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 *Niyikiza* in view of the'*974 Patent* and in further 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	*Niyikiza* discloses administration of pemetrexed disodium to a patient in need thereof: Ex. 1008 at 126 ("The purpose of this study was to assess the relationship of vitamin metabolites, drug exposure, and other prespecified baseline patient characteristics to toxicity following treatment with MTA [pemetrexed disodium]."); *Id.* at 126–27 ("Homocysteine (Hcys), cystathionine and methylmalonic acid were measured in 139 phase II patients with tumors of the colon, breast, pancreas, and esophagus at baseline and once each cycle thereafter. Stepwise regression modeling, multivariate analysis of variance, and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity after one course of MTA. … Toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels (> 10μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA.").
a) administering an effective amount of folic acid and	The '*974 Patent* teaches administering an effective amount of folic acid: Ex. 1009 at 1:46–53 ("We have now discovered that the toxic effects of ... related GAR-transformylase inhibitors [e.g., pemetrexed] and other antifolate agents which bind to folate binding protein (FBP) ... can be significantly reduced by the presence of a FBP binding agent [folic acid], without adversely affecting therapeutic efficacy.").

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

	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. 1025, Bleyer Decl. ¶ 118.
b) an effective amount of a methylmalonic acid lowering agent followed by	*Niyikiza* teaches measuring mehtylmalonic acid levels in patients: Ex. 1008 at 126 ("Homocysteine (Hcys), cystathionine and methylmalonic acid were measured in 139 phase II patients with tumors of the colon, breast, pancreas, and esophagus at baseline and once each cycle thereafter."). *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. 1025, Bleyer Decl. ¶¶ 120–28.
c) administering an effective amount of pemetrexed disodium, wherein	*Niyikiza* discloses administration of pemetrexed disodium to a patient in need thereof: Ex. 1008 at 126 ("The purpose of this study was to assess the relationship of vitamin metabolites, drug exposure, and other prespecified baseline patient characteristics to toxicity following treatment with MTA [pemetrexed disodium]."); *Id.* at 126–27 ("Homocysteine (Hcys), cystathionine and methylmalonic acid were measured in 139 phase II patients with tumors of the colon, breast, pancreas, and esophagus at baseline and once each cycle thereafter. Stepwise regression modeling, multivariate analysis of variance, and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity after one course of MTA. … Toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels (> 10μM) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA.").
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. 1025, Bleyer Decl. ¶¶ 120–28.
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. 1025, Bleyer Decl. ¶¶ 120–28, 149.
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.")

	PL		Folate		B12	
Formulation type	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:-

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