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SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

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**TÍTULO SOLICITADO: COMPOSICIÓN FARMACÉUTICA QUE CONTIENEN
GESTÁGENOS Y/O ESTRÓGENOS Y 5-METIL-(6S)-
TETRAHIDROFOLATO.**

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**SOLICITANTE: BAYER SCHERING PHARMA
AKTIENGESELLSCHAFT Y MERCK EPROVA AG.**

APODERADO: J. IAN RAISBECK.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

Comendidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por

los artículos 14, 16 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario, veamos:

En primer lugar, y ante la revelación textual del uso de 5-metil-(6s)-tetrahidrofolato, uno o varios estrógenos, opcionalmente vitamina B6 y/o vitamina B2 para prolongar la reducción del riesgo de enfermedades provocadas por carencias de folato y malformaciones congénitas condicionadas por carencias de folato; es relevante señalar que dichas revelaciones, explícitamente mencionadas en las reivindicaciones 22 a 35, son inaceptables a la luz de la Decisión 486.

En efecto, a la luz de la normativa subregional resulta inaceptable pretender atribuirse exclusiva sobre un "Uso", categoría no incluida en el concepto de "Productos o Procedimientos" que establece el artículo 14 de la Decisión 486 de 2000. Lo anterior, además, en consonancia con la reiterada interpretación de la SIC sobre este punto.

Sin perjuicio de lo anterior me permito hacer notar que aún si los usos o métodos terapéuticos fueran permitidos en nuestro medio, éstos deberían cumplir necesariamente con los requisitos materiales de patentabilidad, novedad, nivel Inventivo y Aplicación Industrial. Cabe entonces desde ahora anotar que el último resulta de imposible cumplimiento, en tanto la reproducción industrial del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías es del resorte de la profesión médica y no de las actividades industriales.

En otro aspecto, y esta vez refiriéndonos al nivel inventivo de la adición de derivados de tetrahidrofolatos a métodos anticonceptivos orales, es relevante señalar que las deficiencias de folato o ácido fólico en usuarios de dichos sistemas anticonceptivos, así como los trastornos derivados de esta deficiencia, ya se reconocían con anterioridad en el estado de la técnica^{1,2,3,4}, y por lo tanto no constituye de ninguna manera algo ingenioso asociar derivados de folato o ácido fólico (tal y como lo es el 5-metil-(6S)-tetrahidrofolato) a este tipo de sistemas

¹ Streiff RR. Folate deficiency and oral contraceptives. Journal of the American Medical Association, October 5, 1970;214(1):105-108.

² Durand P, Prost M, Blache D. Folate deficiencies and cardiovascular pathologies. Clin Chem Lab Med. 1998 Jun;36(7):419-29.

³ Green D. Thrombophilia and stroke. Top Stroke Rehabil. 2003 Fall;10(3):21-33.

⁴ M. Eichholzer, J. Lüthy b, U. Moser, B. Fowler. Folate and the risk of colorectal, breast and cervix cancer: the epidemiological evidence. SWISS MED WKLY 2001;131:539-549.

anticonceptivos, para reducir el riesgo de la aparición de los diversos trastornos que reivindica la solicitud colombiana en trámite. En el mismo sentido la publicación internacional WO 99/53910 publicada el 28 de Octubre de 199 y titulada "FOLIC ACID-CONTAINING PHARMACEUTICAL COMPOSITIONS ANDE RELATED METHODS AND DELIVERY SYSTEMS" también revela con anterioridad la combinación de un tratamiento anticonceptivo y acido fólico, veamos:

Oral contraceptives are widely available commercially, and classifications thereof include, without limitation, progestin only, fixed dose, and phasics. Oral contraceptives routinely contain one or more estrogen-related compounds and progestin-related compounds. Such contraceptives are preferred in this invention and are listed extensively, along with their respective hormone ingredients, in the IPPF Directory of Hormonal Contraceptives. For the purpose of

(...)

1. A pharmaceutical composition comprising (a) an oral contraceptive for preventing pregnancy in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the oral contraceptive is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.
2. The pharmaceutical composition of claim 1, wherein the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

(...)

9. The pharmaceutical composition of claim 7, wherein the subject is male, and the disorder is a cardiovascular disorder.

Se puede apreciar claramente en esta anterioridad, la combinación sistemas anticonceptivos, que involucran tanto estrógenos como progestinas, con una dosificación de ácido fólico para prevenir trastornos cardiovasculares y teratogénicos tal y como lo reivindica la solicitud colombiana en trámite.

De la misma manera, y esta vez demostrando además la falta de novedad de la invención, la publicación internacional WO 03/070255 publicada el 28 de agosto de 2003 y titulada "PHARMACEUTICAL COMPOSITIONS COMPRISING ONE OR MORE STEROIDS ONE OR MORE TETRAHYDROFOLATE COMPONENTS AND VITAMIN B12" revela un kit anticonceptivo que cubre las características esenciales de lo reivindicado por la solicitud en cuestión, veamos:

1. A kit for use in a hormonal contraceptive method or hormone replacement therapy in mammalian females, said kit comprising at least 10 oral dosage units containing:
 - a) at least 1 µg of one or more steroids selected from the group consisting of estrogens and progestogens;
 - b) at least 0.1 mg of one or more tetrahydrofolate components selected from the group consisting of (6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5-formyl-(6S)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid, pharmaceutically acceptable salts of these tetrahydrofolic acids and glutamyl derivatives of these tetrahydrofolic acids; and
 - c) at least 0.1 mg vitamin B12.

(...)
3. Kit according to claim 1 or 2, wherein the kit additionally comprises one or more dosage units, preferably 3-8 dosage units that contain the one or more tetrahydrofolate components and vitamin B12 in the indicated amounts, but that do not contain an estrogen or a progestogen.

(...)
5. A kit comprising a plurality of steroid containing oral dosage units for use in a hormonal contraceptive method in mammalian females, said method comprising the at least once daily oral administration of one or more of the dosage units to a mammalian female so as to provide steroids in an effective amount to inhibit ovulation, and wherein the dosage units additionally contain at least 0.1 mg of one or more tetrahydrofolate components selected from

the group consisting of (6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5-formyl-(6S)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid, pharmaceutically acceptable salts of these tetrahydrofolic acids and glutamyl derivatives of these tetrahydrofolic acids and at least 0.1 mg vitamin B12.

(...)

11. Kit according to any one of claims 5-10, wherein the method comprises an administration regimen that provides to the female at least 18 consecutive daily dosages of estrogen in an amount equivalent to 3-40 µg ethinyl estradiol and/or progestogen in an amount equivalent to 30 - 750 µg levonorgestrel.

Como se puede apreciar, en esta anterioridad no solo se menciona la combinación de un tratamiento anticonceptivo con un complemento de ácido fólico, sino que explícitamente se menciona la combinación de etinilestradiol y levonorgestrel junto con ácido 5-metil-(6s)-tetrahidrofólico, en formulaciones farmacéuticas que contienen cantidades que incluyen a las mencionadas en la solicitud colombiana en trámite, lo que irrefutablemente afecta la novedad de esta combinación farmacéutica. Además se puede apreciar que se hace mención de la adición de una vitamina del complejo B, en este caso la vitamina B12.

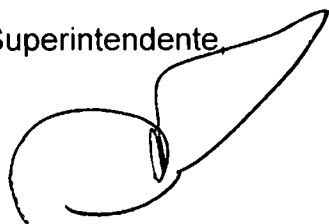
En conclusión, la solicitud colombiana en trámite carece de los requisitos fundamentales para otorgársele el privilegio de patente de invención, en primer lugar porque incurre en una improcedencia directa de patentabilidad al reivindicar un uso a nivel terapéutico; y en segundo lugar porque carece tanto de novedad como de nivel inventivo, puesto que la combinación entre los sistemas anticonceptivos con derivados de ácido fólico, ya se habían descrito en el mismo estado de la técnica y además resultan obvios para cualquier persona medianamente versada en la materia que busque disminuir los riesgos de la aparición de trastornos relacionados por insuficiencia de ácido fólico relacionada a consumo de compuestos hormonales contraceptivos por vía oral.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

III. ANEXOS

- ✦ La publicación internacional WO 99/53910 publicada el 28 de Octubre de 199 y titulada "FOLIC ACID-CONTAINING PHARMACEUTICAL COMPOSITIONS ANDE RELATED METHODS AND DELIVERY SYSTEMS" pagina 10 y capítulo reivindicatorio.
- ✦ La publicación internacional WO 03/070255 publicada el 28 de agosto de 2003 y titulada "PHARMACEUTICAL COMPOSITIONS COMPRISING ONE OR MORE STEROIDS ONE OR MORE TETRAHYDROFOLATE COMPONENTS AND VITAMIN B12" capítulo reivindicatorio.
- ✦ Abstracts de todas las publicaciones científicas mencionadas en el acápite de Complemento de Información.

Señor Superintendente



JOSE LUIS REYES VILLAMIZAR

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(21) International Application Number: PCT/US99/08429 (22) International Filing Date: 16 April 1999 (16.04.99) (30) Priority Data: 60/082,068 17 April 1998 (17.04.98) US (71) Applicants: ORTHO-McNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route 202, Raritan, NJ 08869-0602 (US). THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; c/o Centers of Disease Control and Prevention Technology Transfer Office, 1600 Clifton Road NE (E67), Atlanta, GA 30333 (US). (72) Inventor: KAFRISSEN, Michael, E.; P.O. Box 165, Gladstone, NJ 07934 (US). (74) Agents: CIAMPORCERO, Audley, A. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: FOLIC ACID-CONTAINING PHARMACEUTICAL COMPOSITIONS, AND RELATED METHODS AND DELIVERY SYSTEMS		
(57) Abstract This invention provides folic acid-containing pharmaceutical compositions comprising either an oral contraceptive or a hormone replacement composition. This invention also provides methods of administering folic acid to a subject using the instant pharmaceutical compositions. Finally, this invention provides a drug delivery system useful for administering the instant pharmaceutical compositions.		

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"Subject" shall any animal, such as a primate, mouse, rat, guinea pig or rabbit. In the preferred embodiment, the subject is a human.

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Embodiments of the Invention

This invention provides a pharmaceutical composition comprising (a) an oral contraceptive for preventing pregnancy in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the oral contraceptive is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

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This invention also provides a method of administering folic acid to a subject for whom an oral contraceptive is indicated for preventing pregnancy, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

25

Oral contraceptives are widely available commercially, and classifications thereof include, without limitation, progestin only, fixed dose, and phasics. Oral contraceptives routinely contain one or more estrogen-related compounds and progestin-related compounds. Such contraceptives are preferred in this invention and are listed extensively, along with their respective hormone ingredients, in the IPPF Directory of Hormonal Contraceptives. For the purpose of

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What is claimed is:

1. A pharmaceutical composition comprising (a) an oral
contraceptive for preventing pregnancy in a subject,
5 and (b) folic acid in an amount sufficient to treat
or prevent a disorder which (i) afflicts subjects
for whom the oral contraceptive is indicated at a
higher-than-normal incidence, and (ii) is treatable
or preventable by folic acid administration.
10
2. The pharmaceutical composition of claim 1, wherein
the disorder is selected from the group consisting
of a teratogenic disorder, cervical dysplasia, a
cervical carcinoma, and a cardiovascular disorder.
15
3. A pharmaceutical composition comprising (a) a
hormonal replacement composition for treating or
preventing a menopausal condition in a subject, and
20 (b) folic acid in an amount sufficient to treat or
prevent a disorder which (i) afflicts subjects for
whom the hormonal replacement composition is
indicated at a higher-than-normal incidence, and
(ii) is treatable or preventable by folic acid
administration.
25
4. The pharmaceutical composition of claim 3, wherein
the menopausal condition is a peri-menopausal
condition.
- 30 5. The pharmaceutical composition of claim 3, wherein
the menopausal condition is a post-menopausal
condition.

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6. The pharmaceutical composition of claim 3, wherein the disorder is selected from the group consisting of cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.
- 5
7. A pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a hypogonadal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.
- 10
8. The pharmaceutical composition of claim 7, wherein the subject is female, and the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.
- 15
9. The pharmaceutical composition of claim 7, wherein the subject is male, and the disorder is a cardiovascular disorder.
- 20
10. A method of administering folic acid to a subject for whom an oral contraceptive is indicated for preventing pregnancy, which comprises administering to the subject the pharmaceutical composition of claim 1, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.
- 25
- 30

11. The method of claim 10, wherein the disorder is
selected from the group consisting of a teratogenic
disorder, cervical dysplasia, a cervical carcinoma,
5 and a cardiovascular disorder.
12. A method of administering folic acid to a subject
for whom a hormonal replacement composition is
indicated for treating or preventing a menopausal
10 condition, which comprises administering to the
subject the pharmaceutical composition of claim 3,
wherein the subject is from a population whose
members are afflicted with, or predisposed to become
afflicted with, a disorder at a higher-than-normal
15 incidence, the disorder being treatable or
preventable by folic acid administration.
13. The method of claim 12, wherein the menopausal
condition is a peri-menopausal condition.
20
14. The method of claim 12, wherein the menopausal
condition is a post-menopausal condition.
15. The method of claim 12, wherein the disorder is
25 selected from the group consisting of cervical
dysplasia, a cervical carcinoma, and a
cardiovascular disorder.
16. A method of administering folic acid to a subject
30 for whom a hormonal replacement composition is
indicated for treating or preventing a hypogonadal
condition, which comprises administering to the
subject the pharmaceutical composition of claim 7,
wherein the subject is from a population whose

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members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

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17. The method of claim 16, wherein the subject is female, and the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.
18. The method of claim 16, wherein the subject is male, and the disorder is a cardiovascular disorder.
19. A drug delivery system comprising a pharmaceutical package containing a plurality of dosage units, adapted for successive daily administration, wherein each dosage unit comprises a pharmaceutical composition selected from the group consisting of an oral contraceptive and a hormonal replacement composition.
20. The drug delivery system of claim 19, wherein each dosage unit comprises an oral contraceptive.

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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING ONE OR MORE STEROIDS ONE OR MORE TETRAHY-
DROFOLATE COMPONENTS AND VITAMIN B12

(57) Abstract: The present invention is concerned with a kit for use in a hormonal contraceptive method or hormone replace-
ment therapy in mammalian females, said kit comprising at least 10 oral dosage units containing at least 1 µg of one or more
steroids selected from the group consisting of estrogens and progestogens; at least 0.1 mg of one or more tetrahydrofolate compo-
nents selected from the group consisting of (6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5-formyl-(6S)-tetrahydro-
folic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid,
5 formimino-(6S)-tetrahydrofolic acid, pharmaceutically acceptable salts of these tetrahydrofolic acids and glutamyl derivatives of
these tetrahydrofolic acids; and at least 0.1 mg vitamin B 12. Other aspects of the present invention relate to a hormonal contraceptive
method and a method of hormone replacement therapy comprising the at least once daily oral administration of one or more steroid
containing dosage units to a mammalian female, wherein the dosage units additionally contain at least 0.1 mg of one or more of the
aforementioned tetrahydrofolate components and at least 0.1 mg vitamin B 12.

CLAIMS

1. A kit for use in a hormonal contraceptive method or hormone replacement therapy in mammalian females, said kit comprising at least 10 oral dosage units containing:
 - a) at least 1 μ g of one or more steroids selected from the group consisting of estrogens and progestogens;
 - b) at least 0.1 mg of one or more tetrahydrofolate components selected from the group consisting of (6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5-formyl-(6S)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid, pharmaceutically acceptable salts of these tetrahydrofolic acids and glutamyl derivatives of these tetrahydrofolic acids; and
 - c) at least 0.1 mg vitamin B12.
2. Kit according to claim 1, comprising at least 10 dosage units containing:
 - a) from 2 μ g to 30 mg of the one or more steroids;
 - b) from 0.2 to 15 mg of the one or more tetrahydrofolate components and
 - c) from 0.2 to 20 mg vitamin B12.
3. Kit according to claim 1 or 2, wherein the kit additionally comprises one or more dosage units, preferably 3-8 dosage units that contain the one or more tetrahydrofolate components and vitamin B12 in the indicated amounts, but that do not contain an estrogen or a progestogen.
4. Kit according to any one of claims 1-3, wherein the one or more tetrahydrofolate components are selected from the group consisting of 5-formyl-tetrahydrofolic acid, 5-methyl-tetrahydrofolic acid, as well as pharmaceutically acceptable salts and glutamyl derivatives of these acids.
5. A kit comprising a plurality of steroid containing oral dosage units for use in a hormonal contraceptive method in mammalian females, said method comprising the at least once daily oral administration of one or more of the dosage units to a mammalian female so as to provide steroids in an effective amount to inhibit ovulation, and wherein the dosage units additionally contain at least 0.1 mg of one or more tetrahydrofolate components selected from

the group consisting of (6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5-formyl-(6S)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid, pharmaceutically acceptable salts of these tetrahydrofolic acids and glutamyl derivatives of these tetrahydrofolic acids and at least 0.1 mg vitamin B12.

6. A kit comprising a plurality of steroid containing oral dosage units for use in hormone replacement therapy in peri-menopausal, menopausal or post menopausal mammalian females, said method comprising the at least once daily oral administration of one or more of the dosage units to the female so as to provide steroids in an effective amount to prevent or suppress symptoms of hypogonadism, and wherein the dosage units additionally contain at least 0.1 mg of one or more tetrahydrofolate components selected from the group consisting of (6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5-formyl-(6S)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid, pharmaceutically acceptable salts of these tetrahydrofolic acids and glutamyl derivatives of these tetrahydrofolic acids; and at least 0.1 mg vitamin B12.

7. Kit according to claim 5 or 6, wherein the steroids are selected from the group consisting of estrogens and progestogens.

8. Kit according to any one of claims 5-7, wherein the dosage units are administered to provide a therapeutically effective amount of the one or more tetrahydrofolate components to prevent or remedy deficiencies of a folate component.

9. Kit according to any one of claims 5-8, wherein the method comprises an administration regimen that provides to the female at least 18 consecutive daily dosages of:

- a) from 2 μ g to 30 mg of the one or more steroids;
- b) from 0.2 to 15 mg of the one or more tetrahydrofolate components and
- c) from 0.2 to 20 mg vitamin B12.

10. Kit according to any one of claims 5-9, wherein the one or more tetrahydrofolate components are selected from the group consisting of 5-formyl-tetrahydrofolic acid, 5-

methyl-tetrahydrofolic acid, as well as pharmaceutically acceptable salts and glutamyl derivatives of these acids.

11. Kit according to any one of claims 5-10, wherein the method comprises an administration regimen that provides to the female at least 18 consecutive daily dosages of estrogen in an amount equivalent to 3-40 µg ethinyl estradiol and/or progestogen in an amount equivalent to 30 - 750 µg levonorgestrel.
12. Kit according to any one of claims 5-11, wherein the method comprises essentially continuous administration of the steroid containing dosage units during a time interval of at least 40 days, preferably at least 90 days.
13. Kit according to any one of claims 1-12, wherein the dosage units contain between 3 and 40 µg, preferably between 10 and 30 µg ethinyl estradiol.
14. Kit according to any one of claims 5-13, wherein the method comprises the essentially continuous administration of the one or more tetrahydrofolate components and vitamin B12 during a time interval of at least 40 days, preferably at least 90 days.
15. Kit according to claim 14, wherein the method comprises an interval of 3-8 days during which the one or more tetrahydrofolate components and vitamin B12 are administered, but during which no estrogen or progestogen is administered.
16. Kit according to any one of claims 1-15, wherein the one or more tetrahydrofolate components are selected from the group consisting of folic acid, pharmaceutically acceptable salts of folic acid, glutamyl derivatives of folic acid and precursors of these substances.
17. Kit according to any one of claims 1-16, wherein the dosage units contain at least 3 mg vitamin B6, more preferably from 5 to 250 mg vitamin B6.

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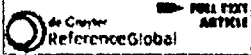
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1: Clin Chem Lab Med. 1998 Jun;36(7):419-29.



Links

Folate deficiencies and cardiovascular pathologies.

Durand P, Prost M, Blache D.

INSERM U 498, Biochimie des Lipoprotéines et Interactions Vasculaires, Faculté de Médecine, Université de Bourgogne, Dijon, France.

Although folates are widely distributed in foods, folate deficiencies may be more frequent than expected because their true availability may be impaired due to their lability under various food cooking and processing conditions. Folate deficiency is frequently observed in elderly people, smokers, alcoholics and oral contraceptive users. It is also associated with the mutation leading to the thermolabile variant of N5,10-methylenetetrahydrofolate reductase which is observed in about 10% of the population. In addition to the essential role of the intracellular pool of polyglutamates in de novo biosynthesis of deoxyribonucleotides which allow cell growth and division, the reduced and methylated form of folate, N5-methyltetrahydrofolate, is required for the remethylation of homocysteine to methionine. By inhibiting this remethylation pathway, folate deficiency induces homocysteine efflux into the circulation. Many studies have shown a negative correlation between plasma folate, particularly N5-methyltetrahydrofolate, and circulating homocysteine levels. In addition, folate deficiency is a major cause of hyperhomocysteinemia which is fully recognised as an independent risk factor for atherothrombosis. Epidemiological and recent experimental studies have demonstrated that folate deficiency might increase the risk of cardiovascular disease by increasing circulating homocysteine levels. Thus, the clinical efficiency of folate supplementation, especially N5-methyltetrahydrofolate, in reducing homocysteine-dependent cardiovascular risk should be evaluated.

PMID: 9746265 [PubMed - indexed for MEDLINE]

Related articles

- Folate deprivation, the methionine cycle, and Alzheimer's disease. [Vitam Horm. 2008]
- Review Impaired homocysteine metabolism and atherothrombotic disease. [Lab Invest. 2001]
- Review [Age-associated changes in the metabolism of vitamin B] [Z Gerontol Geriatr. 2004]
- Review Folate, homocysteine, endothelial function and cardiovascular disease [J Nutr Biochem. 2004]
- Molecular mechanisms of adaptation to folate deficiency. [Vitam Horm. 2008]

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Cited by 1 PubMed Central article

- Structures of Mycobacterium tuberculosis folylpolyγ [Acta Crystallogr D Biol Crystallogr. 2008]

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☐ 1: Top Stroke Rehabil. 2003 Fall;10(3):21-33.

COMPLETE ARTICLE
THOMAS LAND

Links

Thrombophilia and stroke.

Green D.

Atherosclerosis Program, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA.

Thrombophilia is defined as an enhanced tendency to form intravascular thrombi, which may be arterial or venous. Of the inherited thrombophilias, factor V Leiden and the prothrombin 20210 mutation have been associated with stroke, but this association is statistically significant only in children and adults under age 40. The risk of stroke in persons with these mutations is substantially increased by concomitant exposure to oral contraceptives. Hyperhomocystinemia is a major risk factor for stroke as well as Alzheimer's disease; persons with deficiencies of vitamin B12 or folic acid are especially vulnerable to these complications. Of the acquired thrombophilias, the antiphospholipid antibody syndrome is strongly associated with transient ischemic attacks, cerebral infarction, Sneddon syndrome, and dementia. The diagnosis of thrombophilia should be considered in stroke patients who are young, have a family history of thrombosis, suffer venous dural sinus thrombosis, or have recurrent strokes.

PMID: 14681817 [PubMed - indexed for MEDLINE]

Related articles

- Risk of thrombosis associated with oral contraceptives of women frc [Haematologica. 2001]
- Prothrombotic conditions, oral contraceptives, and the risk of ischemic stro[J Thromb Haemost. 2005]
- Review Evidence-based indications for thrombophilia screening. [Vasa. 2008]
- Factor V Leiden and prothrombin G20210A mutations in young adults [Thromb Haemost. 2004]
- Review Oral contraceptives, hormone replacement therapy, thro [Thromb Haemost. 2005]
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306 19

Title: Folate deficiency and oral contraceptives.

POPLINE Document Number: 700259

Author(s):

Streiff RR

Source citation:

Journal of the American Medical Association, October 5, 1970;214(1):105-108.

Abstract:

7 cases of folate deficiency and anemia in women 21-39 years old, taking no medications other than oral contraceptives for at least 1 1/2 years, were studied. Gastrointestinal studies were normal, hematocrit values ranged between 11-32%. Peripheral blood smears were macrocytic and bone marrow examinations showed a striking megaloblastic picture. Serum analysis showed low folate levels, normal Vitamin-B12 levels, and normal to high iron levels. 4 patients responded to orally administered folic acid (monoglutamic folate) at 250 mcq daily while continuing to take oral contraceptives. 2 patients responded to the discontinuation of oral contraceptives alone. To study the absorption of dietary folate (largely polyglutamic folate), absorption tests were performed on 9 men not taking oral contraceptives and 9 women taking oral contraceptives. All had normal serum folate levels and none were anemic. Absorption tests were performed with 200 mcq of folic acid (monoglutamic folate) and the molecular equivalent of polyglutamic folate extracted from brewer's yeast. Absorption of monoglutamic folate does not seem to be effected by oral contraceptives, but the absorption of the polyglutamic folate was decreased approximately 60%. Since polyglutamic folate must undergo an enzymetically induced change before absorption it seems possible that this step is effected by oral contraceptives.

Keywords:

Clinical Research
Oral Contraceptives, Side Effects
Serum Folate Level
Hematological Effects
Contraceptive Methods
Side Effects
Research Methodology
Contraceptive Safety
Safety
Public Health
Health
Hemic System
Physiology
Biology
Contraception
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Treatment

Folate and the risk of colorectal, breast and cervix cancer: the epidemiological evidence¹

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^d Metabolic Unit, University Children's Hospital, Basel

Summary

It is only recently that folate deficiency has been implicated in the development of cancer. The mechanisms by which folate might protect against cancer are not clear but may relate to its role in DNA methylation and DNA synthesis. All case-control, cohort and intervention trials reported in English, French, or German, on folate intake or blood levels in relation to the risk of colorectal, breast, and cervix cancer were reviewed. Twenty case-control, and 12 nested case-control or cohort studies were identified. The epidemiological studies consistently show an inverse association between intake and/or levels of folate and the frequency of colorectal carcinomas, and less clearly of adenomas. Long-term use of supplements of folate seems to be of greater benefit than dietary intake. The effect of folate seems to be modulated by alcohol, methionine, and MTHFR polymorphisms. Results from animal studies suggest that folate supplementation might decrease or increase cancer risk depending on dosage and timing. Recent studies also suggest an inverse association between folate intake and breast cancer among women who regularly consume alcohol. Conversely, epidemiological evidence remains uncertain for the role of folate in cervical cancer prevention; the results of

two intervention trials on rates of cervical intra-epithelial neoplasia regression or progression were negative. An effect of folate later in carcinogenesis is not supported by the few (nested) case-control studies on invasive cervical cancer. Some of the conflicting results may be due to the fact that dietary intake or blood levels of folate do not accurately reflect folate concentrations in the cells of cancer origin. Furthermore, only a few studies have taken into account the modulating effect of alcohol, methionine, and MTHFR polymorphisms in their analyses. The observed inverse associations between folate and risk of cancer, on the other hand, may be confounded by various factors, especially by other potentially protective constituents in fruits and vegetables. Ongoing intervention studies can strengthen evidence for causality by excluding such confounding, but the optimal dose, duration, and stage of carcinogenesis and the appropriate (genetically predisposed) study group for folate chemoprevention are not yet defined.

Key words: folate; cervical; colorectal; breast cancer prevention; gene-nutrition interaction; MTHFR polymorphism

Introduction

Folate deficiency has been associated with neural tube defects, cardiovascular disease, and anaemia [1, 2]. More recently, it has been hypothesized that folate may modulate cancer risk [3-7], notably risk of cervix and colorectal cancer, and less well studied breast cancer and a rapidly growing number of other cancer sites such as lung, pancreas, stomach, oesophagus, leukaemia, skin, and endometrium [8-13].

Mechanisms

Two possible mechanisms by which low folate may increase cancer risk are likely. First, in mediating the transfer of one-carbon moieties, folate is critical for the synthesis of S-adenosylmethionine (SAM), an important compound for DNA methylation. DNA methylation is an epigenetic determinant in gene expression, DNA stability, and mutagenesis. Second, folate is important for normal DNA synthesis and repair. Consequently, folate

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2020
Bogotá, D.C.,

Doctor:
Ian Raisbeck Llinas
Apoderado

Oficio N°: 9853

ASUNTO:	Radicación PCT N°	07-129904
	Trámite	011
	Evento	379
	Actuación	440
	Folios	010

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Gynopharm S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 28 AGO. 2009.

202021

2020
Bogotá, D.C.,

Doctor:
Ian Raisbeck Llinas
Apoderado

Oficio N°: 9854

ASUNTO:	Radicación PCT N°	07-129904
	Trámite	011
	Evento	379
	Actuación	440
	Folios	025

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado del Laboratorio Franco Colombiano Lafranco S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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