IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXO GROUP LIMITED and SMITHKLINE BEECHAM CORPORATION	)	
Plaintiffs,	)	
v.	)	C.A. No. 02-219 GMS
TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICALS INDUSTRIES, LTD.,	)	
Defendants.	)	

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OPINION

Dated: August 20, 2004
Wilmington, Delaware

SLEET, District Judge

I. INTRODUCTION

The court tried the issues of infringement and validity in a five day trial, commencing November 17, 2003 and ending November 21, 2003. Having considered the documentary evidence and testimony adduced at trial, and upon reviewing the parties' arguments and the relevant case law, the court finds that (1) Teva has not adduced sufficient evidence to show that the patents-in-suit are invalid because they would have been obvious to a person of skill in the art, (2) Teva has not shown, by clear and convincing evidence, that the '789 and '628 patents are invalid due to lack of enablement, and (3) the '789 and '628 patents are not anticipated, inherently or otherwise, by any prior art reference. The reasons for these conclusions will be explained in the following findings of fact and conclusions of law made pursuant to Federal Rule of Civil Procedure 52(a).

II. FINDINGS OF FACT

A. Procedural History

1. Plaintiff Glaxo Group Limited ("Glaxo") is an English Company having a registered office at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 ONN, Middlesex, England. Plaintiff SmithKline Beecham Corporation is a Pennsylvania corporation having a principal place of business at One Franklin Plaza, Philadelphia, Pennsylvania, 19102. Plaintiffs collectively hereinafter will be referred to as "GlaxoSmithKline." GlaxoSmitKline is a research-based, multinational pharmaceutical and healthcare company.

2. Defendant Teva Pharmaceuticals USA, Inc. is a Delaware corporation with its principal place of business at 1090 Horsham Road, North Wales, PA 19454-1090. Defendant Teva Pharmaceuticals Industries, Ltd. is an Israeli corporation with its principle place of business at One Hashikma Street, Industrial Area, P.O. Box 353, Kfar-Saba, Israel 44102. Defendants

collectively hereinafter will be referred to as "Teva." Teva is principally engaged in the sale of generic drugs.

3. The patents-in-suit are U.S. Patents Nos. 4,753,789 (issued June 28, 1988, "the '789 patent") and 5,578,628 (issued November 26, 1996, "the '628 patent").[1] GlaxoSmithKline is the record owner of both of the patents-in-suit. The '789 and '628 patents are directed to the synthesis and administration of the molecule known as "ondansetron" to treat and prevent nausea and vomiting.

4. Glaxo presently markets ondansetron in the United states under the product name Zofran.

5. On October 5, 2001, Teva filed application, No. 76-252, under Section 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j) (Teva's "ANDA"), seeking FDA approval to market and sell generic ondansetron hydrochloride tablets prior to the expiration of the '789 and '628 patents.[2]

6. Glaxo thereafter filed this action on March 22, 2002 seeking a finding that the filing of Teva's ANDA constitutes infringement of the '789 and '628 patents and an order that the approval date of Teva's ANDA not be earlier than the expiration dates of the '789 and '628 patents. GlaxoSmithKline also seeks a permanent injunction enjoining Teva (and its officers, agents, servants, employees and privies) from continuing infringement of the '789 and '628 patents.

7. Teva answered GlaxoSmithKline's complaint, alleging invalidity of the '789

[1] The court severed from these proceedings all claims relating to U.S. Patent No. 4,721,720, *see* Order (Nov. 5, 2003) (D.I. 131), and therefore will not discuss them herein.

[2]Glaxo does not specify the expiration date of these patents in its prayer for relief.

and ‘628 patents for obviousness, lack of enablement, and inherent anticipation as its defenses to infringement. It also counterclaimed for a declaratory judgment of non-infringement.

8. On November 5, 2003, the court entered an order construing the claims of the patents-in-suit.

9. On November 17, 2003, the court commenced a five day bench trial on the issues of infringement and validity: specifically, obviousness, lack of enablement, and anticipation.

10. The court held post-trial argument on January 20, 2004.

B. Technology Background

11. Serotonin or 5-hydroxytryptamine (5-HT) has diverse physiological roles–it is a neurotransmitter in the central nervous system (CNS), it regulates smooth muscle function in the cardiovascular and gastrointestinal systems, and it enhances platelet function. Serotonin is found mainly in blood platelets, in enterochromaffin cells in the gastrointestinal tract, and in the CNS. Serotonin is known today to be involved in various functions such as mood, appetite, the perception of pain, the regulation of blood pressure, and vomiting. *See* Peroutka Tr. 125-126, 131-134, 136; Fozard Tr. 452-453; 469; Ex. 490; Ex. 507.

12. The actions of serotonin are mediated through a variety of cell membrane receptors, which, in essence, are recognition sites for the neurotransmitter’s signal. Substances that act as agonists (agents that bind to receptors and elicit a response) and antagonists (agents that prevent neurotransmitters or agonists from binding to the receptor) of 5-HT receptors have proven useful in treating a number of conditions including vomiting and anxiety. Presently, seven 5-HT receptor families have been identified with a number of further subtypes or members.

13. The 5-HT receptor classification system used today categorizes various 5-HT

receptors by the designation "5-HTx." *See* Ex. 248; Ex.490; Ex. 507; Peroutka Tr. 125-126, 141-143.

14. A person of ordinary skill in the art with respect to the patents-in-suit is one with an advanced degree in pharmacology and/or a medical doctor with experience in clinical pharmacology. Fozard Tr. 610-611.

C. 5-HT and Migraine

15. Migraine is a "specific neurological syndrome" that may be defined at its most basic level as " a throbbing (usually unilateral) headache with associated nausea." Peroutka Tr. 1007; Ex. 1449, at p. 487; *see also* Gralla Tr. 903; Tyers Tr. 321.

16. It is presently known that nausea and/or vomiting are the most common nonpainful clinical features of migraine, Ex. 418, and to date, the presence of nausea and vomiting are key criteria for the diagnosis of migraine, Peroutka Tr. 1007-1009; Ex. 1449. With respect to severe migraine attacks, a high percentage, up to 90%, of people suffer from nausea as a symptom. Fewer people with severe migraine, less than 50%, suffer from vomiting. Peroutka Tr. 1011. Other symptoms of migraine include photophobia, ETC.

17. By the late 1970's and early 1980's interest had increased significantly in research into the role of serotonin in the human body. Several pharmaceutical companies, including Glaxo, Beecham, Sandoz and Merrell-Dow, had instituted programs to synthesize selective 5-HT3 receptor agonists and antagonists.

18. At this time, the potential therapeutic application of serotonin agonists and antagonists was still unknown, *see* Peroutka Tr. 135-136, but researchers hypothesized that these compounds might be effective in treating psychological disorders or in managing pain associated

with migraine, *see* Peroutka Tr. 139-140, 142-143; Ex. 490.

19. Beginning, in the early 1970's, Dr. John Fozard became one of the central figures among scientists exploring 5-HT3 receptor antagonism, first in his work at the University of Manchester, England, then later, starting in 1977, with the Merrell-Dow Research Institute in Strasbourg France. Peroutka Tr. 168-69.

20. Throughout the 1970's, Dr. Fozard worked to identify selective antagonists for the 5-HT3 receptor.

21. In an article published in 1977, an Australian doctor indicated that he gave intravenous injections of metoclopramide, a potent drug known as a substituted benzamide, a compound with a phenyl ring and four substitutions around the ring, to four patients suffering from migraine and got complete relief of the symptoms in three out of four patients. Fozard Tr. 469-470; Ex. 1399.

22. Thereafter, in 1978, Dr. Fozard published an article in which he identified the drug metaclopramide as a "selective, surmountable and potent antagonist of 5-HT at the sympathetic neuronal receptor sites." Ex. 1208.

23. By 1978 or 1979, Dr. Fozard had a hypothesis that the pain of migraine arose from activation of 5-HT3 receptors. Fozard Tr. 469.

24. In his work at Merrell, Dr. Fozard identified a new molecule called MDL 72222, which became the first selective neuronal 5-HT receptor antagonist to be published. Peroutka Tr. 169.

25. On May 25, 1982, a United Kingdom patent application directed to Dr. Fozard's work on selective neuronal 5-HT antagonists and disclosing MDL 72222 was filed. Ex. 1209.

26. Dr. Fozard's UK patent application disclosed a preliminary open study of eight patients in which MDL 72222 was tested for its effect on migraine pain and associated symptoms. In two of the eight patients, MDL 7222 was shown to have relieved headache pain as well as nausea and vomiting. However, in one of those two patients, the cause of the headache was unknown. In addition, the application suggests that MDL 72222 be administered with an anti-nauseant. *See* Ex. 1209 at p. 9-11, Table VII.

27. At trial, Dr. Fozard admitted that the UK application for MDL 72222 would not suggest to one skilled in the art that MDL 72222 was an anti-emetic (i.e, an anti-vomiting agent). *See* Fozard Tr. 568-569.

28. After the filing of his UK patent application, Dr. Fozard went on to conduct a second open study of MDL 72222, involving 37 patients. The patients were divided into three categories: moderate headache, severe headache, and very severe headache with vomiting. This trial did not identify the symptoms studied, other than to categorize the patients in the aforementioned manner, nor did it disclose results with respect to any specific symptoms. The study merely indicated that as the dose of MDL 72222 is increased, the response measured increases and results in alleviation of migraine symptoms. Ex. 1221. The trial results disclosed nothing with respect to any ability of MDL 72222 to act as an anti-emetic. Gralla Tr. 874.

29. Following t he second open study, Merrell Dow undertook a full double-blind

placebo-controlled study of MDL 72222 in the symptomatic treatment of migraine.

30. The results of the double-blind placebo study were first disclosed at a meeting of the British Pharmacological Society in April of 1984 and later at a conference on migraine in Paris in August of 1984. Fozard Tr. 476.

31. The results of this study were first published in the book, *Vascular Neuroeffector Mechanisms*, on March 1, 1985, and made available to the public in the United States by the end of May 1985. Ex. 1215. The article discussed serotonin and stated in relevant part that "[i]t seems possible that 5-HT acting through sensory neuronal 5-HT receptors would contribute to the pain of migraine." The passage of the book disclosing the results stated:

> Recently, a compound with considerable potency and selectivity for these [neuronal 5-HT] sites, MDL 72222 . . . has been described and tested as symptomatic treatment for [migraine]. In a double-blind, placebo controlled trial, MDL 72222 was given intravenously to patients undergoing severe or very severe migraine. Doses of 10-20 mg brought .75% relief of symptoms in 15 out of 24 patients, a significantly better result than was obtained with placebo (.75% relief in 5 out of 23 ptients; p=0.007, Fischer exact probability test).

The article nowhere stated what specific symptoms of migraine, other than pain, were relieved. In disclosing that MDL 72222 was tested in symptomatic treatment, Dr. Fozard cited reference 31. Reference 31 is the abstract authored in part by Dr. Tell and Dr. Fozard (hereinafter the "Tell abstract"), which summarizes the results of the controlled study of MDL 72222 relied upon in the article. PTX 422. The Tell abstracts explains that "the severity of the headache was recorded by the investigator as a percent relative to pre-treatment, and by the patients, on a visual analogue scale (extremes = extreme pain v. no pain)."

32. At trial, Dr. Fozard maintained that he disclosed MDL 72222's anti-emetic properties in the following passage from the published article:

> MDL 72222 is not vasoactive, has no analgesic or anti-inflammatory properties and has no dopamine receptor blocking activity which might bestow anti-emetic activity. Moreover, the clinical doses are the

> same as those which in experimental animals are highly selective for afferent neuronal 5-HT receptors. The logical conclusion, is that blockade of these sites leads to symptomatic relief of migraine.

At the time he wrote this passage, Dr. Fozard understood that there were no other known anti-emetics working on the 5-HT pathway. *See* Fozard Tr. 583. He did not take MDL 72222 forward in any studies as an anti-emetic. *See* Fozard Tr. 585.

33. In 1990, Dr. Fozard published an article on 5-HT in migraine in which he wrote that it was still unknown whether or not 5-HT was the underlying mechanism responsible for the nausea and vomiting associated with migraine. Ex. 1222.

34. Migraine has never been a model for the treatment of emesis. Gralla Tr. 849, 857.

D. Knowledge Regarding Anti-Emetics in the 1980's

35. In the early to mid-1980's, researchers focused on neurotransmitters other than 5-HT, namely dopamine, as most likely involved with emesis. *See* Peroutka Tr. 153, 154-156; Ex. 246; Ex. 247. The anti-emetics available at this time, such as metoclopramide, the phenothiazines, and the butyrophenones, were thought to derive their anti-emetic effect from their antagonism or blockade of dopamine receptors in the chemoreceptor trigger zone. *See* Peroutka Tr. 156-157; Fozard Tr. 605; Gralla Tr. 832-833, 834-835, 836-839; Ex. 303. Due to dopamine antagonism, these agents also exhibited severe and undesirable side effects, namely extrapyramidal effects characterized by uncontrolled muscle spasms, which rendered these drugs difficult to use. *See* Gralla Tr. 833-834, 835; Trippett Tr. 1022-1024; Smyth Tr. 384-386; Ex. 304.

36. By the early to mid-1980's, metoclopramide was the most effective anti-emetic available for use at that time.

37. As early as 1978, metoclopramide also was recognized as having weak selectivity at the 5-HT3 receptors.

38. In 1978 Dr. Fozard published studies documenting metoclopramide's selectivity at neuronal 5-HT receptors in the rabbit heart and commenting:

> It remains to be established whether such activity contributes to the unconventional effects of metoclopramide in the CNS, where differences from the classical neuroleptics are observed, or in the gut, where the mechanism of the unique stimulant activity of metoclopramide on propulsive bowel movement is poorly understood.
>
> Ex. 1208.

39. Prior to June 25, 1985, scientists believed that metoclopramide exerted its anti-emetic effect via the dopamine pathway. *See* Peroutka Tr. 151-152, 156-157, 172, 990, 1015; Fozard Tr. 587-588, 605; Gralla Tr. 825-826, 832-833, 839-841, 895-896; Tyers Tr. 232; Gristwood Tr. 808-809; Smyth Tr. 380-382, 384-385; Ex. 246; Ex. 247; Ex. 583, p. 65 Table 3B.

40. In order to exert an anti-emetic effect, metoclopramide had to be given in high doses intravenously, which resulted in a strict and costly dosage schedule that had to be administered on an in-patient basis. This factor, in addition to the severe extrapyramidal side effects, rendered metoclopramide a less than desirable anti-emetic. The extreme side-effects of dopamine antagonists were further exacerbated in children. This prevented the use of more powerful, and more emetogenic, chemotherapy agents. As a result, fewer children were cured. *See* Smyth Tr. 384-385; Gralla Tr. 833-834; Trippett Tr. 1024, 1025-1026; Ex. 302; Ex. 306; Ex. 304.

41. Dazapride, another anti-emetic drug, was initially developed by A.H. Robins as a gastric prokinetic agent. *See* Gristwood Tr. 698-999. It was created to be structurally similar to metoclopramide but without the side effects associated with metoclopramide. Like

metoclopramide, dazopride is in the class of compounds known as substituted benzamides. Both dazopride and metoclopramide have identical substitution at three of the four locations around the benzene ring. *See* Gristwood Tr. 698-702, 811-812.

42. In May of 1985, DuBuois published research on dazopride in which he considered the mechanism of action for the anti-emetic effects of dazopride and concluded that dazopride's mechanism of action was "different from that of anti-emetic agents which block dopamine receptors." Ex. 1261.

43. After concluding that dazopride lacked dopamine activity, researchers concerned with dazopride's mechanism of action next investigated Beta endorphins. *See* Peroutka Tr. 969-971; Ex. 1261.

44. In the early to mid 1980's, there was a great need for a more effective anti-emetic, without side effects characteristic of dopamine agents, particularly to treat emesis resulting from severely toxic cancer treatments. *See* Gralla Tr. 833-834; 895-896; Trippett Tr. 1022-1024; Smyth Tr. 384-386.

45. Ondansetron largely solved the longstanding medical problem of the nausea and vomiting associated with cancer chemotherapy treatments and greatly improved the quality of life for cancer patients. Many times these side effects were so severe that patients, particularly children, would have no other choice but to discontinue chemotherapy treatment. Today, with Zofran, doctors now use more aggressive chemotherapy with confidence that these often prohibitive side effects can be controlled, allowing patients to complete their therapy. *See* Smyth Tr. 379-382, 384-386, 399-400; Gralla Tr. 833-836, 843-844; Trippett Tr. 1022-1024, 1025-1028.

46. From first launch, ondansetron's success far exceeded any expectations, and it has become the most widely prescribed and used drug of its kind. *See* Henely Tr. 1037, 1038-

1039; Ex. 552; Ex. 553.

47. Glaxo has been awarded the Prix Galien (the pharmaceutical industry's equivalent of the Nobel Prize) for ondansetron. *See* Tyers Tr. 270-271; Ex. 351, Ex. 353.

E. Glaxo's Development of Ondansetron

48. Beginning in the late 1970's, like Dr. Fozard at Merrell, Glaxo was researching 5-HT and its relation to migraine as part of its Cardiovascular Project. The goal of the project was to synthesize an S2 (now 5-HT2) agonist, which was believed by Glaxo to mediate vasoconstriction, for treatment of migraine.

49. Scientists from Glaxo, including but not limited to Dr. Michael Tyers, attended conferences at which Dr. Fozard presented his work concerning first the pharmacology of MDL 72222, and the results of later clinical tests administering the compound for the treatment of migraine. Tyers Tr. 315-316, 331.

50. In September of 1983, Glaxo scientists discovered and synthesized the compound ondansetron, a highly selective 5-HT3 antagonist. The chemical name of ondansetron is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-y1)methyl]-4H-carbozol-4-one. *See* Tyers Tr. 228-229; Ex. 91; Ex. 33; Ex. 42.

51. Based on Dr. Fozard's work concerning the role of serotonin in migraine, Glaxo hypothesized that ondansetron might be useful in the treatment of pain and migraine.

52. Ondansetron soon became the lead compound of Glaxo's Cardiovascular Project, and Glaxo began to test the compound in animals.

53. As of early 1984, the toxicology tests carried out in animals showed no adverse side effects of ondansetron. Glaxo thereafter scheduled healthy human volunteer tests to study the safety of ondansetron in humans. The results from the human volunteer studies showed

no adverse effects in doses up to 32mcg/kg. *See* Tyers Tr. 232-234.

54. On January 25, 1984, Glaxo filed a patent application (GB 8401888) in the United Kingdom that disclosed a general chemical formula of compounds that included and specifically disclosed ondansetron. Ex. 1441. This application was not initially disclosed to the public.

55. On November 17, 1986, Glaxo filed a U.S. counterpart application, which eventually matured into the '578 patent, issued on September 22, 1987.

56. The '578 patent explicitly discloses that ondansetron, and other compounds in its class, should be administered in effective amounts to persons suffering from migraine, in order to provide relief from migraine. Tyers Tr. 278-280; Fozard Tr. 512-514; Gralla Tr. 848; Peroutka Tr. 1006; Ex. 574. The '578 patent also teaches that anti-nauseants may need to be used along with ondansetron to treat certain conditions. *See* Ex. 574 (col. 4, ln. 6-21).

57. In January 1985, still believing ondansetron to be effective in migraine treatment, Glaxo organized an uncontrolled, pilot study at a migraine clinic in West Germany to test ondansetron in this capacity. The criteria to be observed after administration of ondansetron were specified by Glaxo and comprised (i) relief of headache, (ii) relief of nausea and vomiting, and (iii) relief of photophobia. Other measurements such as pulse rate and blood pressure and any adverse effects were noted.

58. Although the official results of the pilot study were not published until August of 1985, the initial results were reported to Glaxo in March 1985. These initial results showed no major effects on the patients' headaches but evidenced relief of nausea and vomiting symptoms in certain patients.

59. As a result, Dr. Tyers at this time realized that it could be the 5-HT3

antagonist properties of ondansetron (and similarly for metoclopramide) that were responsible for anti-emetic activity. Thus, he concluded that ondansetron might therefore be useful as an anti-emetic. He postulated that at high doses metoclopramide, after saturating the D2 receptor for which it had a high affinity, acted on the 5-HT3 receptor to prevent emesis, a theory which would explain why metoclopramide had to be administered in such high doses to be effective. *See* Tyers Tr. 253; Ex. 44.

60. Although this hypothesis was initially received with skepticism at Glaxo, Dr. Tyers and his colleagues proceeded to recommend to a senior-level committee that because of the drug's effect on nausea and vomiting, ondansetron should be taken forward and evaluated in patients for anti-emetic activity. The minutes of a meeting at Glaxo held on March 25, 1985 reflect that evaluation of ondansetron on gastric stasis and nausea was a high priority and also indicate that the compound would be evaluated as an anti-emetic. Ex. 39.

61. In April of 1985, Dr. Teresa Challoner of Glaxo was asked to produce a medical development plan for clinical investigation of ondansetron in gastric emptying and anti-emesis. *See* Tyers Tr. 254-255.

62. By May of 1985, Glaxo had obtained evidence in animal tests that ondansetron

possessed gastric emptying properties. *See* Ex. 42 at GSKTEV 008780.

63. On June 21, 1985, Dr. Challoner contacted Professor John Smyth, Chair of the Department of Medical Oncology at the Western General Hospital in Edinburgh, England, by letter. Dr. Challoner disclosed that Glaxo had "a drug undergoing early investigation which increases gastric emptying and which may be anti-emetic." Glaxo sought Professor Smyth's "views on the problem of emesis in patients receiving chemotherapy its assessment and current therapies." Ex.

1179.

F. Glaxo's Patents for the Use of Ondansetron in the Treatment of Nausea and Emesis

64. Based on the initial results of the migraine studies showing relief of nausea and vomiting combined with his knowledge of high dose metoclopramide's effectiveness against chemotherapy induced nausea and emesis, on June 25, 1985, Dr. Tyers, along with his colleagues, filed a United Kingdom patent application, entitled "Heterocylic Compounds." The application stated that it was directed to "a new medical use" for certain tetrahydrocarbazalone derivatives, including ondansetron, "which may be used to promote gastric emptying and as anti-emetics." Ex. 1258.

65. The UK application discloses a group of compounds, namely certain tetrahydrocarbozolone derivatives represented by a general formula and capable of having various combinations. It then identifies a preferred class of compounds among the larger group and also cites a particularly preferred compound, Formula 1b. This is the formulation which now has come to be known as ondansetron. Ex. 1258.

66. On page 1, the application makes reference to metoclopramide as the compound most widely used drug to promote gastric emptying and states that it is also an anti-emetic. It then goes on to mention on page 10 that the compounds may be administered in combination with other therapeutic agents such as cisplatin, a highly emetogenic anti-cancer drug. Ex. 1258.

67. On page 9, the application gives an effective dosage range in a 70 kg human host of 0.05-20 mg, one to four times per day, and then gives a preferable dosage range of 0.1-10 mg, one to four times per day. Ex. 1258.

68. It also lists a toxicity limit of 1 mg per 1 kg in mice on page 6. Ex. 1258.

69. There are eight exemplary dosage forms disclosed in pages 43 through 50 of the application, including 0.50 mg through an inhalation cartridge, .05 mg/800 ml via injection, 2.5 mg of non-sucrose syrup, 2.5 mg of sucrose syrup, 2.5 mg capsules, 2.5 mg sub-lingual tablets, or 2.5 mg conventional tablets. Ex. 1258.

70. On page 3, the application cites examples of animal studies where the disclosed method enhanced gastric emptying. On page 4, it states that results from human patients indicate that the listed class of compounds alleviate the symptoms of nausea. Ex. 1258.

71. After the filing of its UK application, Glaxo continued its discussions with Professor Smyth regarding ondansetron's potential use as an anti-emetic.

72. Specifically, Dr. Challoner met with Professor Smyth at his hospital in Edinburgh on August 12, 1985, to (1) discuss chemotherapy induced emesis and its assessment and (2) find investigators for the anti-emetic activity of ondansetron. Ex. 317.

73. Dr. Smyth suggested to Dr. Challoner and Glaxo that cisplatin-induced vomiting in the ferret would be a useful indicator of ondansetron's potential efficacy as an anti-emetic. He also agreed to sign a confidentiality agreement so that he could review Glaxo's background data on ondansetron. Ex. 317; Ex. 318.

74. In January of 1986, on behalf of Glaxo, the Costall/Naylor group at the University of Bradford carried out investigations to examine the anti-emetic activity of ondansetron against cisplatin-induced vomiting in the ferret. The reports from the studies, issued on April 14, 1986 (Ex. 47) and May 30, 1986 (Ex. 48), respectively, indicate that ondansetron blocked the emetic response to cisplatin. *See* Tyers Tr. 258-259, 262-263; Ex. 47; Ex. 572.

75. Professor Smyth then conducted a series of clinical studies on the efficacy of ondansetron as an anti-emetic in patients being treated with cisplatin. *See* Smyth Tr. 396-397; Ex.

572.

76. It was immediately obvious from the first clinical study that ondansetron was effective in treating the emesis caused by cisplatin. *See* Tyers Tr. 263.

77. Thereafter on June 26, 1986, Glaxo filed U.S. Patent Application No. 06/877,805, directed to the use of ondansetron to treat nausea and emesis. The application claimed priority dating from the June 25, 1985 UK application. This U.S. application matured into the '789 patent which was issued on June 28, 1988.

78. The '789 patent, entitled "Method for Treating Nausea and Vomiting," relates to the use of a class of compounds, which includes ondansetron, "for the relief of nausea and vomiting and/or the promotion of gastric emptying." Ex. 3.

79. The class of disclosed compounds in the '789 patent is represented by the same general formula as disclosed in the UK application. The '789 patent also lists ondansetron as a preferred compound. Ex. 3.

80. The '789 patent specifically claims "a method of treatment for the relief of nausea and vomiting which comprises administering to a human or animal subject in need thereof an effective amount for the relief of nausea and vomiting [the compound known as ondansetron]." Ex. 3.

81. The '789 patent contains the same information as the UK application with several changes and additions. The salient differences between the UK application and the '789 patent center around the '789 patent's more detailed discussion of ondansetron as an anti-emetic, particularly in association with cancer chemotherapy, than the UK application.

82. For example, the '789 patent contains a new section entitled "(B) Anti-Emesis," which discusses the results of Glaxo's ferret studies and lists the doses that were

administered in those studies. It also includes a table of test data from the ferret studies. Ex. 3.

83. Following the filing of the '789 patent, Glaxo conducted the first clinical trials in the United States and eventually submitted a series of Investigational New Drug Applications ("NDA") seeking approval for ondansetron in various forms.

84. The FDA ultimately approved for marketing Glaxo's injectable and tablet formulations of ondansetron. *See* Wood Tr. 97; Henley Tr. 1036.

85. On March 30, 1990, Glaxo filed U.S. Patent Application No. 07/501,974, which was a continuation of U.S. Patent Application No. 07/315,314 and ultimately a division of the '789 patent. This application eventually became the '628 patent. It also derived its priority date from the June 25, 1985 UK application.

86. The '628 patent also relates to the use of ondansetron for the relief of nausea and vomiting.

87. Specifically, the '628 patent claims "a method of treatment of nausea and vomiting which comprises administering to a human or animal subject in need thereof an effective amount for the treatment of nausea and vomiting of [the compound known as ondansetron]." It further claims "a method of treatment of nausea and vomiting induced by an anti-cancer drug which is cisplatin, which comprises administering to a human or animal subject in need thereof an effective amount for the treatment of nausea and vomiting of [the compound known as ondansetron]."

G. Beecham's Interference

88. In April of 1985, Beecham filed a UK patent application disclosing the use of certain compounds, including MDL 72222, for the treatment of cytotoxic-agent induced vomiting. Ex. 1442-B.

89. Glaxo filed its European counterpart application in July 1985. It was then that

the existence of ondansetron was initially revealed. This application matured into the '578 patent, on December 23, 1985. Beecham, another pharmaceutical company researching 5-HT at the time, then claimed the use of ondansetron as an anti-emetic in a UK patent application, and later in a U.S. counterpart filed on March 12, 1986, which eventually resulted in the issuance U.S. Patent No. 4,721,720 (the '720 patent). Ex. 1251. The '720 patent also disclosed that Beecham had successfully tested ondansetron for use in treating chemotherapy induced nausea and vomiting in ferrets.

90. As a result, Glaxo eventually became involved in an interference with Beecham in the early 1990's to determine which party first invented the subject matter of the '628 patent.

91. The issue in the interference was whether Glaxo or Beecham was the first to invent the use of ondansetron to treat nausea and vomiting.

92. In order to defeat Glaxo's claim that its June 25, 1985 UK patent application predated Beecham's invention date, Beecham argued that there were two distinct inventions at issue. First, there was the use of ondansetron to treat nausea and vomiting generally. Second, there was the use of ondansetron to treat nausea and vomiting induced by chemotherapy agents. Beecham asserted that the second use was a "patentably distinct" invention, and noted that Glaxo's 1985 UK application had not disclosed the use of ondansetron to treat nausea and vomiting associated with chemotherapy. Ex. 1442 at 25. Beecham therefore sought to add a second count to the interference, addressed only to chemotherapy induced nausea and vomiting, claiming that it was the first to invent and file for such a use. Ex. 1422.

93. In response, Glaxo argued that there was no "patentable distinction" between a claim to treatment of nausea and vomiting generally, and claims to treat nausea and vomiting induced by a particular cause, including chemotherapy. Glaxo made the following statement in its

response:

> [I]n 1985-1986, the various causes of nausea and vomiting were regarded as being indistinguishable and were not separable. There was no reason to believe that a substance that was effective in the treatment of nausea and vomiting induced by one cause would not be effective in the treatment of nausea and vomiting induced by a different cause . . .
>
> Ex.1251 at 19-20.

94. The PTO ruled in favor of Glaxo on this issue, awarded Glaxo priority over Beecham, and allowed Glaxo's '628 patent to issue. The PTO stated that it agreed with Glaxo "that the invention of proposed count C [ondansetron for nausea and emesis arising from cytotoxic agent induced emesis] would have been prima facie obvious over the invention of count 2 [nausea and emesis from an unspecified cause]." *Wooton v. Tyers*, Final Decision, Patent Interference N. 102,666 (June 9, 1995), at 4-5 (Ex. 1257).

III. CONCLUSIONS OF LAW

The court will first address the issue of obviousness. It will then examine whether Glaxo's UK application sufficiently enabled the claims of the '789 and '628 patents so as to render the June 25, 1985 priority date of those patents valid. Finally, the court will discuss the issue of anticipation, including whether or not Glaxo's '789 and '628 patents were inherently anticipated.

A. Obviousness

Teva contends the '789 and '628 patents are obvious in view of the prior art and therefore invalid. Specifically, it cites the '578 patent and knowledge regarding MDL 72222 and dazopride, and advances that the combination of these references rendered the invention disclosed in the '789 and '628 patents obvious to one of ordinary skill in the art as of the June 25, 1985, or the priority date of the '789 patent.

Whether or not a patent is obvious over the prior art is a question of law. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1479, 1479 (Fed Cir. 1997); *see also Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1384-85 (Fed Cir. 2001). Section 103 provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

35 U.S. § 103. Put simply, an invention is invalid if "the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." *Graham v. John Deere Co.*, 383 U.S. 1, 15 (1966). Obviousness cannot be based on "the hindsight combination of components selectively culled from the prior art to fit the parameters of the invention." *ADT Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed Cir. 1998). The Supreme Court has set forth four factors relevant to determining obviousness: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) other secondary considerations. *Graham*, 383 U.S. at 17-18. Applying the *Graham* factors, and in view of the controlling standards, the court finds that the '789 and '628 patents are not obvious over the prior art references proffered by Teva.

The claimed invention of the '789 patent is a method of treatment for the relief of nausea and vomiting which comprises administering to a human or animal subject in need thereof an effective amount of ondansetron. In contrast, the '578 patent claims the compound ondansetron as a 5-HT3 antagonist and teaches its administration to patients suffering from migraine. Nowhere in the '578 patent does it mention that ondansetron may be used as an anti-emetic or in any way suggest that a 5-HT3 antagonist would provide relief of nausea and emesis. Although nausea and vomiting were

known symptoms of migraine, the testimony of Dr. Fozard and Dr. Gralla makes explicit that a person of ordinary skill in the art on or before June 25, 1985 understood the '578 patent to disclose ondansetron as a 5-HT3 antagonist useful to treat migraine pain, not nausea and vomiting.

Similarly, the published information concerning MDL 72222 at the time also focused on the treatment of migraine pain. Prior to June 25, 1985, MDL 72222 was also known to be a 5-HT3 antagonist. During this time, Dr. Fozard was advancing his theory throughout the international migraine research community that migraine pain functioned through the 5-HT3 pathway. Most relevantly, he discussed his double blind study of MDL 72222 on 47 migraine patients in an article that was made public prior to June 25, 1985. Disclosed in that article are the results of the study discussing the effects of MDL 72222 on the "symptoms of migraine." There is no statement as to which symptoms were actually treated. Again, although the symptoms of migraine were known to include nausea and vomiting, a person of ordinary skill in the art prior to June 25, 1985 would have understood Dr. Fozard's study to be focused on migraine pain. Indeed, the line in which the article mentions symptomatic treatment cites reference 31. Reference 31 is the Tell abstract which states that the severity of the headaches studied in the double-blind test were measured on a visual analog scale, or a scale of extreme *pain* to no *pain*.

The only evidence Teva points to in support of its proposition that Dr. Fozard's double blind study somehow disclosed that MDL 72222 specifically relieved nausea and emesis through its 5-HT3 pathway is the following passage:

> Doses of 10-20 mg brought .75% relief of symptoms in 15 out of 24 patients . . . . MDL 72222 is not vaso active, has no analgesic or anti-inflammatory properties and has no dopamine receptor blocking activity which might bestow anti-emetic activity. . . . The logical conclusion is that blockage of [neuronal 5-HT receptors] leads to symptomatic relief of migraine.

This excerpt does not state what symptoms were being relieved. Moreover, even if the passage did state that it was referring to the symptoms of nausea and vomiting, it nowhere says that the 5-HT3 pathway is responsible for relief of these symptoms. Thus, given the state of the art, it is only hindsight that would support the conclusion that Dr. Fozard's mere elimination of the dopamine pathway as a vehicle for symptomatic relief of migraine would have lead a person of ordinary skill to conclude that blockage of the 5-HT3 receptor achieves an anti-emetic result. Not only does the testimony of Dr. Gralla and Dr. Peroutka unequivocally support such a conclusion, but even Dr. Fozard himself admitted he did not specifically disclose that MDL 72222 as a 5-HT3 antagonist was effective in relieving nausea and vomiting in the above passage or any other article prior to June 25, 1985.

Dr. Fozard's subjective view of his purported disclosure is not only irrelevant but it lacks credibility. The scientific community during the relevant time period thought 5-HT3 to be connected with migraine pain and was closely following Dr. Fozard's work as the leading researcher in the field of 5-HT3 antagonists. Had Dr. Fozard truly discovered and appreciated a completely new property of 5-HT3 receptor sites, as he claims, the court believes he would have disclosed it more clearly than in the cryptic language of the foregoing passage.[3]

Lastly, Teva contends that on or before June 25, 1985, knowledge regarding the compound dazopride rendered obvious the conclusion that 5-HT3 antagonists such as ondansetron produced an anti-emetic effect, and that such an effect would be derived through the 5-HT3 pathway. As substituted benzamides, dazopride and metoclopramide were known during the relevant time period

[3]Also probative of his credibility with respect to this issue, in 1990, five years after the filing date of the '789 and '628 patents, Dr. Fozard published an article in which he stated that it was still unknown whether 5-HT is the underlying mechanism responsible for the nausea and vomiting associated with migraine.

to be structurally similar. According to Teva, because researchers concluded and published before June 25, 1985, that dazopride's anti-emetic activity did not function through a dopamine pathway, which was believed to be the receptor site for anti-emetic activity, it should have been obvious that metoclopramide's anti-emetic effect did not function through the dopamine pathway either. This then would have lead to the conclusion that it was metoclopramide's 5-HT3 pathway that was really responsible for its anti-emetic effect. The knowledge of metoclopramide's true mechanisms, in turn, would have rendered it obvious that 5-HT3 antagonists such as ondansetron would bestow anti-emetic activity through their 5-HT3 pathways and, therefore, be useful as anti-emetics.

Drawing this conclusion from the knowledge about dazopride during the relevant time period requires several leaps, which the court finds would not have been taken by a person of ordinary skill in the art on or before June 25, 1985. Although it is true that dazopride was known prior to June 25, 1985 to have an anti-emetic effect that did not operate through the dopamine pathway, there is simply insufficient evidence to conclude that it would have been obvious to anyone, let alone persons of ordinary skill in the art, that the 5-HT3 pathway was instead responsible for the compound's anti-emetic activity. The references concerning dazopride relied on by Teva do not mention any connection between 5-HT3 receptors and dazopride. They merely conclude that dazopride's mechanism of action is not dopamine. This leaves a vast number of other pathways as possible sites for anti-emetic activity. Dr. Peroutka's testimony at trial amply supports this conclusion. The doctor explained that in 1984, the scientific community researching dazopride thought the next logical step was to distinguish between basal gastric management of solids and liquids and then to investigate Beta endorphins, not 5-HT3, as the drug's possible pathway.

Moreover, even if one of ordinary skill in the art would have drawn the conclusion that dazopride's anti-emetic effect was derived through its 5-HT3 pathway, it would not have been

obvious to conclude that metoclopramide's activity would necessarily follow suit. Although similar, in that they have three out of four substitutions on the phenyl ring in common, dazopride and metoclopramide differ enough in structure that dazopride completely lost its dopamine activity, which is metoclopramide's strongest activity. Again, the conclusions Teva suggests one of ordinary skill in the art would have drawn from the knowledge that dazopride's anti-emetic effect was not derived through the dopamine pathway are far too attenuated to be anything more than impermissible hindsight.

Even though none of the three references independently render obvious the use of ondansetron to treat nausea and emesis, Teva claims that in combination the '578 patent, knowledge regarding MDL 72222, and knowledge regarding dazopride invalidates the'789 and '628 patents on obviousness grounds. "When an obviousness determination is based on multiple prior art references, there must be a showing of some 'teaching, suggestion, or reason' to combine the references." *Winner Intern. Royalty Corp. v. Wang*, 202 F.3d 1340, 1348 (Fed. Cir. 2000) (citing *Gambro Lundia AB v. Baxter Healthcare Corp.,* 110 F.3d 1573, 1579 (Fed. Cir. 1997) (also noting that the "absence of such a suggestion to combine is dispositive in an obviousness determination"))); *see also Echolochem, Inc. v. So. Calif. Edison Co.*, 227 F.3d 1361, 1372 (Fed Cir. 2001) ("Our case law makes clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references."). Whether motivation to combine the references was shown is a question of fact. *Winner Intern. Royalty Corp.*, 202 F.3d at 1348.

The '578 patent teaches administration of ondansetron in combination with an anti-emetic to treat the nausea and vomiting symptoms of migraine, which would suggest that the drug by itself

would not have an effect on nausea and vomiting. In determining whether there was a motivation to combine the prior art references, a finding that a references "teaches away" is indicative of non-obviousness. *Winner Int'l Royalty Corp.*, 202 F.3d at 1349-50. A reference teaches away "if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The court concludes that the '578 patent teaches away from the inventions of the '789 and '628 patents in that it prescribes administration of ondansetron in combination with an anti-emetic and therefore indicates that ondansetron would not function as an anti-emetic on its own. Leading up to June 25, 1985, Dr. Fozard's MDL 72222 studies taught that 5-HT3 antagonists were useful in the treatment of migraine pain, and the '578 patent had affirmatively indicated that those drugs would *not* be useful as anti-emetics. In this regard, the court finds that a person of ordinary skill in the art during the relevant time period would not have had a motivation to combine either of those two prior art references with knowledge about anti-emetics such as dazopride.

Finally, the secondary considerations of long-felt need and commercial success also weigh in favor of a finding of non-obviousness. Metoclopramide was the leading anti-emetic used to alleviate nausea and vomiting in chemotherapy patients prior to the use of ondansetron. It is undisputed that metoclopramide had severe, undesirable, and often debilitating side effects and had to be administered intravenously on an in-patient basis. The introduction of ondansetron, which does not produce the negative side effects of metoclopramide and can be administered on an out-patient basis in a tablet form, has allowed doctors to use more aggressive chemotherapy with confidence that previously prohibitive side effects can now be controlled, allowing patients to complete chemotherapy at greater rates than before. Ondansetron, as a result, has had enormous commercial

success, with Zofran becoming the most prescribed and best-selling drug of its kind.

Considering the disclosures in the individual pieces of prior art, absent a motivation to combine and in view of secondary considerations, the record does not support a finding by clear and convincing evidence that the Teva's three proffered references render obvious each and every element of the '789 or the '628 patents.

B. Enablement

Teva contends that Glaxo's '789 and '628 patents are also invalid because they should have been given a priority date after Beecham's '720 patent and therefore would have been anticipated by that application. Glaxo's '789 and '628 patents derive their priority date from the UK application filed on June 25, 1985 (hereinafter the "priority document"). Teva claims that the priority document could not have enabled a person of ordinary skill in the art to practice the invention. Were the court to agree with Teva , it would have to find that the '789 and '628 patents should have been given a later priority date of June 24, 1986, the date the '789 patent was actually filed in the United States. This later priority date would render the '789 and '628 patents anticipated by Beecham's '720 patent, which was filed during the intervening year between Glaxo's priority document and its United States application. The court does not agree with Teva.

The party seeking to invalidate the patent has the burden to prove by clear and convincing evidence that the patent is not enabled. *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1469 (Fed. Cir. 1993). To be enabled, a patent must satisfy the requirements of 35 U.S.C. § 112, which states in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112. Thus, a patent must set forth a sufficient basis for a person of ordinary skill in the art to conclude that practicing the invention will produce the claimed results. *See In re Cortright*, 165 F.3d 1353, 1355 (Fed. Cir. 1999). To meet the enablement requirement, "the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993) (quoting *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991)). Factors to consider in determining whether or not the experimentation required would be undue include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). Although the question of undue experimentation entails many factual considerations, enablement is ultimately a question of law. *Id.* at 735, 737.

Teva asserts that the information disclosed in the priority document is not sufficient to enable the later claims of Glaxo's '789 patent for the treatment of nausea and emesis with ondansetron as well as the claims of the '628 patent for the same method with respect to cisplatin-induced emesis. According to Teva, the priority document lacks examples in which ondansetron was used to treat nausea and vomiting. Thus, according to Teva, the application cannot satisfy the requirements of 35 U.S.C. § 112. Teva focuses on a single sentence in the priority document: "Results from patients suffering from the symptoms of nausea indicate that the compounds of formula (I) alleviate the symptoms of nausea." Claiming that this text is the priority document's only disclosure of the use of ondansetron to treat nausea or emesis, that the class of compounds disclosed is unduly broad, and

that an appropriate dosage is not specified, Teva argues that the application does not enable a person of ordinary skill in the art to practice the method of use without undue experimentation. Teva further claims that the priority document does not enable a method of using ondansetron to treat nausea and vomiting induced by chemotherapy because it does not specifically disclose or provide examples of such a use. Applying the statutory requirements in view of the *Wands* factors, the court rejects the contention that a person of ordinary skill in the art reading Glaxo's priority document would have to engage in undue experimentation to administer ondansetron to patients suffering from nausea and emesis generally or that induced by chemotherapy.

Considered in context, neither the listed class of compounds nor the cited dosage range in the priority document is so broad as to require undue experimentation. The application's disclosure of a specific, preferred compound (formula 1b, or what later became known as ondansetron) would have offered specific and, indeed, accurate guidance on where to begin practicing the claimed invention. Similarly, the dosage disclosures would also give a person of ordinary skill in the art sufficient guidance to administer ondansetron to achieve the claimed results. The priority document discloses a preferred dosage range of 0.1 to 10 mg per unit of the active ingredient per unit dose administered 1 to 4 times per day. Although the range is broad, the application then goes on to give various examples of specific preparations, including oral, parenteral, and inhalation. These exemplary preparations significantly narrow the range in which a person of ordinary skill in the art would have to experiment to find the effective amount of ondansetron to administer for any given dosage form. As a result, they are sufficiently enabling.

As for the crux of Teva's argument, that the priority document lacks examples, the court likewise is not persuaded. Initially, the court does not find as a matter of law that the application must contain specific examples of the administration of ondansetron to treat emesis to be enabled for

that purpose. Section 112 requires only that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification. "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). There is then no hard and fast rule that examples are necessary to enable an invention for a specific use. Ample guidance will suffice.

Moreover, Teva mischaracterizes the sentence "Results from patients suffering from the symptoms of nausea indicate that the compounds of formula (I) alleviate the symptoms of nausea," as the priority document's only disclosure of using ondansetron to treat nausea. To the contrary, the priority document provides exemplary dosage ranges, forms and frequencies, as well as a toxicity limit, all for the administration of ondansetron. It seems that Teva would have the court believe that the application's disclosures teach only how to use ondansetron to treat gastric emptying. Glaxo, however, specifically states on the first page of the application: "This invention relates to . . . certain tetrahydrocarbazolone derivatives which may be used to promote gastric emptying and as anti-emetics." There is nothing speculative about this sentence. Indeed, it would indicate to any reader, and certainly to one of ordinary skill in the art, that the claimed method may be applied to gastric emptying *or* emesis. This is particularly true in view of the application's reference to metoclopramide–a well-known anti-emetic at the time–establishing that the intended medical use for the claimed compounds was also as an anti-emetic. The priority document also mentions that the compounds may be administered in combination with other therapeutic agents such as cisplatin. Thus, the document again indicates to a person of ordinary skill in the art that ondansetron could also be administered as an anti-emetic in cancer treatment, as claimed by the later '628 patent.

Although it is true that the '789 patent contains a much more detailed disclosure of

ondansetron's effectiveness in treating nausea and emesis, enablement "does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003). Indeed, the level of disclosure necessary to satisfy section 112 will inevitably vary according to the scope of the invention claimed. *Id.* To reiterate, the claimed invention of the '789 patent is a method of treatment for the relief of nausea and vomiting which comprises administering to a human or animal subject in need thereof an effective amount of ondansetron. The '628 patent claims the same method for treatment of nausea and vomiting induced by the anti-cancer drug cisplatin. As is evident from the face of the application, and as established through Dr. Peroutka's and Dr. Gralla's testimony, the priority document gives ample guidance to enable a person of ordinary skill in the art to administer ondansetron to treat emesis. It sets forth that the claimed method can be used to treat gastric emptying and emesis and further references metoclopramide and cisplatin. It provides examples for administration of formula (I), and explicitly cites ondansetron as the particularly preferred embodiment. In this regard, the application is accurate and specific. The court therefore finds that Teva has not carried its burden to establish that a person of ordinary skill in the art would have to unduly experiment to administer ondansetron for the treatment of nausea or emesis, or that he or she would not believe that practicing the invention would produce the claimed results.

C. Anticipation/Inherent Anticipation

Teva argues that the '578 patent anticipates the '789 and '628 patents in that the treatment of migraine with ondansetron, as claimed by the '578 patent, inherently includes the treatment of nausea and vomiting with ondansetron, as claimed by the '789 and '628 patents. The court disagrees.

Anticipation is a question of fact that is shown only by rigorous proof and reviewed under a

clearly erroneous standard. *E.g., Rapoport v. Dement*, 254 F.3d 1053, 1057-58 (Fed. Cir. 2001). A patent claim is invalid for anticipation where each and every element of the claimed invention is disclosed in a single prior art reference. 35 U.S.C. § 102; *e.g., In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994). "[T]he four corners of a single, prior art document [must] describe each and every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." "If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not § 102, but § 103 obviousness." *Id.* At 1577. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). Only claims, as opposed to specifications, may be anticipated. *State Contracting & Eng'g Corp. v. Condotte Am. Inc.*, 346 F.3d 1057, 1067-68 (Fed. Cir. 2003). As a result, the anticipation inquiry must begin with a proper claim construction. *Id.*

The '578 patent claims, in pertinent part, "a method of treating a condition caused by disturbance of 'neuronal' 5HT function which comprises administering to a patient an effective amount of [ondansetron] . . . to relieve said condition." There is no dispute that the condition referred to in the above claim is migraine. The '789 patent, on the other hand, claims a method of treatment for the relief of nausea and vomiting which comprises administering to a human or animal subject in need thereof an effective amount of ondansetron, and the '628 patent the same method for the treatment of nausea and emesis induced by cisplatin. Thus, the '578 patent claims administration to treat patients suffering from migraine, whereas the '789 and '628 patents claim administration of ondansetron to treat patients in need of relief of nausea and emesis. By its plain language, the '578 patent does not contain within its four corners each and every element of the '789 and '628 patents. This conclusion, however, does not end the anticipation inquiry.

Under the theory of inherent anticipation, if an element is not expressly disclosed in the prior art reference, the reference still will be deemed to anticipate the subsequent claim if the missing element "is necessarily present in the thing described in the reference." *Continental Can Co. U.S.A., Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The court, therefore must further determine, keeping in mind the scope of the '578 patent, whether administration of ondansetron to treat migraine, would necessarily treat patients in need of relief of nausea and emesis, as claimed by the '789 and'628 patents.

Inherent anticipation does not require that a skilled artisan recognize the inherent characteristic in the prior art that anticipates the claimed invention. *See Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003). However, "[a] court may resolve factual questions about the references in the prior art by examining the reference through the eyes of a person of ordinary skill in the art, among other sources of evidence about the meaning of the prior art." *Id.* at 1377-78. In other words, although past recognition of the inherent feature is not necessary, the court may still evaluate the opinions of those skilled in the art to determine the scope of the prior art reference. *Id.* at 1378.

Teva contends that administration of ondansetron to migraine sufferers necessarily results in the treatment of patients in need of nausea and vomiting relief. The facts, however, do not support such a conclusion. Without pain, a person does not have a migraine headache. The testimony of Dr. Fozard and Dr. Gralla amply support that a person of ordinary skill in the art understood the '578 patent to claim administration of ondansetron for the treatment of migraine pain, as opposed to other symptoms. Moreover, although nausea and vomiting are the most common symptoms of migraine other than pain, the record clearly establishes that not every migraine patient will experience either of these two symptoms in any given migraine attack. With respect to severe migraine attacks, up

to 90% of patients may suffer from nausea as a symptom and 50% from vomiting as a symptom. Therefore, even the most severe migraine attacks do not produce nausea and vomiting in every case.

Although inherent anticipation does not require the element to be present each and every time, it does require the result to be a necessary and inevitable consequence of practicing the invention claimed in the prior art under normal conditions. *See Schering*, 339 F.3d at 1373. Under normal conditions, all migraine patients suffer from pain, and the '578 patent teaches administration of ondansetron to alleviate this symptom. A significant percentage of *all* migraine sufferers do not experience nausea, and an even greater percentage do not experience emesis. In this regard, the relief of nausea and vomiting is not a necessary consequence of the administration of ondansetron to treat migraine under normal conditions. Nor does treating patients in need of nausea and emesis relief necessarily and inevitably result from treating migraine patients with ondansetron. On this point, Dr. Gralla's testimony makes clear that migraine has never been a good model for testing anti-emetics.

The present case invokes the distinction between a new use and an added benefit. A new use for an existing compound may be the subject of a valid patent. Indeed, there is express statutory authority allowing a patent on a process which is a new use of a known process, composition of matter, or material, provided that the new use is unobvious and not subject to a statutory one year time bar, neither of which apply in this case.[4] *See* 35 U.S.C. §§ 100(b) and 101. On the other hand, an unpatentable, added benefit may be viewed as a "newly discovered result[] of [a] known process[] directed to the same purpose." *Bristol-Myers Squibb Co. v. Ben Venue Labs. Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001).

To highlight this distinction, the court contrasts two exemplary cases addressing new uses for

[4]The court has already found that the administration of ondansetron to treat patients in need of relief of nausea and emesis is not obvious over the prior art.

existing compounds. In the case of *Application of May*, 574 F.2d 1082 (C.C.P.A. 1978), the patent-in-suit claimed a method of treating pain through the use of certain painkillers without producing the side effect of physical dependency on those painkillers. To achieve that result, the patent disclosed the administration of a compound, which a prior art reference had previously disclosed for use as an analgesic (or pain killer), but was not before known to be non-addictive. The court found the prior art reference to anticipate the patent-in-suit because the latter "merely recited a newly discovered result–non-addictiveness–of a known method directed to the same use, i.e., treating pain with an analgesic." *Bristol-Myers Squibb Co.*, 246 F.3d at 1377 (citing *Application of May*, 574 F.2d at 1090, to illustrate an added benefit as opposed to a new use). In contrast, the Federal Circuit in *Rapoport* found that a patent claiming a method of using a known compound to treat sleep apnea was not inherently anticipated by a prior art reference disclosing the use of the same compound in the treatment of anxiety. *Rapoport*, 254 F.3d at 1063. Notably, the court made this determination in spite of the fact that anxiety was a known symptom of sleep apnea, finding too speculative that the reference's dosage regime for treatment of anxiety would necessarily result in a therapeutically effective amount of the drug for the purpose of treating sleep apnea. *Id.* at 1062-63. In other words, although the drug was the same, the implications of its administration for two different purposes ultimately precluded a finding of inherent anticipation.

Similarly, the administration of ondansetron to treat migraine is not directed at the same purpose as administration of the drug to patients in need of nausea and emesis relief. The '789 and '628 patents therefore do not present a mere added benefit of administering ondansetron to treat migraine pain, but rather claim a new use for the compound to treat patients in need of nausea and

emesis relief.[5] The '578 patent accordingly does not anticipate the '789 of '628 patents.

IV. CONCLUSION

For the reasons stated above, the court concludes that the patents-in-suit are not obvious to a person of skill in the art, not invalid for lack of enablement, nor anticipated by any prior art reference. The '789 and '628 patents are therefore valid and infringed by Teva's October 5, 2001 ANDA filing. As a result of this ruling, the effective approval date of Teva's ANDA shall not be earlier than the expiration dates of the '789 and '628 patents.

[5]Teva urges the court essentially to reject the '789 and '628 patent's language "in need thereof" as a separate element of the claim, arguing that it only makes explicit what is already implicit in the method described. *Schering* clarifies that a patent drafter may fashion a claim to cover a method of use so as to avoid anticipation, *see Schering*, 339 F.3d at 1381, and in this regard the addition of the language "in need thereof" is significant. The court need not find that this language adds an intent requirement to the claims of the '789 and '628 patents in order to determine that the phrase is an additional element probative of the issue of the purpose to which the administration of ondansetron is directed in the patents-in-suit.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXO GROUP LIMITED and SMITHKLINE BEECHAM CORPORATION Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICALS INDUSTRIES, LTD., Defendants.	)	C.A. No. 02-219 GMS

ORDER

For the reasons set forth in the court's opinion issued contemporaneously herewith, IT IS HEREBY ORDERED that:

The clerk shall enter judgment in favor of the plaintiffs Glaxo Group Limited and Smithkline Beecham Corporation and against the defendants Teva Pharmaceuticals USA, Inc. And Teva Pharmaceuticals Industries, Ltd.

Dated: August 20, 2004

/s/ Gregory M. Sleet
UNITED STATES DISTRICT JUDGE