-7% in 39 mg; 1.5-8% in 127.3 mg). These researchers concluded that there was no advantage in the speed of treatment on-set or therapeutic outcome associated with the higher dose of 127.3 mg. Thus, it was suggested that the typical 2 mg triterpene glycosides dose per day is sufficient for relief of menopausal symptoms.

Van Breemen *et al.* investigated the maximum tolerated dose of a 75% ethanol extract of Black Cohosh and determined the pharmacokinetics of the 23-epi-26-deoxyactein triterpene glycoside.[11] Single doses of Black Cohosh extract containing 1.4, 2.8, or 5.6 mg of 23-epi-26-deoxyactein were administered to 15 healthy, menopausal women. Serial blood samples and 24-hour urine samples were obtained and blood chemistry, hormonal levels, and 23-epi-26-deoxyactein levels were determined. No acute toxicity or estrogenic hormone effects were observed. Pharmacokinetic analyses of 23-epi-26-deoxyactein in sera indicated that the maximum concentration and area under the curve increased proportionately with dosage, and that the half-life was ~2 hours for all dosages. Less than 0.01% of the 23-epi-26-deoxyactein was recovered in urine 24 hours after administration. No phase I or phase II metabolites were observed either in clinical specimens or in vitro testing.

Originally, Black Cohosh results were understood as evidence for estrogenic effects, attributable to phytoestrogen components.[12] Over the last few years, numerous in vitro and in vivo scientific investigations into the action of Black Cohosh have demonstrated that it does not exert an estrogenic effect, and may be antagonistic.[12-18] Black Cohosh appears to have anti-estrogenic/anti-cancer effects, demonstrable by the inhibition of effects that are induced by estradiol, namely, induced cell cycle arrest at G1 and G1/M, and induced apoptosis in (ER+) MCF-7 cancer cells and in (ER-) MDA-MB231 cancer cells, as well as enhanced Tamoxifen action.[19-22].Data that indicates a non-estrogenic or estrogen-antagonistic effect of Black Cohosh on human breast cancer cells may suggest

that Black Cohosh treatment is a safe, natural remedy for menopausal symptoms in breast cancer.[22]

More recent scientific evidence suggests that Black Cohosh possesses a dopaminergic receptor activity.[23] Borrelli points out that Lohning *et al.*[24] demonstrated that the activity of Black Cohosh was mediated by central nervous system D2-receptors. In another vein, estrogen is known to exert an effect on serotonergic systems and it has been considered possible that hot flashes arise from an alteration in serotonin levels secondary to a declining estradiol level.[25] A possible connection between serotonin and menopausal symptoms is suggested by Slopien *et al.* who found that serum serotonin concentrations in postmenopausal women are related to the severity of climacteric symptoms.[26] Burdette *et al.* have described Black Cohosh as a mixed competitive ligand and partial agonist of the serotonin receptor.[27] Black Cohosh extract was tested against 10 subtypes of the serotonin receptor, revealing the presence of compounds that exhibited strong binding to the 5-HT(1A), 5-HT(1D), and 5 HT(7) receptor subtypes. Subsequent binding studies were carried out using 5-HT(1A) and 5-HT(7) receptors because of their association with the hypothalamus, which has been implicated in the generation of hot flashes. Burdette *et al.* also showed that Black Cohosh extract elevated cAMP levels in the studied cell-line, suggesting the extract acted as a partial agonist at the receptor. These findings suggest that reductions of hot flashes in some women using Black Cohosh may be mediated via dopamine and/or serotonin receptors.

Manufactured product information:

Manufacturer:
WN Pharmaceuticals® Ltd.

Size/UPC:
100's 7 77747 10264 8

NPN:
80007421

Expiry Date:
36 months from date of manufacture

Active Ingredients:
Each softgel contains:

Black Cohosh (Cimicifuga racemosa) (rhizome and root) . . . . . 40 mg
(standardized to 1 mg triterpene)

Non-Medicinal Ingredients (in descending order):
Softgel capsule (gelatin, glycerin, purified water), soybean oil, yellow beeswax, lecithin

Appearance:
Tan or brown coloured suspension of powder in oil (slightly viscous paste, at room temperature), encapsulated in a clear size 4.5 oval soft gelatin shell.

Packaging:
175 cc white round bottle with safety seal under a 38 mm white induction sealed cap with vented interior seal and a label applied to the bottle. Lot number and expiry date are printed on label applied to exterior of bottle.

Storage:
Store in tightly sealed containers at 15 – 25°C.

Dose:

Each 40 mg softgel is standardized to 2.5% triterpene glycosides, calculated as 26-deoxyactein, delivering 1 mg of triterpene glycoside. The established dosage is 1 to 2 mg of triterpene glycoside per day.[10]

Directions:

(Adults): 1 – 2 softgels daily before meals or as recommended by a physician.

Caution:

The caution as approved by *Natural Health Products Directorate* (NHPD): KEEP OUT OF THE REACH OF CHILDREN. Consult a physician if symptoms persist or worsen. Consult a physician prior to use if you are breastfeeding, if you have a liver disorder or if you develop symptoms of liver trouble. Do not use if you are pregnant. STORE AT ROOM TEMPERATURE IN A DARK, DRY PLACE. DO NOT USE IF SEAL UNDER CAP BROKEN OR MISSING.

Deficiency Symptoms:

Not applicable

Drug Interactions/Contraindications :

In a mouse animal study, Black Cohosh appears to decrease the cytotoxic effect of cisplatin on breast cancer cells.[9]

The Natural Medicines Comprehensive Database reports that over 49 cases of hepatotoxicity have been reported in association with Black Cohosh, but that most of these cases are unpublished and poorly documented.[9] Some people may be inexplicably affected by a yet undemonstrated Black Cohosh hepatotoxicity.

Do not use Black Cohosh in patients with compromised liver status or on a potentially hepatotoxic drug or herbal product.[9]

Do not use during pregnancy.

Toxicity/Adverse Reactions:

Black Cohosh has been reported to have caused gastrointestinal upset, rash, headache, dizziness, weight gain, feeling of heaviness in the legs, cramping, breast tenderness, and vaginal spotting or bleeding.[9]

Dog *et al.* performed a comprehensive review of the safety of Black Cohosh for the treatment of menopause symptoms.[28] An extensive database of information was used, including all published literature pertaining to preclinical and clinical safety of various forms of Black Cohosh, the FDA and World Health Organization adverse-event reporting systems, monographs, compendia, internal unpublished data from a major manufacturer, foreign literature, and historical anecdotal reports. They found that uncontrolled reports, post-marketing surveillance, and human clinical trials of more than 2,800 patients demonstrate a low incidence of adverse events (5.4%). Of the reported adverse events, 97% were minor and did not result in discontinuation of therapy. The only severe adverse events were not considered attributable to Black Cohosh treatment.

Studies on Black Cohosh mutagenicity, teratogenicity, and carcinogenicity have been negative.[9]

Concern that Black Cohosh might adversely affect the liver has been expressed originally based on two separate cases from Australia in which herbal blends incorporating Black Cohosh had been used.[29,30] However, no causal connection to Black Cohosh could be established.[9] Thomsen *et al.* express the opinion that it is profoundly doubtful that Black Cohosh could be hepatotoxic given the fact that a German manufacturer has sold more than 350 million daily doses of Black Cohosh preparations worldwide since the pharmacovigilance system was introduced, and no comparable cases had been reported until the two reports in Australia.[31] However, today over 49 cases of hepatotoxicity have now been reported in association with Black Cohosh, most of these cases are unpublished and poorly documented.[9] Hepatitis can occur with no identifiable cause, raising the possibility that in some of these 49 cases hepatitis might be coincident to Black Cohosh use.[9] Also, plant misidentification can occur resulting in the accidental incorporation of hepatotoxic plant material.

Allergen Content/Ingredient Sensitivity:

NO	YES
Artificial Colors	Corn Products
Artificial Flavors	Lecithin
Artificial Sweeteners	Soy Products
Egg Products	Starch/Modified Starch (corn)
Fish	Sulphites (< 10 ppm)
Gluten	
Hydrolyzed Plant Protein	
Milk Products	
Peanuts	
Preservatives	
Sesame Products	
Shellfish	
Tartrazine	
Tree Nuts	
Wheat Products	
Yeast	

NOT ACCEPTABLE FOR THE FOLLOWING DIETARY RESTRICTIONS:

Free of animal products

Kosher

References:

1. Seibel, Machelle M., Treating hot flushes without hormone replacement therapy, *The Journal of Family Practice*, 54(4):291-296, 2003

2. The Editors, The Use of Black Cohosh to Treat Symptoms of Menopause, *Sexuality, Reproduction & Menopause*, 2(1):27-34, March, 2004

3. Blumenthal, M., Busse, W.R., Goldberg, A., Gruenwald, J., Hall, T., Riggins, C.W., Rister, R.S., editors, Klein, S., Rister, R.S, translators, *The Complete German Commission E Monographs – Therapeutic Guide to Herbal Medicines*, Austin, TX, American Botanical Council, Boston, Integrative Medicine Communications, 1998

4. Taylor, M., Botanicals: medicines and menopause, *Clin Obstet Gynecol*, 44:853-863, 2001

5. Philp, Hazel A., Hot flashes – A review of the literature on alternative and complementary treatment approaches, *Alternative Medicine Review*, 8(3):284-302, 2003

6. Borrelli, F., Ernst, E., Alternative and complementary therapies for menopause, Maturitas, Aug; 66(4):333-343, 2010

7. Shams, T., *et al*, Efficacy of black cohosh-containing preparations on menopausal symptoms: a meta-analysis, *Altern Ther Health Med*, Jan-Feb; 16(1):36-44, 2010

8. From the Office of Dietary Supplements, National Institute of Health, http://ods.od.nih.gov/factsheets/blackcohosh.asp

9. Natural Medicines Comprehensive Database, www.naturaldatabase.com

10. Liske, E., *et al*, Physiological Investigation of a unique extract of Black Cohosh (*Cimicifuga racemosa*): A 6-month clinical study demonstrates no systemic estrogenic effect, *Journal of Women's Health & Gender-Based Medicine*, 11(2):163-174, 2002

11. Van Breemen, R.B., *et al*, Pharmacokinetics of 23-epi-26-deoxyactein in women after oral administration of a standardized extract of black cohosh, Clin Pharmacol Ther, Feb; 87(2):219-225, 2010

12. Mahady, G. B., Is Black Cohosh Estrogenic?, *Nutrition Reviews,* 61(5):183-186, 2003

13. Bodinet, C., Freudenstein, J., Influence of marketed herbal menopause preparations on MCF-7 cell proliferation, *Menopause*, 11(3):281-289, May-June, 2004

14. Liu, J. *et al*, Evaluation of estrogenic activity of plant extracts for the potential treatment of menopausal symptoms, *J Agric Food Chem*, 49(5):2472-2479, May, 2001

15. Onorato, J., Henion, J.D., Evaluation of triterpene glycoside estrogenic activity using LC/MS and immunoaffinity extraction, *Anal Chem*, 73(19):4704-4710, Oct 1, 2001

16. Zierau, O., *et al*, Antiestrogenic activities of Cimicifuga racemosa extracts, *J Steroid Biochem Mol Biol*, 80(1):125-130, Jan, 2002

17. Freudenstein,J., *et al*, Lack of promotion of estrogen-dependent mammary gland tumors *in vivo* by isopropanolic *Cimicifuga racemosa extract, Cancer Res*, 62:283-289, 2002

18. Zhang, L., *et al*, In vivo effects of Black Cohosh and Genistein on estrogenic activity and lipid peroxidation in Japanese Medaka *(Oryzias latipes), J Herb Pharmacother*, 3(3):33-50, 2003

19. Einbond, L.S., *et al*, Growth inhibitory activity of extracts and purified components of black Cohosh on human breast cancer cells, *Breast Cancer Res Treat*, 83(3):221-231, 2004

20. Otanska, K., *et al*, Cimicifuga racemosa extract inhibits proliferation of estrogen receptor-positive and negative human breast carcinoma cell lines by induction of apoptosis, *Breast Cancer Res Treat*, 84(2):151-160, Mar, 2004

21. Lupu, R., *et al*, Black Cohosh, a menopausal remedy, does not have estrogenic activity and does not promote breast cancer cell growth, Int J Oncol, 23(5):1407-1412, Nov, 2003

22. Bodinet, C., Freudenstein, J., Influence of Cimicifuga racemosa on the proliferation of estrogen receptor positive human breast cancer cells, *Breast Cancer Res Treat*, 76(1):1-10, Nov 2002

23. Borrelli, F., Izzo, A.A., Ernst, E., Pharmacological effects of *Cimicifuga racemosa, Life Sciences*, 73:1215-1229, 2003

24. Lohning, A., *et al*, Pharmacological studies on the dopaminergic activity of *Cimicifuga racemosa* (Abstract), 23rd Int LOF-Symposium on Phyto-Oestrogens, University of Gent, Belgium

25. Berendsen, Hemmie H.G., The role of serotonin in hot flashes, *Maturitas*, 36:155-164, 2000

26. Slopien, R., *et al*, Relationship between climacteric symptoms and serum serotonin levels in postmenopausal women, *Climacteric*, 6(1):53-57, Mar, 2003

27. Burdette, J.E., *et al*, Black Cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor, *J Agric Food*, 51(19):5661-5670, Sept, 2003

28. Dog, T.L., *et al*, Critical evaluation of the safety of *Cimicifuga racemosa* in menopause symptom relief, *Menopause*, Jul-Aug, 10(4):299-313, 2003

29. Whiting, P.W., *et al*, Black cohosh and other herbal remedies associated with acute hepatitis. *Med J Aust*, 177: 440-443, 2002

30. Lontos, S., *et al*, Acute liver failure associated with the use of herbal preparations containing black Cohosh, *Med J Aust*, 179:390-391, 2002

31. Thomsen, Michael, *et al*, Acute liver failure associated with the use herbal preparations containing Black Cohosh, *Med J Aust*, 180(11), [Letters], 598-600, 2004

Revision #00