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Introducing HMRLignan™: A Novel Enterolactone Precursor and More Digestible Source of Lignans

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On April 19, 2005, the USDA unveiled a new Food Pyramid. In the USDA's introductory report, entitled, "Dietary Guidelines for Americans 2005," under chapter 5, "Food Groups to Encourage," the USDA places emphasis on consumption of whole grains. It reads, "In the grain-refining process, most of the bran and some of the germ is removed, resulting in the loss of dietary fiber (also known as cereal fiber), vitamins, minerals, *lignans*, *phytoestrogens* [emphasis added by author] phenolic compounds, and phytic acid."

This report recognizes the value of the broad range of phytonutrients now missing from the average American diet due to overprocessing of foods or poor diet selection. While most Americans recognize the need for a healthy diet and the consumption of fibers, lignans and other phytonutrients, changes to dietary habits are not always easily achieved. For many people the concept of a daily bowl of flax seed is less than appetizing. However, HMRLignan™, a new generation low-dose, highly bioavailable lignan supplement, may provide a more digestible alternative.

An increasing pool of scientific knowledge and strong epidemiological data has raised the profile of lignan-rich sources such as flax with their relevance in health maintenance being recognized by consumers and dietary supplement formulators alike. Due to the extensive educational and marketing campaign efforts by the flax industry the most recognized lignans by the public are those found in flax seeds. However, lignans are an abundant phytonutrient found in a wide variety of foods and plants, notably unrefined grain products, seeds (sesame and flax), berries, fruits and vegetables. Upon ingestion, lignans make their way into the gastrointestinal tract whereby the microflora convert them into "human lignans," primarily enterolactone, which exerts the weak estrogen-like activity that is primary in their reported prophylactic action in protecting against cardiovascular disease and tumors.

Although lignans are abundant in unprocessed foods, obtaining a sufficient daily dose remains a challenge. Flax seed is used often to supplement the daily intake, but quality and standardization are problematic, relative bioavailability is low and stability is an issue particularly in lignan rich unrefined oils that are prone to rancidity and subsequently carry a short shelf life. In such an environment, the lignan quality can be greatly compromised. The side effects from high consumption of flax seed can also be uncomfortable, including a pronounced laxative effect,

bloating and flatulence. In addition, the high daily dosage, at 20 to 30 grams daily, presents a major challenge to supplement formulators.

Although these challenges exist for flax seed, 7-hydroxymatairesinol (HMRLignan™) is the first commercially available lignan source to overcome these hurdles. 7-hydroxymatairesinol is the prevalent lignan in sesame seeds, but is also particularly abundant in the Norway spruce (*Picea abies*). The Norway spruce is plentiful in the Nordic countries such as Finland, where it is used extensively in the paper industry (a primary local industry), which has led to a strong national industrial and academic interest in the study of wood chemistry.

In addition, Finland is also a center of excellence for the study of phytoestrogens and it was researchers at the University of Helsinki who made the link between the research chemistry and the potential human health benefits of the wood derived lignan 7-hydroxymatairesinol (HMRLignan™) and its metabolism to the protective weak phyto-hormone and lower incidences of breast and prostate cancers and cardiovascular disease. This led to the partnership between Hormos Medical Corporation of Turku, Finland, and Linnea, Switzerland, and the success in bringing HMRLignan™ from the academic arena to the consumer.

HMRLignan™, a patented proprietary lignan product manufactured by Linnea, one of the leading Swiss phyto-pharmaceutical manufacturers, stands out from other lignan sources in several ways.

First, as HMRLignan™ is not in a food matrix, it is characterized by a superior and proven pharmacokinetic and bioavailability. Other lignans, such as flax, are glycosides or diglycosides - bound to sugar molecules that must first be cleaved in the body before they can be metabolized into the target molecule enterolactone. HMRLignan™ is a pure lignan in the aglycone form (not bound to sugars) and upon arrival in a healthy intestinal tract, is more efficiently transformed into enterolactone – HMRLignan™ is the first direct enterolactone precursor dietary supplement.

Second, HMRLignan™ is a pure source of dietary lignans standardized to 90 percent pure lignans as 7-hydroxymatairesinol without the seasonal crop or zonal variations associated with other lignan sources, ensuring exceptional batch-to-batch uniformity.

Third, the dose response of HMRLignan™ is clinically documented with a small single daily dosage of between 10 to 30 mg daily shown to elevate blood enterolactone to protective levels. In addition, as a novel lignan source, the developers undertook extensive safety testing according to pharmaceutical GCP (Good Clinical Practice). In May 2004, New Dietary Ingredient (NDI) clearance from the FDA was obtained for the ingredient, allowing HMRLignan™, containing dietary supplements, to be marketed in the United States.

Population studies and clinical studies present a compelling case for the benefit of raising enterolactone. There is strong epidemiological evidence linking cardiovascular mortality and plasma enterolactone levels in both men and women.

In 2003, the Kuopio Ischaemic Heart Disease Risk Factor Study looked at the associations between serum enterolactone levels and the risk of coronary heart disease (CHD) and cardiovascular disease (CVD) in middle-aged Finnish men. The conclusion was that high serum enterolactone level is dose-dependently positively associated with reduced CHD- and CVD-related mortality in this population.

A 2002 cross-sectional study (Framingham Offspring Study) in the U.S. investigated whether dietary estrogens have similar beneficial effects on metabolic cardiovascular risk factors as estrogen therapies in 939 postmenopausal women. In the highest quartile of isoflavone intake, the mean cardiovascular risk factor metabolic score was 0.43 lower than the lowest quartile. The difference in this score between the extreme quartiles of intake of lignans was 0.55 points. The

study concluded that high intake of lignans in postmenopausal women was associated with a favorable metabolic cardiovascular risk profile.

Studies also support an inverse association between elevated enterolactone levels and rates of breast and prostate cancer. Breast cancer is considered to be a hormone-regulated disease with the female sex hormone estrogen known to increase the risk of development, through a complicated series of pathways.

Enterolactone binds weakly to the estrogen receptors, and as a weak estrogen, appears to block overt estrogen activity in specific selected tissues. In addition, enterolactone stimulates the synthesis and circulating levels of a biochemical called sex hormone-binding globulin (SHBG). Through this activity, enterolactone appears to reduce the free bioavailable pool of circulating estrogen, thereby reducing estrogen penetration in tissues and diminishing risk for adverse estrogen balance. Third, there is evidence that enterolactone may also inhibit biosynthesis of estrogen by blocking aromatase, a key enzyme in biosynthesis of estradiol. Collectively through multiple mechanisms of action, lignans appear to positively influence optimal estrogen balance in the body.

In prostate health, an increasing body of evidence points to the benefits of lignans in the maintenance of prostatic wellness, and suggests that enterolactone may have direct inhibitory effects associated with cancer cell growth and signaling. Research has shown that enterolactone may compete with E2 for the type II estrogen receptor, induce sex hormone binding globulin and may also play a role in steroid metabolism and synthesis, thus reducing proliferation of hormone-dependant prostate. A 2005 study investigated the effect of 7-HMR on LNCaP human prostate cancer xenografts in mice. Results showed that a 7-HMR diet significantly inhibited the growth of LNCaP tumors. Mice that ingested 7-HMR had smaller tumor volume, lower tumor take rate, increased proportion of non-growing tumors and higher tumor cell apoptotic index compared with controls.

Lignans, like 7-hydroxymatairesinol (HMRlignan™), can also make a contribution to the management of menopause. Enterolactone, by binding the estrogen receptor in different target tissues, may bring about either agonist or antagonist type response, depending on the availability and recruitment of tissue-specific co-regulatory proteins to the estrogen receptor signaling complex. When estrogen levels decline, enterolactone may exert a weak estrogen-like effect, mimicking the presence of estrogen). When estrogen levels are high, enterolactone occupies and blocks estrogen receptors, thereby acting to smooth the peaks and valleys. During the climacteric (the several-year period when estrogen levels are in flux, leading to cessation of menstruation) estrogen levels are in flux, so a formula that addresses the body's own production of enterolactone may indeed help lessen symptom severity and frequency.

Bone health is also an emerging area where lignans are being shown to play a positive role. Here too, estrogens are known to play an important role in bone maintenance. Recent studies have shown a link between lignan consumption and bone reabsorption. A 2002 Korean study showed a link between low excreted enterolactone and incidence of osteoporosis in postmenopausal women.

HMRlignan™ is a novel source of lignans offering a variety of advantages and suitable for tablets and capsules. It can be formulated as either as a standalone supplement, or as part of a formula targeted for cardiovascular wellness, and for middle-aged men and women concerned about gender-specific health issues. As a highly efficient source of dietary lignans, HMRlignan™ is a true dietary supplement offering consumers the ideal method of dosing daily lignans.

HMRLignan™ is a patented product developed in Finland by Hormos Medical Corporation, and manufactured and marketed worldwide under license by Linnea, Switzerland. Linnea SA is a specialist manufacturer of botanical extracts and phytochemicals for the pharmaceutical, dietary supplement and cosmetic industries.

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