IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE NEXIUM CONSUMER/PAYOR ADVERTISING LITIGATION	Master File No. 1:05-cv-75 Hon. Sue L. Robinson, USDJ
This document relates to: All Actions	

CONSOLIDATED CLASS ACTION COMPLAINT

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Plaintiffs allege upon personal knowledge as to their own acts, and upon information and belief (based on the investigation of counsel) as to all other matters, as to which allegations Plaintiffs believe substantial evidentiary support will exist after a reasonable opportunity for further investigation and discovery as follows:

I. NATURE OF THE ACTION

1. This is a class action brought against the AstraZeneca group of pharmaceutical companies for unfair and deceptive trade practices and for consumer fraud in the marketing of the brand-name drug Nexium. Plaintiffs seek injunctive relief, monetary damages, and equitable restitution under the laws of the several states.

2. Defendants AstraZeneca Pharmaceuticals LP and Zeneca, Inc. ("AstraZeneca") had a patent for the drug Prilosec which by the year 2000 was the most widely prescribed drug in the world, with annual sales in excess of $6 billion. Prilosec, long-advertised as "the purple pill," is a proton-pump inhibitor ("PPI") or acid-pump inhibitor that is used to treat heartburn and esophageal erosions.

3. A patented drug is also referred to as a "brand name" drug. Brand name drugs which face no competition are the most profitable drugs for drug manufacturers. In the year 2000, the average retail price of a prescription drug was more than three times that of a generic drug.[1]

4. The patent for Prilosec was set to expire in 2001 and AstraZeneca anticipated that it would face stiff competition from generic manufacturers. It is a fact well known to drug manufacturers that entry of generics results in a substantial loss of market share for the brand-name manufacturers, sharply reduced prices, and a decrease in profits. AstraZeneca was thus facing the loss of its most profitable drug.

[1] Kaiser Family Foundation, *Trends as Indicators in the Charges*, Health Care Marketplace 2004 Update (2004).

5. Consequently, years before the Prilosec patent was set to expire, AstraZeneca formed a group of marketers, lawyers and scientists to come up with a solution for what the company believed was a looming patent-expiration disaster. The group called itself the "Shark Fin Project" after the dismal shape the sales chart would form if they did nothing and allowed generic competition to erode Prilosec's market share and price: an inverted V.

6. The Shark Fin Project implemented a multi-prong attack. First, it hauled generic manufacturers into court seeking to delay entry of competition. Second, shortly before the patent on Prilosec was set to expire, the company received FDA approval for a new PPI, Nexium, which was a newly patented brand name drug AstraZeneca intended to position as Prilosec's replacement.

7. AstraZeneca knew that it could not succeed if Nexium was marketed simply as essentially the same drugs as Prilosec. To justify the difference in price between Nexium and generic Prilosec, AstraZeneca had to convince doctors and consumers that Nexium was superior to Prilosec. AstraZeneca set out to do just that. Nexium became the most heavily advertised drug in the United States. Doctors and consumers were blanketed with advertisements for a "new purple pill": "Today's purple pill is Nexium, from the makers of Prilosec." Other advertisements described the "new Nexium" as the "POWERFUL NEW PPI" (emphasis in advertisement). AstraZeneca's advertisements either implicitly or expressly represented that the new purple pill was superior. After all, why market a product as "new" if it were not somehow better than the prior version?

8. AstraZeneca's 6,000 salespeople blitzed doctors with studies proclaiming Nexium's superiority and urging them to "prescribe the new purple pill." The promotional campaign reportedly cost AstraZeneca a half billion dollars in just 2001. Virtually overnight, Nexium – "the new purple pill" – began to replace Prilosec, the old "purple pill." Eventually the company dropped all references to the older drug, Prilosec, in its advertisements.

9. However, Nexium was neither new, nor superior nor more "powerful" than existing PPIs, including Prilosec. Prilosec is comprised of an organic molecule, omeprazole, which – like most organic molecules – exists in two forms (or "isomers") that are mirror images of each other. Prilosec is what is called a "racemic" formulation of this molecule, meaning that it is comprised of a mixture of both mirror images (so-called "S" and "R") of this molecule. In other words, Nexium is simply Prilosec without the less active R-enantiomer. Head-to-head studies comparing Nexium and Prilosec establish they are, chemically and therapeutically, essentially the same.

10. To obtain approval for Nexium from the Food and Drug Administration ("FDA"), AstraZeneca had to test it in several clinical trials. Some of these trials merely compared Nexium with placebos to show that it worked better than nothing, since that is all the FDA requires. But four trials compared Nexium head-to-head with Prilosec and these were crucial to AstraZeneca's marketing strategy. The Company needed to show that Nexium was better than Prilosec – an advance over the older drug.

11. Instead of seemingly comparing equivalent doses, *i.e.*, 20 milligrams ("mg") or less of Nexium, versus the standard 20 mg dose of Prilosec recommended for most indications, the Company included higher doses of Nexium in its studies. AstraZeneca compared Nexium 40 mg to Prilosec 20 mg. With the studies skewed in this way, AstraZeneca expected Nexium to show a significant improvement over Prilosec. This did not happen. As the FDA repeatedly noted in its review of Nexium's New Drug Application ("NDA"), the submitted studies comparing Nexium to Prilosec "do[] not lead to the conclusion that [Nexium] is superior to omeprazole [Prilosec]...."

12. Despite its failure to prove Nexium's superiority over Prilosec, AstraZeneca nevertheless promoted Nexium to doctors and consumers as the "first proton pump inhibitor (PPI) to offer significant clinic improvements over Losec [*i.e.* Prilosec] and its main competitor,

lansoprazole, in terms of acid control and clinical efficacy."[2] It also claimed that Nexium was more effective in acid inhibition than other comparable drugs and provided relief in a shorter period of time. AstraZeneca repeated these messages in a steady stream of marketing directed to patients and doctors.

13. AstraZeneca's campaign worked, with sales of Nexium sky rocketing to reach $3.3 billion by 2003.

14. The truth, however, is that there are no clinical improvements that Nexium offers over Prilosec. The drug was created and promoted solely to maintain AstraZeneca's Prilosec profit stream and not because it offers any medical benefits not available from use of Prilosec or other PPIs. As the FDA reviewers found, "superiority of Nexium over omeprazole was not demonstrated." For consumers, Prilosec is just as effective and at far less cost. As noted by the former administrator of the federal Centers for Medicare and Medicaid services ("CMS"), Thomas Scully, at a convention of the American Medical Association: "You should be embarrassed if you prescribe Nexium because it increases costs with no medical benefits."[3] Mr. Scully noted, "[t]he fact is Nexium is Prilosec ... [i]t is the same drug. It is a mirror compound."[4] Mr. Scully further stated that "Nexium is a game that is being played on the people who pay for drugs."[5] A pharmaceutical industry analyst, in reacting to the recent news that the Pentagon will no longer pay for Nexium, noted "Nexium is not worth the money period.... [Its pretty dubious to pay $4 a pill for Nexium when you can get over-the-counter Prilosec for 67 cents."[6] Unfortunately, as a result of Defendants' promotional and sales practices, billions have been spent on Nexium which should not have been.

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[2] AstraZeneca Annual Report Form 20-F-2000 at p. 11.

[3] NEW YORK TIMES, April 21, 2003.

[4] *Id.*

[5] *Id.*

[6] Pentagon to Drop Nexium From Its List of Covered Drugs For Military Personnel, WASHINGTON POST, May 8, 2005 at A6.

15. In this action, Plaintiffs seek restitution and equitable relief arising out of AstraZeneca's sale and promotion of Nexium pursuant to practices and acts that are unfair, deceptive and unlawful in violation of state laws.

II. PARTIES

16. Plaintiff Pennsylvania Employees Benefit Trust Fund ("PEBTF") is a labor-management trust fund duly organized under the laws of the Commonwealth of Pennsylvania, with its principal place of business at 150 South 43rd Street, Suite I, Harrisburg, Pennsylvania 17111-5700. PEBTF provides comprehensive healthcare benefits, including prescription drug coverage, to 70,000 participants and beneficiaries, which includes active and retired employees of the Commonwealth of Pennsylvania, as well as their spouses and dependents. A number of participants and beneficiaries of PEBTF live in Delaware as well as in Pennsylvania and other states. During the Class Period as described herein, PEBTF paid for some or all of the purchase price of Nexium prescribed to one or more of its participants or beneficiaries, and has thereby been injured, and continues to be injured, as a result of Defendants' conduct.

17. Plaintiff Linda A. Watters, Commissioner, Offices of Financial and Insurance Services for the State of Michigan in her capacity as Rehabilitator of The Wellness Plan ("Wellness Plan") and in her capacity as Liquidator of Michigan Health Maintenance Organization Plans, Inc., formerly known as OmniCare Health Plan, Inc. ("OmniCare") is a Michigan official whose function is to collect and liquidate all assets and liabilities of the former private third party payers Wellness Plan and OmniCare. During the Class Period as described herein, Wellness Plan and OmniCare were private third-party payers whose function was to assume the risk of payment of medical and prescription costs on behalf of the participants in their plan. During the Class Period as described herein, Wellness Plan and OmniCare paid for prescriptions of Nexium and thereby have been injured by Defendants' conduct.

18. Plaintiff AFSCME District Council 47 Health & Welfare Fund ("AFSCME") is a welfare benefit plan duly organized under the laws of Pennsylvania. It is located at 1606 Walnut

Street, Philadelphia, Pennsylvania. Its members include roughly 4,000 active city employees and 700 retirees. During the Class Period as described herein, AFSCME paid for some or all of the purchase price of Nexium prescribed to one or more of its participants and has been injured by Defendants' conduct.

19. Plaintiff Joseph Macken is an individual residing in East Meadow, Nassau County, New York. During the Class Period described herein, Plaintiff purchased Nexium for his own consumption and was injured as a result of Defendant's conduct alleged herein.

20. Plaintiff Victoria Scofield is a resident of Wrightsville, Pennsylvania. She took Nexium until the summer of 2004 and by virtue of making co-payments for Nexium was injured as a result of Defendants' unlawful conduct alleged herein.

21. Plaintiff Janet McGrorty is a resident of Reno, Nevada. She has taken Nexium since 2002 and by virtue of making co-payments for Nexium was injured by the unlawful conduct alleged herein.

22. Plaintiff Richard Tikkuri is an individual residing at Cudahy, Wisconsin. He has taken Nexium since 2004 and by virtue of making co-payments for Nexium was injured by the unlawful conduct alleged herein.

23. Wisconsin Citizen Action ("WAC") is a nonprofit corporation with its headquarters located in Madison, Wisconsin. WAC is the state's premier public interest organization dedicated to social, economic and environmental justice for all. It has as one of its goals working to provide quality, affordable health care for all. Its members have used and paid for Nexium and have been injured by the unlawful conduct alleged herein.

24. United Senior Action of Indiana is a nonprofit organization devoted to issues effecting seniors including affordable health care. Its members have purchased Nexium and been damaged by the unlawful conduct alleged herein.

25. Plaintiff North Carolina Fair Share is a statewide, multi-issue, non-profit corporation located in Raleigh, North Carolina. It has as one of its goals helping the low wealth,

unemployed and underemployed. Its members have used and paid for Nexium and have been injured by the unlawful conduct alleged herein.

26. Defendant Zeneca, Inc. ("Zeneca") is a Delaware corporation with its principal place of business located at 1800 Concord Pike, Wilmington, Delaware. Zeneca is a wholly owned subsidiary of AstraZeneca Group PLC, a limited liability company domiciled in the United Kingdom.

27. Defendant AstraZeneca Pharmaceuticals LP is a Delaware limited partnership, with its principal place of business located at 1800 Concord Pike, Wilmington, Delaware. AstraZeneca Pharmaceuticals LP is owned and controlled by AstraZeneca Group PLC, a public limited liability company domiciled in the United Kingdom.

28. Zeneca and AstraZeneca Pharmaceuticals LP are collectively referred to as "AstraZeneca."

29. AstraZeneca maintains research and development and manufacturing facilities worldwide, including in the United States. AstraZeneca reported annual sales of $18.8 billion in 2003, with an operating profit of $4.2 billion. Its 2003 sales of Nexium were $3.3 billion, or 17% of all sales.

III. JURISDICTION AND VENUE

30. This Court has diversity subject-matter jurisdiction over this class action pursuant to the Class Action Fairness Act of 2005, which, *inter alia*, amends 28 U.S.C. § 1332 to add a new subsection (d) conferring federal jurisdiction over class actions where, as here, "any member of a class of plaintiffs is a citizen of a State different from any defendant" and the aggregated amount in controversy exceeds five million dollars ($5,000,000). *See* 28 U.S.C. § 1332(d)(2) and (6). This Court has personal jurisdiction over the parties because Plaintiffs submit to the jurisdiction of the Court and Defendants systematically and continually conduct business throughout the State of Delaware, including marketing, advertising, and sales directed to Delaware residents.

31. Venue is proper here in that Defendants are incorporated and/or have their principal places of business within the District, Defendants engaged in substantial conduct relevant to the claims within this District, and Plaintiffs suffered substantial loss for purchases of Nexium made within this District.

IV. FACTUAL ALLEGATIONS

A. Prilosec – A Blockbuster Drug for AstraZeneca

32. Prilosec (also known as Losec) is a proton-pump inhibitor ("PPI"). According to AstraZeneca's publicly filed documents, by the year 2000 Prilosec had "set a new global standard in short and long-term treatment of acid related diseases." According to AstraZeneca's publicly filed documents, Prilosec had benefited patients in 530 million patient treatments since 1980 and "is the world's largest selling pharmaceutical." Prilosec was AstraZeneca's most profitable drug with worldwide sales of over $6 billion by 2000.[7]

33. PPIs are used to treat the three gastroesophageal reflux disease ("GERD") indications that require gastric acid inhibition. These three indications are: treatment of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic GERD.

34. Erosive esophagitis is related to heartburn. Heartburn is a gastrointestinal condition caused by acid backflow from the stomach to the esophagus, the swallowing tube from the mouth to the stomach. Normally, a muscular valve at the lower end of the esophagus keeps acid in the stomach and out of the esophagus. When the valve relaxes too frequently, stomach acid flows backward into the esophagus, causing a burning sensation in the chest and throat. This is commonly known as "heartburn" or acid indigestion.

35. More than 60 million Americans experience heartburn/acid indigestion at least once a month, and some studies suggest that more than 15 million Americans experience heartburn/acid indigestion daily. Symptoms are more common among the elderly and pregnant women and can last for several hours, often worsening after eating. Frequent heartburn (two or

[7] 2001 Annual Report at p. 38.

more episodes per week) may be associated with a more severe condition known as gastroesophageal reflux disease or GERD.

36. Without effective treatment, GERD can cause serious complications such as severe chest pain, esophageal stricture (narrowing or obstruction/damage of the esophagus), bleeding, asthma-like symptoms, or Barret's esophagus (a precancerous condition of the esophagus).

37. Another possible complication of GERD/heartburn is erosive esophagitis. This condition is characterized by erosion of the lining of the esophagus caused by chronic backflow of acid from the stomach. Patients with erosive esophagitis usually have the typical symptoms of GERD. An endoscopy is required to diagnose erosive esophagitis. An endoscopy is an outpatient procedure that allows a physician to explore the esophagus and stomach using a small flexible tube with a tiny camera. Once erosive esophagitis is identified as the source of heartburn, physicians can prescribe medications to treat the symptoms and heal the esophagus.

38. Omeprazole, the active ingredient in Prilosec, is a "racemic" mixture containing S- and R-enantiomers. Enantiomers are molecules that have two non-superimposable mirror image forms, *i.e.*, a right and left hand version. Racemic mixtures, such as Prilosec, contain equal proportions of the two enantiomers. Thus, 20 mg of Prilosec (*i.e.*, omeprazole) is really 10 mg of the R-enantiomer and 10 mg of the S-enantiomer.

39. In humans, the S-enantiomer of omeprazole is more active than the R-enantiomer, in part due to its better metabolization.

40. Patent protection for omeprazole, the active ingredient in Prilosec, expired in all major markets by the end of 2000, but patent term extensions extended protection until April 2001 in the United States.

41. With the looming loss of patent protection, AstraZeneca faced the erosion of its number one selling drug. To put this in perspective, Prilosec sales of $5.9 billion in 2000

comprised 39% of AstraZeneca's revenue, with sales of the Company's next best-selling drug comprising 8% of revenue.

B. AstraZeneca Was Keenly Aware That the Loss of Patent Protection Results in Lower Prices and Reduced Profits

42. At the time the Shark Fin Project was underway, AstraZeneca was keenly aware of the financial impact from the loss of brand-name protection.

43. For every year from 1995 through 2002, the pharmaceutical industry was the most profitable industry in the United States, although its profitability declined somewhat in 2002. In 2003, drug companies ranked as the third most profitable industry. Drug companies were more than three times as profitable as the median for all Fortune 500 companies in 2003 (14.3% compared to 4.6%).[8]

44. The most profitable drugs are brand name drugs. Brand name drugs typically sell at three or more times that of a generic drug. Once Prilosec lost patent protection, generic competition would erode Prilosec's price and market share.

C. The AstraZeneca Solution – "The New Purple Pill Nexium"

1. The Shark Fin Project

45. Faced with the catastrophic loss of sales from its flagship drug, AstraZeneca carefully plotted a new strategy. The plotting was done by members of the "Shark Fin Project," a secret group of marketers, lawyers and scientists charged with developing a strategy for averting the Prilosec patent-expiration disaster. The name of the group derives from the dismal shape the sales chart would trace if AstraZeneca did nothing: an inverted V.

46. Eventually the centerpiece of that strategy became the marketing and promotion of the new drug Nexium. Nexium is simply the S-enantiomer of omeprazole, which was patented under the name esomeprazolem. Thus, Nexium is simply Prilosec without the less active R-enantiomer. Nexium was viewed by several AstraZeneca executives as the poorest

[8] Kaiser Family Foundation, *Trends as Indicators in the Charges*, Health Care Marketplace 2004 Update.

solution because internally these executives knew that Nexium was not any better for ordinary heartburn than Prilosec. Nonetheless, with time running out and no other alternatives, Nexium was the chosen replacement.

47. AstraZeneca's plan was to promote Nexium as an improvement over Prilosec to migrate its Prilosec business over to Nexium and to build brand loyalty for Nexium before the expiration of Prilosec's patents. AstraZeneca knew that brand loyalty is critical – once a doctor selects a drug for a certain treatment – he/she is unlikely to change. The same is true for the consumer.

2. Submissions of clinical trials

48. To obtain approval from the FDA for Nexium, AstraZeneca had to test it in several clinical trials. Some of these trials merely compared Nexium with placebos to show that it worked better than nothing, since that is all the FDA requires. But four trials compared Nexium head-to-head with Prilosec for esophageal erosions, and these were crucial to AstraZeneca's marketing strategy. The Company wanted to show that Nexium was better than Prilosec – an advance over the older drug. If it could not show such an advance, there would be no justification for doctors to prescribe and consumers to use an expensive brand-name drug.

49. In total, AstraZeneca submitted 11 efficacy studies and three supportive trials for consideration by the FDA with its NDA for Nexium.[9] Only ***four*** of the eleven studies and the three supportive trials actually compared Nexium with omeprazole. The remaining studies compared Nexium with a placebo.

50. Study 172 compared the efficacy of Nexium 40 mg, Nexium 20 mg, and omeprazole 20 mg in healing erosive esophagitis. A sample size of 500 patients per treatment was chosen in order to ensure the ability to detect a 10% difference in healing with 95% accuracy. Not surprisingly, Nexium 40 mg had a statistically significant higher healing

[9] *See* Stephen G. Hundley, *FDA Pharmacology/Toxicology Review and Evaluation*, Nexium NDA 21-154, 1-2 (October 31, 2000) ("FDA Review").

proportion than omeprazole 20 mg, 87.6% versus 81.4%. However, the targeted therapeutic gain of 10% was not reached. In addition, there was no statistically significant difference between Nexium 20 mg and omeprazole 20 mg according to the FDA reviewer. Thus, according to the reviewer, the superiority of Nexium over Prilosec "was not demonstrated" for this indication, despite the dose of Nexium being "pharmacodynamically thrice" that of Prilosec.

51. Thus, the study that AstraZeneca used to obtain FDA approval concluded that Nexium at twice the standard dose of Prilosec was only slightly more effective for treatment of erosive esophagitis:

> Investigators observed that the time intragastric pH was greater than four during a 24-hour period was longer with Nexium 40 mg once daily than standard healing doses for erosive esophagitis of four other branded proton pump inhibitors currently available by prescription in the United States. On day five, intragastic pH was maintained above 4.0 for a mean of 14.0 hours with Nexium 40 mg, 12.1 hours with Aciphex 20 mg, 11.8 hours with Prilosec 20 mg, 11.5 hours with Prevacid 30 mg, and 10.1 hours with Protonix 40 mg. Nexium also provided a significantly higher percentage of patients with an intragastric pH > 4.0 for > 12 hours relative to the other proton pump inhibitors ($p<0.05$).

52. Acid suppression is, however, only a "surrogate endpoint," meaning that it is not of clinical importance in its own right, but a marker presumed to be of importance. Even if duration of suppression of gastric acid secretion were a valid measure upon which to make a clinical decision, these results show that a single dose of Nexium 40 mg (keeping gastric pH above 4 for 14 hours) cannot be claimed to be "superior" or more beneficial than prescribing or taking Prilosec 20 mg (keeping gastric pH above 4 for 11.8 hours) twice daily.

53. The FDA reviewer, with respect to healing of erosive esophagitis, found that a claim of superiority over Prilosec is "NOT SUPPORTED." (Capitalization in document.)

54. Study 172 also evaluated Nexium 40 mg, Nexium 20 mg and omeprazole 20 mg for heartburn resolution. The study revealed that there was no significant difference in heartburn resolution between 20 mg of Nexium and 20 mg of omeprazole. In fact, there was only a statistical difference at week 4, not at week 8, between 40 mg of Nexium and 20 mg of

omeprazole. The study's authors did claim a statistically significant lower number of heartburn free nights with 20 mg of Nexium versus 20 mg of omeprazole, but there was no significant difference in heartburn free days and more patients using 20 mg of omeprazole had sustained heartburn resolution by day one of the study.

55. Finally, with respect to use of Nexium for GERD, the FDA reviewer found that Nexium is "not very effective in this indication" which "means that a large portion of S-GERD patients (66% in one trial and 58% in another) do not benefit from the administration of this PPI at this daily dose regimen."

56. This finding is particularly important because far more patients are treated for heartburn than those treated for esophageal erosions. Thus, the study did not support the marketing of Nexium for its major market.

57. Possibly to remedy the failure to obtain the targeted therapeutic gain of 10% in Study 172, Study 173 attempted to reproduce the unremarkable, statistically significant difference between 40 mg of Nexium and 20 mg of omeprazole. This time, however, there was no statistically significant difference between 40 mg of Nexium and 20 mg of omeprazole. Even at twice the dose, the study "failed to demonstrate the superiority of [Nexium] over [omeprazole]."[10] Study 173 did not even attempt to compare Nexium 20 mg and omeprazole 20 mg.

58. AstraZeneca attempted yet again to prove that 40 mg of Nexium was better at healing erosive esophagitis than 20 mg of omeprazole in Study 222. This time, however, over 1000 patients per treatment were used. This number of patients reduced the amount of therapeutic gain required to ensure a 95% accuracy rate. With this lower measure of therapeutic gain, AstraZeneca was finally able to show, within the parameters of the study, that 40 mg of Nexium was more effective than 20 mg of omeprazole for treating erosive esophagitis.

[10] *FDA Review* at 10.

59. However, the FDA reviewer noted that "the superiority of [40 mg of Nexium] over [20 mg of omeprazole] was demonstrated by comparing two treatments at different dose level [sic] and does not lead to the conclusion that [Nexium] is superior to omeprazole in healing [erosive esophagitis]."[11]

60. Study 174 compared Nexium 20 mg with omeprazole 20 mg. As with Study 172, the FDA reviewer found no statistically significant difference in healing between 20 mg of Nexium and omeprazole.[12]

61. Of the three supportive trials submitted by AstraZeneca with the Nexium NDA, one compared 40 mg and 20 mg of Nexium with omeprazole 20 mg; one compared Nexium 40 mg and omeprazole 20 mg; and one compared 20 mg of Nexium and 20 mg of omeprazole. "All three studies failed to demonstrate superiority of [Nexium] over [20 mg of omeprazole]."[13]

62. Thus, the FDA gave AstraZeneca approval to market Nexium, the "New Purple Pill," because it worked better than a placebo, not because it was better than Prilosec. All that AstraZeneca's two studies proved was that the "New Purple Pill" was better than a placebo in the treatment of heartburn, not that it was better than omeprazole, *i.e.* Prilosec.

63. In one study that compared Nexium 20 mg to Prilosec 20 mg, the reported increase in efficacy of Nexium over Prilosec was offset by an increase in side effects, including headache, abdominal pain, and diarrhea.

64. The FDA's Medical Review summarized all of the studies – published or not – submitted with AstraZeneca's NDA for three indications for Nexium: healing of erosive esophagitis (four studies), maintenance of healing of erosive esophagitis (two studies), and treatment of symptomatic GERD (gastroesophageal reflux disease) (five studies).[14] The Medical Review reports that:

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[11] *FDA Review* at 14.

[12] *Id.* at 10.

[13] *Id.* at 36.

[14] Hugo E. Gallo-Torrees, MD, PhD, Medical Team Leader, Medical Review(s), FDA Center for Drug Evaluation and Research, Application Number: 21-153/21-154, September 21, 2000, at 3-6.

> All of these studies were well-designed and apparently well-executed, double-blind, randomized, with appropriate: a) controls; b) patient populations; c) consistent inclusion criteria and reasons for exclusion; and d) sufficient sample size for appropriate statistical power.

65. The FDA review found that for healing of erosive esophagitis:

> ... a superiority claim of Nexium over omeprazole [Prilosec] is not supported by either the comparison of H20 [Nexium 20 mg] vs. O20 [Prilosec 20 mg] or the comparison of H40 [Nexium 40 mg] vs. H20 [Nexium 20 mg].

66. For maintenance of healing of erosive esophagitis: The two studies compared various doses of Nexium to placebo only, not to an active comparator, like Prilosec.

67. For treatment of symptomatic GERD:

> ... claims of superiority [of Nexium] to omeprazole are – once again – not supported. Neither H40 [Nexium 40 mg] nor H20 [Nexium 20 mg] could be differentiated from O20 [Prilosec 20 mg].

68. The "SUMMARY OF BENEFITS VS RISKS" section of the FDA's Medical Review of the Nexium new drug application is worth quoting at length as it further demonstrates that Nexium is not superior to Prilosec:

> It is important to point out that in order to determine whether one compound is superior to another, these drugs need to be tested at comparable amounts: H20 [Nexium 20 mg] vs. O 20 [Prilosec 20 mg]; H40 [Nexium 40 mg] vs. O 40 [Prilosec 40 mg]. The sponsor's comparisons of H40 to O 20 do not yield valid conclusions about the superiority of H [Nexium] over O [Prilosec], although these comparisons are adequate to demonstrate that [Nexium] is active in the assessed indications. Therefore the sponsor's conclusions that [Nexium] has been shown to provide a significant clinical advance over [Prilosec] in the first-line treatment of patients with acid-related disorders is not supported by data.[15]

69. The FDA concluded:

> In addition, it is recommended not to allow the sponsor to claim that [Nexium] has any significant clinical advantage over

[15] *Id.* at 171.

> [Prilosec] in the first-line treatment of these acid-related disorders because no data in support of such a claim have been submitted.[16]

3. The failure of the clinical trials to show Nexium's superiority is not surprising given the fact Nexium is a mirror compound of Prilosec

70. An examination of the chemical make-up of Prilosec and Nexium also confirms the lack of superiority over Prilosec.

71. Prilosec (*i.e.*, omeprazole) contains equal proportions of two "mirror image" isomers called enantiomers. Based on a system of mapping and prioritizing the configurations of chemical compounds, the different chemical groupings in enantiomers are priority-ordered in either a clockwise or counter-clockwise direction. Those ordered clockwise are called "R-enantiomers" (from the Latin "*rectus*," or right) and those ordered counter-clockwise are called "S-enantiomers" (from the Latin "*sinister*," or left). A 20 mg dose of Prilosec is really 10 mg dose of the S-enantiomer and a 10 mg dose of the R-enantiomer. However, in humans, the S-enantiomer is more active than the R-enantiomer, in part due to its better metabolization. Thus, when faced with the expiration of its patent on Prilosec, AstraZeneca patented as a "new" clinical compound the S-enantiomer of omeprazole under the name esomeprazole. Nexium is simply Prilosec without the less active R-enantiomer.

72. Even when comparing seemingly "equal" doses, Nexium has a greater proportion of the more active S-enantionmer than Prilosec. "[A] 20 mg tablet of single-isomer esomeprazole [*i.e.*, Nexium] contains the same amount of active ingredient as a 40 mg tablet of race omeprazole [*i.e.*, Prilosec]."[17]

73. Therefore, even in the one study that showed a slight benefit of 20 mg Nexium over 20 mg Prilosec, the results of which the FDA reviewer found non-significant, AstraZeneca compared essentially non-equivalent doses. According to one clinician, "40 mg esomeprazole vs

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[16] *Id.* at 174.

[17] Stephen C. Stinson, *Chiral Drugs*, 78 SCIENT/TECHNOLOGY No. 43, 55-78 (October 23, 2000), available at: http://pubs.acs.org/cen/coverstory/7843/print/7843scit1.html. (last visited February 14, 2005).

20 mg omeprazole is closer to quadruple the dose, not double ... and the 20 mg vs 20 mg study was not a fair comparison of equal doses."[18]

74. Surprisingly, despite the greater amount of S-enantiomer in Nexium, Nexium does not work significantly better when comparing equal 20 mg doses of Nexium and Prilosec according to the FDA reviewer. Even though studies show that Nexium has greater bioavailability and controls gastric pH levels better than Prilosec, these differences do not translate into significantly better clinical outcomes. However, the increased dosage does result in a greater incidence of the most common side effects, including headache, abdominal pain, and diarrhea.

4. Skewing of the studies

75. It is important to note how AstraZeneca slanted the clinical trials. AstraZeneca chose to compare escalating doses of Nexium to the standard 20 mg dose of Prilosec. Instead of comparing likely equivalent doses (which would have been no more than 20 and possibly as little as 10 milligrams of Nexium, versus the standard 20-milligram dose of Prilosec) the Company used higher doses of Nexium. AstraZeneca escalated the dose of Nexium because it knew that the effect of PPIs is dose dependent or dose-related, yet only escalated the dose of Nexium, and did not escalate the dose of Prilosec. To be fair and objective, AstraZeneca should have escalated the dose of Prilosec as well. AstraZeneca acknowledges the dose dependency of PPIs in the package insert of Nexium; "By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion." Thus, with the trials designed in AstraZeneca's favor with escalating doses of Nexium, one would have expected Nexium to do much better than Prilosec. Yet, as noted, in two of the four trials, there

[18] Dr. Barbara Mintzes, Centre for Health Services and Policy Research University of British Columbia, posting on EssentialDrugs.org, June 7, 2002, available at: http://www.essentialdrugs.org/edrug/archive/200206/msg0016.php.

was no significant difference between Nexium 20 mg, Nexium 40 mg, and Prilosec 20 mg for the treatment of erosive esophagitis.

76. The FDA found, "There are no studies which demonstrate that H [Nexium] is superior to O [Prilosec], clinically or even statistically." The significant finding in these trials is that Nexium didn't do better than Prilosec did even at the escalated dose of Nexium 40 mg.

77. The objective conclusion from these studies that should have been part of AstraZeneca's disclosures to doctors and the Class would have been to simply double the standard dose of Prilosec, allow generic competition, sell Prilosec over-the-counter, and forget about the "New Purple Pill." However, such disclosures or treatment would not have helped the profit making objective of AstraZeneca.

78. Another deceptive aspect about using erosive esophagitis in a clinical trial to support the use of Nexium for simple heartburn is that erosive esophagitis can only be diagnosed by an invasive procedure called endoscopy. AstraZeneca knows that physicians are not going to perform an endoscopy, and diagnose erosive esophagitis, when a person first complains of heartburn. In other words, most patients who are given a prescription of Nexium are not being treated for erosive esophagitis, but for symptomatic GERD or simple heartburn, which AstraZeneca knows is just as effectively treated with Prilosec. Nevertheless, AstraZeneca used the data from the erosive esophagitis trials to persuade physicians and patients that the "New Purple Pill" should be prescribed over omeprazole for simple heartburn.

79. Finally, another deceptive aspect of the marketing of Nexium arises from the FDA review of Nexium's clinical trials. The FDA reviewer, for each indication of Nexium, found that 20 mg of Nexium is as effective as 40: "For this indication, as with the previous two, there is no benefit when increasing the H dose from 20 to 40 mg. Thus the recommended dose of Nexium is 20 mg once-a-day."

80. This recommendation presented a problem for AstraZeneca as the studies comparing 20 mg of Nexium with 20 mg of Prilosec showed no clinical difference between the

two. Thus, in order to make any claim, no matter how dubious, that Nexium was better than Prilosec, AstraZeneca had to boost the dosage of Nexium to 40 mg despite there being no clinical reason to do so. Interestingly, to keep 40 mg of Nexium as the dosing standard, so as to keep doctors prescribing Nexium over Prilosec, AstraZeneca prices 40 mg of Nexium at $4.76 and 20 mg of Nexium at $4.96. This discourages use of 20 mg of Nexium and doctors from asking the question of, "I am dosing 20 mg of Nexium at $4.96 per pill, why don't I use 20 mg of Prilosec at $0.67 per pill?"

D. The Promotion of Prescription Drugs

81. Promotional spending by pharmaceutical manufacturers has risen steadily in recent years, more than doubling from $9.2 billion in 1996 to $19.1 billion in 2001, an average annual increase of 16%. While most promotional spending (86%) remains directed at physicians, a growing proportion is directed at consumers, especially through television advertisements.

82. Pharmaceutical manufactures use several types of promotion, each of which has been growing in recent years and was employed by AstraZeneca to promote Nexium:

> ***Detailing*** (29% of spending) is the sales activities of drug representatives directed toward physicians. Most detailing is directed at office-based physicians ($4.8 billion), the rest at hospital-based physicians ($700 million).[19]
>
> ***Sampling*** (55% of spending) is the free drug samples that pharmaceutical representatives provide to office-based physicians. Sampling, valued at retail pharmacy prices, totaled $10.5 billion in 2001. Recently, samples are also being made available through DTC advertising venues like TV, newspapers, and the Internet.[20]
>
> ***Direct-to-Consumer (DTC) Advertising*** (14% of spending) includes advertisements targeted toward consumers through magazines, newspapers, television, radio, and outdoor advertising.[21]

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[19] Kaiser Family Foundation, *Impact of Direct-to-Consumer Advertising on Prescription Drug Spending*, at 3-4 (June 2003).

[20] *Id.*

[21] *Id.*

> ***Medical Journal Advertising*** (2% of spending) is the value of professional journal advertisements.[22]

83. While DTC advertising remains a relatively small part of overall industry promotion, its rapid spending growth in recent years (increasing an average of 28% annually from 1996-2001), frequent presence on television and in magazines, and extensive use in promoting newer, more expensive medications, have attracted the attention of critics who worry that it encourages patients to demand high-cost prescriptions for ailments that could be treated effectively with lower cost options. AstraZeneca's intent was to take advantage of this phenomenon and it succeeded in using its massive Nexium campaign, described below, to encourage consumers to make such demands.

84. A recent study by researchers at the Harvard School of Public Health (M.B. Rosenthal and A.M. Epstein), Massachusetts Institute of Technology (E.R. Berndt), and Harvard Medical School (J.M. Donohue and R.G. Frank) finds that DTC advertising has a significant effect on prescription drug spending.[23]

85. Significant findings from the study include:

> DTC advertising is an important, but not the primary, driver of growth in prescription drug spending. However, DTC advertising produces a significant return for the pharmaceutical industry: every additional $1 the industry spent on DTC advertising in 2000 yielded an additional $4.20 in sales.

E. A Massive Promotional Campaign Is Used to Establish Nexium as a Substitute for Prilosec

86. Having obtained FDA approval, AstraZeneca then promoted Nexium in a massive campaign, the Company deployed thousands of sales employees, made extensive use of sampling, and marketed the product to doctors and directly to consumers.

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[22] *Id.*

[23] The complete report of their study, *Demand Effects of Recent Changes in Prescription Drug Promotion*, May 29, 2003, can be found at www.kff.org. Last visited on May 26, 2005.

1. Promotion to doctors

87. To prepare its pitch to doctors, AstraZeneca flew its entire sales force of 6,000 to Hawaii where they spent an intensive session training on how to pitch Nexium. The sales force was trained to push Nexium even if doctors were resistant or happy with Prilosec. Teleconferences were held whereby the sales force rehearsed, before AstraZeneca sales executives, the sales pitch to be made to doctors.

88. After the training session a 6,000 person sales force flooded doctors' offices with free samples and claims of Nexium's superiority. A July 6, 2002 WALL STREET JOURNAL article depicts one type of pitch made to doctors:

> Peter Halper, an internist at a large group practice in Manhattan, has a computer given him by a drug-marketing firm on condition he chat with drug-company marketers via the Internet from time to time. Recently, he checked in with AstraZeneca. The face of a salesman popped onto his screen, asking him how he was and then launching into a pitch for Nexium.
>
> Dr. Halper asked the salesman why Nexium was better.
>
> "The proof's in the healing rates," said the live salesman, who cited data comparing 40 mg. of Nexium to 20 mg. of Prilosec. "We're safer, with no drug-to-drug interactions. We're also the No. 1 proton-pump inhibitor among gastrointestinal specialists." While he spoke, several graphs flashed on the screen.
>
> "So have I shown you how we differ from the other drugs?" the salesman asked. Dr. Halper said he had. "Do you need any more samples delivered?" No, Dr. Halper said, he had plenty.
>
> Minutes later, two salesmen from AstraZeneca arrived to talk to Dr. Halper about Nexium. They made sure to restock his cabinet with free Nexium. Since many physicians view Prilosec and Nexium as virtually identical, they often prescribe whichever one is in their free-sample closet. Patients who begin with free samples often continue with paid prescriptions, so the freebies are effective marketing tools.

89. AstraZeneca's 2000 Annual Report evidences some of the themes AstraZeneca used in marketing Nexium materials given directly to physicians:

> ***Nexium is the first PPI to offer significant clinical improvements over Losec in terms of acid control*** and clinical efficacy, shown in