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Proactive Disclosure

Proactive Disclosure

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The advisory was met with mixed reaction. The following information explains Health Canada's rationale and provides some background on the issue.

**Information:**

- We recognize that some individuals who suffer from serious central nervous system disorders may be concerned about recent actions taken by Health Canada concerning the drug Empowerplus.
- However, Health Canada is concerned that individuals using Empowerplus could be putting their health at risk. For this reason, Health Canada issued a health advisory on June 6, 2003.
- Health Canada's responsibility is to ensure that drugs sold in Canada are safe and effective. To do that, we require drug manufacturers to provide us with scientific evidence that the drug is safe, effective and of acceptable quality.
- Empowerplus is sold by the company Truehope Nutritional Support Limited (also known as Synergy). The company has not provided evidence of Empowerplus' safety, effectiveness or quality, and has also failed to stop the promotion and sale of Empowerplus - despite Health Canada's request on several occasions that it do so.
- The drug is being sold to treat serious disorders, such as bipolar disorder, anxiety disorder, panic attacks, attention deficit disorder, schizophrenia, autism, Tourette's syndrome, fibromyalgia and obsessive compulsive disorder.
- Serious central nervous system disorders should not be self-medicated or self-diagnosed. They are best treated under the supervision of a health care provider.
- Health Canada's main concerns are the unproven health claims being made for Empowerplus, and the recommendation that patients decrease the dose of, or eliminate altogether, medications prescribed by their doctors. This can result in serious adverse health consequences.
- There are other potential risks associated with Empowerplus. For example, a "full loading dose" of 32 capsules, (i.e., the dose documented by those who have studied the recommended use of the product), provides amounts of vitamins A, D and folic acid that exceed the maximum limit permitted for nonprescription use. Such high amounts could cause adverse effects associated with hypervitaminosis when ingested over an extended period of time. The prolonged intake of products containing germanium, has also been associated with renal failure, and even death in at least 31 reported human cases.
- For these reasons, Empowerplus presents a potential health risk.
- There have been only two studies on Empowerplus that have been reported in the scientific literature to date. Both studies were conducted by the same group of researchers, were exploratory in nature and involved only a small number of subjects. The researchers concluded that more studies were required before the safety and effectiveness of the drug could be determined.
- Health Canada has indicated to Truehope on more than one occasion that it would be willing to evaluate Empowerplus via a new drug submission. Once the supporting evidence has been submitted and assessed, Health Canada will issue a Notice of Compliance and Drug Identification Number (DIN) for the drug product, if the information is deemed to be acceptable.
- The information submitted should provide evidence that the benefits of the drug outweigh the risks. Until such time, it is illegal to sell Empowerplus in Canada.
- Canada's regulatory requirements for the approval of drugs are governed by the Food and Drug Act and Regulations, which are among the best and most rigorous in the world.
- It is important to discuss the use of any drugs, including vitamins, minerals and herbal products, with a health care provider.
patients decrease the dose of, or eliminate altogether, medications prescribed by their doctors. Abandoning conventional therapy while not under the supervision of a doctor can result in serious adverse health consequences.

There are other potential risks associated with Empowerplus. Specifically, a "full loading dose" of 32 capsules, (i.e., the dose documented by those who have studied the recommended use of the product), provides amounts of vitamins A, D and folic acid that exceed the maximum limit permitted for nonprescription use. Such high amounts could cause adverse effects associated with hypervitaminosis when ingested over an extended period of time.

Empowerplus also contains germanium, which could pose a serious health risk if it contains harmful impurities. The prolonged intake of products containing germanium products has been associated with renal failure, and even death in at least 31 reported human cases. In addition, germanium has not been identified as an essential element for humans and no evidence of deficiency of this element has been observed. As such, no level of risk is tolerable.

The greatest safety concern with respect to the "nutritional component" of Empowerplus relates to the fat soluble vitamins, A and D. High storage levels of vitamin A can lead to birth defects, liver abnormalities and reduced bone material density that may result in osteoporosis. Excess vitamin D can lead to hypercalcaemia and its associated effects, including hypercalciuria, ectopic calcification and renal and cardiovascular damage.

In addition, Empowerplus contains dl-phenylalanine (DLPA), which is a mixture of the essential amino acid L-phenylalanine and its mirror image D-phenylalanine. DLPA (or the D- or L-form alone) has been used to treat depression.

This compound can affect mood and the nervous system. Therefore, DLPA should be taken only under medical supervision. Individuals taking prescription or over-the-counter medications should consult a physician before taking DLPA.

DLPA should not be taken during pregnancy or while nursing.

DLPA should be used with caution by people with hypertension, or those taking certain antidepressants, as it may raise blood pressure in some individuals.

DLPA should be avoided by individuals with pigmented melanoma.

Use of DLPA may be contraindicated for individuals with hyperthyroidism or schizophrenia.

**Bottom line:** The main concern with Empowerplus is that the product is being promoted for the treatment of a serious psychiatric disorders without having undergone the rigorous testing necessary for all drug products to demonstrate their safety and efficacy for the advocated purposes, as well as their quality. The distributors of Empowerplus have recommended the discontinuation or lowering of doses of medications prescribed by physicians. This can lead to serious adverse health consequences.

**Questions and Answers**

**Q. What is Empowerplus?**

A. Empowerplus is an unapproved drug containing numerous vitamins and minerals as well as other ingredients such as dl-phenylalanine and germanium. It is sold by Truehope Nutritional Support Ltd (Synergy Group of Canada ) for serious central nervous system conditions like Bipolar disorder, anxiety disorder, schizophrenia, attention deficit disorder etc.

**Q. Is Empowerplus effective?**

A. Health Canada cannot assess the effectiveness of the Empowerplus drug because Truehope Nutritional Support Ltd. (Synergy Group of Canada) has not provided a submission of evidence to Health Canada. Under the Food and Drugs Act and Regulations, companies are required to file a New Drug Submission with Health Canada that provides supportive information regarding the drug's clinical evidence and chemistry and manufacturing to determine the safety and efficacy of
Q. Why is Health Canada concerned about the safety of Canadians with respect to Empowerplus?

A. Health Canada is concerned that individuals using Empowerplus could be putting their health at risk. Serious central nervous system conditions should not be self-diagnosed or self-medicated. People suffering from serious central nervous system disorders should always be under the care of a health care provider.

Health Canada's responsibility is to ensure that drugs sold in Canada are safe and effective. To do that, we require drug manufacturers to provide us with scientific evidence that the drug is safe and effective at meeting its stated claims of effectiveness of treatment. Truehope has not provided evidence of Empowerplus' safety and efficacy, and has also failed to stop the promotion and sale of Empowerplus - despite Health Canada's request that it do so.

Q. How is Health Canada informing consumers about Empowerplus?

A. Health Canada has issued a health advisory (June 6, 2003) to advise consumers that the drug, Empowerplus, has not been authorized for sale as required by legislation. This means that the required safety and effectiveness data has not been submitted to Health Canada for review. Frequently Asked Questions are also being posted to the Health Canada Web site.

How is Health Canada assisting people who are currently using Empowerplus?
Health Canada recognizes the difficult circumstances faced by people with serious central nervous system conditions, and understands that some may have been using Empowerplus. In recognition of the seriousness of this issue, Health Canada is working to provide these individuals with appropriate referral options to health care professionals and services, by setting up a toll-free health assistance referral line. The Health Canada toll-free telephone line is 1-800 504-4156.

Q. What action is Health Canada taking to stop distribution of Empowerplus as well as toward the company Truehope Nutritional Support Ltd. (Synergy Group of Canada)?

A. Health Canada's Inspectorate has placed Import Alerts at Customs on Empowerplus. The alerts relate to commercial shipments. Entry into Canada of a ninety day supply of nonprescription drugs is permitted by Health Canada as per the Importation of Human Use Drugs for Personal Use Directive. Health Canada has issued the company a Warning Letter and is implementing the compliance and enforcement steps as outlined in Health Canada's Compliance and Enforcement Policy.

Q. Why is it necessary for Empowerplus to be regulated as a drug, if the ingredients are "natural"?

A. Being "natural", does not preclude an ingredient from being a drug. Products are drugs because of their representations, their ingredients and their recommended conditions of use. If a product is being sold and represented to treat, mitigate or prevent a disease, disorder or abnormal physical state, then it is a "drug" as defined in the Food and Drugs Act. Empowerplus contains vitamins and minerals which in themselves are drugs in dosage form. It also contains other ingredients such as phenylalanine, boron, germanium and folic acid which are regulated as drugs in Canada.

Q. Is Health Canada restricting access to natural health products?

A. One of the ways Health Canada protects Canadians from potential health hazards and harm is through the administration of the Food and Drugs Act. The Food and Drugs Act and Regulations describe the requirements that a drug must meet before it can be sold to the public to ensure that it is safe and effective. When the new Natural Health Products Regulations come into force on January 1, 2004, they will also fall under the Food and Drugs Act but will describe the requirements that a natural health product will need to meet before sale can occur in Canada.

At the present time, there is no category of drug in legislation called a natural health product. All substances and combinations of substances that are manufactured, sold or represented to treat a disease, or modify an organic function, are drugs. The regulatory requirements do not aim to restrict access, but rather to provide access to drugs that have been...
A. Part of Health Canada's mandate is to ensure that the drugs available in Canada are safe, effective, and of high quality. Under the Food and Drug Regulations, Health Canada evaluates proposals for clinical trials based on scientific and medical information. Drugs used in clinical trials must not present undue risk to the participants, and any known risks must be disclosed. Furthermore, before a clinical trial begins, the sponsor of the trial is expected to obtain an ethics approval from a properly constituted research ethics board.

In 2001, Health Canada investigated unauthorized clinical trials that were conducted using Empowerplus. The trial had begun without a clinical trial application having been filed and authorized. Departmental officials communicated with the researcher at the University of Calgary, and with Synergy/Truehope, to provide information on the regulatory requirements governing clinical trials in Canada. Health Canada provided extensive guidance to Synergy/Truehope to facilitate the filing of a Clinical Trial Application. However, a complete application was not filed and, therefore, authorization was not granted.

Health Canada took compliance action and requested that trials stop. At the same time, Health Canada recommended to the researcher that the trial subjects be assessed and transferred to appropriate professionals who would place them on standard therapy in a manner that would take their health and well being into account.

Q. Can someone use personal importation directive to buy Empowerplus? What exactly does the directive mean?

A. The intent of Health Canada's Importation of Human Use Drugs for Personal Use Enforcement Directive is to allow Canadians access to drugs directly for their own personal use or use by their family, and not for the importation of drugs by a Canadian importer for sale in Canada. To be considered a personal importation, a drug must be ordered or purchased directly by an individual in Canada and shipped directly to that individual. The drug must be imported for their use and not for sale in Canada. The sale of the drug must also not occur in Canada.

In this case, the drug, Empowerplus, is being sold in Canada by Truehope. Orders are taken for the drug by the company and arrangements are made by the company for the importation. This is not personal importation.

Individuals importing Empowerplus who believe their importation should fall within the Personal Importation Directive will be required to demonstrate that the shipment has been ordered by them directly, that there has been no sale, including offer for sale, of the product to them in Canada, and that they are importing it for their personal use. This is Health Canada's standard practice concerning personal importations. For an importation of Empowerplus to qualify as a personal importation, the permitted quantity is limited to 4 bottles of 252 tablets, which represents a 90-day supply of the current formulation. If the shipment is found not to be a personal importation, and the import and sale in Canada would contravene the Food and Drugs Act and Regulations, Health Canada will recommend to the Canada Customs and Revenue Agency (CCRA) a refusal of entry. Although the Personal Importation Directive allows access to drugs from outside Canada, drugs imported for personal use will not have been assessed by Health Canada for their quality, safety and effectiveness. For this reason, we caution against the practice of importing drugs for personal use.

Q. Why doesn't Health Canada consider the views of people who take this drug feel it is safe and effective?

A. Health Canada recognizes the difficult circumstances faced by people with serious central nervous system conditions, and understands that some may have been using Empowerplus. In recognition of the seriousness of this issue, Health Canada is working to provide these individuals with appropriate referral options to health care professionals and services, and to this end, has setup a toll-free health assistance referral line. That number is 1-800 504-4156.

It is up to a company wishing to sell a drug in Canada to follow the requirements stated in the Food and Drugs Act and Regulations. Health Canada is responsible for administering the Food and Drugs Act and Regulations. In order to assess the safety and effectiveness of a drug, a company must supply Health Canada with a new drug submission and approval must be granted before they are permitted to sell the drug. These controls are necessary in order to safeguard the consumers from harm. It is the responsibility of a company wishing to sell a drug in Canada to comply with the requirements of the Food and
A. The Food and Drugs Act and Regulations mandates the process that needs to be followed in order to market a drug in Canada. When a company files a new drug submission, Health Canada evaluates and assesses the merit of the clinical evidence and data from various sources, including information from scientific literature. It is the company's responsibility to provide Health Canada with data that would support the indications (therapeutic claims) being promoted for the drug. As of today, Truehope Nutritional Support Ltd (Synergy Group of Canada) has not provided the required information and supporting data to Health Canada.

While literature reviews can form part of the evidence contained in a New Drug Submission that is filed with TPD in support of the safety and efficacy of a product, to be relevant, this literature must report on findings from well-designed and appropriately-analyzed clinical trials.

There have been only two studies on Empowerplus that have been reported in the scientific literature to date (Kaplan B J et al. J Clin Psychiatry 62:12, 2001 and Kaplan B J et al. J Child Adol Psychopharm 12:3, 2002). Both studies were exploratory in nature and involved only a small number of subjects. Fourteen subjects were enrolled in, but only 11 completed, the 6-month trial in the 2001 study while the 2002 study involved case reports on the use of Empowerplus in two children 8 and 12 years of age.

With respect to the larger 2001 study, the authors indicate that: "The data reported here provide the first, preliminary, scientific validation of the supplement's efficacy and suggest that further research is warranted." The 2002 study is similarly described: "The two cases presented here constitute some of the pilot work carried out to determine whether further research of this micronutrient supplement is warranted."

The investigators acknowledge that there were many weaknesses in the design of the two studies which precludes making any definitive conclusions regarding the safety and efficacy of Empowerplus. They enumerate the following deficiencies with respect to the 2001 study: "Firstly, purely by chance, 10 of these patients were men, thus hindering generalizations to women. Second, as in any case series, there is a weakness in not having a placebo control... A third potential source of bias is from the psychiatrists themselves. As in any open-label study, unblinded assessments can result in exaggerated results... The use of concurrent psychiatric medications was a fourth weakness in this case series: the changes in medications made by psychiatrists as part of normal clinical care make it difficult to attribute symptom changes specifically to the nutritional supplement." The limitations of an unblinded, non-randomized design are echoed in the discussion of the 2002 article where it is stated that: "Open-label trials are inherently subject to expectancy effects and observer bias."

The authors also recognize that there are safety concerns when Empowerplus is being used for the treatment of mental disorders. In their discussion of the 2001 study, the authors recognize that vitamin toxicity is a serious consideration. They state: "..., supplementation with dietary minerals and vitamins that significantly exceed the recommended daily intakes carries with it an unknown risk, and therefore the long-term safety of the nutritional supplement used in this study cannot be definitively proven." The authors were also concerned about possible interactions with medications that patient may be taking at the same time. They note that: "The observation made by many patients and clinicians who have used this preparation is that the supplement interacts with psychiatric medications. The distributor recommends decreasing psychiatric medications in this situation, and despite significant concerns about safety, we have found that this seems to be a reasonable approach." Their overall conclusion regarding safety was summarized as follows: "However, the assurance of safety of this supplement for any healthy patient is not something that can be precisely stated at this time."

Similar views were expressed in the 2002 study where it is stated that: "The safety of this formula has been supported by nutrition and biochemical consultants and reviewers, but there are still safety and toxicity issues that remain to be addressed." "...the micronutrient supplement has not been studied systematically for safety and adverse effects in normal volunteers. In addition, a multi-ingredient formulation could lend itself to unpredictable effects due to the interaction of the individual ingredients, and these need to be studied."

The authors also describe further studies that are being, or will be, undertaken to more clearly define the safety and efficacy of Empowerplus in the treatment of mental disorders. These are as follows: "... a randomized, placebo-controlled trial has..."
In the discussion of the 2002 study, it is noted that: "Much research still needs to be done before the impact of these preliminary findings can be properly evaluated. One randomized, placebo-controlled trial in adults with bipolar disorder is ongoing; another has been funded and will begin shortly. Several other randomized, controlled trials involving children are in the planning stages. Further research into safety and efficacy is also needed, and caution is particularly critical regarding nutrient interactions with psychiatric medications (Popper 2001)."

The authors also note that: "Patients undergoing clinical trials of the supplement should be monitored for adverse reaction and general health, just as they are when undergoing a trial of a new psychotropic medication."

These statements support Health Canada's concerns regarding the safety and efficacy of Empowerplus for treating mental disorders and underscores the need for additional clinical trials.

Q. What is the process and length of time it takes for a drug to be authorized for sale in Canada?

A. New Drug reviews have a performance target of 345 days including screening. If there are serious deficiencies in the New Drug submission the sponsor will be required to provide satisfactory additional data and this will add to the time required for review.

Q. Is the action taken towards Empowerplus similar to the action taken on Kava and Ephedra / ephedrine products?

A. The action taken on kava- and ephedra/ephedrine-containing products included their recall from the market. In the case of Empowerplus, Truehope Nutritional Support Ltd (Synergy of Canada) was instructed to stop the sale and obtain market authorization through the issuance of a Notice of Compliance and a Drug Identification Number (DIN) as is required by the legislation, the Food and Drugs Act and Regulations.

Q. Will Empowerplus be available through Special Access Programme (SAP)?

A. The Special Access Programme is designed to provide limited access to unapproved products for emergency circumstances. The SAP will consider requests for the drug provided that: requests are for the treatment of serious and life-threatening conditions, requests are made by physicians qualified in the treatment of serious mental illnesses.

In the case of Empowerplus, Health Canada strongly recommends that its access be limited at this time to approved clinical trials that seek to ask and answer questions about the relative risks and benefits associated with drugs that are not approved for sale in Canada.

The Special Access Programme (SAP) is committed to dealing with emergency situations but is not a mechanism for physicians and manufacturers to circumvent the important objectives inherent in the conduct of clinical trials:

- Clinical Trials enhance the safety of the participants by ensuring there is a comprehensive informed consent, and a scientifically sound protocol that includes mechanisms for monitoring patients so that they are not exposed to undue risk;
- There is Review Ethics Board approval, which further safeguards the safety of the participants;
- Clinical Trials also ensure that Health Canada has adequate information on the composition and quality of the products; and
- They ensure that valid information on the safety and efficacy of the product is captured.

The SAP may also play a role in providing emergency access to the drug while efforts are made to initiate multi-centre clinical trials in Canada.

The SAP does not conduct a comprehensive evaluation to ensure the validity of drug information or attestations of the
manufacturer respecting safety, efficacy and quality. These are important factors for practitioners to consider when recommending the use of a drug and in making an appropriate risk/benefit decision in the best interests of the patient. If S release were granted, the manufacturer would need to decide on whether or not the drug would be supplied in accordance with the conditions of SAP. The manufacturer must have the capacity to monitor reports of adverse drug reactions and to intervene accordingly when safety issues arise.

**Q. Will Empowerplus be considered a natural health product when the new natural Health Product Regulations are promulgated, and would that mean clinical trials could be conducted for this product under this new set of regulations?**

**A.** The NHP Regulations will not apply to a product that requires a prescription under the Food and Drug Regulations (i.e., a drug or ingredient listed on Schedule F). The ingredients in Empowerplus appear to fall within the NHP definition. However, the recommended dosing regime of certain vitamins and minerals in the product may move the product to prescription status.

The NHP Regulations are designed for products that are intended for over-the-counter use. This intent is also reflected in section 2(2) of the Regulations which clearly states that prescription drugs are not regulated by the NHP Regulations. Therefore, although the product may fall within the NHP definition, the product would likely not be granted a product licence if the data showed that it would not be considered safe and effective under the recommended conditions of use. If it were recommended for the treatment of serious central nervous system conditions, like Bipolar disorder, a product licence would likely be refused.

If the company chose to maintain the same dosing regime (bringing it into prescription status) and health claims, they could then seek marketing authorization under the Food and Drug Regulations.

**Clinical trials**

The clinical trials component of the NHP Regulations is essentially the same as the clinical trial requirements (Division 5) of the Food and Drug Regulations. Some modifications have been made to what is required for a clinical trial application to address the uniqueness of NHPs, i.e., complex ingredients with different profiles.

Since the ingredients appear to fall within the NHP definition, then, so long as the intended dosing regime did not move it to prescription status, the clinical trial application could be submitted under the NHP Regulations.

This would not mean approval for general sale, but would provide the company with clinical data which could then be evaluated. The company would then decide if and how to commercialize the product.

**Q. What kind of products are affected by the new NHP Regulations?**

**A.** NHPs are defined in the Natural Health Products Regulations to include vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines such as Traditional Chinese Medicines, probiotics, and other products like amino acids and essential fatty acids. Under the new Regulations, natural health products are intended for self care and self selection, and do not require a prescription to be sold. Also, to be licensed for sale under these Regulations, the product must be safe and effective for use as an over-the-counter (OTC) product. Any products requiring a prescription will continue to be regulated under the Food and Drug Regulations.

**Q. What can Truehope/Synergy do to ensure individuals in Canada have access to Empowerplus?**

**A.** By way of the *Food and Drugs Act* and its regulations, Health Canada oversees the sale of health products in Canada to ensure products offered to Canadians are safe, effective and of high quality.

Truehope/Synergy can make its product available by complying with the applicable regulations. Truehope/Synergy should file for and receive market authorization for their product.

Health products with market authorization can be sold in retail outlets, via websites, via telephone order desks, etc. A market authorization from Health Canada allows a manufacturer or distributor to make their product widely available. Canadians
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