

Filed on behalf of Gnosis S.p.A., Gnosis Bioresearch S.A.
and Gnosis U.S.A., Inc.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GNOSIS S.p.A., GNOSIS BIORESEARCH S.A. and GNOSIS U.S.A., INC.
Petitioners

v.

Patent Owner of
U.S. Patent 6,011,040 to Muller et al.
Appl. No. 09/095,572 filed June 11, 1998
Issued Jan. 4, 2000

IPR Trial No. TBD

PETITION FOR INTER PARTES REVIEW

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Gnosis S.p.A., Gnosis Bioresearch S.A. and Gnosis U.S.A., Inc. (collectively "Gnosis" or "Petitioners") request *inter partes* review under 35 U.S.C. §312 and 37 C.F.R. §42.108 of Claims 1, 2, 3, 5, 6, 8, 9, 11, 12, 13, 14, 15, 19, 20, 21 and 22 of U.S. Patent No. 6,011,040 (the "'040 patent")(Ex. 1004), which issued on Jan. 4, 2000, to Muller et al. The required fee under 37 C.F.R. §42.15(a) is \$27,200 for the first 20 claims. Petitioner herewith submits the fee of \$27,200 by undersigned deposit account number. This Petition is filed in compliance with the page limit, font size and margin limitations of 37 C.F.R. §§42.6 and 42.24.

I. MANDATORY NOTICES UNDER 37 C.F.R. §42.8(a)(1)

As set forth below and pursuant to 37 C.F.R. §42.8(a)(1), the following mandatory notices are provided as part of this Petition.

A. Real Party-in-Interest Under 37 C.F.R. §42.8(b)(1)

Gnosis S.p.A., Gnosis Bioresearch S.A. and Gnosis U.S.A., Inc. are the real parties-in-interest for Petitioners.

Gnosis S.p.A. has no corporate parent. No shareholder of Gnosis S.p.A. is a publicly held corporation that holds 10% or more of the stock of Gnosis S.p.A. Gnosis Bioresearch S.A., is a wholly-owned subsidiary of Gnosis S.p.A. Gnosis U.S.A., Inc. is a wholly-owned subsidiary of Gnosis S.p.A.

B. Related Matters Under 37 C.F.R. §42.8(b)(2)

The '040 patent has been asserted in two litigations. The first, captioned Merck & CIE, South Alabama Medical Science Foundation and PamLab LLC vs. Macoven Pharmaceuticals, Gnosis S.p.A., Gnosis U.S.A., Inc. and Gnosis Bioresearch S.A., Case No. 6:12-00027-LED (E.D. Texas) was stayed on September 19, 2012. The second, captioned In the Matter of Reduced Folate Nutraceutical Products and L-Methylfolate Raw Ingredients Used Therein, Inv. No. 337-TA-857 (International Trade Commission) is currently pending. Gnosis is a party to both litigations.

The '040 patent is the subject of *ex parte* Reexamination No. 90/011,935, currently pending.

Contemporaneously with the filing of this Petition, Petitioners are filing Petitions for Inter Partes Review of the three additional patents at issue in the above-referenced International Trade Commission proceeding. The three patents, U.S. Patent Nos. 5,997,915 (Ex. 1001), 6,673,381 (Ex. 1002) and 7,172,788 (Ex. 1003) to Bailey et al. are related through continuation applications.

C. Lead and Back-up Counsel Under 37 C.F.R. §42.8(b)(3)

Petitioner's Lead Counsel is Jonathan J. Krit, U.S. Patent and Trademark Office Registration No. 37,164 of Amin Talati LLC, 55 West Monroe St., Suite 3400, Chicago, IL, 60603; Phone (312) 466-1033; Fax (312) 884-7352.

Petitioner's Back-up Counsel is Janine A. Moderson, Registration No. 50,981 of Amin Talati LLC, the same address and phone as shown above.

D. Service Information Under 37 C.F.R. §42.8(b)(4)

Please address all correspondence to the lead counsel at the address shown above. Gnosis also consents to electronic service by email to: patent@amintalati.com.

E. Service on Patent Owner Under 37 C.F.R. §§42.106(a)(2) and 42.105(a)

This Petition is being served by Express Mail on Merck & Cie KG, owner of the '040 patent, at their address of record according to PAIR: Millen White Zelano & Branigan, Arlington Courthouse Plaza I, 2200 Clarendon Boulevard, Suite 1400, Arlington, VA 22201.

II. GROUNDS FOR STANDING UNDER 37 C.F.R. §42.104(a)

Gnosis certifies that the '040 patent is available for *inter partes* review, that Gnosis has not been served with a complaint alleging infringement of the '040 patent more than one year prior to the filing of this Petition, that Gnosis has not filed a civil action challenging the validity of the '040 patent, and that Gnosis is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition.

III. SUMMARY OF ISSUES PRESENTED

This petition primarily presents the Patent Trial and Appeal Board with the following issues:

U.S. Patent No. 6,011,040 claims, *inter alia*, methods of decreasing homocysteine levels in a human subject, or preventing or treating diseases associated with increased levels of homocysteine in a human subject, by administering at least one tetrahydrofolate in natural stereoisomeric form, such as 5-methyl-(6S)-tetrahydrofolic acid. Petitioner contends that the prior art teaches the administration of 5-methyl-(6S)-tetrahydrofolic acid for decreasing homocysteine levels in a human subject, both alone and in combination with other vitamins. Accordingly the issues presented by this Petition are: (1) whether the prior art anticipates the uses of tetrahydrofolates in natural stereoisomeric form claimed by the '040 patent, and (2) whether the uses of tetrahydrofolates in natural stereoisomeric form claimed by the '040 patent would have been obvious to a person of ordinary skill in the art at the time of the invention.

IV. INTRODUCTION

The '040 patent is directed to methods of decreasing homocysteine levels in the human body, and preventing or treating diseases associated with increased levels of homocysteine, by administering at least one tetrahydrofolate in natural stereoisomeric form. Independent claims 1 and 2 of the '040 patent state:

1. A method of decreasing homocysteine levels in the human body comprising administering at least one tetrahydrofolate in natural stereoisomeric form to a human subject.

2. A method of preventing or treating disease associated with increased levels of homocysteine levels in the human body comprising administering at least one tetrahydrofolate in natural stereoisomeric form to a human subject.

The remaining dependent claims at issue in this Petition specify the specific natural stereoisomer(s) of the tetrahydrofolate to be administered (most notably 5-methyl-(6S)-tetrahydrofolic acid) and/or identify specific diseases associated with increased levels of homocysteine.

The term "tetrahydrofolate in natural stereoisomeric form" as used in the '040 patent refers to the active metabolites of folate: 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid. Miller Decl., Ex. 1005, ¶¶8, 12-21. The "6R" and "6S" notations specify that the stereoisomer of the compounds is that of the naturally occurring metabolite. *Id.*

V. IDENTIFICATION OF CHALLENGE PER 37 C.F.R. §42.104(b)

A. List of Exhibits and Prior Art on which Petition is Based

Exhibit 1001 - U.S. Patent No. 5,997,915 to Bailey et al.

Exhibit 1002 - U.S. Patent No. 6,673,381 to Bailey et al.

Exhibit 1003 - U.S. Patent No. 7,172,778 to Bailey et al.

Exhibit 1004 - U.S. Patent No. 6,011,040 to Muller et al.

Exhibit 1005 - Declaration of Joshua W. Miller, Ph.D.

Exhibit 1006 - Curriculum Vitae of Joshua W. Miller, Ph.D.

Exhibit 1007 - "Folic Acid and Vitamin B₁₂", Herbert, V. and Coleman, N., in "Modern Nutrition in Health and Disease," 7th Ed. 1988, pp. 388-416

Exhibit 1008 - "Nomenclature and symbols for folic acid and related compounds," International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology 1986, World Wide Web version prepared by Moss, G.P., retrieved from <http://www.chem.qmul.ac.uk/iupac/misc/folic.html> on January 21, 2013

Exhibit 1009 - European Patent EP 595,005 to Serfontein

Exhibit 1010 - European Patent Application No. 388,827 to Le Grazie

Exhibit 1011 - European Patent Application No. 627,435 to Ambrosini

Exhibit 1012 - U.S. Patent No. 5,194,611 to Marazza et al.

Exhibit 1013 - Ueland, M. and Refsum, H., "Plasma homocysteine, a risk factor for vascular disease: Plasma levels in health, disease and drug therapy," J. Lab. Clin. Med. 1989, Vol. 114, pp. 473-501

Exhibit 1014 - Scott, J. et al., "Folic acid to prevent neural tube defects," The Lancet 1991, Vol. 338, p. 505

Exhibit 1015 - Leeming, R. et al., "Vitamins to prevent neural tube defects," The Lancet 1991, Vol. 338, p. 895

Exhibit 1016 - Barford, A. and Pheasant, A., "Trial of folate treatment to prevent recurrence of neural tube defects," British Medical Journal 1981, Vol. 282, p. 1793

Exhibit 1017 - Lucock, M. et al., "Vitamins to prevent neural tube defects," The Lancet, Vol. 338, pp. 894-95

Exhibit 1018 - U.S. Patent No. 4,959,472 to Wood et al.

Exhibit 1019 - Ubbink, J. et al., "Vitamin B-12, vitamin B-6 and folate nutritional status in men with hyperhomocysteinemia," Am. J. Clin. Nutr. 1993, Vol. 57, pp. 47-53.

B. Claims and Statutory Grounds Per 37 CFR §§42.104(b)(1) and (2)

Gnosis respectfully requests that the Board cancel claims 1, 2, 3, 5, 6, 8, 9, 11, 12, 13, 14, 15, 19, 20, 21 and 22 based on each of the following grounds:

Ground One: All claims challenged in this Petition (1, 2, 3, 5, 6, 8, 9, 11, 12, 13, 14, 15, 19, 20, 21 and 22) are unpatentable as anticipated under 35 U.S.C. §102(b) by Serfontein (Ex. 1009).

Ground Two: All claims challenged in this Petition are obvious under 35 U.S.C. §103 over Serfontein (Ex. 1009) in view of either Marazza (Ex. 1012) or Wood (Ex. 1018) or Ambrosini (Ex. 1011).

Ground Three: Claims 12, 13, 14, and 15 are obvious under 35 U.S.C. §103 over Serfontein (Ex. 1009) in view of either Marazza (Ex. 1012) or Wood (Ex. 1018) or Ambrosini (Ex. 1011) and in further view of Ubbink (Ex. 1019).

Ground Four: All claims challenged in this Petition are obvious under 35 U.S.C. §103 over Serfontein (Ex. 1009) in view of either Marazza (Ex. 1012) or Wood (Ex. 1018) or Ambrosini (Ex. 1011) in further view of Ueland (Ex. 1013).

Ground Five: Claims 12, 13, 14, and 15 are obvious under 35 U.S.C. §103 over Serfontein (Ex. 1009) in view of either Marazza (Ex. 1012) or Wood (Ex. 1018) or Ambrosini (Ex. 1011), in further view of Ueland (Ex. 1013), and in further view of Ubbink (Ex. 1019).

Ground Six: All claims challenged in this Petition are obvious under 35 U.S.C. §103 in view of either Scott (Ex. 1014) or Leeming (Ex. 1015) or Barford (Ex. 1016), in further view of Lucock (Ex. 1017) or Marazza (Ex. 1012).

Ground Seven: Claims 12, 13, 14 and 15 are obvious under 35 U.S.C. §103 in view of either Scott (Ex. 1014) or Leeming (Ex. 1015) or Barford (Ex. 1016), in further view of Lucock (Ex. 1017) or Marazza (Ex. 1012), and in further view of Ubbink (Ex. 1019).

C. Claim Construction Statement Per 37 C.F.R. §42.104(b)(3)

The claim terms in the '040 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation of the claim language. Gnosis does not believe that any special meanings apply to the claim terms in the '040 patent.

D. Ground One: Anticipation Under 35 U.S.C. §102(b) by Serfontein

Serfontein is directed to compositions for providing folate in combination with Vitamins B6 and B12 for the purpose of reducing homocysteine in blood and tissue. Serfontein discloses that its compositions may be comprised of folate "or a

suitable active metabolite of folate or a substance which releases folate in vivo."

See, e.g., Ex. 1009, claim 1, p. 18, ln. 51-56. Serfontein discloses that its compositions are suitable for use as dietary preparations. *Id.* at p. 4, ln. 24. The compositions are for both the treatment and prevention of elevated homocysteine and associated conditions. See, e.g., *Id.* at p. 18, claim 1.

The genus of "suitable active metabolites of folate" at the time of the invention refers to the two natural tetrahydrofolate stereoisomers identified in the discussion of the prior art in the '040 patent: 5-formyl-(6S)-tetrahydrofolic acid (i.e., 5-MTHF) and 5-methyl-(6S)-tetrahydrofolate (i.e., 5-FTHF). Miller Decl., Ex. 1005 at ¶21; Ex. 1001, col. 1, ln. 24-36. As noted in European Patent Application No. 388,827, "[i]n the circulating blood the folate pool is mostly represented by MTHF, but also by FTHF. MTHF represents the main form of folate transport in the blood." Ex. 1010, p. 2, ln. 26-28.

When a genus in a claim consists of a limited number of specific and closely related compounds that enable a person of ordinary skill in the art to at once envisage each member, the individual members are considered to have been explicitly identified in the claims. *In re Schaumann*, 572 F.2d 312, 315 (C.C.P.A. 1978); *In re Petering*, 301 F.2d 676, 682 (C.C.P.A. 1962). One with ordinary skill in the art also would have recognized 5-MTHF to be a racemic mixture that includes the biologically active 6(S)-5-MTHF isomer and the biologically inert

6(S)-5-MTHF isomer. Miller Decl., Ex. 1005 at ¶ 10. Accordingly, the individual active metabolites of folate, including 5-methyl-(6S)-tetrahydrofolic acid, are presumed to be explicitly disclosed in the compositions of Serfontein.

As illustrated by the following claim chart, all limitations of the claims of the '040 patent are disclosed in Serfontein:

U.S. Patent No. 6,011,040	Prior Art
Claim 1	
A method of decreasing homocysteine levels in the human body comprising	Serfontein (European Patent Application No. 0595005) discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising: <ul style="list-style-type: none"> - Vitamin B6; - folate or <i>a suitable active metabolite of folate</i> or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42).
administering at least one tetrahydrofolate in natural stereoisomeric form to a human subject.	Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i> at p. 4, ln. 37-42; Miller Decl., Ex. 1005 at ¶21).
Claim 2	
A method of preventing or treating disease associated with increased levels of homocysteine levels in the human body	Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising: <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo;

<p>comprising administering at least one tetrahydrofolate in natural stereoisometric form to a human subject.</p>	<p>- Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein further discloses that its method is directed towards preventing or treating diseases associated with increased levels of homocysteine:</p> <p>"Elevated homocysteine levels can be correlated with some of the principle cause of morbidity and mortality in the Western world, the so-called "Western" diseases, including such conditions as myocardial and cerebral infarction. Precocious vascular disease is the main single cause of death accounting for the majority of these deaths. (New Eng J. Med, 314 : 488)"</p> <p>"This condition is often associated with high blood levels of homocysteine (often 200 u mole/l or higher) and the associated clinical defects include the following: -</p> <ol style="list-style-type: none"> 1. Disintegration of the vascular elastic interna due to binding of homocysteine to allysine residues of tropoelastin. ... 6. Progressive premature artherosclerosis. ... 8. Pernicious occlusive vascular disease frequently manifested clinically as myocardial infraction, stroke, pulmonary embolism (Am.J.Med.Sc. 1977, <u>273</u>: 120) and peripheral vascular occlusion." <p>(<i>Id.</i>, p.2, ln. 4-7; 34-54)</p> <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i>, p. 4, ln. 37-42; Miller Decl, Ex. 1005 at ¶21).</p>
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Claim 3	
A method according to claim 2, wherein the disease is cardiovascular disease.	<p>See claim 2 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein further discloses that its method is directed towards preventing or treating diseases associated with increased levels of homocysteine including cardiovascular disease:</p> <p>"Elevated homocysteine levels can be correlated with some of the principle cause of morbidity and mortality in the Western world, the so-called "Western" diseases, including such conditions as myocardial and cerebral infarction. Precocious vascular disease is the main single cause of death accounting for the majority of these deaths. (New Eng J. Med, 314 : 488)"</p> <p>"This condition is often associated with high blood levels of homocysteine (often 200 u mole/l or higher) and the associated clinical defects include the following: -</p> <ol style="list-style-type: none"> 1. Disintegration of the vascular elastic interna due to binding of homocysteine to allysine residues of tropoelastin. ... 6. Progressive premature artherosclerosis.

	<p>...</p> <p>8. Pernicious occlusive vascular disease frequently manifested clinically as myocardial infraction, stroke, pulmonary embolism (Am.J.Med.Sc. 1977, <u>273</u>: 120) and peripheral vascular occlusion." (p. 2, ln. 4-7; 34-54).</p>
Claim 5	
<p>A method according to claim 2, wherein the tetrahydrofolate is 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl(6S)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid, or salts thereof.</p>	<p>See claim 2 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i>, p. 4, ln. 37-42; Ex. 1005 at ¶21).</p>
Claim 6	
<p>A method according to claim 3, wherein the tetrahydrofolate is 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl (6S)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-</p>	<p>See claim 3 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo;

formyl-(6R)-tetrahydrofolic acid, 5-formimino(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid, or salts thereof.	<p>- Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i>, p. 4, ln. 37-42; Ex. 1005 at ¶21).</p>
Claim 8	
A method according to claim 2, wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.	<p>See claim 2 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42). <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i>, p. 4, ln. 37-42; Ex. 1005 at ¶21).</p>
Claim 9	
A method according to claim 3, wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.	<p>See claim 3 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a</p>

	<p>patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i>, p. 4, ln. 37-42; Ex. 1005 at ¶21).</p>
Claim 11	
<p>A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S) tetrahydrofolic acid, or a salt thereof.</p>	<p>See claim 2 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein discloses "The clinical condition of homocysteinuria, is an inborn error of metabolism which is either caused by an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine." (<i>Id.</i>, p. 3, ln. 20-23).</p> <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once</p>

	envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i> , p. 4, ln. 37-42; Ex. 1005 at ¶21).
Claim 12	
A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S)tetrahydrofolic acid, or a salt thereof.	<p>See claim 3 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein discloses "The clinical condition of homocysteinuria, is an inborn error of metabolism which is either caused by an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine." (<i>Id.</i>, p. 3, ln. 20-23).</p> <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i>, p. 4, ln. 37-42; Ex. 1005 at ¶21).</p>
Claim 13	
A method according to claim 4,	Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment

<p>(A method of preventing prenatal neural tube deficiencies associated with increased maternal homocysteine levels comprising administering at least one tetrahydrofolate in natural stereoisomeric form to a female human subject.)</p>	<p>of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein further discloses that "the invention is applicable to the lowering of total homocysteine blood levels if elevated by any known cause, including...pregnancy..." (<i>Id.</i>, p. 4, ln. 43-45).</p>
<p>wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.</p>	<p>Serfontein discloses "The clinical condition of homocysteinuria, is an inborn error of metabolism which is either caused by an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine." (<i>Id.</i>, p. 3, ln. 20-23).</p> <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i>, p. 4, ln. 37-42; Ex. 1005 at ¶21).</p>
<p>Claim 14</p>	
<p>A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-</p>	<p>See claim 2 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or

<p>methyl(6S)-tetrahydrofolic acid, or a salt thereof.</p>	<p>a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein discloses "The clinical condition of homocysteinuria, is an inborn error of metabolism which is either caused by an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine." (<i>Id.</i>, p. 3, ln. 20-23).</p> <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i>, p. 4, ln. 37-42; Ex. 1005 at ¶21).</p>
<p>Claim 15</p>	
<p>A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl(6S)-tetrahydrofolic acid, or a salt thereof.</p>	<p>See claim 3 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein discloses that its method is directed towards preventing or treating diseases associated with increased levels of homocysteine:</p> <p>Serfontein discloses "The clinical condition of homocysteinuria, is an inborn error of metabolism</p>

	<p>which is either caused by an enzyme defect in the transsulfuration pathway or a similar defect in the 5-methyl tetrahydrofolate dependent remethylation of homocysteine to methionine." (<i>Id.</i>, p. 3, ln. 20-23).</p> <p>Serfontein discloses a composition containing "a suitable active metabolite of folate" from which one of ordinary skill in the art is able to at once envisage at least one tetrahydrofolate in natural stereoisomeric form, including 5-methyl-(6S)-tetrahydrofolic acid. (<i>Id.</i>, p. 4, ln. 37-42; Ex. 1005 at ¶21).</p>
Claim 19	
A method according to claim 5, wherein the tetrahydrofolate is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.	<p>See claim 5 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are pharmaceutically compatible active substances. (See, e.g., claims 20 and 22 of the '040 patent).</p>
Claim 20	
A method according to claim 19, wherein the pharmaceutically compatible active substance comprises at least one B-vitamin.	<p>See claim 19 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p>

	<ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are B-vitamins.</p>
Claim 21	
A method according to claim 11, wherein the tetrahydrofolate is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.	<p>See claim 11 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are pharmaceutically compatible active substances.</p>
Claim 22	
A method according to claim 21, wherein the pharmaceutically compatible active substance comprises at least one B-vitamin.	<p>See claim 21 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are B-vitamins.</p>

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E. Grounds Two and Three: Serfontein in view of Marazza or Wood or Ambrosini, and in further view of Ubbink

Both the '040 patent and Serfontein are directed to providing folate for the purposes of decreasing homocysteine levels and for treating or preventing diseases associated with elevated homocysteine levels. Serfontein specifically notes the role of correcting a subject's deficiency in folate for these purposes. See, e.g., Ex. 1009, p. 3, ln. 30-39 and p. 18, ln. 51-56.

The prior art explicitly suggests both 5-methyl-(6S)-tetrahydrofolic acid and 5-formyl-(6S)-tetrahydrofolic acid for providing folate for those in a folate deficient state. For example, the Marazza patent stated:

"N⁵-Methyl-5,6,7,8-tetrahydrofolic acid, herein sometimes abbreviated with the denotation N⁵-methyl-THF, is the predominant circulating form of reduced folates in mammals....There exists an increasing interest for the application of this natural metabolite as at least one active compound in a therapeutical agent, *for example as vitamin in folate deficiency states*. Therapeutical agents, containing N⁵-methyl-THF, may also be used for the synergistic exertion of influence of a cancer controlling compound and/or for the reduction of the toxicity of a cancer controlling compound and/or for the protection of human and/or animal cells." Ex. 1012, col. 1, ln. 20-28 (emphasis added).

Even more directly, the Wood patent (Ex. 1018) disclosed that "5-Methyltetrahydrofolate may be used as a dietary supplement." Ex. 1018, col. 5, ln.

17-18. In addition, the Ambrosini reference states: "From the therapeutical point of view, both MTHF and FTHF find an application *in all of the forms of folate-deficiencies*, as general liver protective, and more recently, in antitumor therapies. Ex. 1011, p. 2, ln. 7-8 (emphasis added).

Marazza, Wood and Ambrosini are all directed to substantially chirally pure natural isomers of reduced folates including, *inter alia*, 5-methyl-(6S)-tetrahydrofolic acid. Ex. 1012, col. 3, ln. 31-35; Ex. 1018, col. 2, ln. 28-43; Ex. 1011, p. 4, ln. 50-58.

With respect to Ground Three, claims 11, 13, 14, and 15 of the '040 patent contain the limitation that the increased levels of homocysteine be associated with methylene tetrahydrofolate reductase deficiency, or specifically thermolabile methylene tetrahydrofolate reductase deficiency. Ubbink discloses that this association was known in the prior art, stating: "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine- β -synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." Ex. 1019, p. 50.

Accordingly, one of ordinary skill in the art would be motivated to use 5-methyl-(6S)-tetrahydrofolic acid for the "active metabolite of folate" in Serfontein as disclosed by Marazza, Wood and Ambrosini, as all are directed to the same purpose of providing folate to one in a folate deficient state. One would have a

reasonable expectation of success from the reported suitability of 5-methyl-(6S)-tetrahydrofolic acid for this purpose.

The following claim chart specifies the applicability of the foregoing references:

U.S. Patent No. 6,011,040	Prior Art
Claim 1	
A method of decreasing homocysteine levels in the human body comprising	<p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or <i>a suitable active metabolite of folate</i> or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p>
administering at least one tetrahydrofolate in natural stereoisomeric form to a human subject.	<p>Marazza discloses the use of substantially chirally pure 5-methyl-(6S)-tetrahydrofolic acid as "a vitamin in folate deficiency states." (Ex. 1012, col. 1, ln. 27-28). "Hence, it is a general object of the present invention to provide a simple, cheap and efficient process, by which a mixture of (6RS)-diastereoisomers of a N5-methyl-THF-derivative may be separated into the pure, single (6R) and 6(S) diastereoisomers." (Ex. 1012, col. 3, ln. 31-35).</p> <p>Wood discloses the use of substantially chirally pure 5-methyl-(6S)-tetrahydrofolic acid "as a dietary supplement" (Ex. 1018, col. 5, ln. 17-18). "[T]he present invention provides a process for the preparation of a desired substantially pure (6R or 6S) diastereoisomer of a derivative of tetrahydrofolic acid..." (Ex. 1018, col. 2 ln. 28-32);</p> <p>Ambrosini discloses the therapeutic use of substantially chirally pure 5-methyl-(6S)-tetrahydrofolic acid "in any folate deficient state". (Ex. 1011, p.2, ln. 7-8; Example stating purity at p.4</p>

	<p>ln. 50-58).</p> <p>[Hereafter the above disclosures are identified hereafter as the "Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)"]</p>
Claim 2	
<p>A method of preventing or treating disease associated with increased levels of homocysteine levels in the human body</p>	<p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein further discloses that its method is directed towards preventing or treating diseases associated with increased levels of homocysteine:</p> <p>"Elevated homocysteine levels can be correlated with some of the principle cause of morbidity and mortality in the Western world, the so-called "Western" diseases, including such conditions as myocardial and cerebral infarction. Precocious vascular disease is the main single cause of death accounting for the majority of these deaths. (New Eng J. Med, 314 : 488)"</p> <p>"This condition is often associated with high blood levels of homocysteine (often 200 u mole/l or higher) and the associated clinical defects include the following: -</p> <ol style="list-style-type: none"> 1. Disintegration of the vascular elastic interna due

<p>comprising administering at least one tetrahydrofolate in natural stereoisometric form to a human subject.</p>	<p>to binding of homocysteine to allysine residues of tropoelastin.</p> <p>...</p> <p>6. Progressive premature arteriosclerosis.</p> <p>...</p> <p>8. Pernicious occlusive vascular disease frequently manifested clinically as myocardial infraction, stroke, pulmonary embolism (Am.J.Med.Sc. 1977, <u>273</u>: 120) and peripheral vascular occlusion." (<i>Id.</i>, p. 2, ln. 4-7; 34-54)</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
<p>Claim 3</p>	
<p>A method according to claim 2, wherein the disease is cardiovascular disease.</p>	<p>See claim 2 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein further discloses that its method is directed towards preventing or treating diseases associated with increased levels of homocysteine including cardiovascular disease:</p> <p>"Elevated homocysteine levels can be correlated with some of the principle cause of morbidity and mortality in the Western world, the so-called "Western" diseases, including such conditions as myocardial and cerebral infarction. Precocious</p>

	<p>vascular disease is the main single cause of death accounting for the majority of these deaths. (New Eng J. Med, 314 : 488)"</p> <p>"This condition is often associated with high blood levels of homocysteine (often 200 u mole/l or higher) and the associated clinical defects include the following: -</p> <p>1. Disintegration of the vascular elastic interna due to binding of homocysteine to allysine residues of tropoelastin.</p> <p>...</p> <p>6. Progressive premature artherosclerosis.</p> <p>...</p> <p>8. Pernicious occlusive vascular disease frequently manifested clinically as myocardial infraction, stroke, pulmonary embolism (Am.J.Med.Sc. 1977, <u>273</u>: 120) and peripheral vascular occlusion." (<i>Id.</i>, p. 2, ln. 4-7; 34-54).</p>
Claim 5	
<p>A method according to claim 2, wherein the tetrahydrofolate is 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl(6S)-tetrahydrofolic acid, 5,10-methylene-(6R)tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid, or salts thereof.</p>	<p>See claim 2 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>

Claim 6	
A method according to claim 3, wherein the tetrahydrofolate is 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl (6S)-tetrahydrofolic acid, 5,10-methylene-(6R) tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid, or salts thereof.	<p>See claim 3 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 8	
A method according to claim 2, wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.	<p>See claim 2 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 9	

<p>A method according to claim 3, wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.</p>	<p>See claim 3 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
<p>Claim 11</p>	
<p>A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S) tetrahydrofolic acid, or a salt thereof.</p>	<p>See claim 2 above, incorporated herein.</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50)</p>
<p>Claim 12</p>	
<p>A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S)tetrahydrofolic</p>	<p>See claim 3 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or

acid, or a salt thereof.	<p>a substance which releases folate in vivo;</p> <ul style="list-style-type: none"> - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 13	
<p>A method according to claim 4,</p> <p>(A method of preventing prenatal neural tube deficiencies associated with increased maternal homocysteine levels comprising administering at least one tetrahydrofolate in natural stereoisomeric form to a female human subject.)</p>	<p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein further discloses that "the invention is applicable to the lowering of total homocysteine blood levels if elevated by any known cause, including...pregnancy..." (<i>Id.</i>, p. 4, ln. 43-45).</p>
wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the	<p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019,</p>

tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.	p. 50). Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).
Claim 14	
A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl(6S)-tetrahydrofolic acid, or a salt thereof.	See claim 2 above, incorporated herein. Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising: <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42). Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50). Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).
Claim 15	
A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with	See claim 3 above, incorporated herein. Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical

thermolabile methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl(6S)-tetrahydrofolic acid, or a salt thereof.	<p>conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 19	
A method according to claim 5, wherein the tetrahydrofolate is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.	<p>See claim 5 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are pharmaceutically compatible active substances. (See, e.g., claims 20 and 22 of the '040 patent)</p>
Claim 20	

<p>A method according to claim 19, wherein the pharmaceutically compatible active substance comprises at least one B-vitamin.</p>	<p>See claim 19 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are B-vitamins.</p>
<p>Claim 21</p>	
<p>A method according to claim 11, wherein the tetrahydrofolate is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.</p>	<p>See claim 11 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are pharmaceutically compatible active substances.</p>
<p>Claim 22</p>	
<p>A method according to claim 21, wherein the pharmaceutically compatible active substance comprises at least one B-vitamin.</p>	<p>See claim 21 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p>

	<ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42). Vitamins B6 and B12 are B-vitamins.

F. Grounds Four and Five: Obviousness over Serfontein in view of Ueland in further view of Marazza and in further view of Ubbink

Ueland discloses that increasing intercellular levels of the natural isomer of 5-methyltetrahydrofolate was believed to be responsible for folate's ability to lower homocysteine levels.

"It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." Ex. 1013, p. 489, col. 2.

As discussed *supra*, Marazza, Wood and Ambrosini disclosed the suitability of 5-methyl-(6S)-tetrahydrofolic acid for folate supplementation (Section V.E.). With respect to Ground 5, claims 11, 13, 14, and 15 of the '040 patent contain the limitation that the increased levels of homocysteine be associated with methylene tetrahydrofolate reductase deficiency or thermolabile methylene tetrahydrofolate reductase deficiency. As discussed *supra*, Ubbink discloses that this association was known in the prior art.

Accordingly, one of ordinary skill in the art would have been motivated to choose 5-methyl-(6S)-tetrahydrofolic acid as the "active metabolite of folate" in Serfontein's preparations so as to directly provide the metabolite believed to be responsible for lowering blood homocysteine levels, with a reasonable expectation of success provided by Marazza, Wood and Ambrosini's disclosure of the suitability of 5-methyl-(6S)-tetrahydrofolic acid for providing folate.

U.S. Patent No. 6,011,040	Prior Art
Claim 1	
A method of decreasing homocysteine levels in the human body comprising	<p>Serfontein (European Patent Application No. 0595005) discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or <i>a suitable active metabolite of folate</i> or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p>
administering at least one tetrahydrofolate in natural stereoisomeric form to a human subject.	<p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p. 489).</p> <p>Marazza discloses the use of substantially chirally pure 5-methyl-(6S)-tetrahydrofolic acid as "a vitamin in folate deficiency states." (col. 1, ln. 27-28). "Hence, it is a general object of the present invention to provide a simple, cheap and efficient process, by which a mixture of (6RS)-</p>

	<p>diastereoisomers of a N5-methyl-THF-derivative may be separated into the pure, single (6R) and 6(S) diastereoisomers." (col. 3, ln. 31-35). Wood discloses the use of substantially chirally pure 5-methyl-(6S)-tetrahydrofolic acid "as a dietary supplement" (col. 5, ln. 17-18). "[T]he present invention provides a process for the preparation of a desired substantially pure (6R or 6S) diastereoisomer of a derivative of tetrahydrofolic acid..." (col. 2 ln. 28-32); Ambrosini discloses the therapeutic use of substantially chirally pure 5-methyl-(6S)-tetrahydrofolic acid "in any folate deficient state". (p.2, ln. 7-8; Example stating purity at p.4 ln. 50-58).</p> <p>[Hereafter the above disclosures are identified hereafter as the "Marazza/Wood/Ambrosini Disclosure (see Claim 1; Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)"]</p>
Claim 2	
<p>A method of preventing or treating disease associated with increased levels of homocysteine levels in the human body</p>	<p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Serfontein further discloses that its method is directed towards preventing or treating diseases associated with increased levels of homocysteine:</p> <p>"Elevated homocysteine levels can be correlated with some of the principle cause of morbidity and</p>

<p>comprising administering at least one tetrahydrofolate in natural stereoisometric form to a human subject.</p>	<p>mortality in the Western world, the so-called "Western" diseases, including such conditions as myocardial and cerebral infarction. Precocious vascular disease is the main single cause of death accounting for the majority of these deaths. (New Eng J. Med, 314 : 488)"</p> <p>"This condition is often associated with high blood levels of homocysteine (often 200 u mole/l or higher) and the associated clinical defects include the following: -</p> <ol style="list-style-type: none"> 1. Disintegration of the vascular elastic interna due to binding of homocysteine to allysine residues of tropoelastin. ... 6. Progressive premature artherosclerosis. ... 8. Pernicious occlusive vascular disease frequently manifested clinically as myocardial infraction, stroke, pulmonary embolism (Am.J.Med.Sc. 1977, <u>273</u>: 120) and peripheral vascular occlusion." (<i>Id.</i>, p. 2, ln. 4-7; 34-54). <p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p .489).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 3	
A method according to	See claim 2 above, incorporated herein.

<p>claim 2, wherein the disease is cardiovascular disease.</p>	<p>Serfontein discloses that its method is directed towards preventing or treating diseases associated with increased levels of homocysteine including cardiovascular disease:</p> <p>"Elevated homocysteine levels can be correlated with some of the principle cause of morbidity and mortality in the Western world, the so-called "Western" diseases, including such conditions as myocardial and cerebral infarction. Precocious vascular disease is the main single cause of death accounting for the majority of these deaths. (New Eng J. Med, 314 : 488)"</p> <p>"This condition is often associated with high blood levels of homocysteine (often 200 u mole/l or higher) and the associated clinical defects include the following: -</p> <ol style="list-style-type: none"> 1. Disintegration of the vascular elastic interna due to binding of homocysteine to allysine residues of tropoelastin. ... 6. Progressive premature arteriosclerosis. ... 8. Pernicious occlusive vascular disease frequently manifested clinically as myocardial infraction, stroke, pulmonary embolism (Am.J.Med.Sc. 1977, <u>273</u>: 120) and peripheral vascular occlusion." (Ex. 1009, p.2, ln. 4-7; 34-54).
<p>Claim 5</p>	
<p>A method according to claim 2, wherein the tetrahydrofolate is 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl(6S)-tetrahydrofolic acid, 5,10-methylene-</p>	<p>See claim 2 above, incorporated herein.</p> <p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has</p>

(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid, or salts thereof.	<p>been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p. 489).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 6	
A method according to claim 3, wherein the tetrahydrofolate is 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl (6S)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid, or salts thereof.	<p>See claim 3 above, incorporated herein.</p> <p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p. 489).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 8	
A method according to claim 2, wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.	<p>See claim 2 above, incorporated herein.</p> <p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p. 489).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35;</p>

	Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).
Claim 9	
A method according to claim 3, wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.	<p>See claim 3 above, incorporated herein.</p> <p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p .489).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 11	
A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S) tetrahydrofolic acid, or a salt thereof.	<p>See claim 2 above, incorporated herein.</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50)</p> <p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p.489)</p>

	Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).
Claim 12	
A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S)tetrahydrofolic acid, or a salt thereof.	<p>See claim 3 above, incorporated herein.</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p. 489).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 13	
A method according to claim 4, (A method of preventing prenatal neural tube deficiencies associated with increased maternal	Serfontein discloses that "the invention is applicable to the lowering of total homocysteine blood levels if elevated by any known cause, including...pregnancy..." (Ex. 1009, p. 4, ln. 43-45).

homocysteine levels comprising administering at least one tetrahydrofolate in natural stereoisomeric form to a female human subject.)	
wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.	<p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p. 489).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 14	
A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl(6S)-tetrahydrofolic acid, or a salt thereof.	<p>See claim 2 above, incorporated herein.</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50)</p> <p>Ueland discloses "It is conceivable that folic acid</p>

	<p>administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p. 489)</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 15	
<p>A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl(6S)-tetrahydrofolic acid, or a salt thereof.</p>	<p>See claim 3 above, incorporated herein.</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Ueland discloses "It is conceivable that folic acid administration may increase the intracellular pool of 5-methyltetrahydrofolate which in turn may serve as a methyl-donor in the methionine synthase reaction. Increased 5-methyltetrahydrofolate has been suggested to enhance this transmethylation reaction by so called "mass action effect." (Ex. 1013, p. 489).</p> <p>Marazza/Wood/Ambrosini Disclosure (see Claim 1, (Ex. 1012, col. 1, ln. 27-28 and col. 3, ln. 31-35; Ex. 1018, col. 5, ln. 17-18 and col. 2, ln. 28-32; Ex. 1011, p. 2, ln. 7-8 and p. 4, ln. 50-58)).</p>
Claim 19	
A method according to	See claim 5 above, incorporated herein.

claim 5, wherein the tetrahydrofolate is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.	<p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are pharmaceutically compatible active substances. (See, e.g, claims 20 and 22 of the '040 patent)</p>
Claim 20	
A method according to claim 19, wherein the pharmaceutically compatible active substance comprises at least one B-vitamin.	<p>See claim 19 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are B-vitamins.</p>
Claim 21	
A method according to claim 11, wherein the tetrahydrofolate is administered in combination with at least one pharmaceutically compatible active	<p>See claim 11 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p>

substance or at least one pharmaceutically compatible adjuvant substance.	<ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42). Vitamins B6 and B12 are pharmaceutically compatible active substances.
Claim 22	
A method according to claim 21, wherein the pharmaceutically compatible active substance comprises at least one B-vitamin.	See claim 21 above, incorporated herein. Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising: <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42). Vitamins B6 and B12 are B-vitamins.

G. Grounds Six and Seven: Obviousness over Serfontein in view of Scott (or Leeming or Barford) and Lucock or Marazza and in further view of Ubbink

The '040 patent is directed to decreasing homocysteine levels for both male and female subjects: the claims contain no limitation by gender. The prior art discloses that women who are either pregnant or planning to become pregnant should avoid folic acid supplementation due to the neurotoxicity of unmetabolized

folic acid. Tetrahydrofolates, and 5-methyltetrahydrofolate (5-MTHF) in particular, were suggested as a substitute for folic acid for such subjects.

Scott discloses the use of 5-MTHF instead of folic acid when administering folate for the prevention of neural tube defects in order to avoid exposing the mother and fetus to unmetabolized folic acid, considered to be a neurotoxin. Ex. 1014, p. 505. Leeming echoed Scott's concern about exposure to unmetabolized folic acid causing "damaging effects" and contrasted folic acid to "the major natural folate 5-methyltetrahydrofolic acid." Ex. 1015, p. 895. Barford similarly concluded that "it would be prudent to avoid any problems that may be caused by folic acid by using a reduced folate such as calcium leucovorin. Ex. 1016.

The Scott disclosure is particularly relevant to Claim 13, which is directed to "preventing prenatal neural tube deficiencies associated with increased maternal homocysteine levels." However, the same dangers presented by unmetabolized folic acid would exist for an expectant mother being treated for cardiovascular disease or any other condition.

Racemic 5-MTHF such as that identified in Scott contains both the natural "6S" stereoisomer and the unnatural "6R" isomer, thus providing the natural stereoisomer as required by the claims of the '040 patent. In addition, the Federal Circuit has held that "purifying the 5(S) stereoisomer from a mixture in which it is the active ingredient" is obvious without the need for any additional teaching.

Aventis Pharma Deutschland GMBH et al. v. Lupin, Ltd. et al., 499 F.3d 1293, 1301 (Fed. Cir. 2007).

Here, the unnatural "6R" isomer in racemic 5-MTHF was considered inert or even harmful, establishing a clear preference for the natural isomer 5-methyl-(6S)-tetrahydrofolic acid. For example, Lucock, in commenting on Scott, warned of the unknown and possible negative consequences of the unnatural isomer. Ex. 1017, pp. 894-95 (Lucock mistakenly identifies the unnatural isomer as "6S," but it is clear that the natural isomer is the one that is recommended). Marazza discloses the preferred use of the natural 6(S)-5-MTHF isomer to address folate deficiency states because it was assumed that the unnatural 6(R)-5-MTHF was inert, was excreted in an unchanged form, and also might interfere with the folate transport system through cell membranes in humans. Ex. 1012, col. 2, ln. 8-20.

With respect to Ground Seven, claims 11, 13, 14, and 15 of the '040 patent contain the limitation that the increased levels of homocysteine be associated with methylene tetrahydrofolate reductase deficiency or thermolabile methylene tetrahydrofolate reductase deficiency. Ubbink discloses that this association was known in the prior art, stating: "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine- β -synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." Ex. 1019, p. 50.

Accordingly, one of ordinary skill in the art would have been motivated to use 5-methyl-(6S)-tetrahydofolic acid as the active metabolite of folate in the preparations disclosed by Serfontein when treating an expectant mother to lower homocysteine levels so as to avoid the neurotoxicity dangers identified by Scott, Leeming and Barford. One would have had a reasonable expectation of success because both Serfontein and Scott (and Leeming and Barford) are directed towards the same purpose of supplying folate to expectant mothers.

The following chart shows an element by element comparison of the claims of the '040 patent and the references discussed above:

U.S. Patent No. 6,011,040	Prior Art
Claim 1	
A method of decreasing homocysteine levels in the human body comprising	<p>Serfontein (European Patent Application No. 0595005) discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or <i>a suitable active metabolite of folate</i> or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p>
administering at least one tetrahydrofolate in natural stereoisomeric form to a human subject.	<p>Scott discloses avoiding the risk of exposing a fetus and expectant mother to unmetabolized folic acid by administering 5-MTHF, which includes the natural isomer, 5-methyl-(6S)-tetrahydofolic acid, instead of folic acid. (Ex. 1014, p. 505)</p> <p>Leeming discloses administering 5-methyltetrahydrofolic acid to a human mother's dietary intake of folate instead of folic acid to avoid</p>

	<p>exposure to unmetabolized folic acid. (Ex. 1015, p. 895)</p> <p>Barford discloses administering reduced folates to a human mother's dietary intake of folate instead of folic acid to avoid exposure to unmetabolized folic acid. (Ex. 1016, p.1793).</p> <p>and</p> <p>Lucock discloses increasing a human mother's dietary intake of folate by administering to the mother, the natural isomer of 5-MTHF (Ex. 1017, p. 895, first full paragraph).</p> <p>Marazza (U.S. Patent No. 5,194,611) discloses the preferred use of the natural 6(S)-5-MTHF isomer to address folate deficiency states versus 5-MTHF because it was assumed that the unnatural 6(R)-5-MTHF was inert, was excreted in an unchanged form and could interfere with the folate transport system through cell membranes in humans. (Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)</p> <p>[Due to the repetitious nature of many of the claims at issue, hereafter, the above disclosures are identified hereafter as the</p> <p>"Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793)." and the "Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1, (Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32))."</p>
Claim 2	
A method of preventing or treating disease associated with increased levels of homocysteine levels in the	Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a

	Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1, (Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)).
Claim 3	See claim 2 above, incorporated herein.
A method according to claim 2, wherein the disease is cardiovascular disease.	<p>Serfontein discloses that its method is directed towards preventing or treating diseases associated with increased levels of homocysteine including cardiovascular disease:</p> <p>"Elevated homocysteine levels can be correlated with some of the principle cause of morbidity and mortality in the Western world, the so-called "Western" diseases, including such conditions as myocardial and cerebral infarction. Precocious vascular disease is the main single cause of death accounting for the majority of these deaths. (New Eng J. Med, 314 : 488)"</p> <p>"This condition is often associated with high blood levels of homocysteine (often 200 u mole/l or higher) and the associated clinical defects include the following: -</p> <ol style="list-style-type: none"> 1. Disintegration of the vascular elastic interna due to binding of homocysteine to allysine residues of tropoelastin. ... 6. Progressive premature arteriosclerosis. ... 8. Pernicious occlusive vascular disease frequently manifested clinically as myocardial infraction, stroke, pulmonary embolism (Am.J.Med.Sc. 1977, <u>273</u>: 120) and peripheral vascular occlusion." (<i>Id.</i>, p. 2, ln. 4-7; 34-54).
Claim 5	
A method according to claim 2, wherein the	See claim 2 above, incorporated herein.

<p>tetrahydrofolate is 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl(6S)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid, or salts thereof.</p>	<p>Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793).</p> <p>Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1, (Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)).</p>
Claim 6	
<p>A method according to claim 3, wherein the tetrahydrofolate is 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl (6S)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid, or salts thereof.</p>	<p>See claim 3 above, incorporated herein.</p> <p>Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793).</p> <p>Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1, (Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)).</p>
Claim 8	
<p>A method according to claim 2, wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.</p>	<p>See claim 2 above, incorporated herein.</p> <p>Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793).</p> <p>Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1,</p>

	(Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)).
Claim 9	
A method according to claim 3, wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.	<p>See claim 3 above, incorporated herein.</p> <p>Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793).</p> <p>Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1, (Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)).</p>
Claim 11	
A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S) tetrahydrofolic acid, or a salt thereof.	<p>See claim 2 above, incorporated herein.</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793).</p> <p>Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1, (Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)).</p>
Claim 12	
A method according to claim 3, wherein increased levels of homocysteine in	<p>See claim 3 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels</p>

<p>the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S)tetrahydrofolic acid, or a salt thereof.</p>	<p>of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793).</p> <p>Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1, (Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)).</p>
Claim 13	
<p>A method according to claim 4,</p> <p>(A method of preventing prenatal neural tube deficiencies associated with increased maternal homocysteine levels comprising administering at least one tetrahydrofolate</p>	<p>Serfontein discloses that "the invention is applicable to the lowering of total homocysteine blood levels if elevated by any known cause, including...pregnancy..." (p.4, ln. 43-45).</p>

in natural stereoisomeric form to a female human subject.)	
wherein increased levels of homocysteine in the human body are associated with methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.	<p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793).</p> <p>It is further noted that Scott, Leeming and Barford are specifically directed to the prevention of neural tube defects. <i>Id.</i></p> <p>Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1, (Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)).</p>
Claim 14	
A method according to claim 2, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl(6S)-tetrahydrofolic acid, or a salt thereof.	<p>See claim 2 above, incorporated herein.</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793).</p> <p>Lucock/Marazza Disclosure re: preference for</p>

	natural stereoisomer of 5-MTHF (see Claim 1; Ex. 1017 at p. 895 first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32).
Claim 15	
A method according to claim 3, wherein increased levels of homocysteine in the human body are associated with thermolabile methylene tetrahydrofolate reductase deficiency and wherein the tetrahydrofolate is 5-methyl(6S)-tetrahydrofolic acid, or a salt thereof.	<p>See claim 3 above, incorporated herein.</p> <p>Ubbink discloses "[t]he reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, i.e., cystathionine-β-synthase deficiency (17, 18, 38) or possession of a thermolabile variant of methylenetetrahydrofolate reductase...." (Ex. 1019, p. 50).</p> <p>Scott/Leeming/Barford Disclosure re: 5-MTHF (see Claim 1; Ex. 1014, p. 505; Ex. 1015, p. 895; Ex. 1016, p. 1793).</p> <p>Lucock/Marazza Disclosure re: preference for natural stereoisomer of 5-MTHF (see Claim 1, (Ex. 1017, p. 895, first full paragraph; Ex. 1012, col. 1, ln. 25-28; col. 2, ln. 3-32)).</p>
Claim 19	
A method according to claim 5, wherein the tetrahydrofolate is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.	<p>See claim 5 above, incorporated herein.</p> <p>Serfontein (European Patent Application No. 0595005) discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are pharmaceutically</p>

	compatible active substances. (See, e.g, claims 20 and 22 of the '040 patent)
Claim 20	
A method according to claim 19, wherein the pharmaceutically compatible active substance comprises at least one B-vitamin.	<p>See claim 19 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are B-vitamins.</p>
Claim 21	
A method according to claim 11, wherein the tetrahydrofolate is administered in combination with at least one pharmaceutically compatible active substance or at least one pharmaceutically compatible adjuvant substance.	<p>See claim 11 above, incorporated herein.</p> <p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are pharmaceutically compatible active substances.</p>
Claim 22	
A method according to claim 21, wherein the	See claim 21 above, incorporated herein.

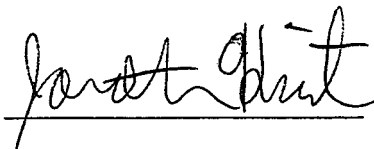
pharmaceutically compatible active substance comprises at least one B-vitamin.	<p>Serfontein discloses a method for lowering levels of homocysteine, or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith by providing a patient with a composition comprising:</p> <ul style="list-style-type: none"> - Vitamin B6; - folate or a suitable active metabolite of folate or a substance which releases folate in vivo; - Vitamin B12, with or without intrinsic factor. <p>(Ex. 1009, p. 4, ln. 37-42).</p> <p>Vitamins B6 and B12 are B-vitamins.</p>

VI. CONCLUSION

In view of the foregoing, Petitioners submit that based upon the prior art presented herein, there has been a showing with a substantial likelihood of success that each of the challenged claims of the '040 patent are invalid under 35 U.S.C. §102 and §103. Accordingly, Petitioners respectfully request that the Board grant this Petition for *inter partes* review and find the claims of the '040 patent are invalid.

Respectfully submitted,

Dated: January 23, 2013

By: 

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **Petition for Inter Partes Review** was served on January 23, 2013, via Express Mail to the correspondence address for the attorney of record for Merck & Cie, the assignee of the '040 patent as recorded on Reel 027464 at Frame 0046 on December 29, 2011:

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Dated: January 23, 2013

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