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AstraZeneca, Prilosec, and Nexium:
Strategic Challenges in the Launch of a Second-Generation Drug

In early spring 2001, Tom McKillop, CEO of AstraZeneca, faced the classic quandary of large pharmaceutical firms. In October of that year, the firm's patent for Prilosec (active ingredient omeprazole) was expiring. Patent expirations were nothing new for the $15.8 billion in revenues drug firm, but Prilosec was the firm's most successful drug franchise, as well as one of the most financially successful drugs in history. In 2000 Prilosec contributed more than a third of AstraZeneca's revenues, with U.S. sales of $4.62 billion and total global sales of more than $6.2 billion. Following patent expirations, drugs quickly lost sales price and volume due to cost-competitive generic manufacturers, in some cases with dramatic impact on the incumbent patent-owning firm.

To combat the potential downside, McKillop considered a range of options, including a number of "franchise-extending" strategies. These included the introduction of a second-generation, follow-on prescription drug (new patent) branded as Nexium, as well as the possibility of introducing an AstraZeneca generic omeprazole and or an over-the-counter (OTC) version of omeprazole. Both the generic and OTC markets were unfamiliar territory for AstraZeneca. However, some of the marketplace goodwill developed during the patent monopoly phase of the life cycle could be used to influence consumer choice post-expiry. Additionally, the myriad of rights inherent in the Prilosec-Nexium patent portfolio could be used to sustain certain invention advantages in the future. But which strategies should be pursued and when? McKillop needed to consider the full range of possibilities.

Drug Development and Pharmaceutical Firm Success

In the high-risk industry of pharmaceuticals, only one in ten thousand new compounds made it to market to become a drug, and only 30 percent of drugs that made it to market recovered the cost of development for the company. On average, it required twelve years and approximately $500 million (this included the cost for failed drugs and opportunity costs) to bring a new drug to market (**Exhibit 1** and **Exhibit 2**).[1] In order to provide the return on investment required by investors, pharmaceutical firms had to introduce approximately five new products and one blockbuster (annual sales greater than $1 billion) per year. Because of the high cost necessary to

[1] J. Carey, "What's a Fair Price for Drugs," *Business Week*, April 30, 2001, 105–106.

bring a mainstream drug to market, a new product had to reach sales of at least $420 million per year in order to be profitable during its life. As a result of the costs and failure rates, large pharmaceutical firms had become reliant on blockbuster drugs for most of their sales and profits.

Moreover, a firm's ability to recover development costs and profit from drugs depended on its ability to acquire patents and trademarks that excluded all others from manufacturing and/or marketing a similar product (**Exhibit 3** and **Exhibit 4**).[2] Furthermore, firms filed patent applications on new drugs before the beginning of clinical trials. The longer the approval process for a new drug, the shorter the period of exclusivity provided by the patent. Once a patent expired, generic drug companies entered the market with a similar (bioequivalent) product at a lower price. This competition usually reduced the price and sales of the incumbent drug manufacturer by at least 50 percent within a year. Industry professionals referred to the sales trend pre- and post-patent expiry curve as the "shark fin."

Sales and Marketing in the Pharmaceutical Industry

In order to encourage doctors to prescribe specific products, companies employed large sales forces to promote their products. Sales calls on doctors, known as *details*, were the first line of attack for drug companies. In 2000 details accounted for almost half of the $15.5 billion drug companies spent on product marketing.

Sales and marketing professionals pitched the product by handing out free samples and promotional items and hosting events where doctors were paid to provide professional testimonials to their colleagues.[3] Unfortunately for the pharmaceutical industry, the effectiveness of these efforts could reach a saturation point as doctors received an increasing volume of sales calls. Industry data suggested that 60 percent of sales details resulted in a meeting with a doctor, and 90 percent of such meetings lasted less than two minutes.

In addition to courting doctors, drug firms had to negotiate with health maintenance organizations (HMOs), insurance companies, and other major payers for inclusion on their formularies (the list of drugs a payer would cover). Similarly, companies had to negotiate with major pharmacies that purchase large volumes. In order to be heard over the noise, drug firms increasingly turned to direct-to-consumer marketing, targeting patients and their families.[4]

Regardless of the channel, a drug could only be marketed for uses (indications) approved by the Food and Drug Administration (FDA). While additional indications could expand the market for a drug, the approval process became more costly and time consuming for each additional indication.[5] However, trials also documented side effects, which could be used to differentiate

[2] M. Hart and H. Zaharoff, "The Protection of Intellectual Property in the United States," Case #9-897-046 (Harvard Business School Publishing, 1996).

[3] J. P. Shapiro and S. Schultz, "Prescriptions: How Your Doctor Makes the Choice," *U.S. News & World Report*, February 19, 2001, 58–61; C. Adams, "Doctors on the Run Can 'Dine 'n' Dash' in Style in New Orleans," *Wall Street Journal*, May 14, 2001; A. Brandenburger, "Bitter Competition: The Holland Sweetener Company versus NutraSweet (A)-(G)," Case #9-794-079 through 9-794-085 (Harvard Business School Publishing, 1993).

[4] L. Belkin, "Primetime Pushers," *Mother Jones*, March/April 2001, 30–37.

[5] S. Hensley and T. M. Burton, "Mind Games: Pfizer, Lilly Spar for Schizophrenia Market," *Wall Street Journal*, May 8, 2001; Z. Moukheiber, "Silencing the Voices," *Forbes*, May 14, 2001, 266–268; R. Langreth, "Reviving Novartis," *Forbes*, February 5, 2001, 90–96.

drugs from competitors. The allergy drug Claritin (loratadine), with sales of $2.7 billion in 1999, dominated its market after arriving to market later than other allergy drugs. Despite exhibiting similar and in some cases *lower* efficacy than competing drugs, Claritin lacked the significant side effect of drowsiness, a fact leveraged heavily in promotions to doctors and consumers.[6] Ultimately, doctors could prescribe drugs for any condition for which they saw fit, whether for approved indications or not, a practice referred to as *off-label* prescription (**Exhibit 5**).

AstraZeneca, Prilosec, and Direct-to-Consumer Marketing

AstraZeneca

Astra had its beginnings in 1913 as a small pharmaceutical company near Södertälje, Sweden, south of Stockholm. In 1982 Astra AB signed an agreement with Merck & Co. for cooperation in the United States. According to the agreement, Astra gave exclusive U.S. rights to develop and market most of its compounds to AstraMerck, a division of Merck.

In 1988 Astra launched its acid-pump inhibitor, omeprazole, in the United States through AstraMerck as Prilosec and internationally as Losec. Losec could not be marketed in the United States under that name because the FDA's division of Drug Marketing, Advertising, and Communications (DDMAC) believed it sounded too similar to Lasix, an unrelated diuretic drug. By 1996 Prilosec/Losec had become the world's top-selling pharmaceutical drug.[7]

In 1994 AstraMerck was spun off from Merck into a separate joint-venture company owned equally by Astra and Merck. In July 1998 the advanced formulation of Prilosec, Prilosec MUPS (multiple unit pellet system) tablets, reached its first markets. Concurrently, Astra AB purchased Merck's share of AstraMerck for $5 billion and consolidated it with Astra's U.S. subsidiary, Astra U.S.A.[8]

On April 6, 1999, Astra AB of Sweden officially merged with London-based Zeneca Group to form AstraZeneca (AZ).[9] Zeneca was formed in 1993 as a result of Imperial Chemical Industries (ICI)[10] spinning out three of its business units—pharmaceuticals, agrochemicals, and specialties—into a separate company. The merger came at a time when many other European and American firms were merging to increase R&D capabilities and sales forces in order to better compete in the growing North American market. Astra brought to the merged company a collection of antiulcer, cardiovascular, antiasthma, and anesthetic products and 2,200 sales representatives. Zeneca offered its strengths in oncology, anesthetic, cardiovascular, and respiratory medicines and 2,000 sales representatives.[11]

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[6] S. S. Hall, "Claritin and Schering-Plough: A Prescription for Profit," *New York Times Sunday Magazine*, March 11, 2001.

[7] http://www.astrazeneca.com/NewsSection/newsreleases/21699_96.htm (accessed December 2000).

[8] J. Weber and A. Barrett, "Volatile Combos: Pharmaceutical Alliances Can Boost Both Players' Health—Or Drag Them Both Down," *Business Week*, October 25, 1999, 122.

[9] http://www.astrazeneca.com/Investors/Annual_and_interim_reports.htm (accessed February 2001), http://www.astrazeneca.com/Annualrep1999/index.htm (accessed December 2000).

[10] ICI was originally formed in 1926 when the British Dyestuffs Corporation merged with three other companies.

[11] McKnight Medical Communications, http://www.pharmrep.com/articles/1999/2/P990210.html (accessed February 2001); AstraZeneca, http://www.astrazeneca.com/AboutUs/Our_history.htm (accessed April 2001).

GERD and Prilosec: The Problem and the Solution

The prescription drug omeprazole that AZ branded as Prilosec was used to treat acid reflux–related indications. In the lining of the stomach millions of cells, known as "pumps," produce and secrete acids required to digest food. Excessive acid secretion can lead to a host of disorders such as duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD, acid reflux disease, or heartburn), and pathological hypersecretory conditions (**Exhibit 6** and **Exhibit 7**). Prilosec was the first marketed product in the class of drugs known as acid pump inhibitors. This class of drug indications was recognized by physicians as far better than previous classes of drugs for the treatment of the diseases mentioned above (**Exhibit 8**, **Exhibit 9**, and **Exhibit 10**).[12] Prilosec was discovered and patented by Astra AB and had been marketed in the United States since 1989.[13] In addition to the efficacy advantages of Prilosec, its market success was related to the direct-to-consumer marketing phenomenon.[14]

Direct-to-Consumer Marketing

Pharmaceutical companies spent approximately $1.7 billion on direct-to-consumer (DTC) television advertising in 2000, 50 percent more than in 1999 and more than double the amount in 1998. In December 1997 twelve drugs were marketed through DTC campaigns. By the end of 2000 more than fifty drugs were being marketed through DTC campaigns.

The FDA's division of Drug Marketing, Advertising, and Communications regulated DTC activities. Its survey research found that among patients that recently visited their doctors, 72 percent recalled having seen or heard an ad for prescription drugs in the previous three months, mostly on television. Close to 25 percent of these people asked their doctors for the first time about the condition or illness. Of those patients who asked for a specific drug by name, nearly half were given a prescription for it, while doctors only recommended a different drug in 21 percent of the cases.[15] Doctors optimized revenue and profitability by maximizing the number of patients they could see on a given day. As such, it was often easier to acquiesce to a patient's demands rather than explain alternatives, assuming the drug in question was appropriate for a patient's condition. The DDMAC monitored DTC marketing in order to protect insufficiently informed patients who might easily be misled or develop unrealistic expectations as a result of inappropriate ads. Likewise, doctors and insurers sometimes expressed concerns to the FDA over the promotion of costly drug use encouraged by DTC marketing.[16]

The explosion of DTC marketing had occurred as a result of the August 1997 changes to some of the FDA's thirty-year-old drug marketing regulations. Prior to that time, the FDA required drug manufacturers to include the entire consumer warning label in any pitch relating a disease indication and the product intended to treat it. Such thoroughness was usually not possible in a thirty-second television slot nor was it a particularly attractive option, given the extent of side effects the FDA required firms to mention. It was possible to fulfill the FDA's requirements in magazine advertisements; however, ads could only mention the disease or the product, not both. After many years of lobbying by advertising agencies, pharmaceutical firms, and television

[12] http://www.priloseconline.com (accessed February 2001).

[13] P\S\L Consulting Group Inc., http://www.pslgroup.com/dg/6f9a.htm (accessed May 2001).

[14] G. Naik, "AstraZeneca Wins U.S. Clearance to Sell Its Follow-Up to Prilosec," *Wall Street Journal*, February 22, 2001.

[15] L. Belkin, "Primetime Pushers," *Mother Jones*, March/April 2001, 30–37.

[16] C. Adams, "FDA to Review Policy Allowing Drug Ads on TV," *Wall Street Journal*, March 28, 2001.

networks, the 1997 rule revisions allowed television commercials to name both the product and disease. Nonetheless, ads had to mention the primary risks of the drug, as well as direct viewers to other sources of information such as Web sites, magazine ads, and toll-free numbers (**Exhibit 11**).

How Did Prilosec Become So Successful?

Merck originally introduced Prilosec in the United States for limited indications, including short-term, nonmaintenance therapy for duodenal ulcer and poorly responsive GERD. The product proved highly effective, but was only marketed to specialists. By 1994 it held 12 percent of total prescriptions in the antiulcer market. At this point, Merck transferred the drug to the newly spun-out AstraMerck. AstraMerck created a new brand image for the product, making Prilosec user friendly for doctors and patients. Sales rose 47 percent in 1995 to $1.2 billion, and market share increased to 18 percent. In 1997 AstraMerck launched a DTC campaign (**Exhibit 12**), and by the following year the firm was spending $50 million on Prilosec DTC marketing. As a result, the product garnered more than 30 percent of the market in 1998. In 1999 AZ spent $79.5 million on Prilosec ads out of the firm's total DTC expenditure of $170.3 million, while sales rose 27 percent to $3.8 billion.[17]

In 1997 Zantac, a competing product, lost its patent protection. Although a much less expensive alternative, most promotional efforts for Zantac had ended as a result of the loss of patent protection. Zantac's market share dropped from 41 percent in 1994 to less than 5 percent in 1998. Concurrent with Prilosec, TAP Pharmaceuticals's Prevacid won an 18 percent market share partly as a result of a DTC campaign. In 2001 Prilosec had about 35 percent of the total antiulcer prescription market ahead of Prevacid's 20 percent.

While promoting Prilosec, AZ was careful to maintain doctors' acceptance by telling consumers to see their doctors about GERD. Moreover, they introduced patient-friendly advertising by naming the drug the "Purple Pill" (Exhibit 3 and **Exhibit 13**), employing cartoon-like images and copy lines such as, "If your heartburn medicine works so well, why do you keep getting heartburn?" The advertising campaign was very successful, with 68 percent of consumers recalling and identifying the print ad, 21.3 percent identifying the product, and 73 percent of physicians recalling the ad and the product. In 1998 physicians granted a prescription for Prilosec to 93 percent of patients that requested the drug.

The Healthcare/Food and Drug Regulatory Environment

The Hatch-Waxman Act and the Generics

In 1984 the U.S. Congress transformed the rules of the game for generic drug makers (generics) with passage of the Drug Price Competition and Patent Term Restoration Act, or Hatch-Waxman Act. Under the Act, the FDA granted an extension to the patent for time lost due to FDA drug review (Exhibit 2). The authorities determined the extension by how long the drug

[17] L. Belkin, "Primetime Pushers," *Mother Jones*, March/April 2001, 33.

spent in each phase of FDA trials, and the patent holder had to show promptness and due diligence during the clinical trial process.

The average patent extension was two and a half to three years, with the maximum allowable extension of five years, or fourteen years from the date of original FDA approval, whichever was less. The FDA granted a five-year exclusivity for newly approved drugs regardless of the patent situation, which was particularly necessary for drugs nearing the end of their patent life at the time of approval.[18] Hatch-Waxman also granted a three-year exclusive marketing period for an approved supplemental new drug application (SNDA) for a new indication of a drug. Thus, besides seeking new indications to expand the market, companies could pursue new indications or formulations with clinical trials simply to get the three-year exclusivity. As a result, firms had the option to wait for the drug to near patent expiration to introduce a new indication, even though such approval might have expanded the market for the drug if introduced earlier.

Perhaps the most substantial impact of Hatch-Waxman was to expand the opportunities for generic drug makers. For the first generic to file and have its abbreviated new drug application (ANDA) approved, the Act gave six months of exclusive generic marketing rights following the expiration of the drug's patent protection. It also gave generic firms the freedom to test and manipulate patented drugs to develop a generic equivalent and seek FDA approval as long as they did not sell the product before patent expiration. This limited the original patent-owning drug firms' power to sue for patent infringement. Generic drug makers could also file for approval if they showed that their product did not infringe other firm's patents or that a patent was invalid. This allowed generic firms to prepare FDA-approved, bioequivalent, generic versions of drugs for release as soon as a patent expired or even earlier.

Since passage of Hatch-Waxman, generics had captured an increasing percentage of the off-patent pharmaceutical market. Soon after generic entry, revenues and prices of the incumbent products declined. Generic substitutes were priced based on production and distribution costs alone. Pharmaceutical incumbent drug prices had to also recover the firm's massive R&D and FDA approval investments. As a result, the price of generics could be substantially lower.

Esomeprazole Magnesium: The New Gold Standard

Faced with the prospect of an expiring patent on Prilosec, its most important product, AZ considered a novel branding strategy in order to extend the Prilosec/Losec franchise. Nexium, the brand name of AZ's new product, represented a reformulated version of Prilosec's active ingredient, omeprazole, called esomeprazole magnesium. After completing clinical trials, the company submitted a new drug application (NDA) to the FDA, which approved Nexium for GERD on February 22, 2001. With new patent protection in hand, AZ planed to launch the drug in the United States in March 2001 and soon thereafter in nine European countries.

[18] Exclusivity was granted upon approval of a drug product if the statutory requirements were met. Some drugs had both patent and exclusivity protection while others had just one or none. Patents and exclusivity might or might not run concurrently and might or might not encompass the same claims. Exclusivity was not added to the patent life. Thus, companies could only pursue various exclusivity strategies when the patent was near expiration to avoid overlap. FDA/Center for Drug Evaluation and Research, http://www.fda.gov/cder/ob/faqs.htm#What is the difference between patents and exclusivity? (accessed June 2001); Michael Strong, "FDA Policy and Regulation of Stereoisomers: Paradigm Shift and the Future of Safer, More Effective Drugs," *Food and Drug Law Journal* 54 (1999): 481, http://www.fdli.org/pubs/Journal%20Online/54_3/art%2011.pdf (accessed September 2000).

AZ's branding strategy positioned Nexium as the new gold standard of acid pump inhibitors.[19] According to the firm, the human body better absorbed the drug and patients could get heartburn relief in five days with Nexium compared to seven to nine days with Prilosec.[20] In addition to promoting the efficacy of the drug relative to Prilosec, generics, and competing drugs, AZ trademarked both Nexium and the "Purple Pill" as trade dress (Exhibit 3 and **Exhibit 14**).[21]

Why Call the New Formulation Nexium?

McKillop and the AZ team believed they could create a new brand to ward off patent expiration by representing Nexium as a new product rather than a simple reformulation.[22] AZ expected the brand identity of Nexium to distance the product from Prilosec in the minds of patients while also leveraging existing brand equity. The firm hoped that the Purple Pill brand identity, developed through years of DTC marketing under the Prilosec name, would transfer to Nexium. Additionally, since Prilosec was called Losec outside the United States, the transition to Nexium offered an opportunity to create a unified, global brand.[23]

Moreover, drug marketing regulations restricted firms from making claims of superiority associated with the name of existing products, for example, Supra Prilosec. AZ could have called esomeprazole magnesium "Prilosec XR" (extended release) or employed a similar name, such as the Clarinex brand of Claritin's next-generation formulation. Such titles tied the product to the original drug but failed to highlight them as new and better products.[24]

Nexium, when marketed as the Purple Pill, created an association with all of the capabilities ascribed to Prilosec. When marketing to doctors, salespeople promoted Nexium as a better formulation of Prilosec. As such, rather than repeating all the clinical trials conducted on Prilosec for conditions in addition to GERD, doctors familiar with Prilosec could similarly prescribe Nexium for off-label indications.

To the Future . . .

The Nexium case highlights several issues concerning the branding and patent protection of pharmaceuticals. If a drug can treat different diseases, it might be useful to market the same drug

[19] AstraZeneca's strategy was similar to Pfizer's when it sought to switch doctors and patients from Procardia XL (nifedipine), a first-generation drug for high blood pressure, to Norvasc (amlodipine), a third-generation drug, and Bristol-Myers Squibb's when it sought to switch people from its diabetes drug, Glucophage (metformin), to an improved version that combined Glucophage with another common diabetes drug, Glucovance (glyburide and metformin). Essentially salespeople flooded doctors' offices and marketed the new improved product as the new gold standard.

[20] However, other sources suggested that Nexium was only 3 percent more effective than Prilosec. As companies come out with new versions or formulations of drugs, many are not necessarily much more effective but rather slightly better or more convenient to take. A possible exception was Prozac Weekly, which unlike other reformulations such as Nexium, Glucovance, and Clarinex, stood to be a major improvement in convenience and could justify the higher price than generics (see Exhibit 5). Another such example would be oral, rather than intravenous, cancer treatments.

[21] http://www.purplepill.com (accessed June 2002). In the pharmaceutical industry, the price of a product did not necessarily correspond to the quantity—at least with patented products—but rather was calculated based on the treatment of a disease that might require different doses at different times or for different severities of the disease.

[22] Pursuing this strategy ran counter to the historic market experience of Zantac and other drugs.

[23] Esomeprazole magnesium (Nexium), as a new formulation of Prilosec, would have to apply for an NDA and Orange Book entry.

[24] Prozac had a Prozac Weekly, which used the old brand but tied into it the idea of increased convenience.

under different brands to avoid confusion in DTC advertising. For example, Eli Lilly marketed the same drug in Prozac as a treatment for PMS in woman under the brand Serafem. This also provided an opportunity to extend patent protection by applying the same drug to different conditions. Patents with different expirations for different indications of the same or substantially similar drugs could effectively extend patent protection beyond a single patent if managed properly.

The Nexium strategy was unlikely to be sufficient on its own, based on consideration of the failure of a similar strategy employed by Bristol-Myers Squibb (BMS) for its diabetes drug Glucophage. BMS's sales force promoted the improved version, Glucovance, as a slightly better drug in the hopes that doctors and patients would prefer it at a higher price to the generic.[25] Additional actual and/or perceived value of an improvement drug might or might not be sufficient to entice patients, doctors, and payers to incur high costs. As such, AstraZeneca needed to consider complementary franchise extension measures.[26]

As of 2001, it remained to be seen how effective the AstraZeneca brand-based approach to Nexium would be over time. With key drug patents expiring throughout the industry, competing firms were waiting anxiously to see if AstraZeneca's strategy succeeded in preserving its lucrative franchise.

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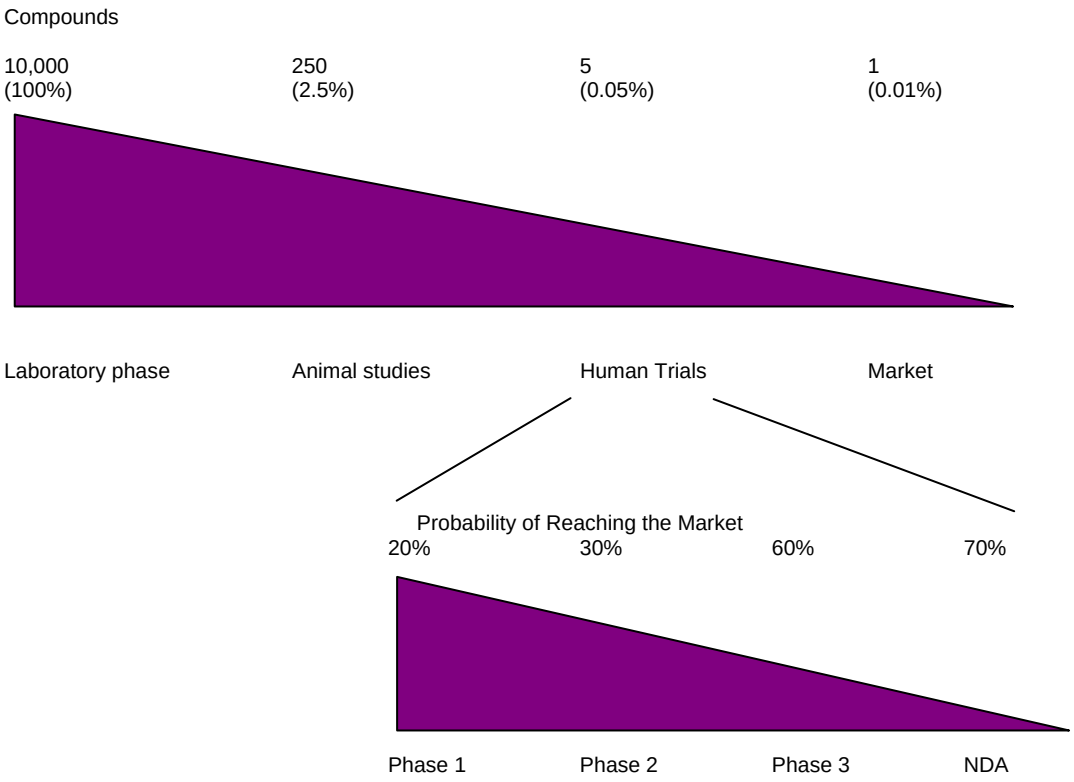
[25] G. Harris, "Bristol-Myers Fights to Lock in Patients Before Generics Hit," *Wall Street Journal*, May 21, 2001.

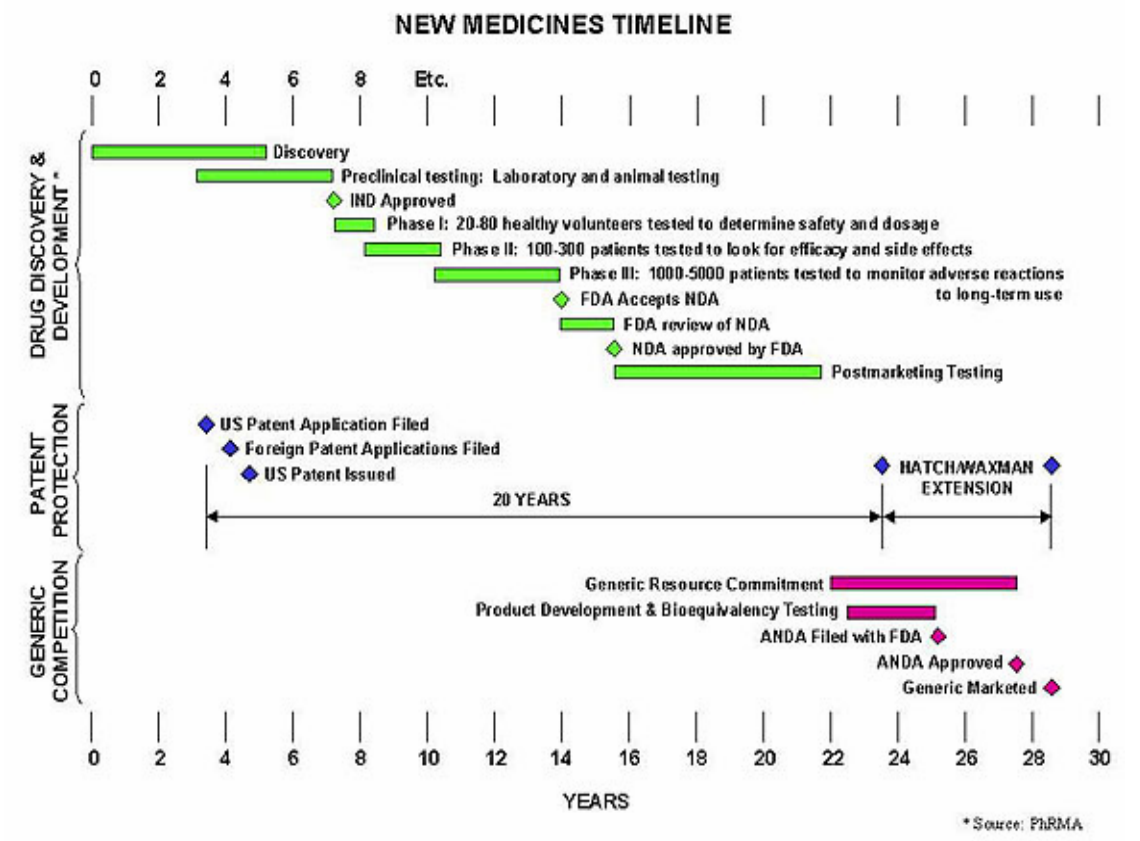
[26] In the case supplement, we review a number of strategic alternatives employed by pharmaceutical firms. If the instructor provides the supplement, think about which alternatives might be compatible or incompatible with the Nexium branding strategy, and how AstraZeneca might employ additional measures to garner more value from the drug.

Exhibit 1: Drug Development Stages and Success Rates



Percentage of compounds and probability of success to make it to market at each stage of drug development and FDA approval (Exhibit 2 and Exhibit 8).

Exhibit 2: Timeline of Patent and FDA Approval, with Hatch-Waxman Extension



An investigative new drug (IND) application to the FDA sought approval to test an agent in humans. There were numerous parallels to patent issuance and FDA approval. In filing a patent(s) for a product with the United States Patent and Trademark Office (USPTO), the applicant sought approval for as many claims as possible in order to broaden protection for a product, much as a drug firm attempted to get as many uses (indications) as possible approved by the FDA. Both had a prosecution phase, where the patent or drug had to show its merits and the FDA or USPTO reviewed the claims or indications associated with the drug or patent application, often limiting them. With patent issuance and FDA approval, certain claims or indications could be expanded with future research. The Hatch-Waxman Act opened up new possibilities for extending drug patents by (1) recovering time lost due to slow FDA approval and (2) receiving a three-year extension of exclusivity by developing a new indication.

Exhibit 3: Prilosec, Nexium, the Purple Pill, and AstraZeneca Trademarks and Trade Dress

www.purplepill.com

While a trademark could not have functional value, it could still hold great value, particularly in the age of direct-to-consumer marketing. Consumers might not understand the science behind a drug, but they could certainly recall a drug's name and understand how it could help. In contrast to a patent, a trademark had indefinite life as long as it was properly used as a unique source identifier. A trademark died if it became a generic noun, for example, elevator, aspirin (U.S. only), and cellophane.

The lifecycle costs of a trademark were related to how unique and descriptive it was. A unique and nondescriptive trademark would have lower costs to maintain than a common descriptive one. As such, drug names were often unique, nondescriptive, and arbitrary. Besides the color, the shape of the pill could also be considered trade dress. Therefore, companies used pills with distinctive shapes and colors.[27]

Nontraditional brand elements such as colors, shapes, sounds, smells, or dynamic animations could, if properly marketed, become secured as trademarks via trade dress. The subliminal aspects of product packaging and promotion could be important cognitive touch points of the user experience upon which brand loyalty could be built in the long run.

[27] Novartis's cancer drug, Gleevec (STI571), was a yellow pill, Pfizer's Viagra (sildenafil) was a blue tablet, Merck's Zocor (simvastatin) was a purple tablet. Both Zocor and Viagra pills came in unique shapes.

Exhibit 4: Patents

Firms filed patents with the USPTO. The policy purpose of patents was to motivate investments in particular inventions that advanced a technology frontier. Successful patent applicants were awarded a limited-life monopoly on their claimed inventions so that they alone could profit and delay market entry of generic cost-based competition. Even with a patent, products remained exposed to competitive pressure from newer and better alternatives.

Relative to drug compounds, a pharmaceutical company could file any of four types of patent claims:

- a compound claim for a chemical entity
- a composition claim for a chemical entity used as a pharmaceutical (a formulation of the drug)
- a method-of-use claim for the use of a chemical compound or composition in a specific manner
- a process claim or method-of-manufacture claim for how to produce a particular compound or composition[28]

The process of drug discovery and development yielded extended protection because firms normally staggered the filing of various patents related to the production and application of a drug over time.

For example, after a firm identified a molecule in the lab and showed it to have a biological effect, the company would file a patent with claim to its structure and method of use. Following further research, the firm would file a patent on the formulation of the drug, stating a composition claim, followed eventually by a production process patent application. Via a *continuation*, it was also possible for new claims to be added to a previous patent if it was still being prosecuted. Since November 2000 the USPTO had granted extensions of the patent life if the prosecution process was slow due to USPTO internal delays and not due to the applicant.

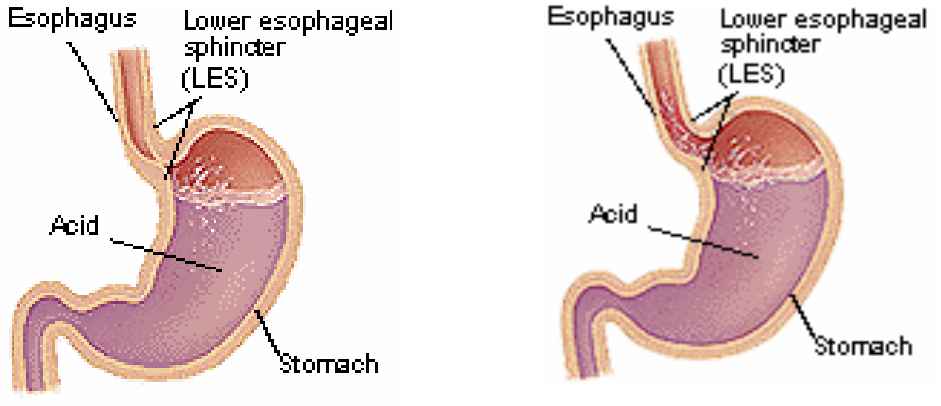
[28] E. Ledbetter, "Cornerstone of an Industry: Part II: Extending the Lives of Key Drug Patents," *Modern Drug Discovery*, May 2000, 81–84.

Exhibit 5: Off-Label Usage and Newly Developed Indications and/or Combinations

Given off-label prescriptions, there was little stopping doctors from prescribing a generic for any of the indications claimed for the original drug, even if these other indications might still be covered by patents. This included patents on new combinations of drugs that had come off their original, individual patents. It could be difficult to enforce combination patents because doctors recognized the availability of generics for each combination component patent. Moreover, a drug company would be very unlikely to attempt to enforce a patent against doctors. They were crucial decision makers influencing drug purchasing behavior.

Furthermore, various payers' formularies could only include the generic so that it was used for all indications, even if some indications remained patent protected. Nonetheless, payers could not specifically list the generic as a covered drug for patent-protected indications, as that would constitute patent infringement.[29]

Exhibit 6: Lower Esophageal Sphincter



The lower esophageal sphincter (LES) opens to allow food and drink to pass from the esophagus to the stomach. Most of the time, the LES remains closed to prevent stomach juices from going up the esophagus. The stomach has built-in protection against the harsh digestive acids present in these juices. This is fine if the juices remain in the stomach, helping with digestion. In people who have acid reflux disease or GERD, the LES relaxes more often than it should and/or at inappropriate times. The term for this is "LES relaxation." This allows harsh stomach juices to back up into the esophagus. Unlike the stomach, the esophagus has no natural protection. When these juices make contact with the esophagus, heartburn or other acid reflux disease symptoms can occur, potentially resulting in damage.

[29] Blue Cross and Blue Shield of Illinois, a division of Health Care Service Corporation, http://www.bcbsil.com/formulary/gastro.htm (accessed March 2001).

Exhibit 7: Prilosec and Ulcers, *H. pylori*, and GERD

An ulcer is a lesion that forms in the stomach lining or the upper small intestine (duodenum). Stomach ulcers are usually larger, causing a higher mortality rate than duodenal ulcers. Ulcers affected approximately 5 million Americans every year, with 1 million requiring hospitalization. Experts calculated that 10 percent of the population would have an ulcer in their lifetime. They were estimated to cost the healthcare system more than $2 billion per year in direct costs and more than $500 million in indirect costs, for example, lost time at work. Symptoms include some combination of a gnawing or burning pain in the upper abdomen, often between meals and early in the morning, nausea, vomiting, and loss of appetite or weight. Ulcers can develop at any age, but they are most prevalent in people over the age of thirty.

Clinical trials showed that Prilosec healed gastric ulcers within eight weeks for 85 percent of the patient population. It had been used in well over 135 million cases worldwide and had a few mild and transient side effects such as headache, diarrhea, abdominal pain, and nausea. The recommended daily dose for gastric ulcers was 20 to 40mg daily for four to eight weeks.

For many years, ulcers were believed to be caused by stress and diet, but later research showed that they are the result of an imbalance in the secretion of digestive fluids by the stomach and its protective lining. The damage to the stomach and duodenal tissue is due to both improper acid secretion and the presence of the bacterium *H. pylori*, which was discovered in 1983. *H. pylori* was found to secrete substances damaging to the protective mucus in the stomach, causing inflammation and ulcers in 90 percent of patients. On April 15, 1996, the FDA cleared Prilosec's use in combination with an antibiotic for the treatment of *H. pylori* infection. Clinical trials showed the combination therapy to be effective at eradicating 83 percent of *H. pylori* cases with ulcer recurrence as low as 5 percent six months after therapy completion. The combination therapy presented only mild side effects, which were similar to those accorded Prilosec. Ulcers could now be cured, whereas prior treatments required many people undergo lifelong, antiulcer treatment.

Many people experienced heartburn, but those who did so more than two to three times a week and had severe enough symptoms might have had GERD, a condition affecting 19 million Americans. Approximately 20 to 30 percent of Americans experienced heartburn at least once a month. About 7 percent of adults in the United States experienced daily heartburn, which might be indicative of acid reflux disease. Estimates showed that 65 percent of adults suffered heartburn and 24 percent had symptoms for more than ten years. GERD sufferers experienced some or all of the following: heartburn (the most common symptom), sour or bitter taste from regurgitation of stomach contents, difficult or painful swallowing, chest discomfort or pain and tightness, nausea, laryngitis, cough, and shortness of breath. The chest discomfort or pain could be severe enough to mimic a heart attack. Besides ulcers, GERD could also lead to pre-cancerous changes within the lining of the esophagus. On December 2, 1996, the FDA cleared Prilosec to be used as the initial therapy for symptoms associated with GERD. It was the first drug in the class of acid pump inhibitors to receive this indication.[30]

[30] P\S\L Consulting Group Inc., "Prilosec Cleared by FDA for Heartburn and Other Symptoms of GERD," Doctor's Guide Global Edition, http://www.pslgroup.com/dg/e556.htm (accessed August 2001); P\S\L Consulting Group Inc., "FDA Clears First Combination Therapy To Cure Cause of Ulcers," Doctor's Guide Global Edition, http://www.pslgroup.com/dg/77b6.htm (accessed August 2001); Allergy Health Care, http://www.allergyhealthcare.com/gastro.htm (accessed July 2001).

Exhibit 8: Prilosec and Its Competitors

Prilosec (omeprazole) and the acid pump inhibitor class of drugs represented a major improvement in reducing acid production over the former class of drugs, namely Tagamet, Pepcid, Axid, and Zantac (cimetidine, famotidine, nizatidine, and ranitidine, respectively). These drugs blocked histamine H_2 receptors in the gut. When histamine acted on these receptors acid was made. Side effects could include diarrhea, dizziness, rashes, and slight enlargement of the breasts.[31] The H_2 blockers were an improvement on the class of drugs known as antacids, for example, Maalox, Mylanta, Rolaids (aluminum and magnesium or calcium carbonate), and metal compounds that bind to acid, reducing the free acid in the stomach.[32] Compared to acid pump inhibitors, the H_2 blockers and antacid classes of drugs were only used for less serious conditions involving excessive stomach acid. They were available over the counter, which meant that buyers did not require a prescription.[33]

Prilosec's primary competition prior to patent expiration came from its own class of acid pump inhibitors. Assuming multiple competing drugs under patent in a particular market (market defined by either a disease or new class of drugs), the first drug to enter a market was typically priced higher and captured 60 percent of the market, while the second drug was priced lower and garnered 30 percent. Remaining drugs in the class were priced even lower and tended to take the remaining 10 percent. In some cases, however, drugs had entered the market second or later and still dominated the market.

It helped for later entrants to show greater efficacy or safety, but it was not always necessary. As none of the other drugs in the acid pump inhibitor class had been proven in clinical trials to be better than Prilosec, competition was largely based on price and sales force. The major competitor for Prilosec in the U.S. market was Prevacid (lansoprazole), marketed by TAP Pharmaceuticals.[34] With similar indications to Prilosec, Prevacid was priced slightly lower. Another drug in the class, Protonix (pantoprazole sodium), had more limited indications than Prilosec or Prevacid, but was substantially cheaper.[35]

Table 1: U.S. Sales of Prescription Gastrointestinal Treatments by Firm, Proton Pump Inhibitor Class

	2000 ($ in billions)	1999 ($ in billions)	% Growth	Dose	Price/Pill
Prilosec (AstraZeneca)	4.18	3.80	10%	20mg	$3.45–$4.10
Prevacid (TAP)	3.15	2.36	33%	30mg	$3.35
Aciphex (Eisai)	0.37	0.03	NA[a]	20mg	$3.15
Protonix (American Home Products)	0.14	NA	NA	40mg	$2.50
Total Market	8.27	6.58	26%	—	

[a] 1999 number partial year only, received FDA approval in August 1999.

[31] http://www.globalchange.com/tagamet.htm (accessed April 2001); http://www.focusondigestion.com/script/main/Ques.asp?li=DIG&QaKey=20178 (accessed October 2006).

[32] Micromedex, Inc., http://www.nlm.nih.gov/medlineplus/druginfo/antacidsoral202047.html#SXX05 (accessed April 2001).

[33] Doctor's Guide Publishing Limited, http://www.pslgroup.com/dg/9afa.htm (accessed June 2001).

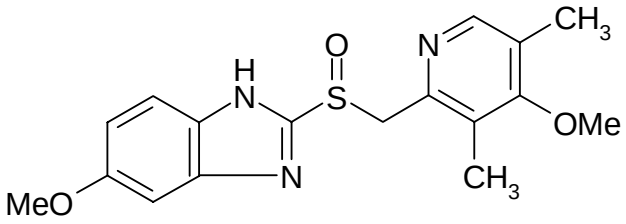
[34] TAP Pharmaceuticals was a 50-50 joint venture between Takeda Chemicals of Japan and Abbott Laboratories.

[35] Wyeth Laboratories, http://www.protonixrx.com/pro_conhomepage.html (accessed June 2001); W. J. Guglielmo, "Prescription Drugs at Bargain Prices," *Newsweek,* April 23, 2001, 62.

Exhibit 8 *(continued)*

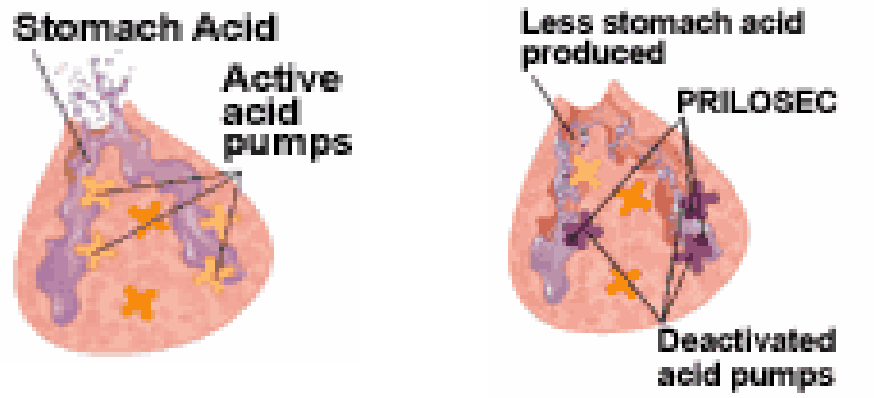
As patents expired, generic drug makers could enter the market after submitting and receiving approval for an abbreviated new drug application (ANDA). The primary control the FDA placed on generic drugs was that they had to be the same as the original drug, known as *bioequivalence*, although this did not mean they had to be produced in the same manner. As a result of bioequivalence, the FDA assumed that the efficacy and safety of the generic was proven by the original manufacturer's original clinical trials (Exhibit 2). Frequently HMOs, insurance companies, and other major payers could switch immediately to pay for only the cheaper generics without consulting doctors or patients.

Exhibit 9: Prilosec Delayed-Release Capsules Active Ingredient



The active ingredient in Prilosec (omeprazole) delayed-release capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1 H-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, slightly soluble in acetone and isopropanol, and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media but has acceptable stability under alkaline conditions. Prilosec is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains either 10, 20, or 40mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, mannitol, sodium lauryl sulfate, and other ingredients.

Exhibit 10: Prilosec's Effect on Stomach Acids



Each acid-producing cell contains millions of acid pumps. Proton pump inhibitors work by decreasing the acid produced by these pumps. As illustrated by the graphic, Prilosec turned off (deactivated) some of the pumps to keep acid production under control. By reducing acid production in the stomach, Prilosec reduced the chance of acid backing up into the esophagus and causing reflux symptoms.

Exhibit 11: Examples of DTC Marketing and FDA Regulation

The Roche Group was able to market its weight loss drug, Xenical (orlistat), without naming the side effects. The company aired two commercials separated by unrelated commercial time. The first ad depicted a baby morphing into a heavyset woman and described the condition of unhealthy weight gain. The second ad employed the same background image and music, only mentioning the drug name and directing people to speak with their doctor. The disease and the drug were not mentioned in the same commercial, so side effects were not mentioned, per the FDA's rules. In Xenical's case, mentioning side effects would have included, "you may experience gas with oily discharge, increased bowel movements, an urgent need to have them and an inability to control them."[36]

In 2001 the FDA ordered Schering-Plough to cease its magazine ads for Claritin employing a similar strategy. Schering-Plough presented back-to-back ads lacking unrelated intervening ads that "convert[ed] the presentation into one full-product ad for Claritin," proving misleading given the lack of side-effect information.[37] Although the FDA regulated DTC advertising content, occasionally intervening to encourage full disclosure, the ads had often already been widely circulated.

[36] On May 18, 2001, the FDA ordered Roche to stop showing the advertisement. Reuters Limited and Yahoo, Inc., May 18, 2001, http://dailynews.yahoo.com/h/nm/20010518/hl/ads_1.html (accessed May 2001).

[37] C. Adams, "Xenical Ads Avoid Listing Unpleasant Side Effects," *Wall Street Journal*, April 3, 2001.

Exhibit 12: The Prilosec DTC Advertisements

Due to former FDA rules, the original Prilosec ads were help-seeking ads describing GERD, recommending consultation with a doctor. A few product reminder ads were used that portrayed a woman in a purple gown in front of a clock surrounded by purple pills, accompanied by the slogan, "It's Prilosec Time." While AstraZeneca's updated Prilosec campaign followed the FDA's new DTC rules, mentioning the disease, drug, and side effects, some ads remained simply product reminder ads. The campaign included television, print, billboard, and Internet media.

Exhibit 13: Examples of Nexium DTC Print Advertising

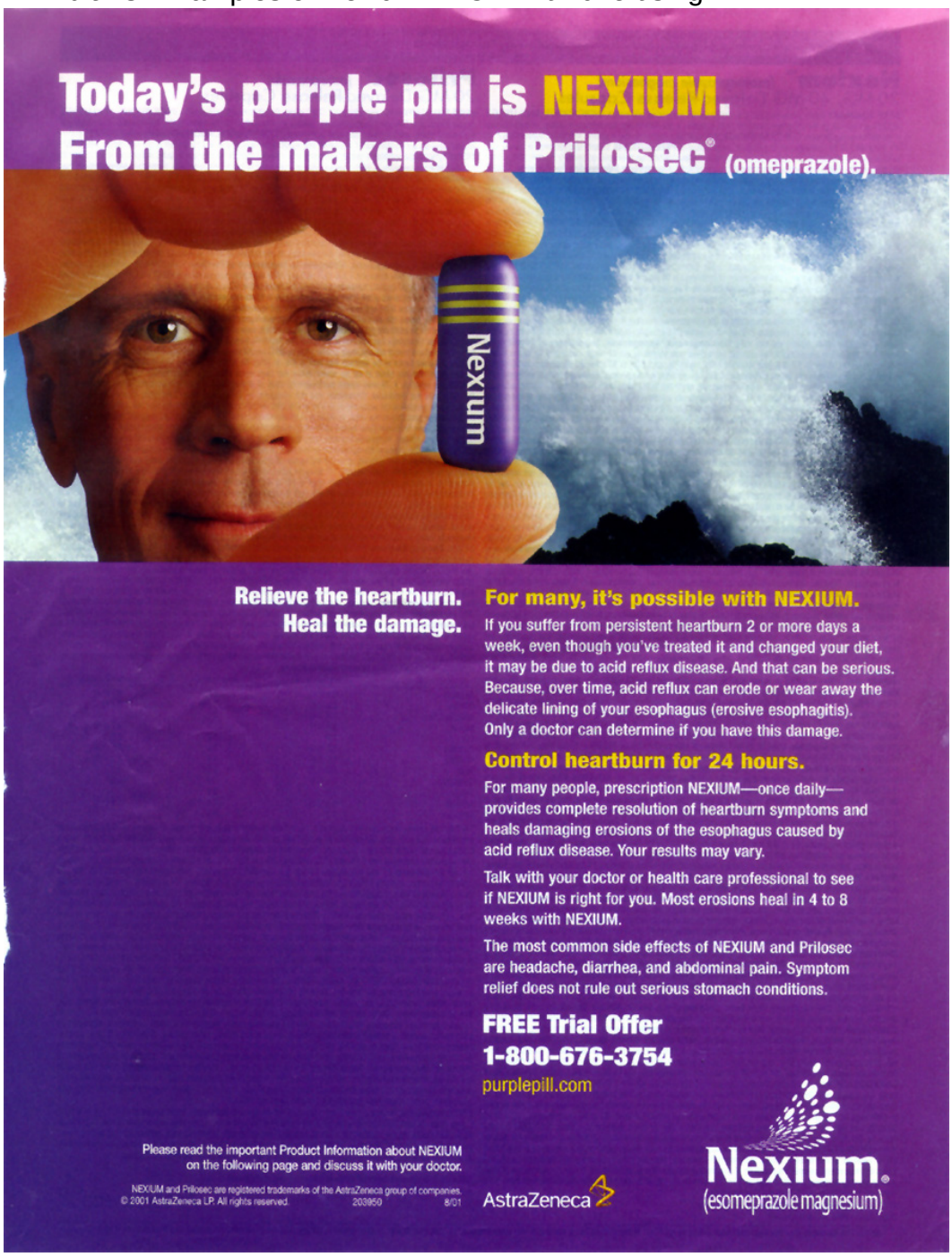
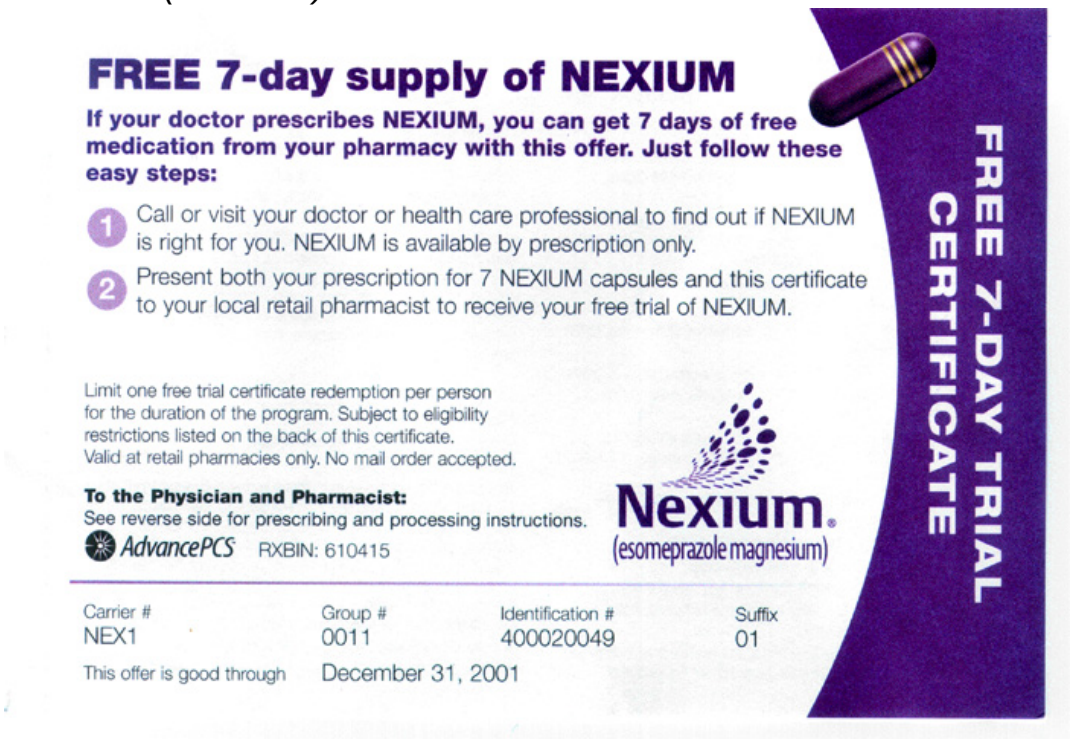


Exhibit 13 *(continued)*



FREE 7-day supply of NEXIUM

If your doctor prescribes NEXIUM, you can get 7 days of free medication from your pharmacy with this offer. Just follow these easy steps:

1. Call or visit your doctor or health care professional to find out if NEXIUM is right for you. NEXIUM is available by prescription only.
2. Present both your prescription for 7 NEXIUM capsules and this certificate to your local retail pharmacist to receive your free trial of NEXIUM.

FREE 7-DAY TRIAL CERTIFICATE

Limit one free trial certificate redemption per person for the duration of the program. Subject to eligibility restrictions listed on the back of this certificate. Valid at retail pharmacies only. No mail order accepted.

To the Physician and Pharmacist:
See reverse side for prescribing and processing instructions.

AdvancePCS RXBIN: 610415

Nexium® (esomeprazole magnesium)

Carrier #	Group #	Identification #	Suffix
NEX1	0011	400020049	01

This offer is good through December 31, 2001

This certificate is part of AstraZeneca's Free 7-Day Trial Program for NEXIUM® (esomeprazole magnesium).

To the Physician:

- In order to use this certificate, your patients will require one prescription for seven (7) free capsules of NEXIUM (20 mg or 40 mg)
- If you wish your patient to continue on NEXIUM beyond the free 7-day trial period, you must also provide a separate prescription based on your recommended therapy
- Refills will not be authorized with this certificate

To the Pharmacist:

- Please dispense this AstraZeneca medication at no copay to the patient. No purchase required
- This certificate must be accompanied by a prescription for seven (7) capsules of NEXIUM (20 mg or 40 mg). No substitutions permitted
- This certificate is good for one fill only. Please process any additional fills for NEXIUM under the patient's primary insurance as a new prescription with a new Rx number
- Limit one free trial certificate redemption per person for the duration of the program

Pharmacists should follow these easy steps:

1. **Transmit the claim to AdvancePCS only.**
2. Remove the Identification #, Carrier #, and Group # from the patient profile after the claim has been adjudicated. Patient confidentiality is maintained.
3. This certificate must be attached to the original prescription and retained by pharmacy for audit purposes for the period of 3 years or the usual period for which your pharmacy records are kept, whichever is longer.
4. For assistance with this claim or rules and regulations governing the AstraZeneca Free Trial Program, please call the AdvancePCS Help Desk at 1-800-345-5413.

I certify that I have received this certificate from an eligible patient, have dispensed the NEXIUM product as indicated, and have not submitted, and will not submit, a claim for reimbursement to the patient or any third-party payor. I certify that my participation in this program is consistent with all applicable state laws and any obligation, contractual or otherwise, that I have as a pharmacy provider.

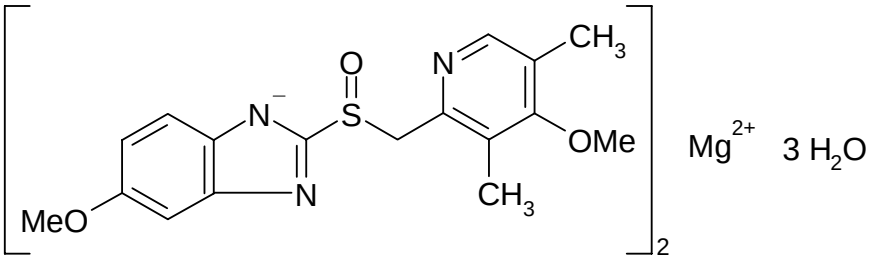
Pharmacist's Signature

Certificate expiration date on reverse side.

Eligibility Restrictions:

This offer is not valid for prescriptions purchased under Medicaid, Medicare, similar federal or state programs, or where prohibited by law. It is a violation of federal law to trade, sell, counterfeit, or to dispense any products other than NEXIUM with this certificate. Not valid if reproduced or submitted to any other payor. No mail orders accepted. Offer good in USA only. AstraZeneca reserves the right to rescind, revoke, or amend this offer without notice.
PerformanceScript is a registered trademark of AdvancePCS.
NEXIUM is a registered trademark of the AstraZeneca group of companies.
 202707B 4/01

Exhibit 14: Nexium Delayed-Release Capsule Active Ingredient



The active ingredient in Nexium (esomeprazole magnesium) delayed-release capsules is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-*1*H-benzimidazole-1-yl) magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R-isomers. Its empirical formula is $(C_{17}H_{18}N_3O_3S)_2$ Mg × 3 H_2O with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The magnesium salt is a white to slightly colored crystalline powder. It contains 3 moles of water of solvation and is slightly soluble in water. The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 2°C and about 8 hours at 3°C. Nexium is supplied as delayed-release capsules for oral administration. Each delayed-release capsule contains 20 or 40mg of esomeprazole (present as 22.3 or 44.5mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40-50, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate.