

PREMARKET NOTIFICATION _SYNTHETICALLY PRODUCED HYDROXYCITRIC ACID |

SUBMITTED BY

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1 NAME AND ADDRESS OF DISTRIBUTOR AND CURRENT MANUFACTURER

Dietary Supplement Distributor:

Broderick & Tourville
26 Washington Street
3rd Floor
Morristown
NJ 07960

Dietary Ingredient GMP Manufacturer:

Mingshen ChemPacific Ltd
741 Moganshan Road
Hangzhou
China

Dietary Supplement GMP Manufacturer/Bottler/Packager

Shannon Minerals Limited
Upper Clare Street,
Limerick,
Ireland

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2. NAME AND IDENTITY OF NEW DIETARY INGREDIENT

Chemical Name: (2S,3S) -2- Hydroxycitric Acid

Other Name: (-)- Hydroxycitric Acid

Common Names: Hydroxycitric acid, HCA, hydroxycitrate, (-)-hydroxycitric acid, (-) HCA, (-)-hydroxycitrate

(See also (-) – *Hydroxycitric Acid – The principal Acid in the fruits of Garcinia Cambogia Desr.*, Lewis and Neelakantan, Central Food Technological Research Institute, Mysore, India, March 1964) – (Appendix A)

The new dietary ingredient is branded APPETRIM™

3. DESCRIPTION OF THE PRODUCT CONTAINING SYNTHETICALLY PRODUCED HCA

The dietary supplement is a 500 mL solution containing 700 mg (-)- HCA, the dietary ingredient. The dietary ingredient is provided by APPETRIM™ synthetic tripotassium hydroxycitrate.

The product is to be sold in individual bottles containing 500 mL of dietary supplement. The product ingredients are water, citric acid, APPETRIM™ synthetic tripotassium hydroxycitrate, natural flavor, aspartame, potassium sorbate and sodium benzoate as preservatives, and asulfame potassium.

The dietary supplement is to be branded TRIM™.

Conditions of use:

The label will recommend use as a dietary supplement by consuming one bottle four times daily (one hour before a meal). It will not be recommended for use by young children or by pregnant or lactating women. The label will provide the phenylketonurics cautionary statement (21 CFR §172.804(d)(2)).

Processing and method of manufacturing

Information on production of the APPETRIM™ synthetic tripotassium hydroxycitrate, the source of the HCA dietary ingredient, including quality checks, tests, and specifications to ensure its identity, is set forth on following pages. Similarly, information on the TRIM™ Dietary Supplement, including its processing and quality control and other procedures in place to ensure its safety, is set forth on following pages. Pages containing trade secret or confidential commercial information believed to be exempt from disclosure when this notification is published at the Dockets Branch are marked "CONFIDENTIAL."

20 P A G E S T O T A L

REDACTED IN ITS
ENTIRETY
CONTAINS
TRADE SECRET
CONFIDENTIAL
COMMERICAL
INFORMATION

4 HISTORY OF USE / SAFETY EVIDENCE

(See also appendices A and B)

HISTORY OF USE

The following extract briefly outlines the history of use of HCA:

Garcinia Cambogia is one of several closely related Garcinia species from the plant family known as Guttiferae. With a thin skin and deep vertical lobes, the fruit of Garcinia Cambogia is about the size of an orange, but looks more like a small yellowish or reddish pumpkin. When the rinds are dried and cured in preparation for storage and extraction, they are dark brown in colour. Another member of the family Garcinia mangostana, is cultivated specifically for its fruit and is not a source of HCA. These Garcinia species are native to Southeast Asia and are usually wild-crafted, although they are cultivated in some areas.

HCA is primarily found in the rind of Garcinia Cambogia, where 10 to (rarely) 30% of the weight of the dried rind is HCA. This acid occurs in nature almost entirely in the form of its lactone, which has a chemical structure and physiologic effects, which are different from those of the free acid.

Along the West coast of Southern India, Garcinia Cambogia is known as "Goroka" or "Katcha puh" (souring fruit). It is employed commercially in fish curing, especially in Sri Lanka (Colombo curing) and various species of Garcinia are used in food preparation in Thailand, Malaysia and Burma. Garcinia Cambogia is considered to be effective in making meals "more filling". Aside from its use in food preparation and preservation, extracts of Garcinia Cambogia are sometimes used as purgatives in the treatment of intestinal worms and other parasites, for tumours, for dysentery and in the treatment of bilious digestive conditions.

Cloutare, Dallas and Michael E. Rosenbaum (1994) **The Diet and Health Benefits of HCA (Hydroxycitric Acid)** (New Canaan, CT: Keats Publishing Inc, 1994) .

Further studies indicate that Garcinia Cambogia has a long history of use as a food

Observational Study:

'The acid rinds of the ripe fruit are eaten, and in Ceylon are dried, and eaten as a condiment in curries'

Drury, Heber (1873) **The Useful Plants of India**, second edition (London: Wiliam H Allen & Co., 1873) 220

Observational Study:

'Fruits are edible, but too acidic, also pickled: rind used as a condiment. Seeds yield an edible fat... A decoction of rind is gien in rheumatism and bowel complaints.'

Publications and Information Directorate, Council of scientific and Industrial Research (1986) **The Useful Plants of India** (New Dehli: Publications and Information Directorate, 1986) 229.

Observational Study:

'Fruit yellowish or reddish, size of an orange having six or eight deep longitudinal grooves in its fleshy pericarp. Pulp acid is of a pleasant flavour. It is dried among the Singalese who use it in curries'

Uphof, J. C. Th. (1968) *Garcinia Cambogia* Desrouss. *Dictionary of Economic Plants*, second edition. (New York: Verlag von J. Kramer , 1968) 237

SAFETY EVIDENCE

As well as having a long history of use in food, there are a vast number of research articles outlining the safety of HCA. The most recent article published by the Burdock Group of Florida states:

In several, placebo controlled, double-blind trials employing up to 2800mg/day HCA, no treatment-related adverse effects were reported. There is sufficient qualitative and quantitative scientific evidence, including animal and human data suggesting that intake of HCA at levels up to 2800 mg/day is safe for human consumption

and

In summary, on the basis of scientific procedures, which include human, animal, analytical, and other scientific studies, and history of exposure and use, the consumption of HCA .. at dose level of 2800mg/day, is considered safe

M. G. Soni, G.A. Burdock, H G. Preuss, S.J. Stohs, S. E. Ohia, D. Bagchi: **Safety assessment of (-)-hydroxycitric acid and Super CitriMax, a novel calcium/potassium salt.** Food and Chemical Toxicology 42 (2004) 1513-1529

An *in vivo* study conducted in 2003 by researchers at Creighton University found that:

Feed intake was significantly reduced in HCA-SX supplemented rats, demonstrating appetite suppression. None of the groups demonstrated any changes in water intake during the 90 days of treatment. HCA-SX supplementation did not alter hepatic and testicular lipid peroxidation or DNA fragmentation. Taken together, these results indicate that HCA-SX is safe and efficacious in weight management under the conditions employed in these studies.

Michael Shara, Sunny E. Ohia, Taharat Yasmin, Andrea Zardetto-Smith, Anthony Kincaid, Manashi Bagchi, Archana Chatterjee, Debasis Bagchi and Sidney J. Stohs: **Dose- and time- dependent effects of a novel (-)- hydroxycitric acid extract on body weight, hepatic and testicular lipid peroxidation, DNA fragmentation and histopathological data over a period of 90 days.** Molecular and Cellular Biochemistry 254: 339 –346, 2003

Another *in vivo* study conducted in 2002 by researchers at the same Creighton University found that:

*Results indicate that the LD₅₀ of HCA-SX is greater than 5,000 mg/kg when administered once orally via gastric intubation to fasted male and female Albino rats. No gross toxicological findings were observed under the experimental conditions. Taken together, these *in vivo* toxicological studies demonstrate that HCA-SX is a safe, natural supplement under the conditions it was tested*

Sunny E. Ohia, Catherine A. Opere, Angela M. LeDay, Manashi Bagchi, Debasis Bagchi and Sidney J Stohs: **Safety and mechanism of appetite suppression by a novel hydroxycitric acid extract (HCA-SX).** Molecular and Cellular Biochemistry 238: 89-103, 2002

SYNTHETICALLY PRODUCED HCA

The similarities between the synthetic development of citric acid and hydroxycitric acid are striking, with citric acid now being almost exclusively produced synthetically. Synthetically produced HCA gives a product that is chemically and structurally identical to the substance found in nature, although contrary to the natural product, synthetically produced HCA contains only 100% HCA. All manufacturers involved in the process are manufacturing the product to GMP standards, and this is also a requirement for any prospective manufacturers.

Since the synthetically produced product is chemically and structurally identical to its naturally occurring counterpart, and since the GMP standards for manufacture are enforced, it is fair to assume that the synthetic product will perform in exactly the same way as the naturally occurring substance.

For detailed information on basic mechanisms of action, including appetite suppression, please see Appendix C. For further information on Quality Control Methodology please see Appendix D

5. Designated Signatory

Brendan O'Mara

Brendan O' Mara
Managing Director
Shannon Minerals Limited

Appendix A

Contents:

Research paper – (-)- Hydroxycitric Acid – The Principal Acid in the fruits of **Garcinia Cambogia Desr.** Y.S. Lewis and S. Neelakantan, Central Food Technological Research Institute, Mysore, India, March 1964