Trends-in-Medicine

June 2002
By Lynne Peterson and Norman Bauman

SUMMARY

An FDA panel has recommended that the agency approve P&G's Prilosec-1, an over-the-counter tablet version of Prilosec (20 mg omeprazole), and it is likely the FDA will follow this advice. Meanwhile AstraZeneca is trying to defend its Prilosec patent in court against generic manufacturers. A court decision is expected within the next couple of months, and the outlook is for the generics to prevail.

When OTC Prilosec and generic omeprazole are both available, managed care companies expect broad usage of both – at the expense of all the brand proton pump inhibitors. Generics will replace Prilosec on formularies, but managed care companies also expect convenience, couponing and advertising to drive OTC use.

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

The Outlook for Prilosec and other Proton Pump Inhibitors

Changes are coming to the more than $9 billion proton pump inhibitor (PPPI) market. An FDA panel recommended the agency approve over-the-counter (OTC) sales of Prilosec, generic manufacturers are awaiting a court decision that may allow them to launch cheaper generic omeprazoles, and managed care firms plan to encourage Americans to choose OTC or generic omeprazole over any brand product. This report examines issues raised by the FDA panel, the status of the legal challenge to AstraZeneca's Prilosec patent, and how managed care firms are likely to handle both generic and OTC Prilosec.

OTC PRILOSEC

OTC Prilosec (20 mg omeprazole), to be sold as Prilosec-1, got a step closer to reality on June 21, 2002, when members of two FDA panels – the Gastrointestinal Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee – voted 16 to 2 in a joint meeting in favor of allowing the first over-the-counter proton pump inhibitor. This was the second time the panels met together on this issue; the first time was in October 2000, when the panel recommended against approval. At the June 2002 meeting, AstraZeneca and Proctor & Gamble companies presented a new labeling proposal and new actual use studies at this meeting but no new safety, efficacy, PK or PD studies.

Comparison of OTC Prilosec Proposals

Prilosec	October 2000	June 2002
Dose	10 mg	20 mg
Target population	>12 years, anyone with heartburn	>18 years, heartburn ≥ twice a week
Uses	Relief and prevention	Prevention of frequent heartburn for 24 hours
Duration	10 days (intermittent)	14 days (continuous)

There is one key difference between OTC Prilosec-1 and prescription brand Prilosec: the OTC product will be a tablet and brand Prilosec is a capsule. However, the panel and the FDA staff dismissed any significance to this formulation difference.

The AstraZeneca/P&G presentation actually was rather boring. Officials didn't break any new ground except to present actual use and label comprehension studies. However, those studies did not satisfy either the FDA or the panel and may have raised as many questions as they answered.

On the other hand, a P&G official did appear to score a few points by suggesting that instead of decreasing patient visits to the doctor, OTC Prilosec actually may increase visits. She commented, "When we looked at physician contact in our study…the rate of physician contact per months was twice what it was in the year

year prior…20% of consumers who are hard to reach – those who never discussed heartburn with their doctor before opted to talk to their doctor when they participated in this study, and 53% of those who took (OTC Prilosec) more than 14 days talked to their physicians during or after the study…We believe increased physician contact was driven by the label and literature...We believe physician visits won't decrease, and there is a chance they will increase (with OTC Prilosec)." A gastroenterologist on the panel said, "It would be nice if people came to the doctor, but a lot of people don't…It is unrealistic to expect an OTC drug to alter the way people think about healthcare."

An Andrx official spoke against the proposal arguing that:

- There are potential food interactions. He said, "There is confusion on how to take prescription Prilosec with food. A study found that over 50% of patients taking PPIs in a community setting were taking them incorrectly due to insufficient information on the relationship to food. It is their opinion that patients have inappropriate dosing habits which lead to inappropriate dose escalation. So how can we expect consumers to take OTC Prilosec safely?" An FDA official responded that new data from AstraZeneca and Proctor & Gamble shows "a significant food effect" (interaction), so the FDA will recommend (require) that Prilosec-1 be administered an hour before meals. A sponsor said, "There is an effect on absorption but no clinical effect."

- There are potential drug-drug interactions, especially with other acid reducers (H2 blockers, antacids, other PPIs).

- The formulation is not identical because Prilosec-1 is a tablet, not a capsule.

The Chairman of the Gastrointestinal Drugs Advisory Committee, Dr. Michael Wolfe, was not allowed by the FDA to participate in the deliberations because of a conflict of interest, but he testified as a member of the public, arguing strongly against approval. He said there is no evidence that PPIs cause esophageal cancer but that new data soon-to-be-published will show that increased levels of gastrin are linked to cancer, and PPIs are known to increase gastrin production. Dr. Wolfe said:

> "I did a study of why patients failed PPIs, and the results were astounding. PPIs are designed to be taken before the first meal of the day, but doctors prescribe them that way in fewer than 30% of cases despite package inserts and lectures. So it is unlikely that consumers will do a better job than doctors. Gastroenterologists did better than other doctors, but they still mis-prescribed, too…Gastrin doesn't cause colon cancer but it does cause pre-existing conditions to worsen…Cancer of the esophagus is the fastest growing cancer in the U.S. for unknown reasons…The function of gastrin receptors on esophageal adenocarcinoma indicates that gastrin may play a role in the pathogenesis of esophageal adenocarcinoma…This is the first study to demonstrate a relationship between PPI use and development of esophageal cancer…but there is no evidence that PPIs cause esophageal cancer."

Company officials denied any causal relationship between Prilosec and development of cancer. A panel member, insisting that the cancer issue was not a serious concern for him or his colleagues, said, "There is no questions the drug is safe." A family practice doctor on the panel told other panel members, "The Prilosec risk is small, and this is approvable. Let's get on with labeling."

Panel members made it clear from their first questions that they were concerned mostly with labeling, though they also had questions about food and drug interactions, the possibility that more serious conditions might be masked or missed, safety during pregnancy, and whether the companies were overly optimistic about actual usage profiles. One panel member worried that HMOs would cover the OTC Prilosec, creating a disincentive for patients to consult a doctor. The biggest panel opposition to OTC Prilosec was expected to come from the gastroenterologists on the panel, but they were surprisingly supportive of the proposal.

Some of the most interesting debate centered on just what the wording "prevent the symptoms of frequent heartburn" on the proposed label meant. To some panel members, that sounded just like GERD (gastroesophageal reflux disease). One panel member asked, "What is heartburn if not a symptom?" Another panel member commented, "I'm having trouble understanding the difference between frequent heartburn and what we call GERD." A third panel member said, "There is no meaningful differentiation…Patients have symptoms, and they don't care what you call it." A fourth panel member said, "I have a lot of confidence in patients with chronic heartburn. They can figure this out…I think we should give a little more confidence to the people out there with chronic heartburn…A physician has to get in the loop, but maybe not soon." A sponsor responded, "Maybe (the labeling) is redundant, but we wanted to convey that we are not preventing heartburn from recurring."

The FDA's focus also was on labeling. The staff wanted to know whether the proposed label was adequate to make it clear to consumers that Prilosec-1 is not for episodic heartburn or meal-induced heartburn. An FDA official indicated the label was less than clear, saying, "There was a high degree of overlap with the diagnosis of GERD in the use and comprehension studies." Another FDA official said, "Our conclusion is that it is not clear whether consumers can apply the label well to their own situation if they require physician consultation…Study participants understood Prilosec is for frequent heartburn, and that they should not use it if they don't have heartburn, have infrequent heartburn, are allergic or are pregnant/nursing. Consumers believe Priolosec-1 can be used episodically to relieve acute heartburn symptoms or to prevent meal-induced heartburn. It is not clear if consumers with medical conditions listed on the label or taking medications listed on the label would seek medical advice before use or decline to use the product."

Among the things that the panel and the FDA want clarified in the label, and so will still need to be worked out with the sponsors:

- Drug interactions.
- How to take the medication in relation to food.
- Concomitant use of other acid blockers.
- When patients should consult a doctor.
- How many courses of Prilosedc-1 patients can safely take in a year.
- Stronger language on other conditions that may be confused with heartburn, such as chest pain.
- The "for 24 hours" phrase.

The FDA asked the panel to vote on five issues:

Ö Self-medication. By a vote of 16 to 2 the panel agreed that it is acceptable for some patients to self-treat with OTC medications.

Ö Heart burn-self selection. By a 15 to 3 vote, the panel decided that the sponsor had not demonstrated that consumers with heartburn can adequately self-select use of Prilosec-1. Several panel members called this a gray question and said they voted no because of a need for better labeling.

Ö Prilosec-1 use for heartburn. By a vote of 12 to 6, the panel found that consumers who had recurrence of heartburn symptoms would respond appropriately to Prilosec-1.

Ö Treatment duration. By a vote of 17 to 1, the panel voted that the treatment duration should be 14 days, not 28 days. An FDA official spoke in favor of a 28-day treatment period, saying the response rate was higher at 28 days than 14 days. However, P&G officials stressed that they were not seeking a 28-day treatment period.

Ö Approval recommendation. By a vote of 16 to 2 the panel voted to recommend approval of Prilosec-1 for the prevention of frequent heartburn, with the understanding that the label (a) would be revised – and retested – prior to marketing and (b) would restrict use to no more than three 14-day courses a year. Panel members were worried that consumers would take to many courses in a year, so they urged the FDA to restrict use to two or three 14-day courses in a year.

It appears that FDA officials are inclined to follow the recommendation of this panel. The question is what types of label studies the agency will require before approval – not whether it will grant approval. A senior FDA official said it is possible the agency will require an "Intent to Heed" study rather than a simple label comprehension study, and that could lengthen the time it takes to get an approved label. The simplest label comprehension study could be done by focus groups, but the most demanding Intent to Heed study could go so far as to put product on some store shelves and test consumer reactions up to but excluding purchase. This official said the staff needs to meet and discuss how to approach the label changes, and she suggested a six- to 12-month time frame for approval is probably accurate but not certain. P&G officials estimated that Prilosec-1 could be on the market by late 2002 or early 2003. A P&G official indicated an Intent to Heed study could push the launch date out but could not estimate how much longer this would take.

The Generic Outlook

The first generic omeprazole is expected to come from Andrx. Other companies with generic omeprazole in the wings include:

- Dr. Reddy-Cheminor
- Eon Laboratories Manufacturing
- GenPharm/Takeda
- Impax Laboratories
- Kremers Urban Development Company (KUDCO)
- LEK Pharmacy
- Mylan Labs
- Schein Pharmaceutical
- Schwarz Pharma

Andrx is nearing the end of a patent battle with AstraZeneca in New York District Court for the Southern District of New York, with Judge Barbara Jones presiding. A decision by Judge Jones is expected in late August or September 2002. That outcome will determine when and if Andrx gets to launch its generic omeprazole. Trends-in-Medicine has been following this non-jury trial closely.

AstraZeneca's original '431 **(4,255,431)** patent for omeprazole expired in October 2001, but a legal minefield of secondary patents has been keeping generics off the market. The Prilosec formulation is covered by the '505 patent, which expires in 2007, and a new pellet formulation is covered by an even newer patent ('281) which was awarded in 2000. Although generic manufacturers, including Andrx, figured out their own pellet formulations, the questions are (1) whether AstraZeneca's patents are **valid** and, if so, (2) whether the generics **infringe**. The answers hinge on formulation and process questions. Omeprazole can't be absorbed in the stomach because stomach acid would destroy it, so Astra devised capsules that would protect omeprazole until it reaches the intestine, where it is absorbed into the bloodstream.

In Re Omeprazole, M21-81 is a consolidated case. AstraZeneca (formerly Astra) is the plaintiff, and the four defendants are Andrx, GenPharm, Dr. Reddy/Cheminor and KUDCO. Andrx and GenPharm have a "Memorandum of Understanding" which gives Andrx sole 180-day exclusivity, with royalties to GenPharm (up to 15% of profits, based on the

number of competitors in the market). The trial, which is divided into four parts, began on December 5, 2001, and a final decision is expected in August or September 2002. It is possible, but unlikely, that Judge Jones will issue her decision piecemeal rather than simply writing one large, final ruling.

Patents Under Litigation

Patent	Patent Type	Trial Part	Issue	Outcome
'505 (4,786,505)	Formulation	Part 1	Infringement and validity	Decision pending
'230 (4,853,230)	Formulation	Part 1	Infringement and validity	Decision pending
'281 (6,013,281)	Process	Part 2	Infringement and validity	Decision pending
'305 (5,629,305)	Use	Part 3	Validity	Mostly withdrawn
'342 (5,093,342)	Use	Part 3	Validity	Ruled Invalid

Part 1. Infringement and/or invalidation of the '505 and '230 formulation patents, covering: (1) the core, (2) an inert subcoating, and (3) an enteric coating, etc. The unique feature of the AstraZeneca formulation of Prilosec is the inert subcoat which resolved stability problems by preventing gastric acid from breaking the capsule down before it reached the intestine where it is absorbed.

All of the defendants admit their product has three layers. GenPharm claims a sugar seed-type core; KUDCO and Cheminor claim an acidic pH rather than alkaline pH in their cores. Andrx claims to have a two-part formulation in its patents but no separate inert subcoat; Andrx's solution to the degradation problem was to put more omeprazole in its product (45.9% vs. 9.4% in Prilosec). AstraZeneca argued that Andrx uses two sublayers – a lactose-enriched layer and an HPMCP salt layer - which Andrx denied. It does not appear that Judge Jones was convinced a salt layer is formed since she wrote, "It is clear to the court that the testimony at trial concerning water in the formation of the HPMCP salt was not an issue in Astra's affirmative infringement case."

Part 2. Validity and infringement of the '281 process patent, which was filed in January 2000. If this patent is held to be valid, it will protect Prilosec until 2017. AstraZeneca claims Andrx infringes the '281 patent because Andrx's omeprazole tablet has a separating layer between the coating and the core. An AstraZeneca witness testified that Andrx, by its own admission, violated the claims of this patent.

There are three claims in '281:

- Claim 1 is for a separating layer: "A process for preparing an oral pharmaceutical formulation comprising the steps of: forming a core material comprising a proton pump inhibitor and at least one alkaline reacting compound...applying an enteric coating polymer layer so as to surround the core material thereby forming *in situ* a separating layer as a water soluble salt product between the alkaline compound and the enteric coating polymer."

- Claim 2 is for general classes of compounds with general structures.

- Claim 3 directly addresses omeprazole specifically.

Andrx offered a two-pronged defense on the '281 patent:

1. Non-infringement – that if there is a separating layer, it forms "spontaneously" by interaction of the coating and the core, so it does not infringe AstraZeneca's patent. An Andrx expert witness offered five reasons the Andrx omeprazole does not infringe: (a) the enteric coat is hydrocarbon, not water-based as in the AstraZeneca formulation; (b) the alkaline-reacting compound is not soluble in hydrocarbon; (c) there is not enough of the compound hydroxypropyl methyl cellulose (HPMC) on the surface of the Andrx core to form the reaction that produces the layer described in the '281 patent; (d) other components on the surface of the core preclude the formation of the layer; and (e) it will not form a separation layer.
2. Invalidity – that the '281 patent is invalid because of obviousness.

Andrx witnesses also claimed a Korean patent case, the CKD case, established prior art. Apparently, a Korean company was making omeprazole, AstraZeneca challenged it for violating the '281 patent with its coating technology, and AstraZeneca lost. Reportedly, the Korean company proved that they had established their coating technology and described it in Korean patent documents before the AstraZeneca patent was issued. Andrx charged that AstraZeneca withheld documents relating to the Korean case, and Judge Jones agreed, accusing AstraZeneca of "utter failure" to provide Andrx with the complete documents. The Judge ordered AstraZeneca to provide those documents to Andrx.

Part 3. Validity of the '305 use patent and the '342 use patent. '342 and '305 use patents. An AstraZeneca attorney said in court, "I agree with GenPharm that we are not trying the case on infringement." Judge Jones ruled the '342 patent invalid, writing: "The court finds that claim one of the '342 Patent is invalid as anticipated under 35 U.S.C. [Section] 102(b) by the Unge Abstract, exhibit G683. Therefore, the court will not hear infringement proof with respect to the '342 Patent. The court reserves decision on issues relating to 35 U.S.C. [Section] 112. An opinion setting for the court's findings of fact and conclusions of law with respect to the validity of the '342 Patent will follow." Most courtroom followers expect Judge Jones to rule the '305 and '342 patents invalid.

'305 is a use patent (filed in 1995) for the "synergistic combination of a substance with gastric acid secretion

inhibiting effect and an acid degradable antibiotic." The '305 patent claims treatment of gastritis and peptic ulcer, caused by H. pylori by omeprazole plus antibiotics. By stipulation, AstraZeneca withdrew most of its '305 claims, except for claims 16-18, which cover treatment of gastritis and peptic ulcer caused by H. pylori. Judge Jones said the stipulation "nearly invalidates" the '305 patent. AstraZeneca said it would appeal any negative '305 ruling.

The **'342** patent (filed in 1997) has just one claim: the use of omeprazole as a single pharmaceutical agent for treating H. pylori infection (an antimicrobial agent). Andrx attorneys argued that the '342 patent is invalid because:

(1) The idea of using omeprazole alone was already disclosed and commonly known to persons skilled in the art (physicians)

(2) '342 claims the use of omeprazole alone, which doesn't work, or omeprazole in combination with an antibiotic.

(3) AstraZeneca didn't disclose prior art. An Andrx witness claimed that Astra invited a "substantial number" of doctors to a symposium where doctors who treat gastrointestinal disease would have learned to use omeprazole to treat H. pylori. He said, "Eradication was a worthy goal, but treatment could also be suppression."

(4) '342 doesn't teach anything.

In the '342 patent, "treatment" is not defined. This is important, Andrx witnesses testified, because AstraZeneca claims that the patent described a method of eradicating H. pylori, not just suppressing it. Since omeprazole doesn't eradicate H. pylori, Andrx witnesses argued that AstraZeneca doesn't have any useful intellectual property to protect. Judge Jones commented that AstraZeneca is not going to get infringement if omeprazole just has an "effect" on H. pylori, saying, "It has to be administered for that 'purpose.'"

Part 4. Whether AstraZeneca is guilty of (1) fraud against the patent office for not disclosing the Korean prior art and/or (2) "inequitable conduct" for not disclosing the Korean documents during the discovery period. The Korean CKD case was decided in September 1994, but the '281 patent was not filed until February 1996. Judge Jones still has to rule on this.

AstraZeneca lawyers responded that they had to review huge collections of documents (more than 1,000, mostly in Korean) by hand, that the review had to be done by a lawyer familiar with the case, and that they were working on it. AstraZeneca lawyers also said they didn't disclose the documents originally because they were "privileged litigation documents" and, thus, protected by attorney-client privilege. Although most if not all of the documents were part of the public court record in Korea, AstraZeneca lawyers argued they were now privileged because the attorneys had reviewed them, underlined them, and made handwritten notes in the margins. The whole delay appeared, at times, to annoy Judge Jones. She finally ordered them to redact the underlined and handwritten notes and turn the documents over to Andrx.

A former Assistant Patent Commissioner who was also the acting Deputy Commissioner of the Patent Office from 1994-1998 testified that Astra was not required to disclose the Korean patents. He said that it was desirable to disclose prior art like the CKD patents, but it wasn't necessary, and if applicants submitted every possible document, the examiners couldn't get their jobs done.

THE MANAGED CARE PERSPECTIVE

Officials of four large managed care firms were asked how they will deal with OTC Prilosec (Prilosec-1) and generic omeprazole. Most do not expect an OTC product to be on store shelves before late 2002 or early 2003, so they assume they still have time to plan for it. However, all have already been discussing this internally. The bottom line is that Prilosec will be taken off formularies, but OTC Prilosec-1 won't go on formularies – at least not immediately. Officials expect the biggest loser to be the other PPI brands – TAP Pharmaceuticals' Prevacid (lansoprazole), Eisai/Johnson & Johnson's AcipHex (rabeprazole), Wyeth's Protonix (pantoprazole) – which will lose share to both Prilosec-1 and generic omeprazole.

PPI Pricing

PPI	Strength	Average Retail Price for 30-day supply*
Prevacid	30 mg	$ 140.84
Prilosec	20 mg	$ 137.29
Nexium	40 mg	$ 121.25
AcipHex	20 mg	$ 117.29
Protonix	40 mg	$ 90.67

**average at 3 national chains, July 2002*

No plans intend to cover Prilosec-1 as a plan benefit – at least in the near term. That is, none plan to put Prilosec-1 on their formulary. One said, "We would encourage use of OTC Prilosec. One of things we are looking at – but have not done yet – is to perhaps drop the whole class once one goes OTC. We haven't taken that step yet." Another said, "We will have guidelines in place: First try OTC, then prescription generic omeprazole, and then a brand…but we haven't made a decision on instituting electronic editing or prior authorization. A third said, "If there is both a generic and an OTC Prilosec available, we would still offer a range of different options, depending on the cost of the OTC. We probably would not put the OTC on the formulary; we didn't do that with the H2 blocker, Zantac (Pfizer, ranitidine)."

If Prilosec-1 is available OTC before generic omeprazole, sources expect prescription Prilosec to disappear. One said, "Prilosec will go off formulary, and there will be no reimbursement for it without pre-authorization exception. Prilosec will lose all prescription market share." Another said, "We don't cover OTC items, regardless of the indication. We would not cover Prilosec once it goes OTC. We only have

coverage for prescriptions, and if the OTC is the same chemical compound, we wouldn't cover it at the same strength by prescription, though we might cover a higher strength." A third said, "Probably prescription Prilosec would go away, and if it didn't, I can't see us covering it. We would encourage doctors to prescribe another brand for ulcer patients – or to tell those patients to take OTC Prilosec off-label, though we might cover another strength of brand Prilosec." Another said, "Prilosec-1, the brand OTC, wouldn't be put on formulary, but when a generic OTC is available, it may get on formulary."

Prilosec-1 is expected to have strong sales. One said, "There will be giant purple kiosks by every pharmacy (counter) in every city. Pricing will be less than the average drug co-pay of $20-$25, and there will be great demand." Another said, "People still have co-pays for brand and generic drugs and for doctors' visits. With couponing and incentives and the lack of office visit, there will be incredible demand for OTC Prilosec. There also will be incredible sampling and couponing for the OTC Prilosec, and those of us responsible for protecting the affordability of healthcare will do what we can to encourage the 60 million Americans who experience heartburn to use OTC Prilosec by providing coupons and different incentives for them to move to OTC Prilosec." A third said, "At this point we are trying to structure a pharmacy benefit with a significant enough co-pay that if something goes OTC, there isn't that much differential. When you add the doctor's visit and the (drug) co-pay, the patient is probably better off to get the drug OTC." The fourth said, "I'm not sure how much share OTC Prilosec will take, but it will have substantial use. A lot will depend on the price of the OTC, which may equal the patient's co-pay."

Managed care executives predicted generic omeprazole will do well, but not as well as it would have done without an OTC product. One said, "If the generic has full indications and is cost effective, then plans will use that on their formulary and ignore the OTC." Another said, "Once there is a generic omeprazole, all other brands will probably have to have prior authorization. If you use the Prozac (Lilly, fluoxetine) model, after six months, a month's supply of generic Prilosec should be <$10. But there will still be demand for OTC Prilosec. People will still have co-pays for both brand and generic omeprazole, and with couponing and incentives and the lack of an office visit, there will be incredible demand for OTC Prilosec." A third said, "Employers covering a brand will shift to generics, especially if there is a significant discount and multiple generic manufacturers. OTC Prilosec will hurt other brands, but generics will hurt brands worse." A fourth said, "If patients really know a brand and that is what they want, then they will demand it. Otherwise, it is up to the doctor to say the person is not covered, but there is an OTC."

Other PPI brands will continue to be on managed care formularies, but managed care officials will be watching just how much usage they get. One source said, "Brands will remain on formulary, but use will require proof that either the OTC or the generic was tried first…Nexium (esomeprazole) can help AstraZeneca if it has enough share, has a position on the formulary, and gives better rebates. We strategized ahead of time, didn't add Nexium to our formulary, taking the short term pain of higher prices. We stayed with the other brands for rebates – so we can go generic." Another official said, "For patients with GERD and chronic diseases, the prescription drugs will be covered. We haven't discussed whether we will implement a prior authorization process on the prescription drugs, but I don't see that happening. There are people with significant GERD, and they will continue to see doctors and be treated by prescription drugs. Only 25%-30% of people take PPIs for episodic heartburn; that still leaves a signification proportion in the prescription realm." A third said, "For now, we would cover other brands…(but) If doctors write a lot of brand prescriptions, that would probably force us to make the whole class a non-covered benefit." The fourth said, "OTC Prilosec will hurt other brands, but generics will hurt brands worse. Patients would move to other brands because manufacturers will be educating doctors on what indications still require a prescription. What we offer will depend on what employers want. We'll offer a variety of options, and some employers will opt not to cover any PPI, and some will cover one or more brands. It will be a mixed bag."

Generic omeprazole pricing will be a key factor in how well that product does. A source said, "When Prilosec goes off patent…a managed care company with a good contract for Protonix, etc., won't rush to generic until the generic price is deeply discounted. A generic will have to price at least 15%-20% below the brand, and we won't add generic Prilosec to our formulary until its 25%-30% lower than the cheapest PPI. Protonix is not on our formulary because its trials don't stand up to the other PPIs – and we have great pricing from the others." Another official said, "When generic omeprazole first comes out, I don't think there will be any pricing advantage to it. It will be equivalent to the cheapest brand. But most plans have different co-pays for generic and for brand – for example, $6 for generic and $12 for brand. So in the first six months, the reality is we won't save any money from brand to generic conversion. After six months, plans will try to move to generics where they can, and I think they will be successful where there are tiered formularies. Where formularies are open, it is more difficult. Half our formularies are open and half are closed or 3-tier." Sources said that the co-payment for the top, or third, tier is often $20 and increasingly $25 or even $30.

Of course, patients might simply change plans if their managed care company didn't cover a popular brand PPI, but managed care officials doubt it. One said, "Employers are starting to take a bigger look at what they are paying for drugs. We never heard about GM asking about drug use and pricing before, but now they are looking for plans to manage high cost products." ♦