

Premarket Notification for Radix Ginseng in VI-28

COMPANY NAME: Vigconic (Intenational) Ltd.
COMPANY ADDRESS: 5B, Cheong Wah Factory Building
39-41, Sheung Heung Road, Tokwawan
Kowloon, HONG KONG

NEW DIETARY INGREDIENT NAME: RADIX GINSENG (Ginseng)

INTENDED USE: Radix Ginseng is intended for use as a dietary ingredient in the dietary supplement product VI-28. The dietary supplement product will contain 75 mg of Radix Ginseng per capsule, for a dietary intake of up to maximum 150 mg per day.

HISTORY OF USE/SAFETY EVIDENCE FOR NEW DIETARY INGREDIENT:

The history of use of Radix Ginseng can be established with a brief review of products currently offered in the United States that contain this ingredient. Examples of such products include FeminiCare™ dietary supplement, Viatexx™ dietary supplement, and Betterman™ dietary supplement. With regard to Betterman™ dietary supplement, attention would like to be directed to the short term study of American men administered the dietary supplement. It was determined that there were no side effects or adverse reactions following administration of the supplement¹.

Radix Ginseng is the dried root of Panax Ginseng (*Panax Ginseng C.A. Meyer, Araliaceae*). Pharmacologically, Radix Ginseng has an "adaptogenic" effect, which produces an increase in the body's defenses against outside stress factors and chemicals. According to Herbal Drugs and Phytopharmaceuticals, Radix Ginseng is not a therapeutic agent, but rather an agent which regulates the resistance of the organism to various outside influences². Further, Herbal Drugs, states that side effects are "...relatively rare and only with high doses and/or use over very long periods of time"³. Side effects include sleepnesses, nervousness, diarrhea, menopausal bleeding, and hypertony. The daily dosage as indicated by the literature is 1-2 grams⁴.

Evidence of the safety of the dietary ingredient is shown in the study performed on the dietary supplement VI-28. A summary of the study and a copy are attached herewith⁵.

¹ See page 3, "Research Studies on the scientific proof that BetterMAN improves erections and prostate...III. Short-term Study with American Men...".

² Wichtl, M. "Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice...", pp. 236-238.

³ Id. at pp. 237.

⁴ Id. at pp. 237, bottom, last column (boxed).

⁵ The letter from Dr. Laurence S.L. Shek and Anti-ageing Study show the results of administration of VI-28.

Based on the literature and in comparison to the intended use of Radix Ginseng in VI-28, it is believed that Radix Ginseng can reasonably be expected to be safe. Namely, literature shows Radix Ginseng administered at doses (1-2 grams daily) significantly higher than that of VI-28 (maximum 150 mg daily), with the result being no ill effects.

Premarket Notification for Cornu Cervi Pantotrichum in VI-28

COMPANY NAME: Vigconic (Intenational) Ltd.
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NEW DIETARY INGREDIENT NAME: CORNU CERVI PANTOTRICHUM
(Pilose Antler⁶)

INTENDED USE: Cornu Cervi Pantotrichum is intended for use as a dietary ingredient in the dietary supplement product VI-28. The dietary supplement product will contain 75 mg of Cornu Cervi Pantotrichum per capsule, for a dietary intake of up to maximum 150 mg per day.

HISTORY OF USE/SAFETY EVIDENCE FOR NEW DIETARY INGREDIENT:

The history of use of Cornu Cervi Pantotrichum can be established via a review of literature. In China, the red deer species is raised for their young pilose antlers⁷. According to the literature, red deer, a member of the Cervus species, has been farmed to produce velvet antler teas, extracts, capsules and tablets for health related products⁸. Currently, many countries produce velvet antler including New Zealand (450 tons/year), China (400 tons/year), Russia (80 tons/year), United States (20 tons/year), and Canada (20 tons/year)⁹. Velvet antler supplements have been the subject of numerous studies¹⁰.

Evidence of the safety of the dietary ingredient is shown in the study performed on the dietary supplement VI-28. A summary of the study and a copy are attached herewith¹¹.

In one study, Senescence-Accelerated Mice were administered subchronic oral doses of hot-water extract of pilose antler (Rokujo)¹². Doses were given orally for 8 successive days in amounts of 0, 100, or 200 mg/kg/d¹³. In a scientific review, researchers studied acute and sub-chronic toxicity of powdered deer velvet at dose levels of 2000 mg/kg for single oral treatment, and 500 mg/day orally for 90 days in rats¹⁴. It was reported that there were no

⁶ Monograph, "Cornu Cervi Pantotrichum", www.healthlink.com.au/ant_lib/htm-data/htm-herb/bhp927.htm.

⁷ "Young Pilose Antler- A Precious Crude Drug", pp. 43-45.

⁸ Batchelder, H. "Velvet Antler: A Literature Review", www.natraflex.com/studies/VA2.htm.

⁹ Id. at pp. 1.

¹⁰ Id., Antler extract was orally administered to rat and dog to determine plasma level of chondroitin sulfate (pp. 8-9), Antler extract was administered to rats to study level of monocytes (pp. 11), antler was administered to male athletes to determine effect (pp. 14).

¹¹ The letter from Dr. Laurence S.L. Shek and Anti-ageing Study show the results of administration of VI-28.

¹² Wang et al. "Effects of Repeated Administration of Deer Antler Extract on Biochemical Changes Related to Aging in Senescence-Accelerated Mice", Chem Pharm. Bull. 36, pp. 2587-2592.

¹³ Id. at pp. 2589.

¹⁴ Suttie, J. and Harris, S. "Clinical Properties of Deer Velvet",

pathological findings. Further, deer velvet powder was tested on reproduction and developmental toxicity, which was shown to have no effect on conception rates¹⁵.

Bovine Spongiform Encephalopathy (BSE) and Cornu Cervi Pantotrichum

During a telephonic meeting held with the FDA on 20 April 2004 regarding the dietary ingredient Cornu Cervi Pantotrichum, concern was expressed for the ingredient being infected with BSE, a transmissible spongiform encephalopathy (TSE), and its transmission to users of the ingredient.

Firstly, it is important to note that BSE is not known to infect deer, rather Chronic Wasting Disease (CWD) is known to infect deer¹⁶. Second, in view of current studies, it is the Notifier's contention that use of Cornu Cervi Pantotrichum in VI-28 is reasonably safe.

CWD is known to be an infectious agent present in free-ranging deer and elk in Wyoming and Colorado. As for transmission to humans, current epidemiologic and laboratory investigations have concluded there is no strong evidence for a causal link between CWD and Creutzfeldt-Jakob disease (CJD-the form of TSE in humans)¹⁷. In developing such conclusion, the researchers reviewed several cases of humans who died of apparently rare neurological disorders. The patients did not appear to possess a common history with regards to exposure to deer or elk. Some patients apparently consumed venison, however it was not clear that the meat was infected with CWD. In some cases, the meat was from areas not known to be infected with CWD (Michigan)¹⁸. In addition, the report concluded that because there has not been an increase in the cases of CJD in Colorado and Wyoming (areas known to be infected with CWD), the risk of transmission to humans is low.

Further research has shown that a barrier at the molecular level likely limits the susceptibility of non-cervid species to CWD¹⁹.

Cornu Cervi Pantotrichum as used in VI-28 is obtained from the People's Republic of China, an area not known to contain instances of CWD-infected deer. It is also believed the method of preparation of Cornu Cervi Pantotrichum likely addresses potential prion proteins.

www.positivehealth.com/permit/Articles/Nutrition/sut54.htm.

¹⁵ Id.

¹⁶ "Commonly Asked Questions About BSE in Products Regulated by FDA's Center for Food Safety and Applied Nutrition (CFSAN)", U.S. Food and Drug Administration, January 14, 2004.

¹⁷ Belay et al. "Chronic Wasting Disease and Potential Transmission to Humans", Emerging Infectious Diseases, Center for Disease Control and Prevention, Vol. 10, No. 6 (2004).

¹⁸ Id. at pages 4-5

¹⁹ Raymond et al., "Evidence of a molecular barrier limiting susceptibility at humans, cattle, and sheep to chronic wasting disease", The EMBO Journal, Vol. 19, No. 17 (2000).

Cornu Cervi Pantotrichum is boiled and dried, then ground into a powder and incorporated into VI-28. The entire VI-28 mix is then dried at 80°C for 24 hours.

Based on the literature and in comparison to the intended use of Cornu Cervi Pantotrichum in VI-28, it is believed that Cornu Cervi Pantotrichum can reasonably be expected to be safe. Namely, the literature shows Cornu Cervi Pantotrichum administered at doses (2000mg/kg and 500 mg/day for 90 days) that are significantly higher than that of VI-28 (maximum 150 mg daily), with no ill effects. Further, through the method of preparing Cornu Cervi Pantotrichum, it is believed that prion proteins are likely eliminated.

Premarket Notification for Semen Cuscutae in VI-28

COMPANY NAME: Vigconic (Intenational) Ltd.
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NEW DIETARY INGREDIENT NAME: SEMEN CUSCUTAE (Cuscuta
Chinensis Lam.; Cuscuta japonica
Choisy)

INTENDED USE: Semen Cuscutae is intended for use as a dietary ingredient in the dietary supplement product, VI-28. The dietary supplement product will contain 60 mg of Semen Cuscutae per capsule, for a dietary intake of up to maximum 120 mg per day.

PRESENT IN FOOD SUPPLY

Semen Cuscutae has likely been present in the United States food supply, most likely in staple crops including soybean, potato, and pumpkin²⁰. Specifically, Semen Cuscutae has been known to parasitize such staple crops. While being considered a parasite, it is a likely fact that during harvest, Semen Cuscutae was harvested along with the staple crop, and unknowingly utilized during the production of foods.

Further to its past use, Semen Cuscutae has frequently been known as a medicinal herb that is sold under a variety of names include "Dodder Seed Semen", "Cuscutae" and "Tu Si Zi"²¹.

HISTORY OF USE/SAFETY EVIDENCE FOR NEW DIETARY INGREDIENT:

The history of use of Semen Cuscutae can be established from a review of scientific literature. In one study, a dietary supplement, EquiguardTM, currently available in the United States, concluded that the ingredients of the dietary supplement were effective in prohibiting the effects of carcinoma²². Notably, EquiguardTM ingredients include Cuscuta Chinensis Lam. (Semen Cuscutae).

Evidence of the safety of the dietary ingredient is shown in the study performed on the dietary supplement VI-28. A summary of the study and a copy are attached herewith²³.

²⁰ NPAG DATA: Cuscuta Japonica (Japanese Dodder) 11/2001, pp. 5.

²¹ Id. at pp. 8.

²² Hsieh, T. et al. "Effects of herbal preparation Equiguard on hormone-responsive...", Intern. Jour. of Oncology 20: pp. 681-689 (2002).

²³The letter from Dr. Laurence S.L. Shek and Anti-ageing Study show the results of administration of VI-28.

Safety evidence for the use of Semen Cuscutae is stated in the American Herbal Products Associations Botanical Safety Handbook (BSK)²⁴. The BSK, in arranging herb ingredients, positions them in classes according to their safety. A list of the classes is attached herewith. *Cuscuta chinensis* Lam. is classified in Class 1, which refers to herbs which can be safely consumed when used appropriately.

²⁴ McGuffin, M et al. (ed.) "American Herbal Products Association's Botanical Safety Handbook".

Premarket Notification for Fructus Cnidii in VI-28

COMPANY NAME: Vigconic (Intenational) Ltd.
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NEW DIETARY INGREDIENT NAME: FRUCTUS CNIDII (Cnidii Monnieri
Fructus (*Cnidium monnieri* *cusson*,
Matsuda); Dried Fruits of Cnidium
monnieri)

INTENDED USE: Fructus Cnidii is intended for use as a dietary ingredient in the dietary supplement product, VI-28. The dietary supplement product will contain 60 mg of Fructus Cnidii per capsule, for a dietary intake of maximum 120 mg per day.

HISTORY OF USE/SAFETY EVIDENCE FOR NEW DIETARY INGREDIENT:

The history of use of Fructus cnidii is established from a review of current products in the U.S. marketplace. Examples of such products include Stamina-Rx, a dietary supplement for "enhancing sexual performance", which contains 25 mg of Cnidium monnieri and instructions that use should not exceed 4 tablets in a 24-hour period, for a total dietary intake of 100 mg²⁵. Watkins "Male Formula" is currently being sold in the U.S. to aid in optimizing male health. The formula includes a proprietary herbal blend in an amount of 500 mg that includes Cnidium monnieri²⁶. Vagistatin is a product useful for "cervical dysplasia, HPV, and candidiasis". The ingredients of the supplement include cnidium fruit. No information is given as to the amount used or frequency of administration²⁷.

Evidence of the safety of the dietary ingredient is shown in the study performed on the dietary supplement VI-28. A summary of the study and a copy are attached herewith²⁸.

Evidence of safety of Fructus cnidii is also shown in the scientific literature. In one study, the anti-inflammatory effects of a dietary supplement were determined upon application to rats. The dietary supplement, *Xuan-Ju*, contains in its ingredients Fructus cnidii. The supplement was administered at doses of .20, .40 and .80 g/kg²⁹. Another report detailed the use of Cnidium monnieri in

²⁵ Available at www.stamina-rx.com/about.html.

²⁶ Information available at www.watkinsonline.com.

²⁷ Information available at www.emersonecologics.com

²⁸ The letter from Dr. Laurence S.L. Shek and Anti-ageing Study show the results of administration of VI-28.

²⁹ Wei J et al. "Anti-Inflammatory effects of an herbal medicine (Xuan-Ju agent)...", Journal of Ethnopharmacology, 89(1) pp. 139-141 (2003).

the prevention of hepatotoxic effects of tacrine (1,2,3,4-tetrahydro-9-aminoacridine hydrochlorid)³⁰.

Based on the presence of Fructus cnidii in current herbal supplements sold on the U.S. market used in an amount similar to the amount used in VI-28 supplement, and studies performed on VI-28, it is believe that Fructus cnidii as present in VI-28 can reasonably be expected to be safe.

³⁰ Oh, H. "Sesquiterpenes with Hepatoprotective Activity from *Cnidium monnieri*...", *Planta Med* 68, pp. 748-749 (2002).

Premarket Notification for Kaempferiae Rhizoma in VI-28

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NEW DIETARY INGREDIENT NAME: KAEMPFERIAE RHIZOMA (rhizomes of
Kaempferia galanga)

INTENDED USE: Kaempferiae Rhizoma is intended for use as a dietary ingredient in the dietary supplement product VI-28. The dietary supplement product will contain 30 mg of Kaempferiae Rhizoma per capsule, for a dietary intake of maximum 60 mg per day.

HISTORY OF USE/SAFETY EVIDENCE FOR NEW DIETARY INGREDIENT:

The history of use of Kaempferiae Rhizoma is established from a review of various Asian cultures. *Kaempferia galanga* (**Kaempferia galanga chekur, Vimala**) is cultivated in India, China, Malaysia, Indonesia, and Singapore. It is widely used as a flavoring in food, as well as a health aid. The rhizomes of Kaempferiae Rhizoma have been used to aid in abdominal pain, swelling, and rheumatism³¹.

Evidence of the safety of the dietary ingredient is shown in the study performed on the dietary supplement VI-28. A summary of the study and a copy are attached herewith³².

Evidence of safety for Kaempferiae Rhizoma is also shown in the scientific literature. In one study, the cytotoxicity effect of rhizomes of *Kaempferia galangal* against EBV genome carrying human lymphoblastoid cells (Raji) was performed. It was determined that *Kaempferia galangal* exhibited no cytotoxicity effect³³. In another study, the various constituents of Kaempferiae Rhizoma were determined³⁴. Safety information regarding many of the constituents can be found in the literature including cineol (which is major component of sage oil, an ingredient used in the U.S.³⁵), borneol³⁶, 3-carene (in which dairy farmers during

³¹ Othman et al. "Vasorelaxant Effects of Ethyl Cinnamate Isolated from *Kaempferia galangal*...", *Planta Med.* 68, pp. 655-657 (2002).

³² The letter from Dr. Laurence S.L. Shek and Anti-ageing Study show the results of administration of VI-28.

³³ Vimala et al. "Anti-tumor promoter activity in Malaysian ginger...", *British Journal of Cancer* 80, pp. 110-116 (1999).

³⁴ Kiuchi et al. "Studies on Crude Drugs effective on Visceral Larva..." *Chemical and Pharmaceutical Bulletin*, 36 (1) pp. 412-415 (1988). Constituents include cineol, borneol, 3-carene, camphene, kaempferol, kaempferide, cinnamaldehyde, p-methoxycinnamic acid, ethyl cinnamate, and ethyl p-methoxycinnamate.

³⁵ Farhat et al. "Seasonal changes in the composition of the essential oil...", (Abstract), PubMed record no. 11478969.

milking are regularly exposed to the compound³⁷), kaempferol (in which guinea pig enterocytes were exposed to the compound in concentration of 50-450 microM, and kaempferol was determined to be less toxic³⁸), and ethyl cinnamate (EC) (in which it was determined that EC, which is present in red wines as flavor, may be responsible for the vasorelaxant activity of the rhizome of *Kaempferia galanga*³⁹).

Based on the current use of *Kaempferia Rhizoma* in cooking in many Asian cultures, studies conducted on the toxicity of the ingredient, scientific articles disclosing and researching many of the constituents of the ingredient, and the study performed on VI-28, it is believed that *Kaempferia Rhizoma* as used in the VI-28 dietary supplement can reasonably be expected to be safe.

³⁶ Id.

³⁷ Sunesson et al. "Airborne chemical compounds..." (Abstract), PubMed record no. 11354733.

³⁸ Canada et al. "The toxicity of flavonoids..." (Abstract), PubMed record no. 2734797.

³⁹ Id. at 26.

CHEMICAL COMPOSITION OF COMPONENTS OF VI-28

Radix Ginseng

- 2-3% Ginsenosides (triterpene saponins)
- 0.05% essential oil (limonene, terpineol, citrol, polyacetylenes)
- sugar
- starch

Cornu Cervi Pantotrichum

- 34% Ash
- 12% moisture
- nitrogen
- fats
- collagen
- glycosaminoglycans (chondroitin sulfate, keratin sulfate, hyaluronic acid, dermatan sulfate, chondroitin sulfate proteoglycan, decorin)
- lipids (polysaccharides)
- growth hormone and prostaglandins (IGF-1, IGF-2)

Semen Cuscutae

- quercetin 3-O-beta-D-galactoside-7-O-beta-D-glucoside (I)
- quercetin 3-O-beta-D-apiofuranosyl-(1-->2)-beta-D-galactoside (II)
- hyperoside (III)
- isorhamnetin (IV)
- kaempferol (V)
- quercetin (VI)
- d-sesamin (VII)
- 9(R)-hydroxy-d-sesamin (VIII)
- Vitamin A

Fructus Cnidii

- osthol
- imperatorin
- xanthotoxin
- isopimpinellin
- bergapten

Kaempferiae Rhizoma

- cineol
- borneol
- 3-carene
- camphene
- kaempferal
- kaempferide
- cinnamaldehyde
- p*-methoxycinnamic acid
- ethyl cinnamate
- ethyl *p*-methoxycinnamate

Inactive Ingredient

- rice powder

Capsule

- Gelatin Capsule

METHOD OF MANUFACTURE

Phase A

Radix ginseng; Cornu Cervi pantotrichum and Rhizome kaempseriae are ground to a fine powder under low temperature.

Phase B

Fructus cnidii and Semen cuscutae are water decocted, filtered, the solution is oven dried, and reduced to a fine powder via grinding process.

Phase A and B are mixed in proper proportion to form the final mix. The final mix is heat treated at 80°C for 24 hours, and then filled into gelatin capsules.

MICROBES AND PESTICIDE CONTROL

In the control of microbes, it is believed the method of manufacture, namely the use of heat treatment 80°C for 24 hours, is sufficient to address any microbes that may be present.

Regarding pesticide monitoring, the final mix is subject to pesticide monitoring in accordance with the Hong Kong Standards and Testing Centre (report of 2003-02-14 enclosed herewith).

TEST ARTICLES UTILIZED IN STUDIES

The FDA has asserted in its reply to the original Notification that, at page 3, second full paragraph, there are discrepancies with the description of the test articles used in studies submitted with the original Notification. Specifically, the FDA states that one study reported was conducted with VI-28, and other studies were conducted with test substances similar to VI-28, however "the relationship of these test materials to the botanical preparations that are the subject of the notification was not stated".

With reference to the letter faxed to Dr. Walker on 21 January 2004 (attached herewith), it was previously stated that VI-28 to be marketed consists of the botanical preparations that were the subject of the original Notification (and subsequently this re-submitted Notification). Because the botanical preparations are not modified chemically in the preparation of VI-28 and the preparations are believed to be safe, it is believed that VI-28 to be marketed is safe. The test materials used in the studies are qualitatively and quantitatively akin to VI-28 to be marketed in the U.S., i.e., it consists of the same botanical preparations used in the same amounts as stated in this Notification.