Claim Chart for the Petition for Inter Partes Review of U.S. Patent No. 7,772,209

Ground 1: Claims 1–22 of U.S. Patent No. 7,772,209 are obvious over *Rusthoven* in view of *EP 005* and the knowledge of a POSA.

Element	Prior Art
1pre[1]**.** A method for administering pemetrexed disodium to a patient in need thereof comprising	*Rusthoven* discloses a phase II study with pemetrexed disodium: Ex. 1011 at 1194 ("Multitargeted Antifolate LY231514 [pemetrexed disodium] as First-Line Chemotherapy for Patients with Advanced Non-Small-Cell Lung Cancer: A Phase II Study."); *Id.* ("Eligible patients … initially received MTA 600 mg/m^2 intravenously (IV) for 10 minutes every 3 weeks."). Ex. 1024, Bleyer Decl. ¶ 106.
a) administering an effective amount of folic acid and	*EP 005* teaches administering an effective amount of folic acid: Ex. 1010 (*Passim*). For example, *id.* at Cover ("Pharmaceutical preparations for lowering blood and tissue levels of homocysteine are disclosed, comprising: … b) folate or a suitable active metabolite of folate or a substance which releases folate in vivo...."); *Id.* at 4 ("[A] pharmaceutical preparation for lowering levels of homocysteine or for the prophylaxis or treatment of elevated levels of homocysteine in a patient of a combination which comprises … b) folate or a suitable active metabolite of folate or a substance which releases folate in vivo...."); *Id.* at 19 ("A pharmaceutical preparation which comprises in combination, each in a concentration and form effective to suppress homocysteine levels in plasma … b) folate or a suitable active metabolite of folate or a substance which releases folate in vivo…."). Ex. 1024, Bleyer Decl. ¶¶ 107–09.

[1] Claim 1 is divided into elements for ease of explanation.

b) an effective amount of a methylmalonic acid lowering agent followed by	*EP 005* teaches administering an effective amount of vitamin B12 (methylmalonic acid lowering agent): Ex. 1010 (*Passim*). For example, *id.* at Cover ("Pharmaceutical preparations for lowering blood and tissue levels of homocysteine are disclosed, comprising: … c) vitamin B12...."); *Id.* at 5, 19 ("[T]he preparation is formulated to make available to the patient … an effective dosage of the vitamin B12 in less than 1 hour after administration."); *Id.* at 6 ("the vitamin B12 … to be galenically formulated for the preparation to release an effective dosage…."); *Id.* at 19 ("A pharmaceutical preparation which comprises in combination, each in a concentration and form effective to suppress homocysteine levels in plasma … c) vitamin B12…."). Ex. 1024, Bleyer Decl. ¶¶ 111–18.
c) administering an effective amount of pemetrexed disodium, wherein	*Rusthoven* discloses administering an effective amount of pemetrexed disodium: Ex. 1011 at 1194 ("Eligible patients … initially received MTA [pemetrexed disodium] 600 mg/m^2 intravenously (IV) for 10 minutes every 3 weeks."). Ex. 1024, Bleyer Decl. ¶ 106.
d) the methylmalonic acid lowering agent is selected from the group consisting of vitamin B12, hydroxycobalamin, cyano–10–chlorocobalamin, aquocobalamin perchlorate, aquo–10–cobalamin perchlorate, azidocobalamin,	*EP 005* teaches that methylmalonic acid lowering agent (vitamin B12) is selected from cyanocobalamin or hydroxycobalamin: Ex. 1010 (*Passim*). For example, *id.* at 6 ("Vitamin B12 may be used in the form of cyanocobalamin or hydroxycabalamin or both…."); *Id.* at 12 ("The tablets containing vitamin B12 (20 µg cyanocobalamine) only were formulated as immediate release tablets…."); *Id.* at 13 ("Invention "B": prepared as described in Example 3, however, with the following changes in composition: cyanocobalamin 400 µg, folic acid 1 mg.");

cobalamin, cyanocobalamin, or chlorocobalamin.	*Id.* at 16 ("One dosage unit of injectable solution contains 1000 µg hydroxycobalamin, 1100 µg folic acid and 5,0 mg pyridoxine, dissolved in saline for intramuscular injection."); *Id.* at 20 ("[V]itamin B12 is used in the form of cyanocobalamin or hydroxycobalamin or both.…"); Ex. 1024, Bleyer Decl. ¶¶ 111–18.
2. The method of claim 1, wherein the methylmalonic acid lowering agent is vitamin B12.	*EP 005* teaches vitamin B12 (methylmalonic acid lowering agent): Ex. 1010 (*Passim*). For example, *id.* at 2 ("[P]harmaceutical preparations for lowering levels of homocysteine or for the prophylaxis or for treatment of elevated levels of homocysteine in patients and for counteracting the harmful effects associated with homocysteine contain … vitamin B12."); *Id.* ("Three pathways exist by means of which blood and tissue levels of homocysteine are controlled to ensure homocysteine homeostasis: … 2. Remethylation to methionine which requires folate (as substrate) and vitamin B12 as co-factor …."); *Id.* at 3 ("[I]t is known that … vitamin B12 and folate play a role in regulating the methionine - homocysteine pathway and controlling levels of homocysteine.…"). Ex. 1024, Bleyer Decl. ¶¶ 111–18, 139.
3. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 500 µg to about 1500 µg.	*EP 005* teaches administering various dosages of vitamin B12 by intramuscular injection: Ex. 1010 at 2 ("[P]harmaceutical preparations for lowering levels of homocysteine or for the prophylaxis or for treatment of elevated levels of homocysteine in patients and for counteracting the harmful effects associated with homocysteine."); *Id.* at 5, 19 ("The preparation may be galenically formulated for parenteral administration, preferably by infusion or by intramuscular injection.");

Id. ("The preparations in accordance with the invention are formulated to provide approximate daily dosages as follows (µg/d/kg body weight).

	a) Vitamin B6	b) Folic Acid	c) Vitamin B12
Broadest range	15-750	1,5-150	1,5-75
preferred range	30-400	7,5-50	3-15
more preferred range	75-250	10-30	7-10
typical example	150	15	7,5

These dosages may be exceeded somewhat for short durations, e.g. at the beginning of the treatment.");

Id. at 8 ("The following quantities refer to one daily dose for an adult patient of approximately 70kg body weight. (PL=pyridoxal; Fol=folate; B12=Vitamin B12) Quantities are given in milligrams per day.")

Formulation type	PL		Folate		B12	
	Range mg	Preferred mg	Range mg	Preferred mg	Range mg	Preferred mg
Normal (no absorption problem)	2-5	5	0,2-15	1,0	0.1-2	0.5
Special (to overcome absorption problems)	2-50	5	2-15	5	0.2-5	1,0

;

Id. at 9 ("a pharmaceutical formulation comprising … folic acid and vitamin B12 … is provided for as illustrated in the following table:-

	<table><tr><th>Compound</th><th>Range (mg)</th><th>Preferred (mg)</th><th>For Example (mg)</th></tr><tr><td>B6, preferably as</td><td></td><td></td><td></td></tr><tr><td>Pyridoxal</td><td>2-50</td><td>5-15</td><td>5,0</td></tr><tr><td>Folate</td><td>0,2-15</td><td>0,5-3</td><td>1,0</td></tr><tr><td>Vitamin B12</td><td>0,2-5</td><td>0,5-1,5</td><td>0,5</td></tr><tr><td>Anti-oxidants</td><td></td><td></td><td></td></tr><tr><td>ß-carotene</td><td>1-12</td><td>5-15</td><td>7,0</td></tr><tr><td>d-α-tocopherol acetate</td><td>10-1000</td><td>50-700</td><td>500</td></tr><tr><td>Ascorbic acid</td><td>30-1000</td><td>100-700</td><td>500</td></tr><tr><td>Coenzyme Q10</td><td>10-100</td><td>15-50</td><td>20</td></tr></table> ; *Id.* at 16 ("One dosage unit of injectable solution contains 1000 µg hydroxycobalamin … dissolved in saline for intramuscular injection."). Ex. 1024, Bleyer Decl. ¶¶ 125–28, 141.
4. The method of claim 2, wherein the vitamin B12 is administered as an intramuscular injection of about 1000 µg.	*See supra* Claim 3.
5. The method of claim 2, 3 or 4, wherein the vitamin B12 administration is repeated about every 6 to about every 12 weeks following the administration of vitamin B12 until the administration	*EP 005* discloses time programmed dosage regimen for vitamin B12 administration: Ex. 1010 at 19 ("[T]he preparation is formulated to make available to the patient … an effective dosage of the vitamin B12…."); *Id.* at 5 ("The preparation may be galenically formulated for parenteral administration, preferably by infusion or by intramuscular injection. The latter form inherently provides for a retarded availability of the ingredients….");

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