

PETITIONERS' DEMONSTRATIVE EXHIBITS

Gnosis v. Merck & Cie, IPR 2013-00117
Gnosis Exhibit No. 1148

Serfontein, Ex. 1009, p. 18, Claim 1

Claims

1. The use in the manufacture of a pharmaceutical preparation for lowering levels of homocysteine or for the prophylaxis or treatment of elevated levels of homocysteine or of clinical conditions associated therewith in a patient of a combination comprising
 - a) vitamin B6;
 - b) folate or a suitable active metabolite of folate or a substance which releases folate in vivo;
 - c) vitamin B12, with or without intrinsic factor.

IPR Petition, Paper 2, pp. 10-11

Claim 2	<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;
	<ul style="list-style-type: none"> - Vitamin B12, with or without intrinsic factor. (Ex. 1009, p. 4, ln. 37-42). <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 arteriosclerosis. ... 8. Pernicious occlusive vascular disease frequently manifested clinically as myocardial infraction, stroke, pulmonary embolism (Am.J.Med.Sc. 1977, 273: 120) and peripheral vascular occlusion." <p>(<i>Id.</i>, p.2, ln. 4-7; 34-54)</p>

IPR Petition, Paper 2, p. 11, Claim 2 (continued)

comprising administering
at least one tetrahydrofolate
in natural stereoisometric
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. (*Id.*, p. 4, ln. 37-42; Miller Decl, Ex. 1005 at ¶21).

'040 Patent, Ex. 1004, Claim 8

8. A method according to claim 2, wherein the tetrahydrofolate is 5-methyl-(6S)-tetrahydrofolic acid, or a salt thereof.

Board Decision to Institute, Paper 12, pp. 8-9

Dr. Miller states that the phrase “active metabolite of folate” as used in Serfontein is “a phrase one of ordinary skill in the art would recognize to constitute a genus of no more than eight compounds.” Miller Decl. ¶ 10. To support his statement, Dr. Miller refers to the textbook *Modern Nutrition in Health and Disease*, 7th Ed. (1988), which, according to Dr. Miller, describes “the biochemistry and metabolism of the active metabolites of folic acid . . . within the text and in Figure 21-4.” *Id.* at ¶ 18. Chapter 21 of *Modern Nutrition* is reproduced as Exhibit 1007. The paragraph bridging the columns on p. 391 of Ex. 1007 identifies eight compounds, not including variants resulting from glutamylation, as those that are “normally found . . . in foods or in the human body in significant concentrations”:

- (1) 7,8-dihydrofolate (“DHF”);
- (2) 5,6,7,8-tetrahydrofolate (“THF”);

and six “one carbon adduct[]” forms of THF, listed in Figure 21-3 (Ex. 2007, p. 392):

- (3) N⁵formyl tetrahydrofolic acid (“THFA”);
- (4) N¹⁰formyl THFA,
- (5) N⁵formimino THFA,
- (6) N^{5,10}methenyl THFA,
- (7) N^{5,10}methylene THFA, and
- (8) N⁵methyl THFA.

Board Decision to Institute, Paper 12, pp. 9-10

Fig. 21-4 in *Modern Nutrition* illustrates how each of these eight compounds participates in a human folate metabolism pathway. Ex. 1007, p. 399. *Modern Nutrition* does not address the stereo-specificity of the tetrahydrofolates, but Dr. Miller notes that it does refer (p. 391) to an IUPAC nomenclature recommendation (submitted as Exhibit 1008), which identifies the “natural” folates as those having the same 6-carbon configuration as (6*S*)-tetrahydrofolate. Miller Decl. ¶ 18. From this disclosure, Dr. Miller concludes that one of ordinary skill in the art would have recognized “active metabolites of folate” as embracing “no more than” DHF and the naturally-occurring stereoisomers (i.e., those having the L-configuration at carbon 6) of the other seven compounds listed above. Miller Decl. ¶¶ 19-20.

Board Decision to Institute, Paper 12, p. 15

1. Overview of Marazza

Marazza (Ex. 1012) describes methods for the chiral resolution of 5-methyl-THF into its (6*R*) and (6*S*) diastereomers. Marazza, col. 1, ll. 12-16. Marazza specifically identifies 5-methyl-(6*S*)-THF, i.e., [II] 5-methyl-(6*S*)-tetrahydrofolic acid recited in claims 5, 6, 8, 9, and 11-15, as a “natural metabolite” of folate that may be used “as at least one active compound” in a vitamin therapy for folate deficiency. *Id.* at ll. 21-28, 55-67. Marazza cites a number of earlier studies expressing concern that the unnatural (6*R*) diastereomer of 5-methyl-THF interferes with folate uptake in mammalian cells. Col. 2, ll. 15-32. Marazza therefore seeks improved methods for separating the (6*R*) and (6*S*) diastereomers from one another, and describes a method that employs fractional crystallization of ammonium salts of the diastereomers. *Id.* at col. 3, ll. 32-40. In this regard, Marazza states that it provides “a simple, cheap and efficient process, by which a mixture of (6*RS*)-diastereoisomers of a N⁵-methyl-THF-derivative may be separated into the pure, single (6*R*) and (6*S*)-diastereoisomers.” *Id.* at ll. 32-36.

Marazza, Exhibit 1012, Col. 1, ln. 25-28, Col. 2, ln. 8-33

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, con-

There exists no agreement about the function of the (6R)-diastereoisomer of N⁵-methyl-THF. It has been assumed, that the unnatural (6R)-diastereoisomer of N⁵-methyl-THF is inert and is excreted as such in an unchanged form; see, for example, D. G. Weir et al., "The Absorption of the Disastereoisomers of N⁵-methyl-THF in Man: A Carrier-Mediated Process." *Clinical Science and Molecular Medicine* (1973) 45, 625. But there has also been postulated, that the unnatural (6R)-diastereoisomer could interfere to the folate transport system through the cell membranes of mammals, including humans; see, for example, Chello P. L. et al., "Further Studies of Stereospecificity at Carbon 6 for Membrane Transport of Tetrahydrofolates". *Biochem. Pharmacol.* (1982) 31, 1527; White J. C. et al., "Lack of Stereospecificity at Carbon 6 of N⁵-methyl-THF Transport in Ehrlich Ascite Tumor Cells." *Journal of Biol. Chem.* (1978) 253, 242-245; and White J. C. and I. D. Goldman, "Lack of Stereospecificity at Carbon 6 of N⁵-methyl-THF Transport: Possible Relevance to Rescue Regimens with Methotrexate and Leucovorin." *Chemistry and Biology of Pteridines* (Kisliuk/Brown eds./1979), 625.

Board Decision to Institute, Paper 12, p. 17

C. Obviousness of claims 11, 12, 14, 15, 21, and 22 over Serfontein, Marazza, and Ubbink

1. Overview of Ubbink

Ubbink (Ex. 1019) presents a study assessing vitamin B₁₂, vitamin B₆ and “folate nutritional status” in men with hyperhomocysteinemia. Ubbink, p. 47, Title and Abstract. Ubbink states that “[n]umerous studies have indicated that elevated plasma homocysteine concentrations are associated with increased risk for premature occlusive vascular disease.” *Id.* at p. 50, 2nd col. Ubbink further teaches that the “reasons for hyperhomocysteinemia may be varied; it may be due to enzyme polymorphisms and variants, [i.e.,] cystathionine- β -synthase deficiency or possession of a thermolabile variant of methylenetetrahydrofolate reductase [], an enzyme required in the remethylation of homocysteine to methionine.” *Id.* (citation omitted).

Re: Prior Art “As A Whole”

Zittoun and Cooper, Ex. 1029, p. 195, 4th ¶

Howard examined vitamin requirements in six patients under total parenteral nutrition at home [16]. The doses of folinic acid used (5 mg intravenously twice a week = 1.4 mg/24 h) appeared to be adequate for maintaining serum levels at normal values. The study was, however, very short (limited to 3 days after injection).

Zittoun and Cooper, Ex. 1029, pp. 195-196

In our own work in 105 patients admitted to a general intensive care unit, we assessed on folic acid status the effect of the administration of folinic acid at various doses and with two dosage schemes: 5mg/24 h intravenously for 7 days in sequence, or 50 mg given in single intravenous dose at the start of the trial. We found that a daily injection of 5 mg of folinic acid always normalized serum and erythrocyte levels of folate, whereas a single dose of 50 mg did not regularly correct folate levels when measured on the 8th day, at least in patients who were initially deficient. Like the majority of authors, we found that pre-existing hypo-

Zittoun and Cooper, Ex. 1029, p. 208

copies of the gene. At least three cases have been described which have been presumed to be deficient in DHFR [56–59]. These children were 0–6 weeks old and had megaloblastic anemia with better response to folinic than to folic acid.

Re: Prior Art “As A Whole” (continued):

Godfrey , Exhibit 1024, p. 392, first ¶ and p. 394, last ¶

41 (33%) of 123 patients with acute psychiatric disorders (DSM III diagnosis of major depression or schizophrenia) had borderline or definite folate deficiency (red-cell folate below 200 µg/l) and took part in a double-blind, placebo-controlled trial of methylfolate, 15 mg daily, for 6 months in addition to standard psychotropic treatment. Among both depressed and schizophrenic patients methylfolate significantly improved clinical and social recovery. The differences in outcome scores

We thank Bioresearch, Milan, for supplies of methylfolate.

Zittoun and Cooper, Ex. 1029, p. 210

transmitter deficiency, and this can be treated with BH₄. Many BH₄-deficient patients have had low folate levels [5] and have improved clinically when treated with folinic acid. As indicated above, defects in BH₄-

Re: Prior Art “As A Whole” (continued):

Scott, Ex. 1014, p. 505

We suggest an increased risk apart from that from a high level of circulating folate. The normal daily median intake of dietary folate for British women is 209 μg .¹ At these levels the various forms of dietary folate are converted, during their passage through the intestine and liver, to the single circulating form of 5-methyltetrahydrofolate (5-MTHF).² This process is easily saturated and at higher levels of synthetic folic acid progressively more of it appears unmetabolised in the urine.³ After an oral dose of 500 μg a small but detectable level of unmetabolised folic acid appears in the urine but at levels of 4000 μg urinary folic acid amounts to more than one-quarter of the dose administered.^{3,4} This excess has to pass through the systemic circulation to get from the gut to the kidney. Thus a developing embryo would probably be exposed to unmetabolised folic acid—a form of the vitamin which it would not normally encounter. Folic acid is a neurotoxin⁵ and convulsant⁶ in laboratory animals. Although the blood/brain barrier normally restricts access of folic acid so that very high doses are required to produce these effects, similar toxicity occurs at much lower doses if the blood/brain barrier is damaged.⁷ In epilepsy,

Re: Prior Art “As A Whole” (continued):

Pattini et al., Ex. 1077, pp. 296, 305

Group A was treated for 60 days with oral sodium ferric gluconate 230 mg/day. Group B received the same treatment as Group A, plus 50 mg/day of 5-methyltetrahydrofolic acid (5-MTHF) orally during the first 30 days. Group C received 50 mg/day of oral 5-MTHF for the first 30 days and every second day for the following 30 days. Fasting blood samples were taken prior to

In conclusion, our study showed that a significant percentage of iron-depleted subjects is found among top-trained cross-country skiers, in particular during the period of hard agonistic activity. In such athletes, supplementation with high doses of iron and 5-MTHF seems to be more effective than iron alone in improving the haematological parameters related to iron status and erythropoiesis.

Furthermore, the administration of high dosage 5-MTHF may also improve haemoglobin levels in iron-repleted subjects.

Re: Prior Art “As A Whole” (continued):

LeGrazie, Ex. 1010, pp. 1

⑤ This invention relates to the use of 5-methyltetrahydrofolic acid, 5-formyltetrahydrofolic acid and their pharmaceutically acceptable salts in the preparation of pharmaceutical compositions in controlled-release form which are active in the therapy of organic mental disturbances and in particular in the treatment of senile and presenile primary degenerative dementia of Alzheimer type and multiinfarctual dementia, and to the pharmaceutical compositions concerned.

* * *

In the present text, for greater clarity and simplicity, the expression 5-methyltetrahydrofolic acid and the initials MTHF refer to compounds having the following complete chemical denomination: (±)-L-5-methyl-5,6,7,8-tetrahydrofolic acid and (-)-L-5-methyl-5,6,7,8-tetrahydrofolic acid and their salts, whereas the expression 5-formyltetrahydrofolic acid and the initials FTHF refer to compounds having the following

BIOAVAILABILITY:

Gregory, Ex. 1028, p. 1148

1148

GREGORY

TABLE 1

Apparent bioavailability of various monoglutamyl folates in humans:
summary of published data*

Folate	Response criterion	Apparent bioavailability†
% relative to folic acid		
(6S)-H ₄ folate	Urine folate	105 (1)
(6S)-5-methyl-H ₄ folate	Urine folate	121 (1)
(6S)-5-formyl-H ₄ foalte	Urine folate	70 (1)
(6-ambo)-5-formyl-H ₄ folate	Serum folate	101 (23)
(6-ambo)-5-methyl-H ₄ folate	Serum folate	135 (23)
(6-ambo)-H ₄ folate	Serum folate	40 (23)
(6-ambo)-10-formyl-H ₄ folate	Serum folate	159 (23)
(6-ambo)-5,10-methenyl-H ₄ folate	Serum folate	150 (23)
(6-ambo)-H ₄ folate	Urine folate	120 (24)
(6-ambo)-5-formyl-H ₄ folate	Urine folate	179 (24)
(6-ambo)-5-methyl-H ₄ folate	Urine folate	218 (24)
(6-ambo)-H ₄ folate	Serum folate	26 (24)
(6-ambo)-5-formyl-H ₄ folate	Serum folate	59 (24)
(6-ambo)-5-methyl-H ₄ folate	Serum folate	78 (24)

* H₄folate, tetrahydrofolate; 6-ambo signifies the racemic form of tetrahydrofolate.

† Expressed as a percentage of the observed response to tested folate (biologically active 6S isomer) relative to the response to the folic acid control. References cited in parentheses.

SUBSTRATE ACTIVITY:

Chicowicz, Ex. 1080, p. 515

Table VI: Folate Compounds as Substrates for Folylpolylglutamate Synthetase^a

substrate	relative activity			
	10 μ M	50 μ M	100 μ M	1 mM
H ₂ Pte ^b	3.1	11	<i>c</i>	24
PteGlu	5.7	17	33	47
H ₂ PteGlu	128	122	83	22
(6 <i>RS</i>)-H ₄ PteGlu	62	100	89	33
(6 <i>RS</i>)-5-methyl-H ₄ PteGlu	10	36	<i>c</i>	61
(6 <i>RS</i>)-5-formyl-H ₄ PteGlu	0.8	5.3	<i>c</i>	61
(6 <i>RS</i>)-5,10-methylene-H ₄ PteGlu	10	38	<i>c</i>	36
(6 <i>RS</i>)-10-formyl-H ₄ PteGlu	18	29	<i>c</i>	13
PteGlu ₂	<i>c</i>	45	116	120
PteGlu ₃	<i>c</i>	<i>c</i>	52	80
PteGlu ₄	<i>c</i>	<i>c</i>	4.4	5.7
PteGlu ₅	<i>c</i>	<i>c</i>	0.3	1.0
PteGlu ₆	<i>c</i>	<i>c</i>	0	0.5
PteGlu ₇	<i>c</i>	<i>c</i>	0.2	0.6
H ₂ PteGlu ₂	<i>c</i>	55	47	<i>c</i>
H ₂ PteGlu ₅	0.4	<i>c</i>	0.4	0.4
(6 <i>RS</i>)-H ₄ PteGlu ₂	86	127	139	127
(6 <i>RS</i>)-H ₄ PteGlu ₃	39	56	63	65
(6 <i>RS</i>)-H ₄ PteGlu ₅	3.4	1.4	1.7	1.7
(6 <i>RS</i>)-H ₄ PteGlu ₇	2.6	1.8	0.4	0.9

^a The assay mixture was as described under Experimental Procedures and contained 5 mM ATP and 250 μ M L-[¹⁴C]glutamate. Folate substrates were added at 10, 50, 100, and 1000 μ M, as indicated. Activities are expressed relative to that obtained with (6*RS*)-H₄PteGlu (50 μ M) as substrate. ^b Activity due to <0.2% contamination with H₂PteGlu. ^c Not determined.

UNREGULATED AMOUNTS:

Barford, Ex. 1016, p. 1793

We therefore feel that it is time that the practice of giving folic acid, particularly in large doses, is reviewed. A dose of 4 mg of folic acid would have some inhibitory effect on dihydrofolate reductase.

Additionally, folic acid has been shown to inhibit dihydropteridine reductase² a key enzyme in neurotransmitter biosynthesis. This enzyme is missing in some forms of atypical phenylketonuria,³ with very serious results. The action of folic acid on the developing fetus could therefore be similar to that of aminopterin, a potent inhibitor of dihydrofolate reductase and dihydropteridine reductase, and preparations which contain trimethoprim, which also inhibits these reductases.²

We would like to suggest 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.

Scott, Ex. 1014, p. 505

After an oral dose of 500 µg a small but detectable level of unmetabolised folic acid appears in the urine but at levels of 4000 µg urinary folic acid amounts to more than one-quarter of the dose administered.³⁴ This excess has to pass through the systemic circulation to get from the gut to the kidney. Thus a developing embryo would probably be exposed to unmetabolised folic acid—a form of the vitamin which it would not normally encounter. Folic acid is a neurotoxin⁵ and convulsant⁶ in laboratory animals.

STABILITY:

Reggev (1986), Ex. 1023, p. 251

A
new and stable preparation of MTHF has become available for clinical trials (Bio-Research, Milan, Italy).

Godfrey (1991), Ex. 1024, p. 392, first ¶ and p. 394, last ¶

41 (33%) of 123 patients with acute psychiatric disorders (DSM III diagnosis of major depression or schizophrenia) had borderline or definite folate deficiency (red-cell folate below 200 µg/l) and took part in a double-blind, placebo-controlled trial of methylfolate, 15 mg daily, for 6 months in addition to standard psychotropic treatment. Among both depressed and schizophrenic patients methylfolate significantly improved clinical and social recovery. The differences in outcome scores

We thank Bioresearch, Milan, for supplies of methylfolate.

STABILITY (continued):

Muller (1991), Ex. 1029, Col. 1, ln. 5-18

The invention relates to a process for the preparation of 5,10-methenyl-(6R)-tetrahydrofolic acid [5,10-CH-(6R)-THF; “(6R)-I”], of biologically active tetrahydrofolates, especially of 5-formyl-[5-CHO-(6S)-THF] and 5-methyl-(6S)-tetrahydrofolic acid [5-Me-(6S)-THF] as well as of the salts thereof, especially the physiologically well tolerated calcium, magnesium, sodium and potassium salts thereof.

The said (6S)-tetrahydrofolates [(6S)-5,6,7,8-tetrahydropteroyl-L-glutamates] are the sufficiently stable natural biologically active forms of folic acid (folic acid cofactors).

LONG FELT NEED:

Godfrey, Ex. 1024, p. 392

41 (33%) of 123 patients with acute psychiatric disorders (DSM III diagnosis of major depression or schizophrenia) had borderline or definite folate deficiency (red-cell folate below 200 µg/l) and took part in a double-blind, placebo-controlled trial of methylfolate, 15 mg daily, for 6 months in addition to standard psychotropic treatment. Among both depressed and schizophrenic patients methylfolate significantly improved clinical and social recovery. The differences in outcome scores

In this study we used the methyl derivative of folate for treatment as it is this form which is actively transported across the blood-brain barrier and which is detectable in the cerebrospinal fluid in concentrations three times greater than in serum.^{12,13}

LONG FELT NEED (Continued):

Guaraldi, Ex. 1053, p. 104

In summary, this open-label pilot study showed a markedly significant reduction in depressive symptoms in a sample of depressed elderly patients treated with MTHF 50 mg per day. If our findings were to be confirmed by double-blind, placebo-controlled studies, the antidepressant efficacy of this compound may present several advantages. MTHF, being a naturally occurring molecule, could enhance patient acceptance of antidepressant treatment and be safe in overdose. In addition, the relative absence of side effects could make this compound particularly helpful in treating depressive disorders in elderly populations that are often undertreated because of concerns about potentially serious side effects (e.g., cardiac toxicity, orthostatic hypotension, and drug-drug interactions) of standard antidepressants.

LONG FELT NEED (Continued):

DiPalma, Ex. 1054, p. 565

However, the clinical results reported in our study appear to support our hypothesis that methylfolate (30 mg TID) has a positive effect on depressive signs and symptoms in alcoholics. Our preliminary results should be verified in controlled trials.

LONG FELT NEED (Continued):

Ex. 2162

DEPLIN® 7.5mg Tablets
DEPLIN® 15mg Caplets

DEPLIN® is indicated for the distinct nutritional requirements of individuals who have suboptimal L-methylfolate levels in the cerebrospinal fluid, plasma, and/or red blood cells and have major depressive disorder (MDD) with particular emphasis as adjunctive support for individuals who are on an antidepressant.²⁻⁵

REFERENCES

1. United States Food and Drug Administration Title 21 Code of Federal Regulations (8).
2. Godfrey PSA et al. The Lancet. 1990;336:392-5.
3. Passeri M et al. Aging Clin Exp Res. 1993;5(1):63-71.
4. Guaraldi GP et al. 1993;5(2):101-5.
5. Di Palma C et al. Is Curr Ther Res. 1994;55(5):559-68.

COMMERCIAL SUCCESS - NEXUS:

METANX®

Ex. 2078

PATENTS

Some or all of the following patents may apply:

U.S. Patent No. 5,997,915
U.S. Patent No. 6,011,040
U.S. Patent No. 6,254,904
U.S. Patent No. 6,441,168B1
U.S. Patent No. 6,673,381
U.S. Patent No. 7,172,778
U.S. Patent No. 7,674,490

NEEVODHA®

Ex. 2080

Patents

Some or all of the following patents may apply:

U.S. Patent No. 5,407,957	U.S. Patent No. 6,441,168B1
U.S. Patent No. 5,492,938	U.S. Patent No. 6,451,360
U.S. Patent No. 5,563,126	U.S. Patent No. 6,673,381
U.S. Patent No. 5,795,873	U.S. Patent No. 7,163,811
U.S. Patent No. 6,011,040	U.S. Patent No. 7,172,778
U.S. Patent No. 6,254,904	U.S. Patent No. 7,674,490
U.S. Patent No. 6,297,224	and other pending patent applications

NÉEVO® Caplets

Ex. 2079

Patents

Some or all of the following patents may apply:

U.S. Patent No. 6,207,651	U.S. Patent No. 5,563,126
U.S. Patent No. 6,254,904	U.S. Patent No. 5,795,873
U.S. Patent No. 6,297,224	U.S. Patent No. 5,997,915
U.S. Patent No. 6,528,496	U.S. Patent No. 6,011,040

and other pending patent applications.

DEPLIN® 7.5mg Tablets
DEPLIN® 15mg Caplets

Ex. 2162

PATENTS

Some or all of the following patents may apply:

U.S. Patent No. 6,011,040
U.S. Patent No. 6,441,168B1
and other pending patent applications

COMMERCIAL SUCCESS – NEXUS:

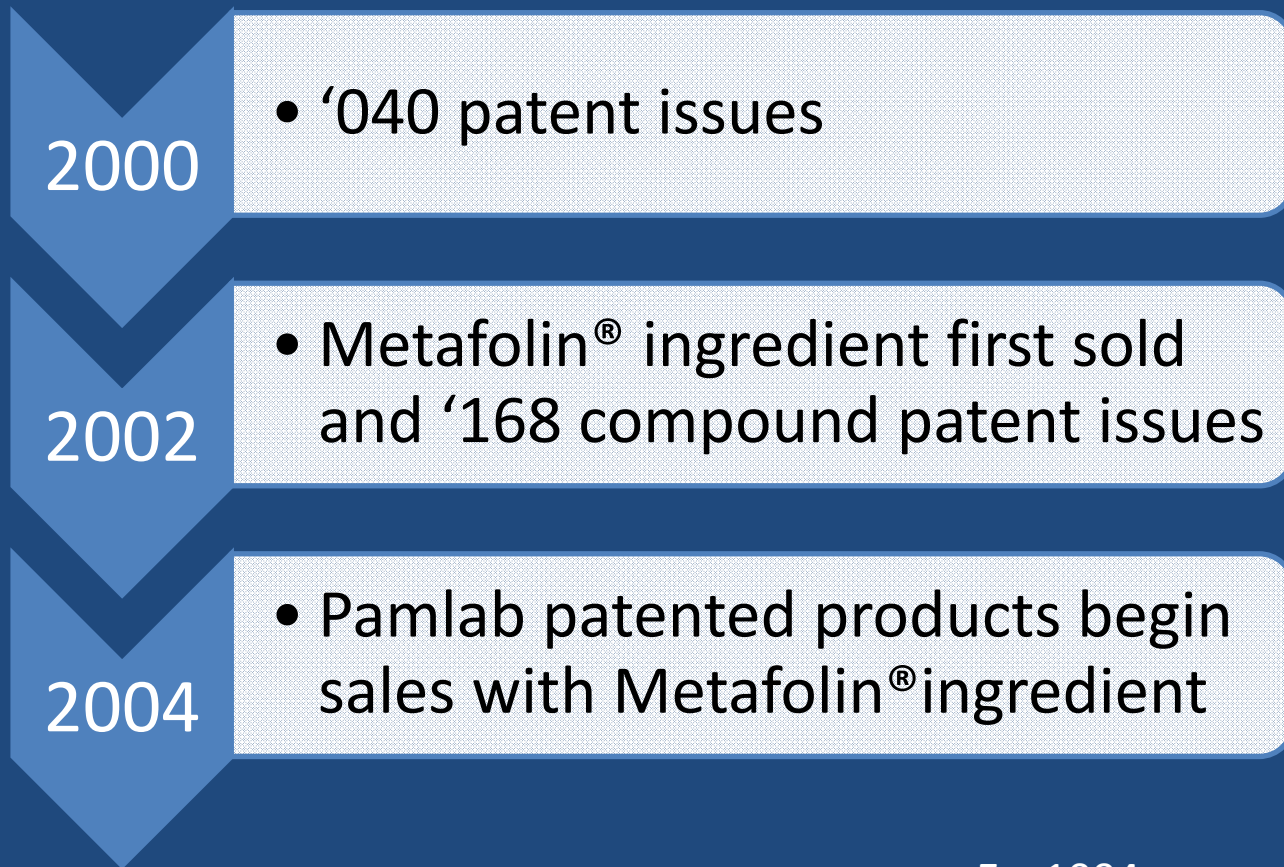
Merck and SAMSF Complaint (E.D. Tex.), Ex. 1102

60. Neevo DHA®, METANX®, Cerefolin NAC® and DEPLIN® are covered by one or more claims of the '915, '904, '381, '778, '490 and/or '040 patents.

Pamlab Complaint (E.D. La.), Ex. 1103

27. In the mid-1990's, Merck & Cie (formerly known as Merck Eprova AG) ("Merck") made a key breakthrough, and invented a process to synthesize L-methylfolate in a stable form. Offered under the name Metafolin® (METAFOLIN), L-methylfolate calcium¹ is the crystalline, stable and diastereoisomerically pure form of folate directly usable by cells in the body.

COMMERCIAL SUCCESS - NEXUS



Ex. 1004
Ex. 2015, ¶12
Ex. 2311, ¶ 65-72

COMMERCIAL SUCCESS - NEXUS:

Katz Declaration, Ex. 2015, par. 13

13. I consider Metafolin® to be a successful product, because Metafolin® offers unique biological benefits as it is a substantially pure, stable, active form of folate. As I noted earlier, it is one of the most important products in Merck & Cie's portfolio because it is such a key component of our customers' products.

Frost & Sullivan, Ex. 2182

Stability issues have deterred the use of natural folates in many applications. However, Merck Eprova AG has made significant advancements in this field, with the introduction of Metafolin®. Metafolin® provides a stable, naturally occurring predominant form of folate

COMMERCIAL SUCCESS– NEXUS:

'168 patent (2002), Ex. 1044, Col. 1, ln. 1-10, 44-49

STABLE CRYSTALLINE SALTS OF 5-METHYLTETRAHYDROFOLIC ACID

FIELD OF THE INVENTION

This invention relates to crystalline salts of N-[4-[(2-amino-1,4,5,6,7,8hexahydro-4-oxo-5-methyl-(6S)-, -(6R)- and -(6R,S)-pteridinyl)methyl]amino]benzoyl-L-glutamic acid (hereinafter called salts of 5-methyltetrahydrofolic acid), to the use thereof, and to a method of producing them.

Accordingly, it has not been possible hitherto to identify a commercially feasible method which is suitable for the production of salts of 5-methyltetrahydrofolic acid which are satisfactorily stable and which are of high purity.

UNEXPECTED RESULTS

Marazza, Ex. 1012, Col. 2, ln. 9-20

(6R)-diastereoisomer of N⁵-methyl-THF. It has been assumed, that the unnatural (6R)-diastereoisomer of N⁵-methyl-THF is inert and is excreted as such in an unchanged form; see, for example, D. G. Weir et al., "The Absorption of the Diastereoisomers of N⁵-methyl-THF in Man: A Carrier-Mediated Process." *Clinical Science and Molecular Medicine* (1973) 45, 625. But there has also been postulated, that the unnatural (6R)-diastereoisomer could interfere to the folate transport system through the cell membranes of mammals, including humans; see, for example, Chello P. L. et al., "Further

Zittoun and Cooper, Ex. 1029, p. 200

In some other cells, the concentration of folic acid required to generate adequate concentrations of intracellular folates is 100–200 times that of reduced folates such as 5-methyl tetrahydrofolate (THF) and 5-formyl THF (folinic acid) [9].

INDUSTRY PRAISE:

Ex. 2182, Frost & Sullivan

2006

Product Differentiation Innovation Award

o Natural and Stable Product

Stability issues have deterred the use of natural folates in many applications. However, Merck Eprova AG has made significant advancements in this field, with the introduction of Metafolin®. Metafolin® provides a stable, naturally occurring predominant form of folate

LICENSING:

Stipulation, Ex. 2311, par. 12 (public version)

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INDUSTRY SKEPTICISM:

Godfrey, Ex. 1024, p. 393, Table IV

TABLE IV—SERUM AND RED-CELL FOLATE AND SERUM VITAMIN B₁₂ CONCENTRATIONS

	Mean (SD)		
	Baseline	3 mo	6 mo
<i>Serum folate (μg/l)</i>			
Placebo	5.3 (3.2)	8.7 (5.4)	7.2 (5.3)
Methylfolate	6.5 (4.5)	> 18.0	> 18.0
<i>Red-cell folate (μg/l)</i>			
Placebo	143 (45)	226 (116)	271 (148)
Methylfolate	150 (45)	> 800	> 800
<i>Serum vitamin B₁₂ (ng/l)</i>			
Placebo	388 (171)	344 (119)	333 (132)
Methylfolate	322 (130)	301 (128)	347 (142)

Pattini, Ex. 1077, pp. 296

Group A was treated for 60 days with oral sodium ferric gluconate 230 mg/day. Group B received the same treatment as Group A, plus 50 mg/day of 5-methyltetrahydrofolic acid (5-MTHF) orally during the first 30 days. Group C received 50 mg/day of oral 5-MTHF for the first 30 days and every second day for the following 30 days. Fasting blood samples were taken prior to supplementation, after 15, 30 and 60 days of therapy, and on the 15th day after treatment withdrawal.

INDUSTRY SKEPTICISM (continued):

LeGrazie, Ex. 1010, p. 3

The purpose of this trial was to verify the therapeutic effects of prolonged administration of controlled-release MTHF compared with the administration of MTHF not in controlled-release form and of a placebo to elderly subjects affected by organic mental disturbances with depression of mood in accordance with the definitions given in DSM-III-R. This was a multi-centre perspective randomized trial of double-blind controlled type. The trial was carried out in 7 centres, each of which involved 30 patients giving a total of 210 patients. The patients were divided randomly into three sub-groups, these receiving MTHF in controlled-release form, MTHF not in controlled-release form and placebo respectively.

Passeri, Ex. 1052, p. 63

ABSTRACT. 5'-Methyltetrahydrofolic acid (5'-MTHF) in addition to standard psychotropic medication significantly improved clinical recovery in depressed patients with borderline or definite folate deficiency, and significantly reduced depressive symptoms in elderly normofolatemc patients after 3 weeks of treatment. In this equivalence study the effect of 5'-MTHF on depressive symptoms and cognitive status was compared to Trazodone (TRZ) in normofolatemc elderly patients with mild to moderate dementia and depression.