(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 December 2007 (13.12.2007)

PCT

(10) International Publication Number
WO 2007/142973 A1

(51) International Patent Classification:
A61K 31/714 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2007/012747

(22) International Filing Date: 29 May 2007 (29.05.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/809,517	30 May 2006 (30.05.2006)	US
60/834,641	31 July 2006 (31.07.2006)	US
60/855,785	31 October 2006 (31.10.2006)	US

(71) Applicant and
(72) Inventor: **HALEY, Jeffrey, T.** [US/US]; 13434 Se 27th Place, Bellevue, WA 98005-4211 (US).

(74) Agents: **KING, Joshua** et al.; Graybeal Jackson Haley Llp, 155-108th Ave Ne, Suite 350, Bellevue, WA 98004-5973 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2007/142973 A1

(54) Title: COBALAMIN COMPOSITIONS AND METHODS FOR TREATING OR PREVENTING MUCOSITIS

(57) Abstract: The present invention relates to troches, patches, gels, or viscous liquids for topical treatment or prevention of mucosal surfaces containing as an active ingredient molecules of cobalamin for the treatment of inflammatory, ulcerative and painful conditions of mucosal surfaces such as mucositis, stomatitis, vestibulitis, aphthous ulcerations, and Behcet's syndrome. For reducing the incidence, duration, and pain levels of recurrent aphthous ulcers, bioactive cobalamin may delivered with adhering discs that stick to a tooth.

COBALAMIN COMPOSITIONS AND METHODS FOR TREATING OR PREVENTING MUCOSITIS

This application claims priority from US provisional applications 60/809,517, filed 30 May 2006; US 60/834,641, filed 31 July 2006; and US 60/855,785, filed 31 October 2006, each of which is incorporated by this reference.

FIELD OF THE INVENTION

The present invention relates to compositions containing cobalamin suitable for topical delivery to moist epithelial surfaces for treatment of inflammatory, ulcerative and painful conditions such as mucositis, stomatitis, vestibulitis, aphthous ulcerations, and Behcet's syndrome.

BACKGROUND OF THE INVENTION

Mucositis is an inflammation of the mucous membranes. Stomatitis is an inflammation of mucous membranes in the mouth. About 20 percent of people suffer from recurrent stomatitis in the form of aphthous ulcers, also called mouth ulcers, mouth sores, canker sores, denture sores, and sores from braces. Many women get oral aphthous ulceration at specific times of the menstrual cycle and some simultaneously get similar ulcers in the genital tract, in particular the vulva and vagina. This is sometimes very severe and can cause retention of urine and require strong painkillers and sedatives. The most severe form is called Behcet's syndrome.

Aggressive cancer treatment may have toxic effects on normal cells as well as cancer cells. The gastrointestinal tract, including the mouth, is especially affected because these cells are replaced by the body continuously. Mucositis in the mouth (stoamatitis), is one of the most common oral problems occurring after chemotherapy and radiation therapy. Oral mucositis can contribute to oral infections, inability to taste normally and pain arising from the resulting open sores that can develop. Oral mucositis can become so painful that the patient will not eat or drink, contributing to dehydration and malnutrition.

Oral mucositis frequently also occurs in HIV patients, particularly when associated with Kaposi's sarcoma, in patients affected with non-Hodgkin's lymphoma, in debilitated elderly patients and in patients receiving BRM treatments like interleukin-2, TNF, interferons, lymphokine-activated lymphocytes and the like.

Mucositis typically manifests as an erythematous, burn-like lesion or as random, focal-to-diffuse, ulcerative lesions. Stomatitis refers to an inflammatory reaction affecting the oral mucosa, with or without ulceration, that may be caused or intensified by pharmacological, particularly chemotherapeutic treatments, or by radiotherapy. Stomatitis can range from mild to severe; the patient with severe stomatitis is unable to take anything by mouth.

There is a need to provide method and compositions for treating and preventing inflammatory conditions of the moist epithelial surfaces, such as the mouth, particularly treatment of mouth sores, and other mucosa including vagina and rectum.

SUMMARY OF THE INVENTION

The present invention fills this need by providing compositions that topically apply cobalamin (vitamin B12) to epithelial tissues that are subject to mucositis. The cobalamin may be in the form of cyanocobalamin, which is not a bioactive form and must be converted to a bioactive form before it is used by human tissues. It may be a bioactive form of cobalamin, such as methylcobalamin (a/k/a mecobalamin), deoxyadenosylcobalamin (a/k/a adenosylcobalamin) or hydroxocobalamin.

The composition may be a liquid, gel or paste. Or it may be a troche, such as a lozenge or "drop" as shown in Figure 1. As used herein, the term "troche" encompasses chewing gum and solid forms suitable for use in the vagina or rectum, sometimes called suppositories. It may be an adhering troche, such as a troche with adhesive on one side suitable for adhering to mucosa or to teeth or gums as shown in Figure 2. It may be an adhering troche that is thin and often flexible, called a patch, as shown in Figure 3.

The composition contains an amount of cobalamin that is effective for prevention or treatment when delivered topically to the mucosal tissues. For prevention, the delivery is typically at least once each day.

In one aspect, the invention is a troche comprising bioactive cobalamin in a quantity effective to reduce mucositis when used regularly on moist epithelial tissues.. The troche may comprise at least 100 micrograms of bioactive cobalamin. The troche may be adherent, perhaps using acacia gum as an adhesive, and it may be thin in the shape of a patch, perhaps comprising collagen which aids flexibility.

In another aspect, the invention is an adhering troche comprising cyanocobalamin in a quantity effective to reduce oral mucositis when used regularly by dissolving in the mouth.

In another aspect the invention is a composition of liquid, gel or paste comprising bioactive cobalamin in a quantity effective to reduce mucositis when used regularly. The

composition may comprise at least .02 percent by weight molecules of cobalamin. It may comprise at least one thickener selected from the group comprising polyvinylpyrrolidone, xanthan gum, konjac gum, locust bean gum, guar gum, gelatin, collagen and aloe vera, wherein the viscosity of the composition is from about 50 to about 10,000 centipoise. It may be a mouthwash or toothpaste. It may be packaged in an aerosol spray bottle. It may be packaged in a container of dry powder with directions to add water to the container to make the composition. It may be packaged in a pump bottle or a single dose size plastic bag.

In another aspect the invention is a method for treating or preventing mucositis in a patient by regularly applying to a mucosal surface of a patient in need thereof an effective amount of a composition comprising cobalamin. The cobalamin may be selected from the group comprising cyanocoblalmin, methylcobalamin, hydroxocobalamin, and adenosylcobalamin. The composition may be a liquid, gel, paste, dissolving troche, suppository, or patch, including an oral patch. The composition may comprise at least 100 micrograms of cobalamin or at least .02 percent by weight molecules of cobalamin. The composition may be administered at least once a day every day for prevention. The mucositis may occur in the mouth as stomatitis or aphthous ulcers. The mucositis may occur in the oro-pharynx or the oesophagus or the vagina or the rectum.

The present invention can be more fully explained by reference to the following detailed description and illustrative examples.

DRAWINGS

Figure 1 shows a troche in a typical shape, often called a lozenge.

Figure 2 shows a cross section of an adhering troche in a shape designed to adhere to a tooth or orthodontic brace.

Figure 3 shows an edge view of a troche in the form of an oral patch designed to adhere to the cheek or lip.

DETAILED DESCRIPTION OF THE INVENTION

Without being bound by a particular mode of action, the favorable therapeutic results obtained by the use of the compositions of the present invention are believed to be due to interactions between molecules of cobalamin with elements of the inflammatory process, which is best achieved with a topical application of bioactive cobalamin. It is helpful if the delivery vehicle can adhere to the oral mucosa providing a protective coating

for the exposed nerve endings and holding the active molecules in topical application. Furthermore, the moisturizing or mucous releasing effects of some the compositions have beneficial effects as they protect mucous membranes from further irritations.

These compositions can be used by themselves or in an admixture with one or more medicaments, excipients and/or adjuvants, preferably forming a viscous and lubricating substance that remains adherent to the surface epithelium.

Preferably, the compositions of the present invention are administered by topical application. In a particular embodiment in which the composition is administered to the oral cavity, the patient, after applying to the oral mucosa by applying a dissolving troche or by pressing, squeezing, swishing or gargling with a liquid or gel, if desired, may refrain from eating or drinking for a certain time, ranging from minutes up to hours. Alternatively, the patient, if desired, may eat or drink immediately after applying the composition.

An effective level of use of the composition as a viscous liquid, paste, oral patch, or other composition comprises enough cobalamin to deliver a dose to mucosa where it is applied equal to at least 0.1 milligrams (100 micrograms) of cobalamin spread over the surfaces of an average size human mouth or an equal amount per unit area in the vagina or rectum. To minimize cost of the bioactive cobalamin, it may be delivered in a gel or paste that a person can spread to all surfaces with little left over. The longer the gel is left in place on the mucosa so the bioactive cobalamin can absorb into the mucosal tissues, the better. In a dissolving troche used once a day as a preventive, 500 micrograms of cobalamin is a suitable dose.

For release of cobalamin in the mouth, some people will prefer chewing gum and some people will prefer a troche, such as a "mint" or "lozenge" or an adhering troche that contains cobalamin and completely dissolves. More precisely, the binder molecules erode as they become hydrated and the bioactive cobalamin molecules dissolve. In the mouth, the troche may have a feel and texture like gummy candies. It may be made with slowly dissolving hydrocolloids so that that it typically lasts in the mouth for at least ten minutes to six hours. The troche can be formed in the shape of a tablet or a lozenge, as shown in Figure 1, or a wafer or any other desired shape. A preferred shape is a thin lentil, nearly flat on one side, as shown in Figure 3, which may be called a patch. A detailed description of such a troche/patch and how to make it are disclosed by the same inventor in US patent application serial number 10/287,843 filed November 5, 2002.

To cause the troche to dissolve (erode) very slowly in saliva, a binder that dissolves slowly in saliva is incorporated. Binders that have been tested and found to work include carrageenan (preferably kappa), xanthan gum, xanthan gum combined with konjac gum, agar, and carboxymethylcellulose (CMC). Other gums similar to those listed,

such as locust bean gum which has properties similar to konjac gum, and guar gum should also work, as well as starches, such as corn starch or, particularly pregelatinized corn starch, sometimes called zea mays.

A method of manufacturing troches in the shape of patches is to use gum drop manufacturing equipment, squirting a hydrated mixture heated above the gel melting temperature through nozzles onto a sheet of plastic or wax coated paper, allowing the troches to cool and gel, and drying the troches. The troches are preferably dried until the water activity level is lower than 0.8 so that the troches will not grow mold or other organisms. The drops are allowed to cool and then the sheets of plastic or coated paper with the drops on them are dried in a drying chamber. The product is sold still adhered to the plastic or paper and the user pulls it off the plastic or paper.

One troche formulation is made by combining cobalamin and xylitol with collagen and with other binder ingredients. Collagen, which is the organic molecule that makes up skin and the lining of the mouth (a form of skin), tends to adhere very well to itself, making it glutinous, and therefore adheres very well to the lining of the mouth. An effective and cost effective form of collagen is food grade gelatin which is made from animal skins.

Testing shows that, if the primary binders are xanthan gum and konjac gum, preferred dry weight formulations have between 10% and 50% xylitol, between 30% and 50% food grade gelatin, between 5% and 15% xanthan and konjac gums, between 5% and 30% cellulose fiber.

Other methods for making adherent troches include extrusion of a sheet and then die cutting. The cobalamin can be incorporated in other forms of troches including suppositories, lozenges, mints and other candies.

Troches in the form of dissolving muco-adhesive tablets may be made by pressing powders including mucoadhesive hydrocolloids. A preferred form of such an adhering troche may be made by mixing dry powders consisting of 80 percent acacia gum (gum arabic) for adhesive and 20 percent xylitol for flavor, then adding up to 1 percent carboxymethylcellulose (CMC), to enhance mouth feel, moderate adhesiveness of the acacia gum, and slow dissolution, and about 500 micrograms of cobalamin. The tablet may be pressed into the shape shown in Figure 3 for good adhesion to a tooth. Such a tablet is preferably about 8 mm in diameter and about 85 milligrams in weight.

The preferred instruction to users is to stick a troche in their mouths, just before they go to sleep, between teeth and cheek, placing it on the tongue side of the teeth if the patient suffers particularly from ulcers on or under the tongue and otherwise placing it on the cheek side. In greater detail, the instructions state: "Use after brushing teeth, at least one disc per day, and allow to dissolve for 30 minutes with nothing else in your mouth. In

an area of your mouth where you experience sores, use your tongue to hold the dimpled side of the disc against a tooth until it adheres. The disc will slowly dissolve over 10 to 40 minutes, releasing cobalamin which is absorbed directly into the mouth lining tissues. When you first start using the discs, use three discs the first day to quickly boost the level of cobalamin in your mouth tissues. Thereafter, use at least one disc each day. If you miss a day, use at least two discs the next day. If you miss two or more days, begin with three discs the first day you resume. Vary the spots you place the disc from day to day in the places where you frequently experience sores, such as a front tooth against your lip, on the inside of a lower tooth to protect under your tongue, and on the outside of a molar in each cheek. If you have a sore, place the disc near the sore."

Such discs were given to test subjects with the above instructions, generating the following results: Fifteen subjects with minor RAU at least monthly were given 30 adhering dissolving discs and instructed to use one each day. Seven received discs with 500 mcg methylcobalamin and eight received discs with red food coloring. In the placebo group, two out of eight (25%) reported a benefit consisting of reduced frequency of minor RAU, reduced duration of ulcers, or reduced peak pain levels; two out of eight were unsure; and four out of eight (50%) were confident they experienced no benefit. In the active group, all seven (100%) reported a benefit. Twenty-five additional non-blinded subjects were given active discs with 500 mcg methylcobolamin. Approximately 3 to 7 days of daily use was required for the preventive effects to reach full strength. Twenty-four subjects (96%) reported a benefit of using the discs. Five subjects who reported a benefit stopped using the discs and all five reported that, within 4 to 7 days (mean=4.8), they each had an ulcer with a pain level like before they started using the discs.

Other tests were run with cyanocobalamin in oral patches and in a gel with similar results. The gel formulation was about 93.5% water, 0.5% Ticalose carboxymethylcellulose, about 6% xylitol for flavor, and about 0.05% cyanocobalamin.

In liquid formulations, the liquid is preferably more viscous than water, such as by using partially evaporated aloe vera sap or including a hydrophilic gum such as polyvinylpyrrolidone, xanthan gum, locust bean gum, konjac gum, guar gum, collagen from any source including food grade gelatin, or carboxymethylcellulose (CMC) such as Ticalose from Tic Gums. In one embodiment, the viscosity of the composition is from about 50 to about 2000 centipoise. In an embodiment, the polyvinylpyrrolidone is from about 3 to about 10% by weight of the composition. In another embodiment, the polyvinylpyrrolidone is from about 7 to about 10% by weight of the composition. In yet another embodiment, the viscosity of the composition is from about 2000 to about 10,000 centipoise. In this embodiment, the composition is so viscous as to be considered a gel.

The cobalamin is at least 0.02 percent by weight. There is no upper limit to the amount of cobalamin in the liquid, except for economic limitations of cost and practical limitations that it must still be a liquid. In one embodiment, the viscosity of the liquid is from about 50 to about 1000 centipoise. In an embodiment, the primary thickener is polyvinylpyrrolidone which is from about 6 to about 12% by weight of the composition. In another embodiment, the thickener is Ticalose cellulose from about 0.5% to about 4%.

The liquid or gel or paste may be packaged in a pump bottle that pumps a roughly equal dose with each pump stroke. Because cobalamin will degrade more quickly in solution than when stored as a dry powder, in one embodiment, the bottle is delivered to the consumer with about 1.5 grams of dry powder comprising, by dry weight, about 20% pre-hydrated xanthan gum, about 78% xylitol for flavor, and about 2% methylcobalamin. The consumer then adds about 13.5 grams of water and lets the mixture sit until the gum is fully hydrated to make a gel.

The composition may be provided in a flexible packet comprising a liquid comprising at least 0.02 percent by weight of bioactive cobalamin with a viscosity substantially greater than water. In an embodiment, the packet is a sealed pouch comprising from about 10 to about 30 milliliters of the composition. In another embodiment, the pouch is delivered with two separate sections, one containing dry powder as specified above and the other containing water. The consumer forces the two sections to merge and lets the packet sit until the cellulose is fully hydrated to make a gel.

In an embodiment, the composition further comprises a surfactant, stabilizing agent/preservative, flavor, fragrance, sweetening agent, bioadhesive agent, or a co-solubilizer. The composition may also further comprise any of the various cellulose derivatives, acrylic or methacrylic acid polymer or copolymer, ethylene or propylene glycol, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrin, sodium saccharin, aspartame, sorbitol, xylitol, or erythritol.

The composition may be a chewing gum, toothpaste, mouthwash, or beverage additive intended to release an effective amount of cobalamin molecules in the mouth to treat or prevent stomatitis, particularly including aphthous ulcers.

The compositions can comprise a pharmaceutically acceptable excipient, preferably for topical administration, such as one or more of the following:

viscosity-increasing agent;

surfactant;

stabilizing agent/preservative;

flavor, fragrance, sweetening agent;

bioadhesive;

co-solubilizer.

Examples of said excipients comprise cellulose derivatives, acrylic or methacrylic acids polymers or copolymers, ethylene or propylene glycols, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrins, sodium saccharin, aspartame and other excipients conventionally used in the formulation of collutories or liquid oral forms. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, sorbitol, xylitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Additional examples of suitable excipients are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

The compositions may further comprise one or more other active ingredients, such as an antibacterial, disinfectant, antifungal, analgesic, other anti-inflammatory, emollients, local anesthetics and the like. Suitable antimicrobials include, but are not limited to, quaternary ammonium salts such as benzalkonium chloride.

The method for treating or preventing mucositis inflammation in a patient comprises administering to a patient in need thereof an effective amount of a composition comprising molecules with at least 100 micrograms of cobalamin if in troche from or at least 0.02 percent by weight, with a thickener such as cellulose, polyvinylpyrrolidone or xanthan gum, if in liquid form. The composition may be administered at least once daily for at least three consecutive days. In yet another embodiment, the composition is administered at least once daily for at least seven consecutive days. In yet another embodiment, the composition is administered at least once daily every day without end to prevent or reduce the effects of mucositis. In addition to its ordinary meaning, the term treatment encompasses inhibition of progression of symptoms or amelioration of symptoms of inflammation and mucositis. The liquid may be squeezed or swished or gargled. These methods may provide an effective therapeutic or preventive treatment for mucositis and stomatitis of various origin and severity and, more generally, of the lesions of the oro-pharynx cavity and oesophagus, particularly those caused by recurrent aphthous ulceration, dental devices, by radio- or chemotherapy, and by surgery.

The precise dose to be employed in the composition will depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. In principle, however, for oral applications, a coating, wash or gargle with 1 - 5 ml of solution, perhaps after dilution with water, at least once but up to three times or more daily, will be sufficient to provide an optimal therapeutic or preventive response. The treatment can be protracted until remission of symptoms, usually for at least 2 days, but preferably 5-10. More prolonged treatments are not contraindicated, considering zero

toxicity of the components of the formulations, and once daily use as a preventive is effective for many conditions.

The composition may be provided a pharmaceutical pack or kit comprising one or more containers, e.g. a flexible packet, vial, ampoule, bottle and the like, filled with one or more of the ingredients of the compositions of the invention. In an embodiment, the compositions can be presented as single- or multi-dose forms in a flexible packet or pump bottle. The compositions are packaged in a powder or concentrated liquid form with a capacity of from about 10 to about 30 ml per container that can be diluted with water to create liquid or gel for use by the patient.

The following series of examples are presented by way of illustration and not by way of limitation on the scope of the invention.

EXAMPLE 1

Qualitative-quantitative composition percent composition, delivered in a bottle or packet: about 1.5 grams of dry powder comprising, by dry weight, about 40% Ticalose cellulose, about 58% xylitol for flavor, and about 2% methylcobalamin or hydroxocobalamin. The consumer then adds about 50 grams of water and lets the mixture sit until the cellulose is fully hydrated to make a gel.

EXAMPLE 2

Qualitative-quantitative composition percent composition: Ingredient % By Weight: bioactive cobalamin (methylcobalmin) 0.2, partially evaporated aloe vera sap with preservative: the balance. For a concentrated version of the invention, 10 ml to 30 ml of the above composition is distributed in a packet or bottle.

EXAMPLE 3

Qualitative-quantitative composition percent composition: Ingredient % By Weight: bioactive cobalamin (methylcobalmin) 0.2, glycerin 40, guar gum 9.0, water: the balance. For a concentrated version of the invention, 10 ml or 15 ml of the above composition is distributed in a packet or mono-dose vial.

EXAMPLE 4

Qualitative-quantitative composition percent composition: Ingredient % By Weight: bioactive cobalamin (methylcobalmin) 0.2, PVP (K60 to K100) 8.0, Maltodextrin 4.0, Propylene glycol 2.9 Potassium sorbate 0.3, Sodium benzoate 0.3, Hydroxyethyl cellulose 1.5, Hydrogenated castor oil PEG-40 0.3, Disodium EDTA 0.1, Benzalkonium chloride 0.5, Perfume 0.16, Xylitol 1, Depurated water: the balance.

EXAMPLE 5

Manufacturing of an oral patch containing methylcobalamin

The following were mixed together in the percentages listed by dry-weight:

Methylcobalamin 1.35%
Konjac and Xanthan gum 9.0%
Xylitol – 22%
Cellulose 26%
Gelatin 41.6%

To this dry mixture 5 times by weight of water was added and the mixture stirred and heated to 140 – 200° F so as to produce a uniform viscous liquid. Drops of the mixture were deposited onto sheets to form blobs at a temperature of about 140° F. The resultant oral patches each containing 500 micrograms methylcobalamin were then dried at room temperature.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

I claim:

1. A troche comprising bioactive cobalamin in a quantity effective to reduce mucositis when used regularly on moist epithelial tissues.

2. The troche of claim 1 wherein the bioactive cobalamin is selected from the group comprising methylcobalamin, hydroxocobalamin, and adenosylcobalamin.

3. The troche of claim 1 or 2 comprising at least 100 micrograms of bioactive cobalamin.

4. The troche of claim 1 or 2 or 3 wherein the troche is adherent.

5. The troche of claim 4 comprising acacia gum as an adhesive.

6. The troche of claim 4 wherein the troche is a patch.

7. The troche of claim 6 further comprising collagen.

8. The troche of claim 1 or 2 or 3 wherein the troche one of a lozenge, a drop, a mint, or a piece of chewing gum.

9. The troche of claim 1 or 2 or 3 wherein the troche is a suppository.

10. An adhering troche comprising cyanocobalamin in a quantity effective to reduce mucositis when used regularly by adhering proximate to affected tissues.

11. The adhering troche of claim 10 comprising at least 100 micrograms of cyanocobalamin.

12. The adhering troche of claim 10 or 11 comprising acacia gum as an adhesive.

13. The adhering troche of claim 10 or 11 or 12 wherein the troche is a patch.

14. The adhering troche of claim 13 further comprising collagen.

15. A liquid, gel or paste composition comprising bioactive cobalamin in a quantity effective to reduce mucositis when applied regularly on affected tissues.

16. The composition of claim 15 wherein the bioactive cobalamin is selected from the group comprising methylcobalamin, hydroxocobalamin, and adenosylcobalamin.

17. The composition of claim 15 or 16 comprising at least .02 percent by weight molecules of cobalamin.

18. The composition of claim 15 or 16 or 17 comprising at least one thickener selected from the group comprising polyvinylpyrrolidone, xanthan gum, konjac gum, locust bean gum, guar gum, gelatin, collagen and aloe vera, wherein the viscosity of the composition is from about 50 to about 10,000 centipoise.

19. The composition of claim 15 or 16 or 17 or 18 packaged in an aerosol spray bottle.

20. The composition of claim 15 or 16 or 17 or 18 wherein the composition is a mouthwash.

21. The composition of claim 15 or 16 or 17 or 18 or 20 packaged as a container of dry powder with directions to add water to the container to make the composition.

22. The composition of claim 15 or 16 or 17 or 18 wherein the composition is a toothpaste.

23. The composition of claim 15 or 16 or 17 or 18 or 20 or 21 or 22 packaged in a pump bottle.

24. A method for treating or preventing mucositis in a patient comprising:
regularly applying to a mucosal surface of a patient in need thereof an effective amount of a composition comprising cobalamin.

25. The method of claim 24 wherein the cobalamin is selected from the group comprising methylcobalamin, hydroxocobalamin, and adenosylcobalamin.

26. The method of claim 24 wherein the cobalamin is cyanocobalamin.

27. The method of claim 24 or 25 or 26 wherein the composition is a dissolving troche.

28. The method of claim 27 wherein the troche is adherent.

29. The method of claim 27 or 28 wherein the troche comprises at least 100 micrograms of cobalamin.

30. The method of claim 24 or 25 or 26 wherein the composition is a liquid, gel or paste.

31. The method of claim 30 wherein the composition comprises at least .02 percent by weight molecules of cobalamin.

32. The method of claim 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 wherein the composition is administered at least once a day every day for prevention.

33. The method of claim 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 wherein the mucositis is stomatitis or aphthous ulcers.

34. The method of claim 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 wherein the mucositis occurs in an oro-pharynx or an oesophagus.

35. The method of claim 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 wherein the mucositis occurs in a vagina or a rectum.

Figure 1

Figure 2

Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/012747

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/714(2006.01)i, A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC8 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN(REGISTRY, CA), eKIPASS(KIPO internal)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VOLKOV, I. et al., "Vitamin B12 could be a "master key" in the regulation of multiple pathological processes", Journal of Nippon Medical School, 2006, Vol.73, No.2, pp.65-69, CODEN: JNMSF5; ISSN: 1345-4676 See the whole document.	1-23
A	BJOERKEGREN, K. et al., "Reported symptoms and clinical findings in relation to serum cobalamin, folate, methylmalonic acid and total homocysteine among elderly Swedes: a population-based study", Journal of Internal Medicine, 2003, Vol.254, No.4, pp.343-352, CODEN: JINMEO; ISSN: 0954-6820 See the whole document.	1-23
A	WO 2003002148 A1 (EVERETT LABORATORIES, INC.) 09 JANUARY 2003 See the whole document.	1-23

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 NOVEMBER 2007 (13.11.2007)	**13 NOVEMBER 2007 (13.11.2007)**

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

KIM, EUN HEE

Telephone No. 82-42-481-5609

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2007/012747

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03002148 A1	09.01.2003	EP 01406661 A1	14.04.2004
		US 20030012826 A1	16.01.2003
		US 2004086574 A1	06.05.2004
		US 6660293 BB	09.12.2003
		US 6863904 BB	08.03.2005

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/012747

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 24-35
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 24-35 pertain to methods for treatment of the human or animal body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.