

**CORTITROL STRESS CONTROL FORMULA™**  
- TECHNICAL PRODUCT BULLETIN –  
(HEALTHCARE PROFESSIONALS VERSION)

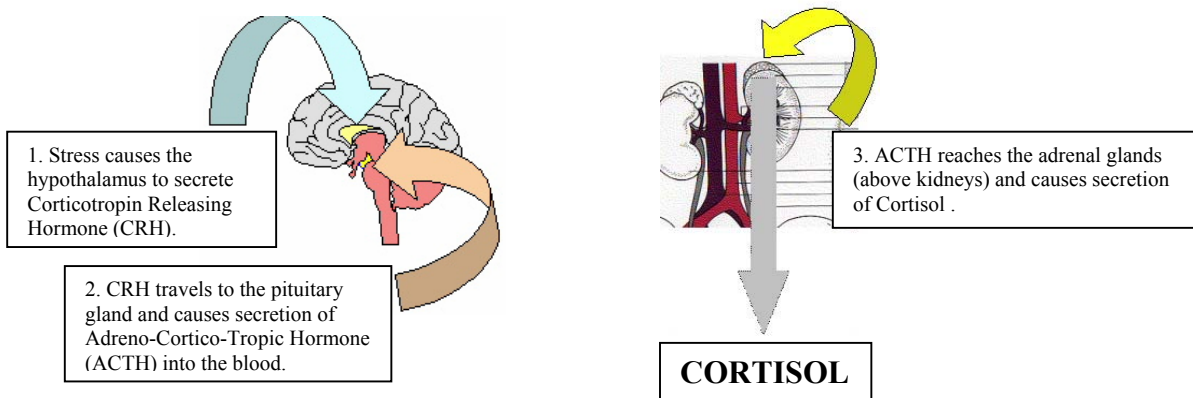
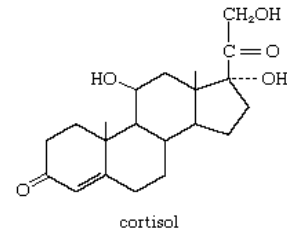
**SUMMARY**

Cortitrol Stress Control Formula™ is a dietary supplement developed and manufactured by Pharmanex, LLC, to help the body modulate healthy levels of cortisol. This revolutionary product is a patent-pending cortisol-controlling dietary supplement that combines natural ingredients that have been scientifically shown to have direct cortisol-balancing effects. Ingredients included in Pharmanex Cortitrol that may have cortisol-lowering effects include magnolia bark (*Magnolia officinalis*), epimedium (*Epimedium koreanum*), theanine, beta sitosterol and phosphatidylserine.

This technical bulletin reviews the scientific rationale behind the formulation of Cortitrol. It also discusses the purported health benefits, mechanisms of action, published scientific studies, and proprietary processing. This is an educational bulletin provided to help licensed healthcare professionals understand the science upon which Cortitrol is based. This bulletin should not be used to sell Cortitrol, and it should be distributed only to licensed healthcare professionals. The only claims that can be made for Cortitrol are those that have been approved by Pharmanex.

**ABOUT CORTISOL**

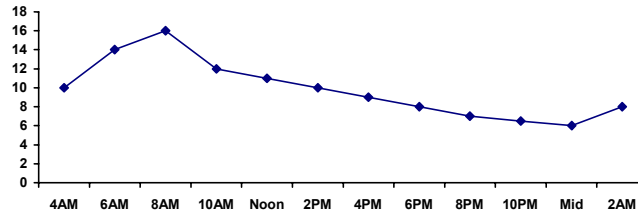
Cortisol, also known as Cortisone and Hydrocortisone, is a steroid hormone produced in the adrenal gland in response to stress. As such, cortisol is often referred to as the primary “stress hormone.” In the body, cortisol is needed to maintain normal physiological processes during times of stress—without cortisol, the body would not be able to respond effectively to stress. With an effective cortisol metabolism, cortisol secretion releases amino acids from muscle, glucose from the liver and fatty acids from adipose tissue into the blood stream for use as energy.



\*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Normal cortisol metabolism undergoes a “diurnal rhythm,” meaning that cortisol levels vary throughout a 24-hour period with the highest levels typically observed in the early morning and the lowest levels in the early hours (about midnight – 2 am). Cortisol levels usually show a rapid drop between 8 am and 11 am and a continued gradual decline throughout the day. From those lowest levels around 2 am, cortisol again begins to rise to help us wake up and prepare for another stressful day. The normal range for blood cortisol levels is a fairly wide range of 6-23 mcg/dl, but these levels can vary tremendously in response to stress, illness and even following meals (Bjorntorp 1995, Epel 2001).

**Cortisol Levels Throughout the Day**



## Stress and Cortisol

There are three main stages of stress; Acute Stress, Chronic Stress and Adrenal Exhaustion.

**Stage 1 Acute stress.** When the brain perceives a stressful event, it responds by stimulating hormonal (endocrine) glands throughout the body to release hormones including both adrenaline and cortisol (resulting in the fight-or-flight response). Stress causes the rapid mobilization of the body’s energy reserves of fat, protein, and carbohydrates. Levels of adrenaline and cortisol increase, while DHEA (dehydroepiandrosterone) and testosterone decrease. Acute stress also typically involves increased heart rate and blood pressure, increased breathing rate, increased body temperature and sweating, feelings of anxiety and nervousness, headaches, heartburn and irritability.

**Stage 2 Chronic Stress.** As acute stress becomes more chronic, cortisol levels continue to increase and DHEA levels continue to decrease. The dual effect of high cortisol and low DHEA lead to muscle loss and fat gain and can have detrimental effects on bone and other tissues. Typical symptoms associated with chronic stress may include weight gain, fatigue, fluctuations in blood sugar, increased appetite, carbohydrate cravings, and reduced immune system function. Scientific studies have shown that chronic stress leads to overeating (Bjorntorp 2001, Epel 2001, Peeke 1995). During periods of chronic stress, levels of both cortisol and insulin rise and together send a potent signal to fat cells to store as much fat as possible. They also signal fat cells to hold on to fat stores, so stress can reduce the ability of the body to release fat from fat stores to use for energy. Several recent studies have demonstrated that cortisol secretion is increased with aging and that elevated cortisol levels reduce sensitivity to insulin. Reduced insulin sensitivity is clearly linked to obesity, diabetes and Metabolic Syndrome X. The early stages of chronic stress can be considered more of a “hyper-catabolic” situation characterized by accelerated tissue destruction.

**Stage 3 Adrenal Exhaustion.** The later stages of chronic stress cause the body to shift to a “hypo-anabolic” state where the body’s ability to rebuild vital tissues is impaired. At this later stage, much of the damage has already be done, so muscle and bone tissues are weaker and a vicious cycle of increased appetite, reduced caloric expenditure and accelerated fat accumulation occur.

Cortisol can have detrimental effects when there is either too much cortisol or the body is exposed to cortisol on a regular basis. Scientific evidence shows that chronically elevated cortisol levels are associated with obesity (Bjorntorp 1999), hypertension (Rosmond 2000), diabetes (Bjorntorp and Rosmond 2000), fatigue (Rosmond 1999), depression (Raikkonen 1994), moodiness (Epel 1999), irregular menstrual periods (VanItallie 2001) and increased appetite (Epel 2001, Peeke 1995). Stress-related diseases occur because of an excessive activation of our stress-response in the brain and the endocrine system to common, everyday sources of physical and psychological stress.

There are many different ways to help control cortisol levels. Eat a balanced diet, get adequate rest, and regular exercise can help the body adapt and respond to stressful events. Controlling individual stress responses with various relaxation techniques can help modulate cortisol secretion and normalize metabolism. There are a variety of dietary supplements that can help control the hyper-secretion of cortisol. Studies have shown that some dietary supplements can assist the body mount its own adaptive response to stress and help minimize or control some of the systemic effects of stress. Bringing cortisol levels back into a normal range will bring caloric expenditure back to normal levels, reduce body fat levels, preserve muscle mass, reduce appetite, and increase energy levels. Other benefits include reducing cholesterol and blood sugar, maintaining brain power, reducing bone loss, and strengthening immune function.

#### **PRIMARY ACTIVE CONSTITUENTS**

The key active constituents found in Cortitrol include Magnolia bark (*Magnolia officinalis*), Epimedium (*Epimedium koreanum*) Water Extract 6:1, L-Theanine (from *Camellia sinensis*, Extract 70:1 (TheaPure™), Beta Sitosterol and Phosphatidylserine. The Magnolia bark in Cortitrol is standardized to 2% Honokiol – a constituent with known anxiolytic properties (Kuribara 2001). Theanine is a unique amino acid found in the leaves of green tea (*Camellia sinensis*). Theanine acts as a non-sedating relaxant to help increase the brain's production of alpha-waves. Phosphatidylserine (PS) is a phospholipid, a molecule made up of two fatty acids and a phosphate group attached to a glycerol backbone. Phosphatidylserine is concentrated in cells of the brain, where it may be related to brain cell function and neurotransmitter metabolism. Magnolia bark (*Magnolia officinalis*) is a traditional Chinese medicine used since 100 A.D. rich in two biphenol compounds, magnolol and honokiol. Epimedium is a genus of 21 related plant species. Epimedium is grown as an ornamental herb in Asia and the Mediterranean region.

#### **HEALTH BENEFITS**

The constituents of Cortitrol address various aspects of cortisol control. Cortitrol combines natural ingredients that have been scientifically shown to have direct cortisol-balancing effects. Cortitrol helps provide enhanced feelings of well-being and control in response to stressful situations, and helps improve performance and increase vigor throughout the day by the anxiolytic effects of magnolia bark and the relaxation effects of theanine. Cortitrol helps support weight maintenance efforts and allows better mental concentration and focus through the natural ingredients theanine, epimedium, beta sitosterol and phosphatidylserine. Epimedium helps restore normal cortisol levels during stress, phosphatidylserine helps control cortisol elevation during stress, and beta-sitosterol helps reduce cortisol levels during exercise stress.

Many of the ingredients found in Cortitrol have multiple mechanisms of action to address various aspects of cortisol control, which are described below.

#### ***Phosphatidylserine***

Phosphatidylserine (PS) is a phospholipid that is concentrated in the brain cells, where it is thought to be related to brain-cell function. But it is also found in all cell membranes where it is thought to play key roles in muscle metabolism and immune-system function. Phosphatidylserine has also been shown to modulate many aspects of cortisol overproduction, especially following intense exercise.

There is ample scientific evidence that phosphatidylserine supplements can help improve mental function and depression, even in cases as severe as Alzheimer's disease and other forms of age-related mental decline. More recent studies have shown phosphatidylserine to reduce cortisol levels by 15–30 percent following heavy exercise (Monteleone 1990). Because cortisol is catabolic toward muscle tissue, athletes frequently use PS supplements to help promote recovery from exercise and help slow muscle loss. Because of its benefits in improving cognitive function, phosphatidylserine could also be considered a general antistress nutrient, providing benefits not only for athletes subjected to the physical stress of exercise, but also for individuals who are under chronic emotional stress from hectic lifestyles, job deadlines, and many of the other stresses of a modern lifestyle.

### ***Beta-sitosterol***

Beta-sitosterol has a structural similarity to cholesterol, but none of the artery-clogging effects. In the diet, plant oils contain the highest concentration of beta-sitosterol, nuts and seeds contain fairly high levels, and all fruits and vegetables generally contain some amount of beta-sitosterol. Perhaps the best way to obtain beta-sitosterol is to eat a diet rich in fruits, vegetables, nuts, and seeds.

Beta-sitosterol appears to help modulate immune function, inflammation, and pain levels through effects on controlling the production of inflammatory cytokines. In athletes competing in marathons and other endurance events, beta-sitosterol is known to reduce cortisol levels, maintain DHEA levels, and prevent the typical suppression of immune-system function seen after endurance events. From test-tube and animal studies, it appears that beta-sitosterol can influence the structure and function of cell membranes in both healthy and cancerous tissue. This effect is known to alter cellular signaling pathways that regulate tumor growth and apoptosis (cell death) and provide a possible explanation for the stimulation of immune function observed following beta-sitosterol supplementation.

In terms of general immune function, beta-sitosterol has been shown in humans to normalize the function of T-helper lymphocytes and natural killer cells following stressful events, such as marathon running, that normally suppress immune-system function. In addition to alleviating much of the postexercise immune suppression that occurs following endurance competitions, beta-sitosterol has also been shown to normalize the ratio of catabolic stress hormones (i.e., those that break down tissue, such as cortisol) to anabolic (rebuilding) hormones such as DHEA. In one study, seventeen endurance runners completed a sixty-eight-kilometer run (about forty miles) and afterward received either 60 mg of beta-sitosterol (nine runners) or a placebo (eight runners) for four weeks. Those runners receiving the beta-sitosterol supplements showed a significant drop in their cortisol-to-DHEA ratio (indicating less stress) as well as reduced inflammation and a markedly lower immunosuppression. Using the ultramarathon as a model for overall stress, researchers concluded that beta-sitosterol is effective in modulating the stress response by managing cortisol levels within a more normal range.

### ***Magnolia Bark***

Magnolia bark (*Magnolia officinalis*) is a traditional Chinese medicine used since 100 A.D. for treating stagnation of qi (low energy) as well as a variety of syndromes, such as digestive disturbances caused by emotional distress and emotional turmoil. The two active compounds, magnolol and honokiol, are thought to contribute to the primary antistress and cortisol-lowering effects of the plant.

Numerous animal studies have demonstrated honokiol to act as a central nervous system depressant at high doses, but as a nonsedating anxiolytic (antianxiety and antistress) agent at lower doses. When compared to pharmaceutical agents such as Valium (diazepam), honokiol appears to be as effective in its antianxiety activity, yet not nearly as powerful in its sedative ability.

### ***Theanine***

Theanine is a unique amino acid found in the leaves of green tea (*Camellia sinensis*) and acts as a nonsedating relaxant to help increase the brain's production of alpha waves. As such, theanine may be effective for combating tension, stress, and anxiety—without inducing drowsiness. Clinical studies show that theanine is effective in dosages ranging from 50 to 200 mg per day. Three to four cups of green tea are expected to contain 100–200 mg of theanine.

In addition to being considered a relaxing substance (in adults), theanine has also been shown to have benefits for improving learning performance (in mice), and promoting concentration (in students). No adverse side effects are associated with theanine consumption, making it one of the leading natural choices for promoting relaxation without the sedating effects of depressant drugs and herbs. When considering the potential benefits of theanine as an antistress or anticortisol supplement, it is important to distinguish its nonsedating relaxation benefits from the tranquilizing effects of other “relaxing” supplements such as valerian and kava, which are actually mild central nervous system depressants.

As mentioned previously, one of the most unique aspects of theanine activity is its ability to increase the brain's output of alpha waves. Alpha waves are one the four basic brain-wave patterns (delta, theta, alpha,

and beta) that can be monitored using an electroencephalogram (EEG). Each wave pattern is associated with a particular oscillating electrical voltage in the brain, and the different brain-wave patterns are associated with different mental states and states of consciousness (see Table below).

Brain-Wave Oscillation Patterns (Speeds)		
Brain-Wave Pattern	Cycles per Second	Mood/Emotional State
Delta	0–4	Deep sleep (stages 3 and 4)
Theta	4–8	Drowsy/light sleep (stages 1 and 2)
Alpha	8–13	Relaxed/wakeful/alert
Beta	13–40	Stress/anxiety/difficulty concentrating

### ***Epimedium***

Epimedium is a genus of twenty-one related plant species. Epimedium is grown as an ornamental herb in Asia and the Mediterranean region, and various species are used for medicinal purposes, including *Epimedium sagittatum*, *Epimedium brevicornum*, *Epimedium wushanense*, *Epimedium koreanum*, and *Epimedium pubescens*.

The use of epimedium as a medicinal herb dates back to at least 400 A.D. It has been used as a tonic for the reproductive system (boosting libido and treating impotence) and as a rejuvenating tonic (to relieve fatigue). Animal studies have shown that epimedium may function like an adaptogen by increasing levels of epinephrine, norepinephrine, serotonin, and dopamine when they are low (an energy-promoting effect), but reducing cortisol levels when they are elevated (an antistress effect). There is also evidence that epimedium can restore low levels of both testosterone and thyroid hormone to their normal levels; this may account for some of the benefits of epimedium in improving libido. Animal studies using epimedium have shown a reduction in bone breakdown, an increase in muscle mass, and a loss of body fat—each of which may be linked to the observed reduction of elevated cortisol to normal levels.

In a series of studies conducted in humans and animals by Chinese researchers, immune-system function was directly suppressed and bone loss was accelerated by using high-dose glucocorticoids. Subsequent administration of epimedium extract reduced blood levels of cortisol and improved immune-system function (in the humans) and slowed bone loss and strengthened bones (in the animals) (Wu 1996).

### **PROPRIETARY PROCESSING**

The combination of quality ingredients, qualified manufacturers, certified independent laboratory verification, and a continuous drive to supply leading-edge products, ensures our distributors and consumers the highest quality products available in the industry. The constituents in Cortitrol are standardized through scientific and analytical methods to ensure that every capsule contains the specific level of constituents, every time.

Cortitrol is one of the first cortisol-controlling dietary supplements. Cortitrol is a proprietary blend of ingredients that both lowers cortisol and improves mental function. Cortitrol contains a proprietary mixture of theanine. Cortitrol is a patent-pending formula for cortisol control.

All ingredients are tested for purity, and where applicable, ingredients are certified pure by microbial testing, such as tests for *Salmonella*, *E. coli*, other coliforms, *Staphylococcus aureus*, total plate counts, yeasts, molds and pesticide residues. Our manufacturers go through a detailed selection and certification process to assure their compliance with Good Manufacturing Practice (GMP) standards set by the Food and Drug Administration (FDA).

### **SIDE EFFECTS**

No known side effects at recommended dosage.

### **SAFETY AND TOXICITY**

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Cortitol is safe and well tolerated at the recommended dosage. L-theanine has been approved in Japan for unlimited use in all foods, except infant foods, after favorable toxicology studies. There are no limitations to duration of administration or known adverse drug interactions (Mason 2001).

#### **CONTRAINDICATIONS/DRUG INTERACTIONS**

If you are pregnant or lactating, or taking a prescription medication, or allergic to any component of this product, please consult a physician prior to use. Because Cortitol is indicated for stress relief, consult a physician if you are taking prescription "anti-stress" medications such as anxiolytics, sedatives, or hypnotics. Consult a physician if you are taking other CNS depressants, tricyclic antidepressants, anti-epileptics, muscle relaxants, anticoagulants, corticosteroids and quinalone antibiotics. Use of l-theanine concomitantly with chemotherapeutic agents must be done under medical supervision. L-theanine may enhance the effects of doxorubicin, idarubicin, adriamycin, and picarubicin and may ameliorate some of their side effects (PDR for Nutritional Supplements 2001, Sadzuka 1996, Sugiyama 1998, 1999). This supplement should be discontinued two weeks prior to surgery.

#### **DIRECTIONS FOR USE**

As a dietary supplement, take two to three capsules daily. Take two (2) capsules with your evening meal. For optimal results take an additional (1) capsule with your morning meal.

#### **HOW SUPPLIED**

Cortitol is supplied in a 20-30 day supply of 60 capsules.

#### **STORAGE**

Store in a cool, dry place. Avoid excessive heat. Protect from light.

#### **SHELF LIFE**

Expiration date and lot code numbers are stamped on the bottle.

#### **WARNINGS**

Keep out of reach of children. If you are pregnant or nursing, or taking a prescription medication, consult a physician before using this product.

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