



3 Δ XIS Advisors

PURPLE HAZE

How a little purple pill called Nexium exposes
big problems in the U.S. drug supply chain

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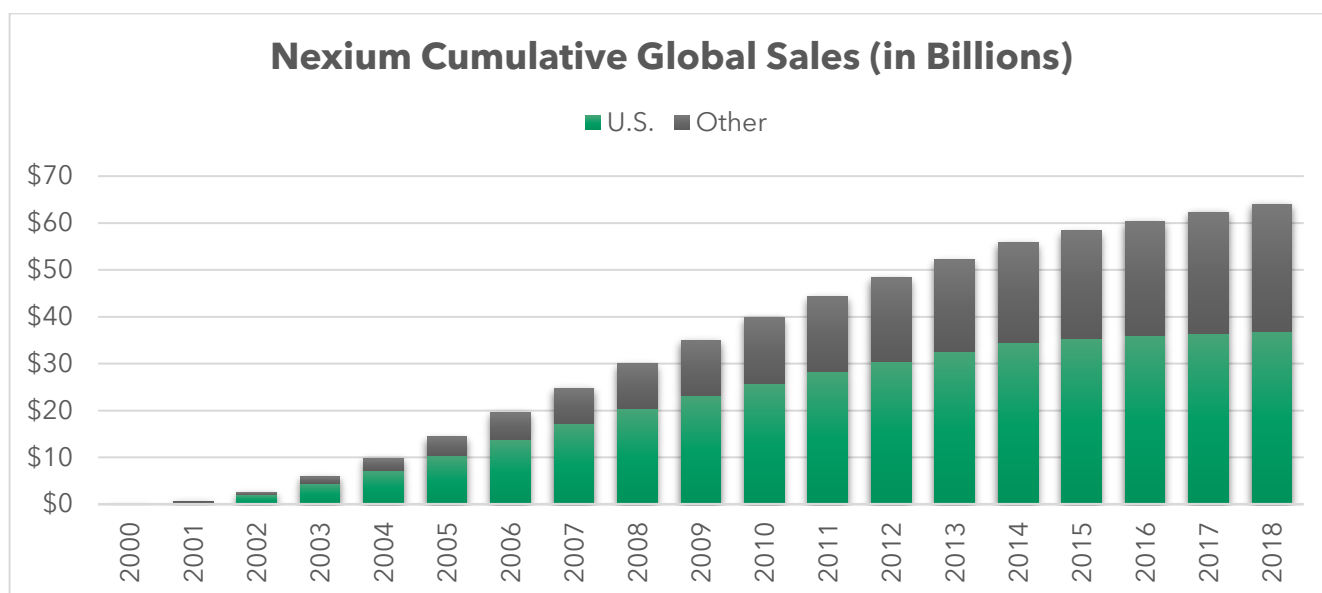
1 ABOUT THIS REPORT

In 2018, the U.S. Department of Health and Human Services (HHS) released a report detailing Medicare Part D spending on brand-name drugs that were also available as multi-source generics.ⁱ At the top of that list was a popular medication known as Nexium, for which Medicare spent \$1.06 billion (pre-rebate) in 2016, despite its manufacturer losing its patent exclusivity in early 2015.

When HHS released this report, we were fascinated by the fact that the highly competitive Medicare Part D program collectively produced such a perplexing outcome. Nexium not only had ample generic competition in 2016, but it had significant therapeutic competition from other inexpensive medications prescribed to regulate and/or suppress gastric acid secretion.

Motivated to understand the root cause of the elevated spending on this high-profile brand-name drug in 2016, we started to research the story of Nexium, and the old drug from which it was derived, Prilosec. It didn't take long to figure out that Nexium has been a lightning-rod of a topic for more than a decade. Numerous journalists have written about the myriad tactics used by its manufacturer, AstraZeneca, to block the generic market for Prilosec from taking hold while it transitioned patients from Prilosec to Nexium. But the press has not been completely negative. AstraZeneca was lauded by business school strategists and national marketing agencies for its ability to manifest a \$35+ billion U.S. Nexium franchise (**Figure 1**) out of the ashes of Prilosec - a drug that had lost its exclusivity, and as a result, essentially all its value for AstraZeneca in the U.S.

Figure 1: Nexium Cumulative Global Sales



Source: AstraZeneca annual reports (2000-2018)

Despite ample media coverage over the past two decades, we struggled to find a comprehensive overview of the entire Nexium story that was supported by data and analytics needed to fully understand its many moving parts. To fill this void, we received funding from Waxman Strategies through a grant provided by Arnold Ventures to complete and publish this work. Our goal was simply to provide a full data-driven analysis of the Nexium story to help educate lawmakers and the general

public on how a drug commonly viewed as a line extension first became a blockbuster drug for AstraZeneca and then exposed a host of warped incentives across the U.S. drug supply chain that continue to be exploited today. The information in this report can serve as the foundation for a more constructive debate on what regulation is needed to help reduce waste in the drug supply chain without sacrificing innovation.

Part of Arnold Ventures' grant was for Waxman Strategies to develop issue briefs that directly propose policy solutions informed by our research to help close the more egregious loopholes exploited by companies throughout the Nexium saga. Such issue briefs will be published and provided in the coming months to lawmakers and the general public in a shorter, more digestible, and more actionable format than this report.

However, this report serves as the full "cradle-to-grave" Nexium story. We found it fascinating to explore Nexium's story from start to finish. It was very much like watching a spider build its web. This immensely complex story was simply easier for us to digest and understand one strand at a time.

This report is organized chronologically to build a step-by-step narrative for the reader. It is divided into five sections that correspond to different stages in Nexium's lifecycle. Each section starts with a summary of what we view to be the section's key takeaways.

The sections are:

1. Prilosec - the precursor to Nexium
2. Nexium comes to market
3. Nexium patent battles
4. AstraZeneca prepares for Nexium's patent expiration
5. Nexium goes generic - where are all the savings?

We apologize in advance for either directly or tacitly casting blame on any one character in this story. While AstraZeneca happens to be the central player, and many of its decisions and actions were, in our view, troubling; concluding that AstraZeneca is to blame or not to blame for what transpired would be incredibly shortsighted. It would miss the opportunity to use Nexium as a case study to better understand the many loopholes and flaws in the current design of the U.S. drug supply chain. We hope that the reader will read the following pages through this lens, rather than looking to reinforce or support any existing prejudices on who is to blame for our nation's drug pricing conundrum. In our view, we must look past the current participants, and instead study the inner workings of the system as a whole. Only then will we be able to objectively understand the flaws in its design and be able to work to remedy them. The story of Nexium provides a golden opportunity to reflect on what went wrong (and what went right) across the lifecycle of one of the best-selling (and arguably, one of the most controversial) drugs of all time. We hope it is used as such.

2 EXECUTIVE SUMMARY

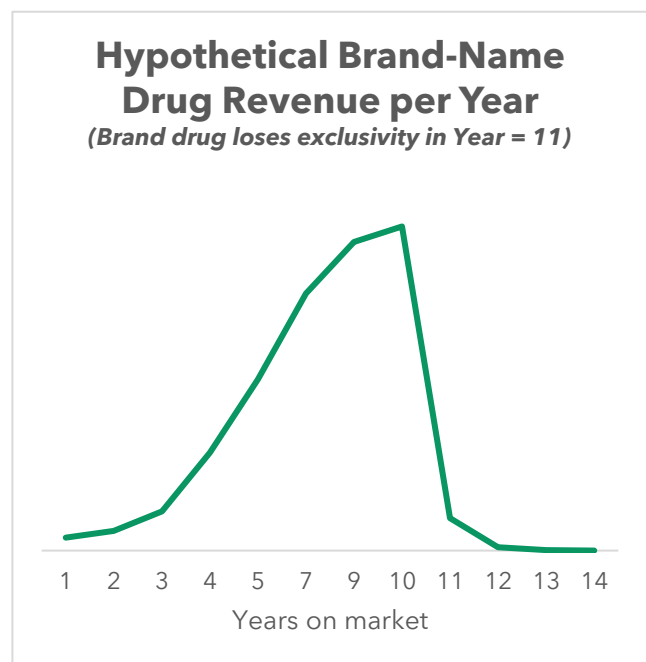
“In the political uproar over prescription-drug costs, Nexium has become a symbol of everything that is wrong with the pharmaceutical industry. The big drug companies justify the high prices they charge – and the extraordinary profits they enjoy – by arguing the search for innovative, life-saving medicines is risky and expensive. But Nexium is little more than a repackaged version of an old medicine.”ⁱⁱ

- **Malcolm Gladwell (2004)**

In 1995, Astra’s back (now AstraZeneca) was firmly against the wall. Prilosec – by far and away Astra’s best-selling product – was approaching the end of its patent exclusivity (April 2001). If Astra were to do nothing to fend off generic competition, more than half of the company’s revenue would be at risk. So, Astra assembled a diverse team of experts – internally referred to as the “Shark Fin” team – to avert the precipitous revenue drop that when charted out, would very much resemble a shark fin (**Figure 2**).

The Shark Fin team settled on Nexium as Prilosec’s replacement. Nexium is “one-half of the Prilosec molecule -- an isomer of it.”ⁱⁱⁱ According to several of the executives from the Shark Fin team, it was, “among the poorest of the many drug solutions ... pondered back in 1995.”^{iv} Even the Medical Team Leader of the Center for Drug Evaluation and Research’s Medical Officer’s Review of AstraZeneca’s Nexium new drug application (NDA), Dr. Hugo Gallo-Torres, concluded his assessment of Nexium by writing, “this reviewer reiterates that ... this s-enantiomer of omeprazole (i.e. Nexium) is of similar efficacy to omeprazole (i.e. Prilosec).”

Figure 2: The Shark Fin

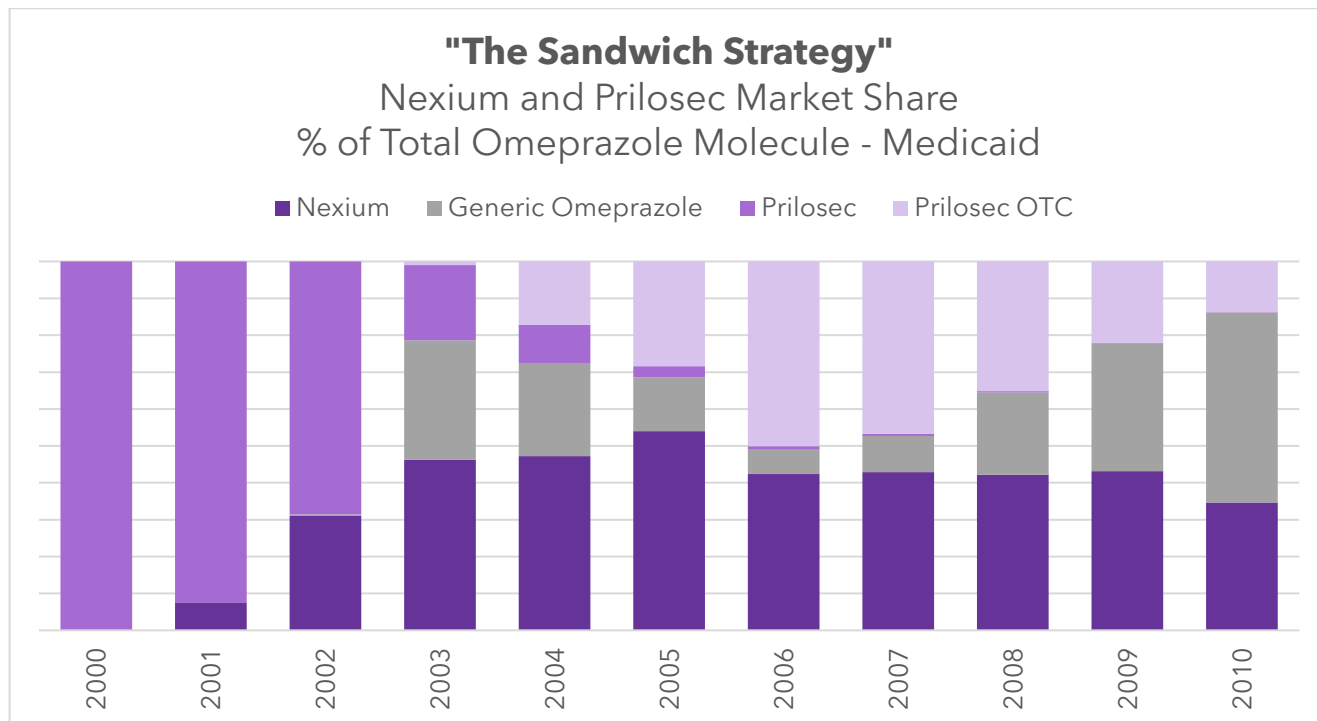


Not to be dissuaded, AstraZeneca developed internally-generated studies – called “stacked” by Forbes – demonstrating Nexium’s clinical superiority over Prilosec.^v AstraZeneca armed its sales force with these results and put nearly \$500 million behind a 2001 marketing campaign targeted at consumers and physicians. Meanwhile, AstraZeneca’s legal team successfully fended off generic competition until late-2002, giving the company much needed time to convert patients to “the new purple pill.” Ultimately, Nexium was “one of the most successful launches ever of a new medicine,” generating \$64 billion in revenue for AstraZeneca between 2001 and 2018 (**Figure 1** on previous page).^{vi}

The company also worked with Procter and Gamble to introduce an over-the-counter version of Prilosec. Former Northwestern Kellogg School of Management Dean Dipak Jain used AstraZeneca’s management of Prilosec’s patent cliff as one of the prime examples of an effective execution of a “sandwich strategy.” This is when a company “sandwiches” its competition (in this case, the generic

market for omeprazole) between two similar products at different price points.^{vii} This resulted in generic omeprazole only obtaining a 7% market share of the omeprazole molecule in Medicaid in 2006 - **four years** after the generic was available (see **Figure 3**).

Figure 3: The "Sandwiching-out" of Omeprazole in Medicaid



Source: 3 Axis Advisors analysis – derived from data obtained from Data.Medicaid.gov and Medispan PriceRx

Just under a decade later, Nexium was approaching its patent cliff. AstraZeneca once again deployed similar tools to fend off generic competition (patent infringement lawsuits) and extend the revenue stream from the brand (OTC introduction, direct-to-consumer marketing).

But arguably the most powerful tool this time around were the rebates and discounts negotiated between AstraZeneca and pharmacy benefit managers (PBMs) that may have bought preferential formulary placement, extending the life of brand-name Nexium and hindering a robust development of the generic marketplace for esomeprazole. While we cannot prove causality between rebates and formulary placement, our work has uncovered two glaring facts that suggest interplay between rebates and formulary placement. We found that in 2015 (the year Nexium lost its exclusivity), AstraZeneca discounted Nexium in the U.S. by nearly 75%. Meanwhile, the following year, more than 50% of Medicare Part D plans kept brand-name Nexium on their formularies despite ample generic competition in the marketplace.

Compounding matters, even when generic Nexium (esomeprazole) was dispensed, we found that PBMs were charging inflated prices to federal and state programs rather than prices based on an actual market-clearing drug ingredient cost. Exaggerated generic prices set by PBMs, typically driven by inflated generic Average Wholesale Prices (AWPs), distorted the relative attractiveness of the generic relative to brand-name Nexium, potentially extending the life of the brand even further.

3 KEY LEARNINGS

After exhaustive research and analysis on Nexium, we recognize that this is only one of many cases of the U.S. drug supply chain delivering questionable value relative to cost. Billions of dollars were spent on something flagged within its initial review as no more efficacious than the medication it was designed to replace. To this end, we believe that the knowledge gained within this case study can inform a broader discourse on U.S. drug spending. Specifically, we believe enough evidence exists that demonstrates the following:

1. The approval of new drugs within the U.S. fails to adequately assess the value that new therapies provide to the healthcare system. Approving drugs based on safety and efficacy alone provides drug manufacturers with the incentive to bring to market line extensions that may be slightly more beneficial than currently available treatments, but with price tags that far exceed their incremental value. Meanwhile, in many instances, PBMs and health plans not only lack the proper incentives to block utilization on drugs like Nexium, but they have the financial incentive to actually promote their usage (i.e. rebates). In our view, **one of the primary drivers of rising U.S. drug costs are the lack of proper incentives for 1) manufacturers to exclusively focus their efforts on the development of innovative new therapies with exceptional value propositions; and 2) PBMs, health plans, and providers to discourage utilization of poor cost/benefit drugs.**
2. The use of artificial prices allows the supply chain to incentivize the use of one medication over another in ways not necessarily commensurate with a drug's relative value. Nexium offered a 75% discount off its list price to incentivize its use over its U.S. competition (brand and generic). Similarly, reliance on AWP-based payment models for generic medications obscures the savings generic medications could otherwise provide to both patients and payers. Such pricing distortions are very concerning in our view. They provide a means for the drug supply chain to disproportionately profit off the volume of drugs dispensed, creating the incentive to dispense more drugs rather than to create better outcomes. In our view, **the current design of the U.S. drug supply chain is highly reliant on sick people to generate rebates, price concessions, and pricing spreads that can then be used to help subsidize premiums for healthy people and generate excess profits for shareholders.**

We highly recommend that policymakers fix these glaring, perverse incentives embedded at the core of the U.S. prescription drug supply chain.

4 TABLE OF CONTENTS

1	About this report.....	1
2	Executive summary.....	3
3	Key learnings.....	5
5	Table of figures.....	8
6	Table of tables.....	9
7	Prilosec – the precursor to Nexium.....	10
7.1	Omeprazole – the first proton pump inhibitor.....	10
7.2	Racemic mixture versus single isomer.....	11
7.3	Pricing of Prilosec, Nexium, and the controversial impact of rebates.....	13
8	Nexium – the second coming of Prilosec.....	16
8.1	Majority of FDA approvals are for reformulations of existing drugs.....	16
8.2	The Shark Fin Project.....	18
8.2.1	Meet the “The Son of Prilosec”.....	20
8.2.2	Creating perceived value.....	21
8.2.3	Keeping generic competition at bay.....	22
8.2.4	The bottom slice of bread.....	24
8.2.5	Stronger = Longer.....	27
8.2.6	A near complete and perfect crippling of the generic marketplace.....	29
9	Nexium Patent Battles.....	31
10	AstraZeneca Prepares for Nexium’s Patent Expiration.....	35
10.1	AstraZeneca’s OTC agreement with Pfizer.....	35
10.1.1	The risks of self-medication.....	37
10.2	Nexium Direct.....	40
10.3	Nexium gets granular.....	42
10.4	Vimovo.....	43
10.4.1	Pozen’s agreement with AstraZeneca.....	43
10.4.2	Vimovo’s value proposition.....	44
10.4.3	A dud of an investment.....	45
10.4.4	Horizon Pharma takes over.....	45
10.4.5	Horizon’s strategy – in its own words.....	47
10.4.6	Is this legal?.....	49
10.4.7	A commercial strategy... that somehow resulted in \$150 million in Part D sales.....	50

10.5	Ranbaxy – the gift that keeps giving (for AstraZeneca)	51
11	Nexium goes generic. Where are all the savings?	52
11.1	Brand over generic	54
11.1.1	Plans kept Nexium on formulary.....	55
11.1.2	Assessing the role of reinsurance, rebates, and low-income subsidy (LIS)	56
11.1.3	Case study: Comparing Nexium to Abilify.....	59
11.2	Distortions in generic unit costs	60
11.2.1	10% cheaper	61
11.2.2	Unchanging AWP	63
11.2.3	The fallout of AWP-linked contracts – PBMs can set generic prices to optimize profit.....	66
11.2.4	Omeprazole pricing in Medicaid and Medicare	67
11.2.5	Esomeprazole pricing in Medicaid and Medicare	70
11.2.6	Incentives driving generic pricing distortions.....	72
12	Key Learnings.....	78
13	Acknowledgements	79
14	About 3 Axis Advisors.....	80
15	Appendix A: Pricing History of the omeprazole molecule (1990 – 2018).....	81
16	Appendix B: AstraZeneca’s Prilosec and Nexium Sales (2000-2018)	82

5 TABLE OF FIGURES

Figure 1: Nexium Cumulative Global Sales	1
Figure 2: The Shark Fin.....	3
Figure 3: The "Sandwiching-out" of Omeprazole in Medicaid	4
Figure 4: Omeprazole Enantiomers.....	12
Figure 5: The \$64 Billion Enantiomer	12
Figure 6: Prilosec WAC versus CPI-U (1989 - 2002).....	13
Figure 7: Prilosec/Nexium WAC versus CPI-U (2002 - 2008).....	14
Figure 8: Prilosec/Nexium WAC versus CPI-U (2008 - 2015).....	14
Figure 9: "Line Extensions" as a Percentage of Overall NDA/BLA Applications	17
Figure 10: The Shark Fin	19
Figure 11: Omeprazole 20mg Capsule WAC Pricing vs. Unique ANDAs	27
Figure 12: Omeprazole 40mg Capsule WAC Pricing vs. Unique ANDAs	29
Figure 13: AstraZeneca's Generic Omeprazole Sandwich Strategy in Medicaid.....	30
Figure 14: Prescription vs. OTC Nexium 20 mg WAC Pricing in May 2014	37
Figure 15: PubMed Articles on PPIs and Kidney Disease by Year	39
Figure 16: Medicaid Spending on Nexium Oral Packets (in Millions).....	42
Figure 17: Line Extension Status in Medicaid Drug Rebate Program Q2 2019 Single-Source Innovator Drugs	43
Figure 18: Launch Price Comparison of Vimovo vs. its Component Drugs	45
Figure 19: Cost of 60-count Package of Vimovo vs. its Sum of the Parts.....	46
Figure 20: Cumulative Net U.S. Vimovo Sales	47
Figure 21: 2018 Horizon Pharma Gross Sales.....	49
Figure 22: Gross Sales of Vimovo in Medicare Part D	50
Figure 23: Generic Esomeprazole Discount to Nexium vs. # of Generic Manufacturers.....	53
Figure 24: 2016 Medicare Part D Esomeprazole Units and Expense	54
Figure 25: Nexium Tier Placement by Part D Plans in 2014	55
Figure 26: 2016 Medicare Part D Plan Coverage of Nexium and Esomeprazole	56
Figure 27: 2016 Part D Nexium 40mg Capsule Cost Share	57
Figure 28: 2016 Part D Omeprazole 40mg Capsule Cost Share.....	58
Figure 29: U.S. Gross and Net Nexium Expense and Estimated Nexium Discounts/Rebates	59
Figure 30: Percent of Part D Plans with Nexium and Abilify on Tiers 1-4	59
Figure 31: Spending on Nexium and Abilify in Part D.....	60
Figure 32: Medicaid Managed Care Generic Dispensing Ratio (GDR).....	60
Figure 33: Relationship of Generic Launch AWP to Equivalent Brand AWP.....	63
Figure 34: Esomeprazole 40mg Capsule Average AWP vs. Average NADAC.....	64
Figure 35: Medicaid Annual Weighted Average AWP vs. NADAC per Unit (Oral Solids).....	65
Figure 36: Medicaid Managed Care and Medicare Part D Cost per Unit vs. NADAC per Unit (Omeprazole 40 mg Capsule).....	68
Figure 37: Cost of Omeprazole 40mg Capsules in Top 20 Medicaid Managed Care Programs (Q4 2018).....	69
Figure 38: Omeprazole 40mg Capsule Cost per Unit by Part D Plan (Q4 2018).....	70
Figure 39: Medicaid MCO and Medicare Part D Cost per Unit vs. NADAC per Unit (Esomeprazole 40 mg Capsule).....	71

Figure 40: Cost of Esomeprazole 40 mg Capsules in Top 20 Medicaid Managed Care Programs (Q4 2018)	71
Figure 41: Esomeprazole 40 mg Capsule Cost per Unit by Part D Plan (Q4 2018).....	72
Figure 42: Esomeprazole 40 mg Cost Comparison - NY Medicaid Managed Care	73
Figure 43: Esomeprazole 40 mg Cost Comparison - MI Medicaid Managed Care.....	74

6 TABLE OF TABLES

Table 1: All approved NDAs derived from omeprazole	18
Table 2: Chronology of Generic Challengers to Nexium.....	31
Table 3: Esomeprazole Marketing Start Dates, Labelers, and Application Numbers (2015-2016) ...	53
Table 4: 2014 to 2016 Savings on Generic Esomeprazole - NADAC vs. Medicare Part D.....	54
Table 5: Launch Pricing for Nexium versus generic esomeprazole	62
Table 6: Pricing per Unit of Generic Esomeprazole NDCs brought to market in 2015 and 2016	64
Table 7: Change in Price Benchmarks between Q1 2016 and Q1 2018 for Medicaid Generic Oral Solid NDCs.....	65
Table 8: Aetna Part D esomeprazole 40 mg capsule Pharmacy Adjudicated Payment and DIR fees	76
Table 9: Aetna Part D omeprazole 40 mg capsule Pharmacy Adjudicated Payment and DIR fees...	76

7 PRILOSEC – THE PRECURSOR TO NEXIUM

Section Key Takeaways

- Proton Pump Inhibitors (PPIs) inhibit acid secretion
- Astra's Prilosec/Losec was the first PPI and developed into the world's largest selling gastrointestinal treatment
- Prilosec (omeprazole) is a **racemic mixture** - it is comprised of two "mirror image" enantiomers (S and R enantiomers) of the omeprazole molecule
- Nexium (esomeprazole) is the isolated S-enantiomer of omeprazole
 - It was approved by the FDA with a "Type 2" classification - a new active ingredient that is not a new molecular entity
- AstraZeneca generated \$64 billion in global revenue from Nexium between 2001 and 2018
- AstraZeneca's list price increases on Prilosec - during its exclusivity period - tracked inflation
- Starting in 2008, AstraZeneca's list price increases on both Prilosec and Nexium (7.6% and 8.0% 2008-2015 CAGR) diverged from inflation (1.4% 2008-2015 CAGR)
 - The median brand-name drug increased at a 9.3% CAGR over the same period
 - Part D rebates grew from 11% to 18% over the period, and are forecasted to eclipse 25% in 2018

It is estimated that up to 60 percent of Americans experience heartburn or similar symptoms over the course of a year.^{viii} As Americans become more and more impacted by problematic levels of gastric acid and acid reflux, demand has grown for a medication to help regulate acid secretion. In the 1960s, a pharmaceutical company called Astra began pursuing methods to inhibit acid secretion.^{ix}

7.1 OMEPRAZOLE – THE FIRST PROTON PUMP INHIBITOR

The Second Edition of Drug Discovery and Development provides an illuminating history on Astra's early work towards developing what would become the first proton pump inhibitor (PPI):^x

"In 1966 Astra started a project aimed at developing inhibitors of gastric acid secretion, having previously developed profitable antacid preparations ... Compounds with weak activity were quickly identified; initial hepatotoxicity problems were overcome, and a potential development compound was tested in humans in 1968. It had no effect on acid secretion, and the project narrowly escaped termination. In the meantime, good progress was being made by Smith, Kline and French in developing histamine H₂ antagonists for the same indication, thereby adding to the anxiety within Astra. At the same time Searle reported a new class of inhibitory compounds, benzimidazoles, which were active but toxic. Astra began a new chemistry programme based on this series, and in 1973

produced a highly active compound which was proposed for further development. To their dismay, they found that a Hungarian company had a patent on this compound (for a completely different application). However, upon entering licensing negotiations they found that the Hungarian patent had actually lapsed because the company had defaulted on payment of the fees to the patent office! Further studies with this compound revealed problems with thyroid toxicity, however, and more demands to terminate this hapless project were narrowly fought off. The thyroid toxicity was thought to be associated with the thiouracil structure, and further chemistry aimed at eliminating this resulted, in 1976, in the synthesis of picoprazole, the forerunner of omeprazole. After yet another toxicological alarm - this time vasculitis in dogs - which turned out to be an artefact, picoprazole was tested in human patients suffering from Zollinger-Ellison syndrome and was found to be highly effective in reducing acid secretion. At around the same time, an academic group showed that acid secretion involved a specific transport mechanism, the proton pump, which was strongly inhibited by the Astra compounds, so their novel mechanism of action was established."

As such, after years of study and research, instead of Astra pursuing picoprazole, the first proton pump inhibitor (PPI) was officially synthesized in 1979 under the generic name **omeprazole**.^{xi} PPIs work by inhibiting gastric acid secretion at the H⁺/K⁺/ATPase pump in the gastric parietal cell, blocking the last step in acid production. PPIs are generally favored over other classes of acid reflux medications such as H₂ receptor antagonists, because they have greater acid suppression and a longer duration of action.

Phase II/III clinical trials began in 1981, and Astra's omeprazole was finally approved by the FDA in September 1989 under the brand name **Losec**.^{xii xiii} Later, due to prescribing and dispensing mix-ups with similarly named Lasix, Astra modified the name to **Prilosec** in the United States.^{xiv}

Omeprazole approval was granted for the healing and treatment of duodenal and gastric ulcers, gastroesophageal reflux disease (GERD), and the maintenance of healing erosive esophagitis.

7.2 RACEMIC MIXTURE VERSUS SINGLE ISOMER

Omeprazole is what is called a **racemic** mixture. In other words, it is comprised of equal amounts of two **enantiomers** - an "S-enantiomer" and an "R-enantiomer." An enantiomer is one of two molecules that are mirror images of each other. However, as shown in **Figure 4** (on next page)^{xv}, much like a right and left hand, enantiomers are not identical. They cannot appear identical simply by reorientation.^{xvi} Usually, one enantiomer is more active than the other and produces a better result. According to a study published by AstraZeneca R&D in 2003, the pure S-enantiomer (which would eventually be brought to market as **Nexium**) has a "higher and more consistent bioavailability" (i.e. the extent to which a medication can be used by the body^{xvii}) than a racemic mixture of the two enantiomers (i.e. Omeprazole) and therefore exhibits "superior clinical efficacy" to Omeprazole.^{xviii} However, 12 years later, a study published in the DARU Journal of Pharmaceutical Sciences (funded by a University of Alberta Self-Directed Grant), concluded that the S-enantiomer "offers little or no advantage over its parent racemic product."^{xix}

Whether AstraZeneca or the DARU researchers are correct is ultimately a moot point, because it was the **perceived** difference in bioavailability between the two omeprazole enantiomers that became the basis for the immensely successful launch of Nexium in 2001, which isolated the single S-enantiomer.

In early 2001, Nexium was approved by the FDA with a Type 2 classification - a new active ingredient that was not a new molecular entity (NME). Nexium went on to generate \$64 billion in worldwide revenue (\$37 billion in the U.S. alone) for AstraZeneca through 2018 (see **Figure 5**). Billions more have been spent on generic Nexium (esomeprazole) since Nexium lost patent protection in 2015.

Figure 4: Omeprazole Enantiomers

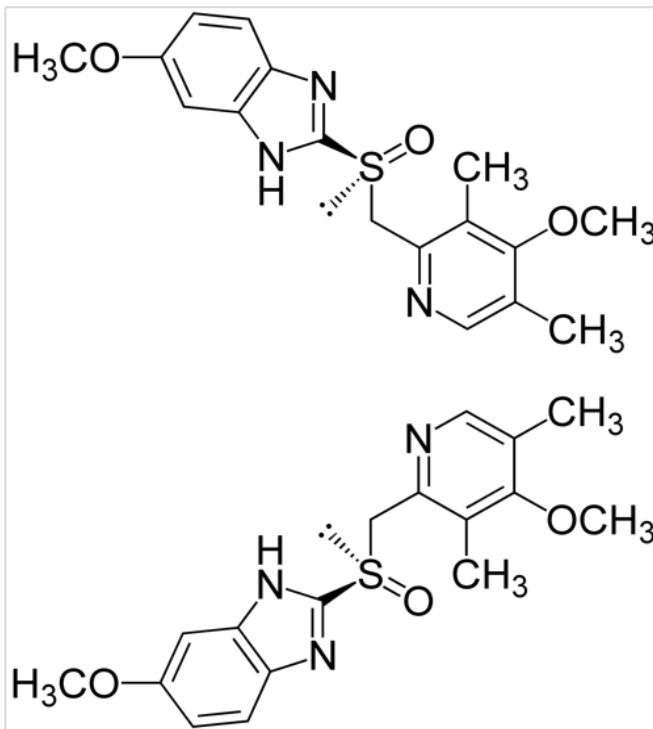
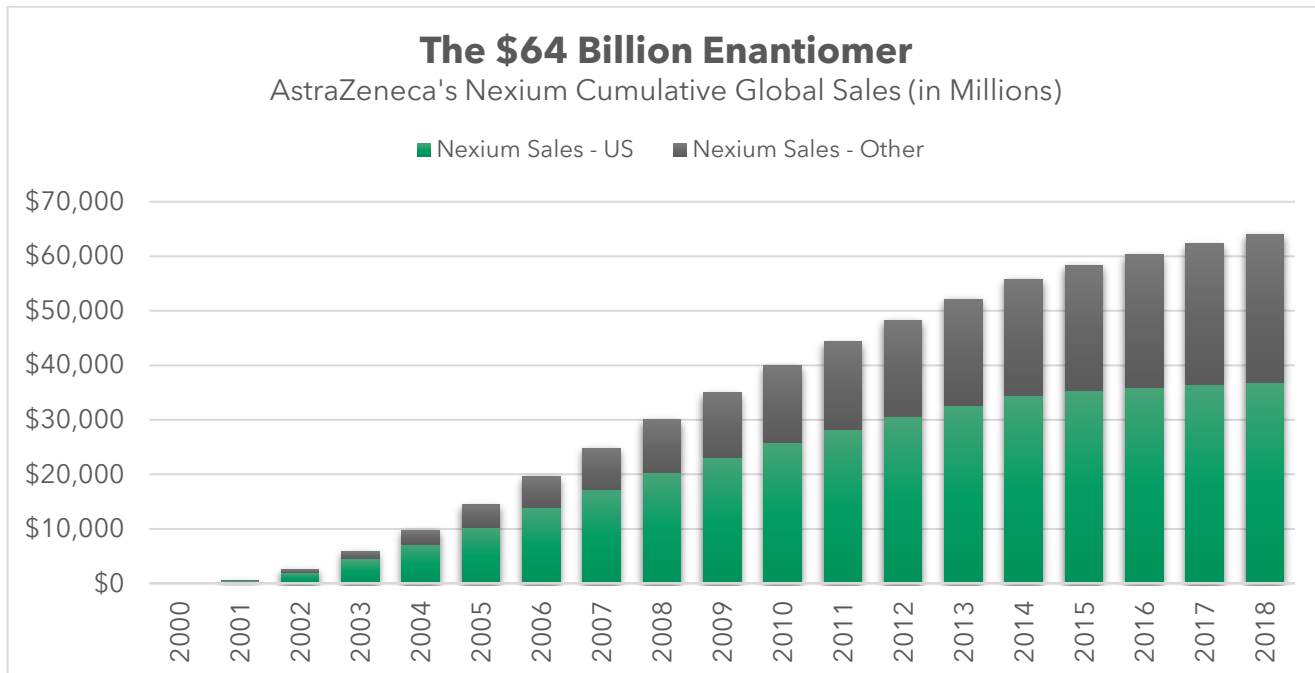


Figure 5: The \$64 Billion Enantiomer



Source: AstraZeneca annual reports (2000-2018)

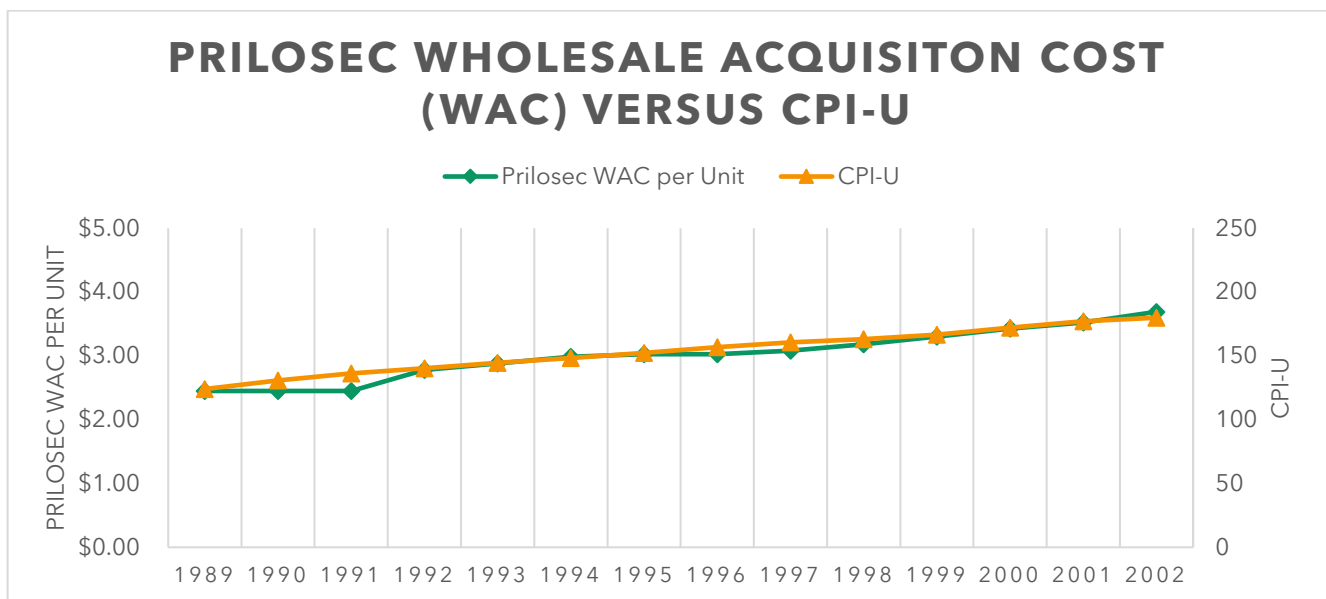
7.3 PRICING OF PRILOSEC, NEXIUM, AND THE CONTROVERSIAL IMPACT OF REBATES

Back in 1989, the controversy surrounding the relative efficacy of omeprazole’s enantiomers was still a decade away from having any relevance. With the introduction of Prilosec, Astra had effectively created an entirely new class of drugs (PPIs) for treatment of acid-related disorders. It was a class of drugs that exhibited “generally superior acid suppressing capability than prior agents.”^{xx}

Overall, Prilosec developed into the world’s largest-selling GI product with 665 million treatments from its launch through 2002.^{xxi} Over this period, Prilosec generated \$26 billion in U.S. revenue for AstraZeneca.^{xxii}

However, this financial windfall was not aided by egregious price increases. Despite its market dominance within the GI treatment class, AstraZeneca largely limited price increases on Prilosec to inflationary adjustments (as measured by CPI-U). As shown in **Figure 6**, AstraZeneca launched Prilosec in 1989 with a Wholesale Acquisition Cost (WAC) of \$2.45 and increased its WAC to \$3.69 by 2002 - a 3.2% CAGR over the 13-year period. Meanwhile, CPI-U increased from 124 in 1989 to 180 in 2002 - a 2.9% CAGR over the same period.^{xxiii}

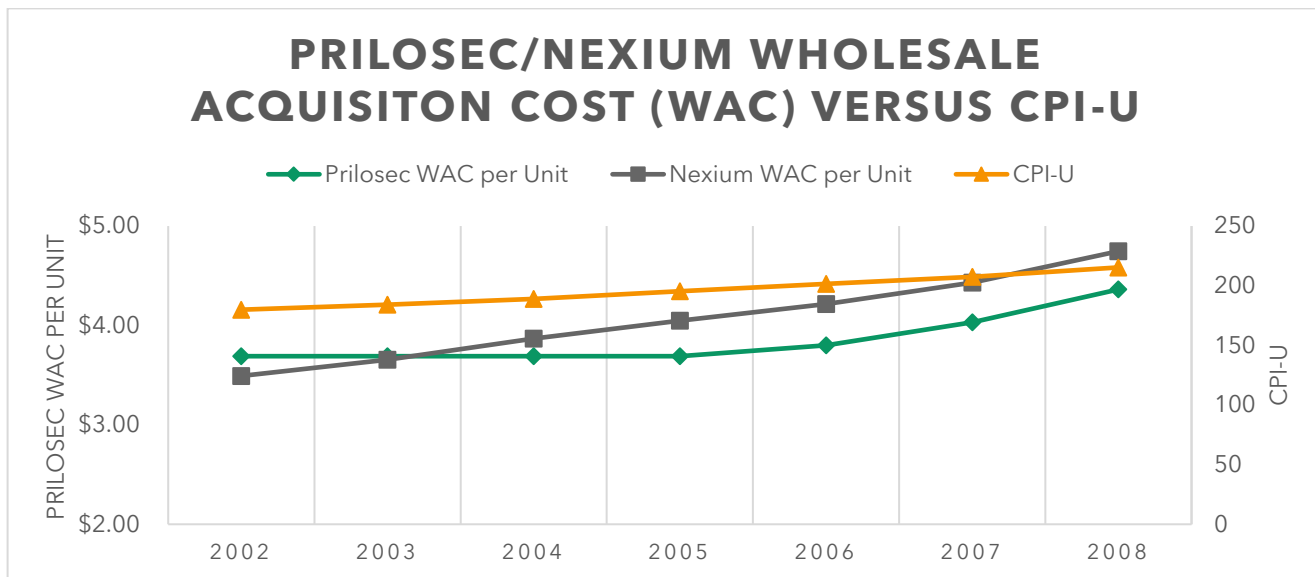
Figure 6: Prilosec WAC versus CPI-U (1989 - 2002)



Source: 3 Axis Advisors analysis – derived from data obtained from Medispan PriceRx

In early 2002, AstraZeneca lost its exclusivity on Prilosec, and omeprazole generic copy-cats began to come to market. But, before that, AstraZeneca successfully brought Nexium to market in early 2001 to replace Prilosec, setting its initial price at a 6% discount to Prilosec. However, as shown in **Figure 7** (next page), neither development appears to have materially impacted AstraZeneca’s pricing strategy through 2008. The company increased Prilosec’s WAC by a 2.8% CAGR between 2002 and 2008, lagging the 3.0% CPI-U CAGR over the same period. AstraZeneca was apparently more aggressive on Nexium’s price increases, raising its price at a 5.2% CAGR over the same period.

Figure 7: Prilosec/Nexium WAC versus CPI-U (2002 - 2008)

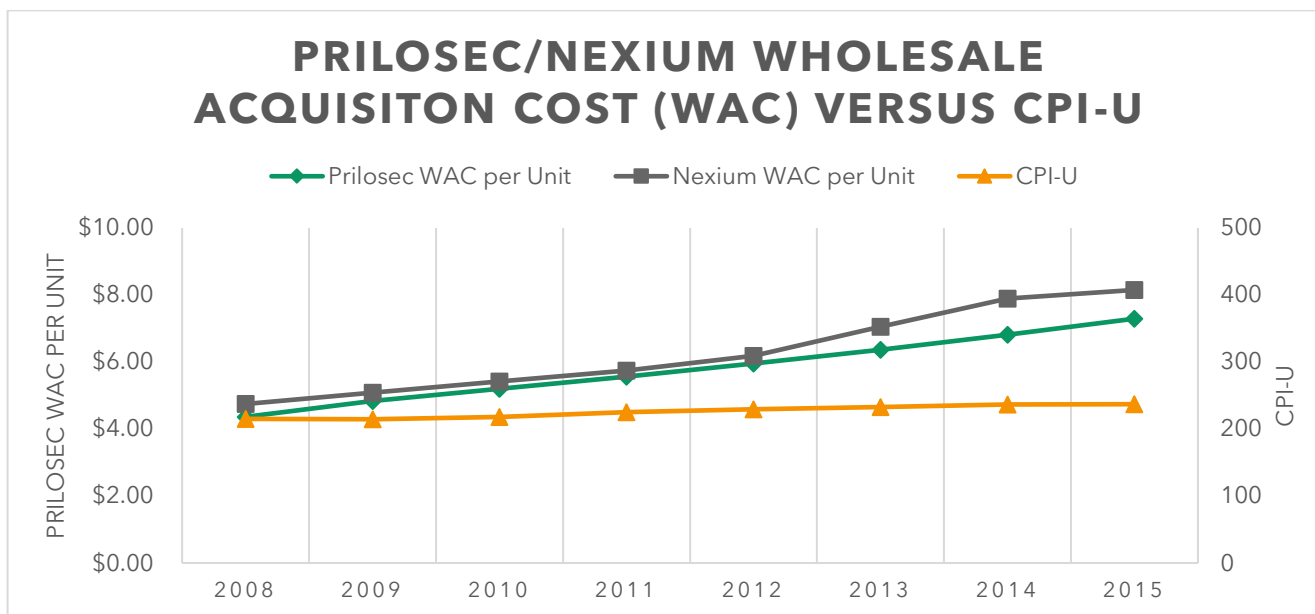


Source: 3 Axis Advisors analysis – derived from data obtained from Medispan PriceRx

It wasn't until 2008 when AstraZeneca's price increases really started to diverge from CPI-U. As a result of the Great Recession, CPI-U stepped down (0.4%) in 2009 and never recovered to its pre-recession run-rate - from 2008 through 2015, CPI-U grew at a CAGR of just 1.4%.

Meanwhile, AstraZeneca ramped up pricing increases on both Prilosec and Nexium to a CAGR of 7.6% and 8.0%, respectively, over the same period. The divergence in AstraZeneca's pricing on Prilosec/Nexium and CPI-U is shown in **Figure 8**.

Figure 8: Prilosec/Nexium WAC versus CPI-U (2008 - 2015)



Source: 3 Axis Advisors analysis – derived from data obtained from Medispan PriceRx

In our view, these aggressive price increases cannot be fully blamed on AstraZeneca. At the same time inflation was slowing, rebates between drug manufacturers and pharmacy benefit managers (PBMs) were increasing. According to the latest Medicare Trustees Report, in 2008, rebates were 11.1% of total Medicare Part D drug cost. By 2015, rebates had increased to 18.2% of total Part D drug cost. In 2018, rebates are expected to eclipse 25% of total Medicare Part D drug cost.^{xxiv} There is significant concern from the federal government that the rapid rise in rebates has played an instrumental role in inflating drug list prices.^{xxv} Rebates introduce the risk that drug manufacturers will simply boost list prices to offset greater PBM and government program demands for rebates, subjecting patients and smaller employers to overinflated list prices for medications. This was likely a contributing factor behind the steep increases on Prilosec and Nexium starting in 2008. A more extensive analysis of brand-name drugs suggests that AstraZeneca's pricing behavior was not abnormal; **between 2008 and 2018 the median brand drug unit cost increased at an 9.3% CAGR, six times the rate of inflation (2008-2018 CPI-U CAGR = 1.6%).**^{xxvi}

Unfortunately, it is not possible with the data available to the public to prove causality between high rebates and high list prices. But it is, in our view, irrefutable that there is a correlation between the two. AstraZeneca's pre-2008 pricing strategy offers an interesting historical case study that suggests that absent substantial rebate pressure, it is plausible that manufacturers could link price increases to inflation even on market dominant brand-name drugs.

8 NEXIUM – THE SECOND COMING OF PRILOSEC

Section Key Takeaways

- Over the past 29 years, an average of 65% of all original applications approved by the FDA have been for “line extensions”
- In 1998, 55% of Astra’s sales came from Prilosec/Losec, which was set to lose patent exclusivity in April 2001 in the U.S.
- Astra launched the Shark Fin Project in 1995 to avert the steep revenue decline expected when generic omeprazole came to market
- AstraZeneca put \$478 million behind the 2001 launch of Nexium to build brand awareness and aggressively switch market share from Prilosec
- Through a spate of patent infringement lawsuits, AstraZeneca was able to hold off omeprazole generic entry until November 2002
- AstraZeneca partnered with Procter and Gamble to launch Prilosec OTC, further undermining development of the generic marketplace
- In 2006 - four years after the launch of generic omeprazole - AstraZeneca still produced 93% of all omeprazole molecule dispensed units in Medicaid

In 1998, Astra’s overall company sales were \$7.2 billion.^{xxvii} Of this, 55% came from sales of Prilosec/Losec. Meanwhile, Prilosec’s U.S. patent was expiring in April 2001, after which generic manufacturers would flood the U.S. market with inexpensive generic omeprazole.

To clarify, this is the natural, designed lifecycle of a drug in the U.S. A brand-name manufacturer (AstraZeneca) is rewarded handsomely (\$27 billion in revenue) for bringing an innovative drug (Prilosec) to market that improves patients’ quality of life. But eventually, a brand-name manufacturer will lose its exclusivity, and generic manufacturers will come to market, driving the cost of the medication down to cents on the dollar. In our view, this design works very well “on paper.” Brand-name manufacturers need a financial incentive to develop treatments that significantly improve patients’ quality of life. Patent protection provides such an incentive. But when exclusivity expires, robust generic competition must rapidly drive the cost of off-patent drugs down to an efficient market-clearing price. Such generic deflation is critical in providing the savings to collectively fund the next generation of drugs needed to further improve patients’ quality of life.

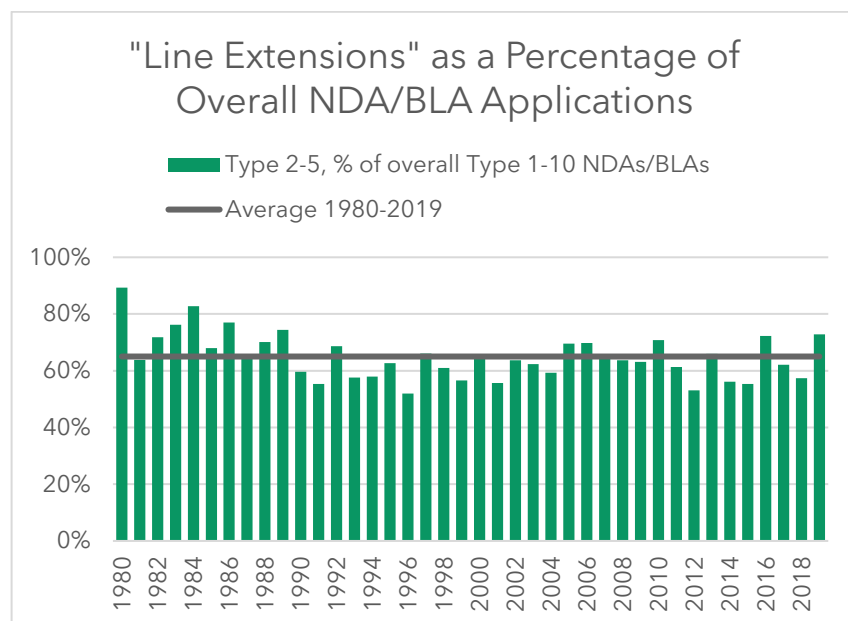
8.1 MAJORITY OF FDA APPROVALS ARE FOR REFORMULATIONS OF EXISTING DRUGS

Unfortunately, the system does not actually work as it was naturally designed. Not all drugs developed and patented are innovative. Not all drugs developed and patented significantly improve patients’ quality of life. But all drugs patented and approved by the FDA are rewarded with the ability

to set monopolistic pricing for ten or so years.^{xxviii} As such, brand-name manufacturers are theoretically incentivized to bring to market any drug that is safe, effective, and **perceived to be** incrementally beneficial versus existing treatments. These drugs go by many names - line extensions, reformulations, or follow-on products, to name a few.

We tested this theory on incentives. As shown in **Figure 9**, we found an average of 65% of all Type 1-10 NDA/BLA applications each year were classified as Type 2-5, or as “line extension” products (as per the side panel).^{xxix} This would suggest that only one-third of all new drug applications each year are truly for “innovative” new molecules.

Figure 9: “Line Extensions” as a Percentage of Overall NDA/BLA Applications



Source: 3 Axis Advisors analysis – derived from data obtained from FDA.gov

FDA CLASSIFICATION TYPE 2-5

- Type 2:** New Active Ingredient (e.g. Nexium)
- Type 3:** New Dosage Form (e.g. Suboxone Film)
- Type 4:** New Combination (e.g. Truvada)
- Type 5:** New Formulation or Other Differences (e.g. Glumetza)

Identifying “line extensions”

In 2017, Annabelle Fowler, Ph.D. candidate in Health Policy and Economics at Harvard University published a report entitled, “Pharmaceutical Line Extensions in the United States: A Primer on Definitions and Incentives.” In the study, Ms. Fowler provides “rules of thumb” to identify line extensions based on the FDA approval classification code. She explains that if an application is coded as Type 2, 3, 4, or 5, it is likely that it is for a line extension.

We applied this rule of thumb to the complete Drugs@FDA database. To do so, we first had to perform several joins of the tables within the Drugs@FDA database, in the following order:

1. Inner join between “Submissions” table with “SubmissionsClass_Lookup” table on “SubmissionClass CodeID”
2. Inner join between table created in Step 1 and “Applications” table on “ApplNo”
3. Inner join between table created in Step 2 and “Products” table on “ApplNo.” Before joining filter Products table to ProductNo = “001” to ensure only one Product row per application

We then used the merged database to test our theory. We filtered “Appl Type” to only include “NDA” and “BLA” applications. Then we simply counted the number of applications each year that were classified as Type 2-5 as a percentage of the total Type 1-10 applications. We performed this analysis from 1980-2019.

Omeprazole offers a helpful case study on how this percentage can be so high. **Table 1** - based exclusively on data retrieved from Drugs@FDA - shows that there have been 12 different Type 2-5 derivatives of omeprazole brought to market by a variety of manufacturers. All of applications listed in the following table are NDAs (i.e. ANDAs are not included). The year corresponds to the year each NDA was first approved by the FDA.

Table 1: All approved NDAs derived from omeprazole

Year	Appl No	Drug Name	Active Ingredient	Form	Sponsor Name	Submission Class Code
1989	019810	PRILOSEC	OMEPRAZOLE	CAPSULE, DELAYED REL PELLETS; ORAL	ASTRAZENECA PHARMS	TYPE 1
2001	021153	NEXIUM	ESOMEPRAZOLE MAGNESIUM	CAPSULE, DELAYED REL PELLETS; ORAL	ASTRAZENECA PHARMS	TYPE 2
2003	021229	PRILOSEC OTC	OMEPRAZOLE MAGNESIUM	TABLET, DELAYED RELEASE; ORAL	ASTRAZENECA PHARMS	TYPE 2/3
2004	021636	ZEGERID	OMEPRAZOLE; SODIUM BICARBONATE	FOR SUSPENSION; ORAL	SALIX	TYPE 3/4
2005	021689	NEXIUM IV	ESOMEPRAZOLE SODIUM	INJECTABLE; INTRAVENOUS	ASTRAZENECA PHARMS	TYPE 3
2006	021849	ZEGERID	OMEPRAZOLE; SODIUM BICARBONATE	CAPSULE; ORAL	SANTARUS INC	TYPE 4
2006	021957	NEXIUM	ESOMEPRAZOLE MAGNESIUM	FOR SUSPENSION, DELAYED RELEASE; ORAL	ASTRAZENECA PHARMS	TYPE 3
2007	022032	OMEPRAZOLE	OMEPRAZOLE	TABLET, DELAYED RELEASE; ORAL	DEXCEL PHARMA	TYPE 5
2008	022056	PRILOSEC	OMEPRAZOLE MAGNESIUM	FOR SUSPENSION, DELAYED RELEASE; ORAL	COVIS PHARMA BV	TYPE 3
2008	022101	NEXIUM	ESOMEPRAZOLE MAGNESIUM	FOR SUSPENSION, DELAYED RELEASE; ORAL	ASTRAZENECA PHARMS	TYPE 3
2010	022511	VIMOVO	ESOMEPRAZOLE MAGNESIUM; NAPROXEN	TABLET, DELAYED RELEASE; ORAL	HORIZON	TYPE 4
2013	202342	ESOMEPRAZOLE STRONTIUM	ESOMEPRAZOLE STRONTIUM	CAPSULE, DELAYED RELEASE; ORAL	R2 PHARMA LLC	TYPE 2
2015	207920	NEXIUM 24HR	ESOMEPRAZOLE MAGNESIUM	TABLET, DELAYED RELEASE; ORAL	ASTRAZENECA LP	TYPE 3

Source: Drugs@FDA

For more discussion on esomeprazole's "for suspension" new dosage form (application numbers 021957 and 022101) see the [Nexium gets granular](#) section. For more discussion on the esomeprazole / naproxen combination drug called Vimovo, see the [Vimovo](#) section.

8.2 THE SHARK FIN PROJECT

Let's now return to Astra's dilemma in the late 1990s - a looming U.S. patent cliff in 2001 that was a threat to the product delivering over half of the company's revenue.

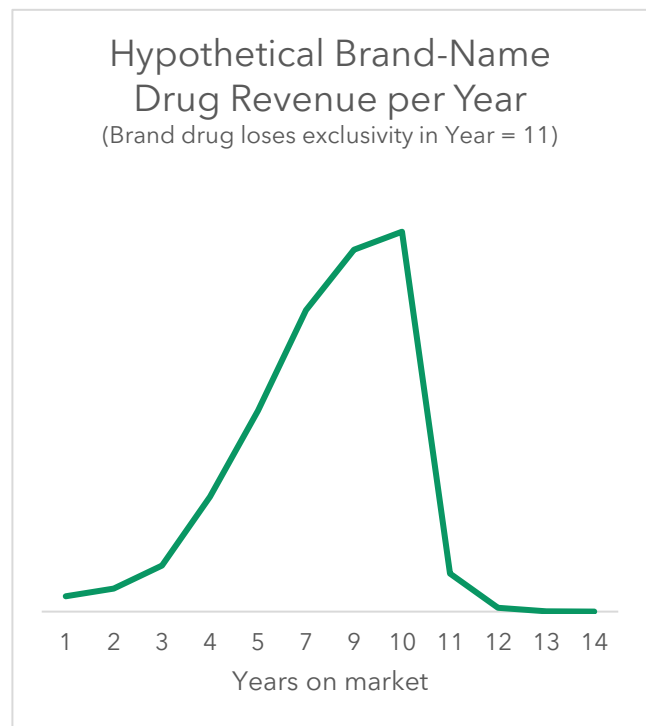
This risk, according to Wall Street analysts, could have been one of the main factors leading to the late-1998 merger between Astra AB and Zeneca group.^{xxx} While Zeneca's portfolio brought a bit of much-needed diversification, Prilosec/Losec sales still comprised nearly 40% of the merged company sales in 2000.^{xxxi} It was clear that Astra was not going to be able to merge its way out of the damage caused by the Prilosec patent cliff.

Back in 1995, Astra saw this dire situation looming on the horizon. That year, Astra proactively formed a team of experts that included marketers, lawyers, and scientists who “studied Prilosec and came out with around 50 possible solutions to outsmart the patent-expiration peril.”^{xxxii} This group was known inside the company as the Shark Fin Project.^{xxxiii}

The goal of the Shark Fin team was simple - avert the dreaded revenue drop that when charted out, would resemble a shark fin. To avoid this intentionally designed fate, the team had to:

1. Develop a drug that performed at least incrementally better than Prilosec
2. Execute an aggressive marketing campaign touting the benefits of the new drug
3. Stave off generic competition on Prilosec for as long as possible to get as many patients as possible switched to the new drug

Figure 10: The Shark Fin



As we already know, AstraZeneca pulled off this hat trick with unprecedented results. AstraZeneca’s odds-defying success in averting the shark fin was so compelling that it is being used to train business school students at one of the top business schools in the country. Northwestern Kellogg Business School published a case in 2005 called “AstraZeneca, Prilosec, and Nexium: Strategic Challenges in the Launch of a Second-Generation Drug,” in which it posed the question, “how could the company use its entire portfolio of intellectual properties—including patents and trademarks—to actively manage the priced-based competition and achieve a revenue growth strategy in the GERD market?”^{xxxiv} Former Northwestern Kellogg School of Management Dean Dipak Jain used AstraZeneca’s management of Prilosec’s patent cliff as one of the prime examples of an effective execution of a “sandwich strategy,” in which a company “sandwiches” its competition between two similar products at different price points.^{xxxv}

Much has been written about AstraZeneca’s epic success in transitioning from Prilosec to Nexium. Our goal with the remainder of this section is simply to collect, organize, and present the extensive work performed by the media on this topic in the first few years after Nexium’s launch. We’ve categorized the details of AstraZeneca’s work into five subsections:

- **Meet the “The Son of Prilosec”** discusses how AstraZeneca ended up patenting Nexium as a single isomer of omeprazole
- **Creating perceived value** details the wildly successful marketing campaign launched to shift consumers from Prilosec to Nexium
- **Keeping generic competition at bay** explains how AstraZeneca’s legal team was able to extend Prilosec’s exclusivity for an additional 17 months

8.2.2 Creating perceived value

Whether or not Nexium was clinically superior to Prilosec, and by how much, was irrelevant in hindsight. AstraZeneca just needed to create the perception of incremental value and convince prescribers and patients of such value.

Without tools to evaluate overall prescription costs to both the payer and patients, or incentives to reduce such costs, all but the most noble of physicians are completely insensitive to the cost of a new medication. Therefore, if a pharmaceutical sales representative touts the benefits of a new product, there is no downside for prescribers to shift patients over to a new drug, even if the improvement is debatable.

Exacerbating this dynamic are the payments made by drug manufacturers to doctors. In 2010, the Sunshine Act required these payments to be made publicⁱ - CMS now publishes them in its Open Payments database.ⁱⁱ ProPublica reports that between August 2013 and December 2016, pharmaceutical and medical device companies disclosed \$9.1 billion in payments to a variety of doctors and teaching hospitals.ⁱⁱⁱ We suspect this number was much higher when AstraZeneca launched its Nexium marketing blitz - before disclosure requirements of such payments were in place.

To characterize Nexium's marketing efforts as a blitz is an understatement of epic proportions. The Nexium marketing campaign was more like an "avalanche."

Dovetailing on the immense success of Prilosec's "purple pill" campaign, AstraZeneca branded Nexium as the "new purple pill" and "the healing purple pill."^{liii} ^{liv} Nexium's "ubiquitous TV spots" distilled the core message down to a very simple and powerful takeaway - "Better is better."^{lv} AstraZeneca threw \$478 million behind Nexium's marketing campaign in the critical 2001 Prilosec-to-Nexium transition year and then shelled out another \$183 million and \$257 million in 2002 and 2003, respectively.^{lvi} In the summer of 2002, Nexium was the most heavily advertised drug in the U.S.^{lvii}

According to the Wall Street Journal, AstraZeneca's sales representatives also played a critical role in the uptake of Nexium:

Nexium's Critics

Kaiser Permanente, the largest managed-care group at the time, pushed back on doctors prescribing Nexium. The reason, said David Campen, a Kaiser physician and pharmacy executive: "Nexium clearly is no value-added drug."

Modern Healthcare Editor Emeritus Merrill Goozner, who also authored the book **The \$800 Million Pill: The Truth Behind the Cost of New Drugs** called Nexium "medically irrelevant"

According to the New York Times, "Thomas A. Scully, administrator of the federal Centers for Medicare and Medicaid Services ... admonished doctors for prescribing Nexium when Prilosec is functionally identical and will soon be much cheaper"

In a Forbes feature from 2006, Robert Langreth and Matthew Herper called the Nexium trials "stacked," explaining that, "in three of the big trials AstraZeneca pitted high doses of Nexium versus half the dose of Prilosec; it never bothered to test whether twice the Prilosec dose would be equally effective."

“AstraZeneca’s 6,000 salespeople, who have nine products they sell to U.S. primary-care physicians, talk about Nexium during a third of their sales calls, according to ImpactRx, a research firm in Mt. Laurel, N.J. Its numbers show doctors get more pitches for Nexium than for any other heartburn drug. Trying to switch doctors to the new drug with years of patent protection ahead, the salespeople now bring up Prilosec only to compare it unfavorably to Nexium.”

To reduce patient-switching cost and further promote brand awareness among consumers, AstraZeneca also offered free trials of Nexium through inserts in magazines and directly through its PurplePill.com website. In 2004, more than five million people visited the site and 500,000 people registered for free trials of the drug.^{lviii}

AstraZeneca’s marketing efforts around Nexium continued for years after its launch. In 2007, its “Purple Plus Adherence” program won the Silver in the MM&M awards in the “Best Use of Direct Marketing to Consumers” category.^{lix} The MM&M awards are “regarded as healthcare marketing’s highest accolade ... (it) recognizes and champions both creativity and effectiveness in healthcare marketing and communications.”^{lx}

But such awards and accolades came well after the true success of the Shark Fin project. According to AstraZeneca’s 2002 annual report, during 2002 – less two years after Nexium’s launch – U.S. sales of Nexium overtook Prilosec.^{lxi} According to AstraZeneca’s 2004 annual report, “Nexium confirmed as the most successful U.S. pharmaceuticals launch with in excess of \$3.5 billion sales in 30 months.”^{lxii}

Not everyone was pleased with AstraZeneca’s direct-to-consumer marketing efforts. In October 2014, the AFL-CIO, the Congress of California Seniors, and the California Alliance for Retired Americans filed a lawsuit on behalf of consumers nationwide who purchased Nexium, alleging that, “AstraZeneca initiated a misleading advertising campaign about Nexium that claimed the new treatment was significantly better than Prilosec. The consumer group claims Nexium is ‘nearly identical’ to Prilosec.”^{lxiii}

Two years later, eight retailers, including Walgreens, Kroger, and Safeway filed a civil suit in federal court “alleging that AstraZeneca used fraud and ‘exclusionary conduct’ to hold on to its dominant position by switching patients from Prilosec to its nearly identical, patent-protected drug Nexium.”^{lxiv}

8.2.3 Keeping generic competition at bay

Absent the success of AstraZeneca’s legal team in blocking Prilosec’s generic competition, Nexium may have never been able to gain a toehold in the GI market. Had several manufacturers brought cheap generic versions of Prilosec to market starting in April 2001 (as scheduled), the pricing discrepancy between generic omeprazole and branded esomeprazole may have been so extreme that health plans may have never added Nexium to their formularies. In other words, the drug could have been blocked by insurers, PBMs, and government payers, leaving AstraZeneca in dire straits.

Of course, this is not what happened. It wasn’t until November 4, 2002, that Kremers Urban Pharmaceuticals (now part of the Lannett Company) brought the first version of generic omeprazole to market. As mentioned earlier, by that time, Nexium didn’t just have a toehold on the U.S. GI market, Nexium had overtaken Prilosec.

Here's how AstraZeneca's lawyers bought enough time to render Prilosec obsolete.

First, in 1999, AstraZeneca filed lawsuits against four generic pharmaceutical manufacturers for alleged patent infringements in the manufacturers' Abbreviated New Drug Applications (ANDAs) that sought to bring generic Prilosec to market. Just a year later, four more generic manufacturers seeking ANDAs were sued by AstraZeneca as well. Despite protests from AstraZeneca, all eight cases were consolidated and referred to a single U.S. District Court Judge.^{lxv}

On March 23, 2000, the FDA granted tentative approval to Andrx, the first manufacturer to file an abbreviated application, for the production and distribution of the 10 mg, 20 mg, and 40 mg strengths of omeprazole. However, the FDA noted that since action had been brought against Andrx for patent infringement, it could not grant final approval until expiration of a 30-month stay, the date of the court decision, or the date each patent expired.^{lxvi}

As of July 2001, there were ten different manufacturers angling for a slice of the omeprazole pie, and AstraZeneca was suing each one of them. AstraZeneca insinuated that any generic pill would infringe on the company's "metabolite" patent, a highly controversial process that essentially involves patenting human-produced chemicals that are generated in response to drug absorption.^{lxvii lxviii}

The Wall Street Journal summarized the quagmire of metabolite patents well at the time:^{lxix}

"The metabolite defense, which first surfaced in the mid-1990s, relies on manufacturers' ability to identify and separately patent chemical compounds created naturally in the body when a drug is digested. With one or more metabolite patents in hand, the company's lawyers sue generic makers, contending that the knock-off companies seek to induce patients to unwittingly produce the metabolite in their bodies."

But the metabolite patent debate would have to wait. On May 1, 2001, AstraZeneca scored an extra six months of exclusivity for pediatric trials, thanks to a provision included in the FDA Modernization Act of 1997.^{lxx lxxi} AstraZeneca ended up generating \$306 million per month in revenue from U.S. sales of Prilosec in 2001.^{lxxii} Assuming ratable sales over the year, we estimate that this six-month extension was worth over \$1.8 billion – a significant sum of money, but insignificant relative to the long-term value creation associated with a successful launch of Nexium.

Nonetheless, on November 16, 2001, the FDA approved Andrx's application for the 10 mg, 20 mg, and 40 mg strengths of omeprazole. In the approval letter, the FDA stated, "you further informed the Agency that litigation is underway in the United States District Court for the Southern District of Florida involving challenge to the '499, '505, and '230 patents ... With respect to this litigation, the Agency recognizes that the 30-month period ... during which time the FDA was precluded from approving your application, has expired." Shares of Andrx Corp. jumped 8% on the news. Wall Street analyst Adam Greene estimated that omeprazole could generate \$570 million in revenue over 12 months for Andrx.

But before Andrx could realize such a windfall, it had to prove its application did not infringe on those three patents ('499, '505, and '230). Greene was optimistic that the court would side with the contingent of generic manufacturers, "Predicting any legal outcome is difficult, but in my view the legal difficulty is more manageable."^{lxxiii} Robert Langreth noted at that time (based on an analysis by Wachovia Securities) that generic firms had historically won about 80% of court disputes over brand-name patents. He called a potential win by AstraZeneca an "upset."^{lxxiv}

On December 6, 2001, the patent infringement trial between AstraZeneca and generic drug manufacturers Andrx Group, Merck/Pharmaceutical Resources Inc/Genpharm, Dr. Reddy's Laboratories/Cheminor, and Schwarz Pharma/Kremers Urban Development Company commenced.^{lxxv} While the generic companies argued that AstraZeneca was abusing the regulatory process and unjustly holding onto a patent that should have been dissolved more than three and a half years earlier, AstraZeneca claimed that the companies were just seeking "to take away AstraZeneca's legitimately obtained right for money."^{lxxvi}

As the trial rolled into May 2002, the stakes for AstraZeneca, generic drug makers, and plan sponsors couldn't have been higher. And the precedent from the case would have wide-ranging impacts on the entire industry.

The generic manufacturer contingent and AstraZeneca were fighting down to microscopic levels of legal differences.^{lxxvii} Those differences ended up taking what was supposed to be a quick decision in May 2002 all the way to September 2002. For a drug that was originally supposed to lose its exclusivity in April 2001, AstraZeneca had already gained 17 months of additional Prilosec exclusivity and, more importantly, had successfully moved droves of patients over to Nexium, registering \$830 million in Nexium sales in just the first half of 2002.^{lxxviii}

In October 2002, Federal District Court Judge Barbara S. Jones finally delivered her verdict - and it was an upset. She ruled that Andrx, Cheminor, and Genpharm had each infringed on AstraZeneca's Prilosec patent rights. However, she ruled that Schwarz Pharma, an affiliate of Kremers Urban Development Company did not.^{lxxix} Andrx's share price plummeted 40% on the news.^{lxxx}

An important detail that appears to not have been picked up by the media at the time was that Andrx's application - which, after the verdict, was effectively "blocked" - was for the 10 mg, 20 mg, **and 40 mg** strengths of omeprazole. Kremers' application was only for the 10 mg and 20 mg strengths - strengths that AstraZeneca and Proctor and Gamble were already actively working to move to over-the-counter.

Eventually, Andrx, Genpharm and Schwarz Pharma/Kremers cut a deal since Andrx and Genpharm had been previously awarded a six-month period of co-exclusive marketing rights for omeprazole from the FDA.^{lxxxi} This was a helpful marriage for both sides, as Andrx and Genpharm didn't lose out completely when the court blocked them from manufacturing omeprazole (each received a 15% share of Schwarz profit on omeprazole), and Schwarz got to utilize Andrx and Genpharm's generic exclusivity rights. They began working hard to bring the drug to market to stave off AstraZeneca from further moving patients to Nexium. On November 1, 2002, the FDA finally approved the Kremers abbreviated new drug application (ANDA) for omeprazole, ushering generic competition into the marketplace. Just three days later, generic omeprazole was finally introduced into the marketplace. But it was too late - Nexium had already overtaken Prilosec in the U.S.^{lxxxii}

8.2.4 The bottom slice of bread

Let's return to Dipak Jain's sandwich strategy. To effectively sandwich out your competition, you need a "premium" version of a product that you can market to less price-sensitive consumers. AstraZeneca had that with Nexium, which its army of 6,000 sales representatives marketed to physicians. But you also need what we'll call the "bottom slice of bread" - a discounted version of a

product that you can market to more price-sensitive customers (i.e. patients who were paying out-of-pocket for the drug). Of course, generic competition was just around the corner. Had it taken hold as expected, it would have rapidly gained market share among the more price-sensitive crowd. In other words, AstraZeneca would have been left with only half a sandwich.

What AstraZeneca needed was a way to capture the price-sensitive customer segment. Its solution was to work with Procter and Gamble to bring an OTC version of Prilosec to market. On January 27, 2000, Procter and Gamble submitted a new drug application for Prilosec OTC (omeprazole magnesium 20 mg delayed-release tablets).^{lxxxiii} According to the New York Times, Procter and Gamble “would market (Prilosec OTC) under a contract with AstraZeneca.”^{lxxxiv} While the financial terms of Procter and Gamble’s arrangement with AstraZeneca were not disclosed, we got a hint that the royalty payments were material in its fiscal-2015 10-K in which P&G disclosed that, “earnings were also negatively impacted by a higher royalty expense rate for Prilosec OTC.”^{lxxxv}

The next challenge was to get approval from an FDA advisory panel to allow over-the-counter sales of Prilosec in the U.S. According to the Wall Street Journal, “FDA approval to sell Prilosec without a prescription has been long sought by AstraZeneca.” Apparently, a positive outcome was not guaranteed as, “the same group of FDA advisers in 2000 recommended against over-the-counter status for Prilosec as an immediate treatment for heartburn.”^{lxxxvi}

However, in June 2002, the advisory panel eventually gave the green light to Prilosec OTC, qualified by some labeling concerns.^{lxxxvii lxxxviii} It took Procter and Gamble just about a year to fully address these concerns. Finally, on June 20, 2003, the FDA issued its approval for Prilosec OTC.^{lxxxix} Less than a month later (July 14, 2003), the product hit shelves across the country.^{xc} Procter and Gamble put a \$100 million marketing campaign behind the launch,^{xc} which generated a fantastic return on investment – according to Procter and Gamble’s fiscal-2014 10-K (emphasis added), “Prilosec OTC became the leading over-the-counter heartburn remedy in the U.S. **within five days of launch**. First year retail sales are expected to approach \$400 million.” Procter and Gamble / AstraZeneca was granted three years of exclusivity on Prilosec OTC since they performed “new clinical investigations” as part of the application. Expiration was set for June 20, 2006.

In February 2006, Dexcel Pharma Technologies filed an abbreviated application to bring generic Prilosec OTC to market after AstraZeneca’s exclusivity expired. Before that could happen, AstraZeneca fired off a patent infringement suit against Dexcel, starting the clock on the 30-day stay. In the 12 months ending May 13, 2007, Prilosec OTC registered sales of approximately \$700 million, meaning that each extra month of exclusivity was worth roughly \$60 million to the Procter and Gamble / AstraZeneca partnership.^{xcii}

In November 2007, AstraZeneca and Dexcel settled the ongoing litigation, giving Dexcel, and its partner company, Perrigo Company, “exclusive marketing rights to store-branded OTC version of omeprazole.”^{xciii} Dexcel/Perrigo’s product hit the market in late February 2008.

To be clear, introduced at a WAC of roughly \$0.60 per pill, Prilosec OTC was significantly cheaper than Prilosec (which carried a WAC of ~\$3.70 per pill in 2013). There is no debate that AstraZeneca and Procter and Gamble’s pricing strategy saved money for consumers versus branded Prilosec. Rather, a potential concern with this tactic is that \$0.60 per pill was still a unilaterally-set price. It was not a market-clearing price that could have been produced through efficient competition between multiple generic manufacturers.

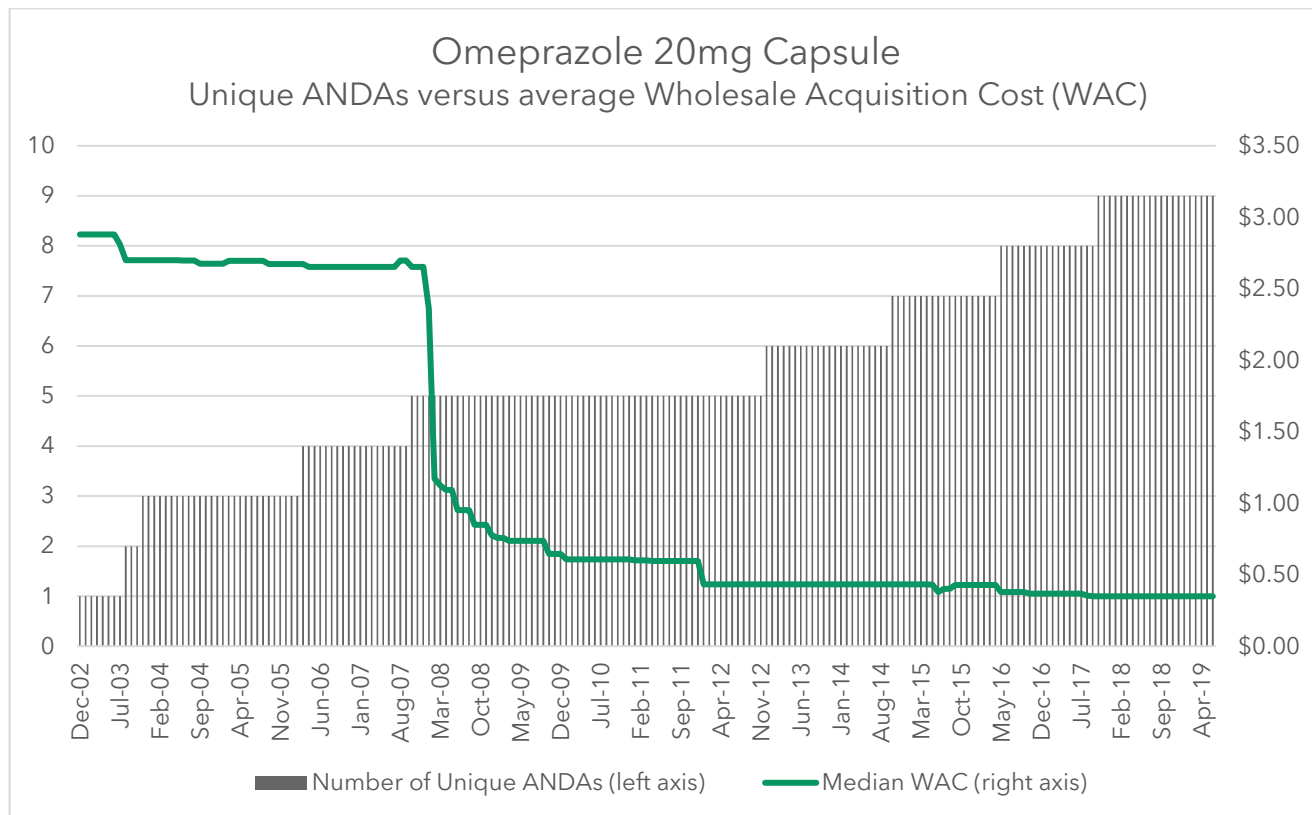
In addition, the launch of an over the counter version of Prilosec was expected to undermine the development of the generic marketplace for omeprazole. This is because once a brand-name drug becomes available over the counter, insurers may be less likely to cover the generic. The Wall Street Journal illustrated this dynamic with Aetna's actions around the launch of generic Prilosec in 2003 (emphasis added).^{xciiv}

"The product will get another edge from Aetna Inc. and other big insurers eager to reduce a major source of drug outlays. As of next week, Aetna will stop covering Prilosec (**and any other prescription omeprazole sold in a 20-milligram dose**, as Prilosec OTC is) for the majority of members in its drug plans, **steering them instead to Prilosec OTC**. Patients filling prescriptions for competing PPIs will pay a co-payment ranging from \$20 to \$35, making Prilosec OTC a good deal. In part because of the insurance advantage, **many doctors anticipate that about 25% of PPI users will switch to Prilosec OTC.**"

Conceptually, if the brand-name manufacturer can (through a partner) bring the OTC to market before the generic comes to market, it can influence plan coverage decisions. This effectively will shift market share from the nascent generic, in which it has no financial interest, to the OTC, in which it has a meaningful financial interest.

Figure 11 (on next page) shows how AstraZeneca's sandwich strategy effectively blocked out generic competition on omeprazole 20mg capsules, delaying price decreases on one of the most anticipated generic releases. After Kremers brought its version to market in late 2002, Mylan and Apotex came to market in 2003. All three set their Wholesale Acquisition Costs (WACs) around \$2.70 per pill. But prices did not start to fall until the fifth ANDA was brought to market, which was not until late 2007, just months before Dexcel brought OTC omeprazole to market. As of May 2019, the Median WAC for Omeprazole 20mg Capsules was \$0.35 per pill. National Average Drug Acquisition Cost (NADAC) - a more accurate measure of pharmacy invoice acquisition cost - was \$0.05 per pill.^{xcv}

Figure 11: Omeprazole 20mg Capsule WAC Pricing vs. Unique ANDAs



Source: 3 Axis Advisors analysis – derived from data obtained from Medispan PriceRx

8.2.5 Stronger = Longer

On February 26, 1996 – the year after the formation of the Shark Fin project^{xcvi} – AstraZeneca submitted a supplemental application for the 40mg strength of omeprazole to the FDA.^{xcvii} On January 15, 1998, the FDA approved AstraZeneca’s application and the new double-strength Prilosec hit the market on June 8, 1998.^{xcviii xcix}

This strength change (and its timing) was significant for a couple reasons:

First, all the trials AstraZeneca had submitted to the FDA in its December 3, 1999 application comparing Nexium (esomeprazole) to Prilosec (omeprazole) relied on the 20 mg version of omeprazole, despite esomeprazole pharmacodynamically being a “higher dose” version of omeprazole. This fact did not go unnoticed in the Center for Drug Evaluation and Research’s Medical Officer’s Review. In Section B (“Efficacy”), Dr. Hugo Gallo-Torres wrote (emphasis added) “**superiority** of NEXIUM over omeprazole **was not demonstrated** because ... in the two studies where (esomeprazole) is shown statistically different to (omeprazole), the dose of (**esomeprazole**) **is pharmacodynamically thrice** that of the S-isomer in (omeprazole).” Dr. Gallo-Torres concluded his assessment by writing, “this reviewer reiterates that ... this s-enantiomer of omeprazole is of similar efficacy to omeprazole.”^c

Meanwhile, the application for the 40 mg strength of omeprazole was submitted three years before, and approved one year before, Nexium’s application was submitted. So, it appears that AstraZeneca could have designed trials comparing Nexium to omeprazole 40 mg (still not a

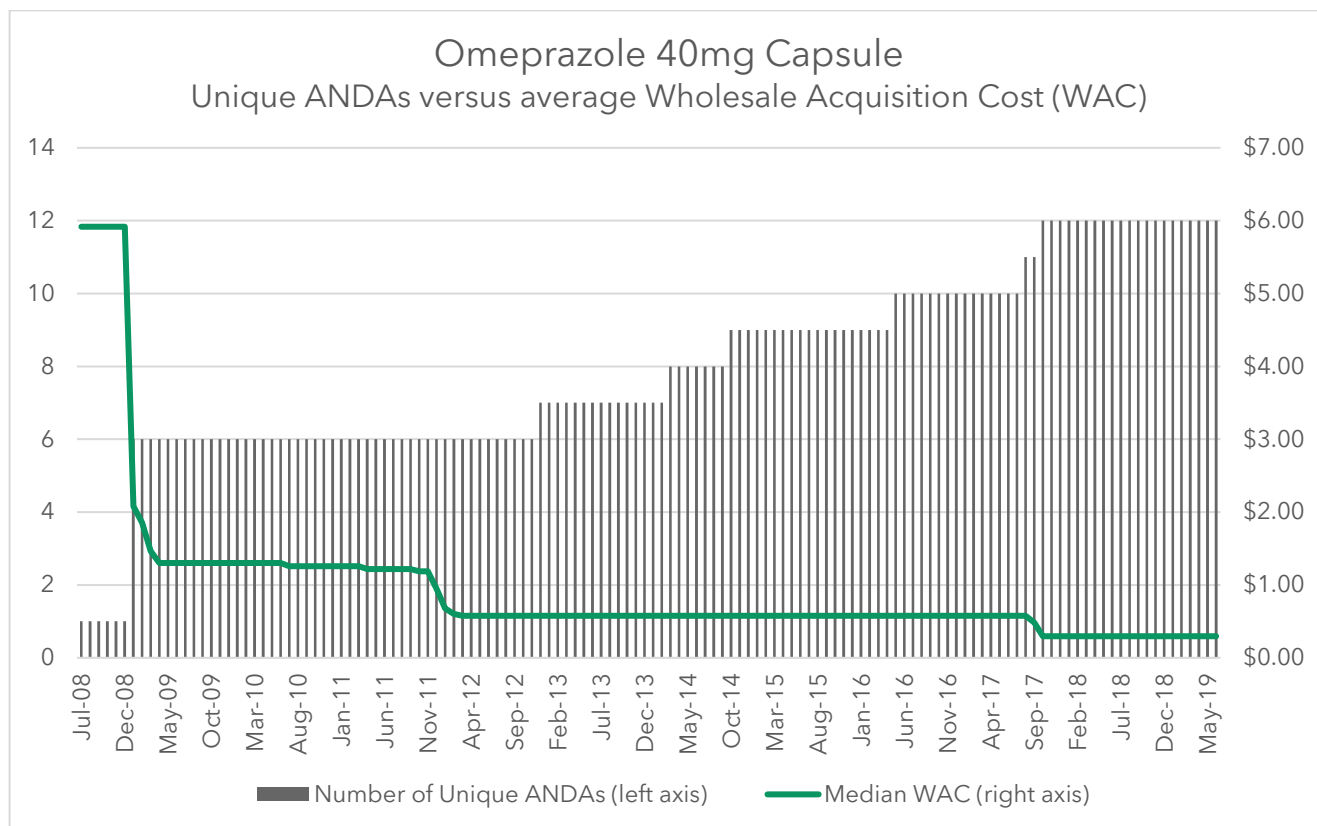
pharmacodynamically equivalent comparison, but at least closer), yet it chose not to. The answer why AstraZeneca made this choice came more than a decade later. In 2015, an evaluation of trials only comparing equal doses of both omeprazole and esomeprazole was conducted and found, “no differences between 20 mg and 40 mg of either omeprazole or S-omeprazole with respect to both therapeutic and pH control outcomes.”^{ci}

Second, as discussed in the prior section, AstraZeneca was already forming plans to shift Prilosec 20 mg to over the counter (and to get exclusivity on the new over the counter) from which it would generate royalties well into the next decade. This had a crippling effect on the formation of the generic marketplace for omeprazole since health plans have little incentive to cover drugs that are available over the counter. But the 40 mg strength was not part of AstraZeneca’s OTC application. So, by introducing Prilosec 40 mg toward the end of Prilosec’s original exclusivity, the company created a new “middle-tier” product option, which it also exclusively owned. To be clear, this would have been a moot point had Judge Barbara S. Jones sided with Andrx in late 2002. As noted earlier, Andrx’s abbreviated application included the 40 mg strength of omeprazole, while Kremers’ application did not. So, in late 2002, the 10 mg and 20 mg versions both came to market – again, a largely irrelevant development given the then-imminent OTC shift of the 20 mg strength – **but the 40 mg version remained available only as a brand for nearly six more years.**

To clarify, we do not believe that this move was intended to drive sales of Prilosec 40 mg – with Nexium touted as “the better purple pill,” it would be illogical to expect plans to cover a perceived-to-be inferior product that carried a similar price tag. Instead, we believe this was likely a move to further block robust generic competition for a stronger version of omeprazole that was, 1) more comparable to Nexium; and, 2) not approved for OTC sales. Had Andrx prevailed and brought the 40 mg strength of omeprazole to market in 2002, this could have forced health plans and their PBMs to more critically evaluate coverage of Nexium, or at the very least, demand more significant rebates in return for its coverage.

We struggled to find any documentation explicitly stating why it took nearly six years for Watson Pharmaceuticals (who acquired Andrx in 2006) to bring the 40 mg version of omeprazole to market. All we know for sure is that it was not until May 30, 2008, that the FDA issued final approval for Watson/Andrx’s application.^{cii} Watson/Andrx’s generic hit the market on July 25, 2008, with 180-days of exclusivity and nearly a \$6 per unit price tag (see **Figure 12** on next page). Six months later, labelers marketing off five different applications hit the market, cutting the price by 80%. As of May 2019, the 40 mg strength is priced at a median WAC of \$0.30 per unit and a median NADAC of \$0.07 per unit.

Figure 12: Omeprazole 40mg Capsule WAC Pricing vs. Unique ANDAs



Source: 3 Axis Advisors analysis – derived from data obtained from Medispan PriceRx

While we do not know exactly how much profit Watson generated off its exclusivity, it was significant enough for the company to call out as one of the key drivers of its increase in gross profit in its 2008 10-K.^{ciii}

8.2.6 A near complete and perfect crippling of the generic marketplace

In summary, the ultimate impact of the Shark Fin project was a near complete and perfect crippling of the marketplace for generic omeprazole. **Figure 13** (on next page) helps visualize the success of AstraZeneca’s sandwich strategy by using Medicaid State Drug Utilization Data (SDUD) published by CMS. We downloaded 11 years of SDUD (which shows utilization and cost in all state Medicaid programs across the country), identified all Prilosec, Nexium, and generic omeprazole National Drug Codes (NDCs) within the database, and aggregated the units reimbursed across the U.S. for such NDCs.

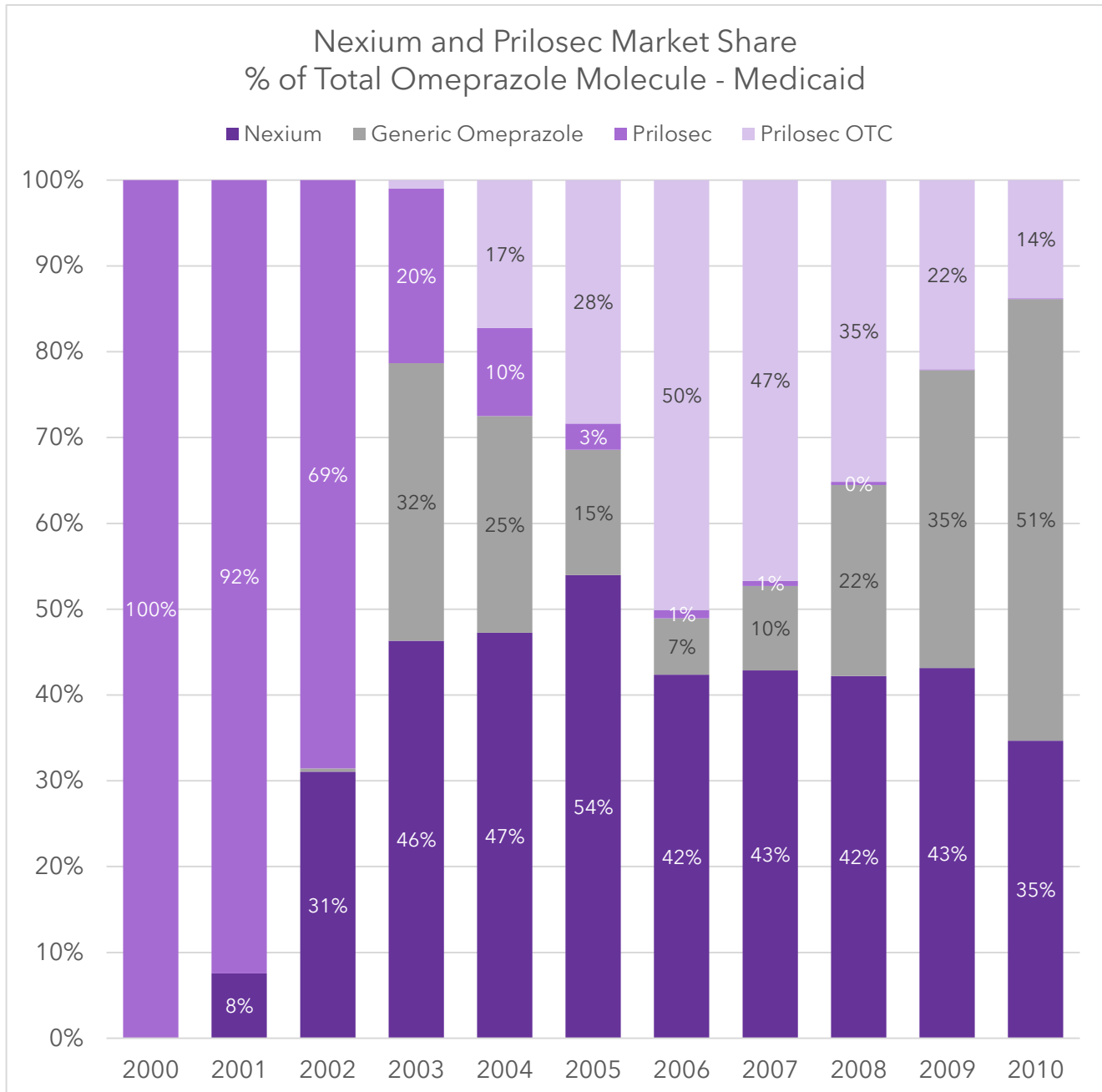
As expected, in 2000, with only prescription Prilosec available, it had 100% market share of all units reimbursed based on the omeprazole new molecular entity (NME). While Nexium was brought to market in early 2001, its uptake in Medicaid appears to have been relatively slow, resulting in Prilosec retaining a 92% market share in 2001. Moving to 2002, Nexium’s market share rose by nearly four times to 31% - as expected, there was effectively no generic omeprazole uptake given its late introduction that year.

However, generic omeprazole’s market share soared in 2003 to 32%. Recall that Prilosec OTC did not hit shelves until the second half of the year, which likely allowed generic omeprazole to capture

a significant amount of the market. Meanwhile, Nexium’s market share continued to grow, approaching half of the market.

Over the next few years, Prilosec OTC market share exploded, cannibalizing prescription Prilosec (as expected) but also significantly cutting into generic omeprazole’s market share. The most stunning takeaway from this chart, in our view, is that **four years after AstraZeneca lost its Prilosec exclusivity (2016), products either directly or indirectly marketed by AstraZeneca still controlled 93% of the Medicaid market for omeprazole-derived products.**

Figure 13: AstraZeneca’s Generic Omeprazole Sandwich Strategy in Medicaid



Source: 3 Axis Advisors analysis – derived from data obtained from Data.Medicaid.gov and Medispan PriceRx

9 NEXIUM PATENT BATTLES

Section Key Takeaways

- In 2005 and 2006, three large generic manufacturers that tried to break Nexium’s patent exclusivity – all ended up agreeing with AstraZeneca to delay entry until May 27, 2014
- Ranbaxy’s agreement with AstraZeneca was estimated to be worth \$1 billion. In a class action antitrust suit brought against AstraZeneca and the three generic manufacturers, the “reverse payment” was found to be “large and unjustified”
- However, Ranbaxy’s serious quality control issues drew into question its ability to bring the generic to market before May 27, 2014 – with or without a large and unjustified reverse payment
- The Court ultimately sided with the Defendants in the case, citing the lack of “causality” between the reverse payment and Ranbaxy’s delay
- The FDA granted 180-day exclusivity rights to produce generic Nexium to Ranbaxy despite ongoing investigations into Ranbaxy quality control issues

Between its 2001 introduction and 2005, Nexium generated over \$14 billion in global **net** revenue for AstraZeneca – \$10.3 billion of which came from U.S. In 2003, AstraZeneca CEO Sir Tom McKillop called Nexium, “one of the most successful launches ever of a new medicine.”^{civ} AstraZeneca had created a multi-billion-dollar market for its single isomer omeprazole, a market that generic manufacturers desperately tried to break into.

Table 2 presents the chronology of the multiple failed attempts to bring generic Nexium to market.^{cv cvi} Overall, three generic manufacturers attempted to break AstraZeneca’s Nexium exclusivity between 2005 and 2006. All three ended up settling with AstraZeneca agreeing to delay introduction of their versions until May 27, 2014.

AstraZeneca was rightfully most concerned with Ranbaxy, given its possession of first-to-file 180-day exclusivity rights. As such, “AstraZeneca

Table 2: Chronology of Generic Challengers to Nexium

DATE	EVENT
FEB-01	FDA approves New Drug Application to AstraZeneca, granting it exclusive rights to market Nexium
OCT-05	Ranbaxy is first to file an ANDA, containing Paragraph IV certifications to market a generic version of Nexium
NOV-05	AstraZeneca files a patent infringement suit against Ranbaxy in the District of New Jersey
NOV-05	Teva files Paragraph IV ANDA
MAR-06	AstraZeneca sues Teva for alleged patent infringements
APR-06	Dr. Reddy’s Laboratories files ANDA, but did not challenge three AstraZeneca patents expiring in 2014 and 2015
APR-08	AstraZeneca and Ranbaxy settle. Ranbaxy agrees to delay generic launch until May 27, 2014. Since Ranbaxy had first-to-file exclusivity rights, this settlement created “a bottleneck in the generic Nexium market until May 27, 2014”
JAN-10	Teva agrees to postpone entry until May 27, 2014
JAN-11	Dr. Reddy’s Laboratories defers from entering market until May 27, 2014

began an effort in 2007 and 2008 to launch its own authorized generic version of Nexium, in order to maintain revenue that it would otherwise lose upon Ranbaxy's entry into the market."^{cvii}

However, if AstraZeneca could placate Ranbaxy, it would be able to create "a bottleneck in the market that postpones the date on which any generic product will become available."^{cviii} That eventually happened on April 14, 2008 when the two companies settled their ongoing patent infringement suit. According to the Nexium Antitrust Litigation Memorandum and Order:

"As was the case in all of the Nexium settlements, AstraZeneca agreed to end its patent infringement lawsuit against Ranbaxy in exchange for certain legal admissions and an agreement to delay launch of Ranbaxy's generic product until May 27, 2014."^{cix}

In addition to "refraining from producing its own authorized generic version of Nexium during Ranbaxy's 180-day exclusivity period," AstraZeneca also entered a series of other business agreements with Ranbaxy as part of the settlement: ^{cx}

1. "Two agreements under which Ranbaxy would distribute authorized generic versions of AstraZeneca's brand drugs, Plendil and 40 mg Prilosec"
2. "An agreement under which Ranbaxy would store AstraZeneca's products for a nominal fee"
3. "An agreement under which Ranbaxy would supply AstraZeneca with significant amounts of esomeprazole magnesium, the active pharmaceutical ingredient in Nexium, for sale in the United States"
4. "An agreement under which Ranbaxy would supply AstraZeneca with branded Nexium capsules for sale in the United States"

The potentially "large and unjustified" nature of these agreements (estimated to be worth \$1 billion to Ranbaxy^{cx}) in return for its delayed launch, coupled with identical negotiated launch dates set by Teva and Dr. Reddy's, became the core components of class action antitrust litigation against all four manufacturers.

Ultimately, the Court sided with the Plaintiffs on its claim that such "reverse payments" to Ranbaxy were "large and unjustified." According to the Memorandum, the Plaintiffs evinced "the proper economic evaluation and factual support to **suggest** that Ranbaxy was induced to delay its generic launch in exchange for certain lucrative side business arrangements with AstraZeneca." It went on to state that, "A reasonable jury would be able to find that these side arrangements amounted to an illegal reverse payment to Ranbaxy."^{cxii}

"A reasonable jury would be able to find that these side arrangements amounted to an illegal reverse payment to Ranbaxy."

However, precedent set by the landmark Supreme Court case *FTC vs. Actavis* held that (emphasis added), "the existence of a reverse payment is neither presumptively lawful nor unlawful." The Court had to find a "**causal nexus** between the Ranbaxy Settlement and their alleged antitrust injury." In other words, the Plaintiffs had to **prove** that the reverse payments induced Ranbaxy to delay introduction of generic Nexium to the market.^{cxiii}

This critical argument was significantly complicated by Ranbaxy's "serious quality control issues" at its Paonta Sahib facility - the facility specified by Ranbaxy for production of generic Nexium in its pending ANDA. In February 2009, these quality issues culminated in the FDA's decision to invoke its

Application Integrity Policy (AIP) against Paonta Sahib, which “halted the FDA’s substantive review and approval of all pending ANDAs,” including generic Nexium. In 2010, the FDA and Ranbaxy began to negotiate a consent decree to resolve enforcement issues against the company. The decree set out certain milestones that had to be met before review of Ranbaxy’s Nexium ANDA would continue. By the middle of 2012, Ranbaxy had satisfied the first of the milestones and was working on a site transfer amendment to move production to a facility in New Jersey (filed in November 2013). However, the decree also included significant data integrity review protocols that Ranbaxy had not satisfied at the time the case was being evaluated.^{cxiv}

Meanwhile, in May 2013, Ranbaxy pled guilty to felony charges related to the distribution of adulterated drugs from two of their production facilities in India.^{cxv} The settlement with the United States resulted in Ranbaxy forking over \$500 million in fines for safety issues, a lack of adequate quality testing, and making false statements to the FDA, among other violations. The findings stemmed from an internal whistleblower at Ranbaxy, who reported his findings to the FDA in 2005.^{cxvi}

In 2011, CBS News heavily criticized the FDA in regards to another popular drug being manufactured by Ranbaxy, reporting that, “while one arm of the FDA was investigating Ranbaxy for serious criminal violations, another arm of the FDA was approving Ranbaxy for the exclusive rights to make the generic version of one of the most popular pharmaceuticals of all time: Lipitor. That decision by the FDA would earn the company a reported \$600 million in the first six months.”^{cxviii} A year later, the FDA found major quality issues with Ranbaxy’s manufacturing of generic Lipitor as well. Similarly, quality issues held up Ranbaxy’s release of a generic form of Novartis’ Diovan.^{cxix}

Fortune’s Katherine Eban was even more brutal in her criticism of the FDA in 2014:^{cxx}

“Given the parade of bad medicine coming out of Ranbaxy’s laboratories – pills with unexplained black spots, human hairs, and glass particles in them – can we believe the FDA’s continued reassurance that despite an import alert on four of Ranbaxy’s overseas factories, the medicine already on U.S. pharmacy shelves made at those factories is safe to take?

And can Congress continue to sit on its hands, after starting an investigation into the FDA’s handling of Ranbaxy in 2008 and then letting it peter out, even though the FDA continued to approve the company’s drug applications, and even allowed it to proceed with its exclusive generic launch of America’s most popular drug, atorvastatin (better known by the name of the brand version, Lipitor)?”

As far as the antitrust case, the ongoing Ranbaxy / FDA drama seriously drew into question whether, in any scenario, the company would have been able to bring generic Nexium to market before May 27, 2014. This was the critical question. If the Plaintiffs could not prove Ranbaxy’s ability to bring the generic to market before that date, it would break the causality link between the reverse payment and the launch delay. In other words, there would be proof of “Pay” and “Delay,” but not “Pay-for-Delay.”

The Plaintiffs in the Nexium antitrust case were able to prove there was “Pay” and “Delay,” but failed to prove it was “Pay-for-Delay”

Ultimately, on February 12, 2014, the Court sided with the Defendants in summary judgement, citing a “lack of causation.”^{cxxi}

While the ruling was perceived at the time to have broad implications in protecting pharmaceutical manufacturers from future accusations of anticompetitive pay-to-delay schemes, this case was quite unique. “The plaintiffs did enough to prove their case,” said Michael Carrier, a Rutgers University School of Law professor who specializes in intellectual-property issues and has filed a brief in another pay-to-delay case on behalf of consumer groups. “It just came down to one thing—the generic company was not ready to launch before 2014.”^{cxix}

10 ASTRAZENECA PREPARES FOR NEXIUM'S PATENT EXPIRATION

Section Key Takeaways

- In preparation for Nexium's patent expiration, AstraZeneca entered another branded OTC agreement - this time with Pfizer. The agreement was worth at least \$793 million to AstraZeneca
 - As Nexium OTC was being released, concerns over the linkage between prolonged usage of PPIs and kidney disease started to rise. It is unknown to what extent OTC availability has exacerbated this problem
- AstraZeneca also partnered with Eagle Pharmacy to manage Nexium *Direct*, a direct-to-consumer sales channel that provided consumers with subsidies to remain on branded Nexium
- Meanwhile, Ranbaxy missed its May 27, 2014 target to bring generic Nexium to market. However, the FDA didn't officially revoke its 180-day exclusivity until January 27, 2015 - delaying Teva's eventual launch until February 2015.
- AstraZeneca ended up boosting its profit outlook for 2014 "based on lack of competition for Nexium"

After staving off multiple attacks from generic manufacturers, it appeared that the generic would come to market on May 27, 2014. Ranbaxy, the first to file with the FDA for the generic had 180-day exclusivity, after which the likes of Teva and Dr. Reddy's would enter the market and drive down the cost of the generic.

But as we have already seen with Prilosec, there are several ways that brand manufacturers can extend the life of a brand that go beyond patent litigation. As Nexium's patent cliff was approaching, AstraZeneca employed four such methods:

1. Launching a combination drug called Vimovo, and later selling its rights away
2. Introducing a new dosage form, which garnered new patent exclusivity
3. Entering into an exclusive licensing agreement for the branded OTC
4. Launching a direct-to-consumer program called "Nexium *Direct*"

This section first discusses these two tactics AstraZeneca employed to proactively protect Nexium market share. We then conclude the chapter with a discussion on how Ranbaxy's troubles with the FDA resulted in a nearly \$2 billion windfall for AstraZeneca.

10.1 ASTRAZENECA'S OTC AGREEMENT WITH PFIZER

On August 13, 2012, AstraZeneca announced an agreement to sell over the counter rights for Nexium to Pfizer Inc. Recall that when AstraZeneca sold rights to Procter and Gamble to produce Prilosec OTC, the financial terms were not disclosed. More than a decade later, the public received more detail on the terms between AstraZeneca and Pfizer to sell Nexium OTC. Pfizer launched

Nexium OTC into the marketplace on May 27, 2014 - the exact same day generic esomeprazole was initially slated to launch. Once again, AstraZeneca was granted three years of OTC exclusivity.^{cxxiii}

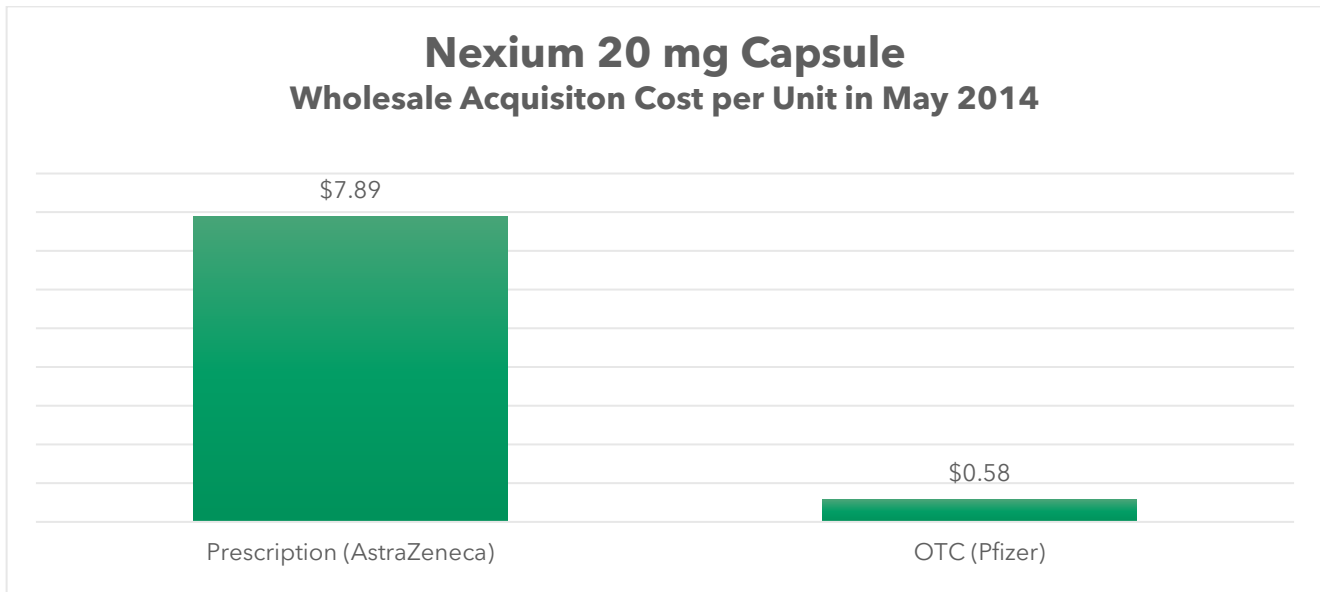
According to the agreement, Pfizer made a \$250 million up front payment, and AstraZeneca was “eligible to receive milestone and royalty payments based on product launches and sales.”^{cxxiv} This was the extent of the compensation disclosed by AstraZeneca in its press release. However, our review of Pfizer’s annual reports provides a more complete disclosure of the financial remuneration AstraZeneca received for Nexium OTC. The following excerpt is from Pfizer’s 2016 Financial Report filed with the SEC^{cxxv} (emphasis added to highlight compensation):

“License of Nexium OTC Rights--In August 2012, we entered into an agreement with AstraZeneca PLC (AstraZeneca) for the exclusive, global, over-the-counter (OTC) rights for Nexium, a leading prescription drug approved to treat the symptoms of gastroesophageal reflux disease. In connection with this Consumer Healthcare licensing agreement, we made **an upfront payment of \$250 million** to AstraZeneca, which was recorded in Research and development expenses when incurred. On May 27, 2014, we launched Nexium 24HR in the U.S., and on July 11, 2014, we paid AstraZeneca a related **\$200 million product launch milestone payment**. On August 1, 2014, we launched Nexium Control in Europe, and on September 15, 2014, we paid AstraZeneca a related **\$50 million product launch milestone payment**. These post-approval milestone payments were recorded in Identifiable intangible assets, less accumulated amortization and are being amortized over the estimated useful life of the Nexium brand. Included in Other current liabilities at December 31, 2015 are **accrued milestone payments to AstraZeneca of \$93 million**. AstraZeneca is eligible to receive **additional milestone payments of up to \$200 million**, based on the level of worldwide sales **as well as quarterly royalty payments** based on worldwide sales.”

Based on Pfizer’s disclosure, as of the end of 2015, it had not only paid the previously disclosed \$250 million up front payment, but another \$250 million in product launch milestone payments, and \$93 million in additional milestone payments, which appear to be related to 2015 sales activity. All told, by the end of 2015, Pfizer had paid \$593 million to AstraZeneca for global rights to Nexium OTC and was still on the hook for “additional milestone payments of up to \$200 million... as well as quarterly royalty payments based on worldwide sales.”

Just as was the case with Prilosec OTC, the push to Nexium OTC clearly was, on the surface, favorable for payers. Based on analysis of historical pricing data from MediSpan PriceRx, Pfizer brought “Nexium 24Hr Oral Capsule Delayed Release 20 mg” to market in May 2014 with a Wholesale Acquisition Cost (WAC) of \$0.58 per unit (**Figure 14** on next page). This was a 93% discount to the \$7.89 WAC placed on the prescription version of the drug by AstraZeneca in the same month.

Figure 14: Prescription vs. OTC Nexium 20 mg WAC Pricing in May 2014



Source: Medispan PriceRx

However, the problem (once again) is that \$0.58 was not a market-clearing price, and the introduction of the OTC hindered development of a robust generic marketplace capable of arriving at an efficient market-clearing price.

Earlier in this report, we illustrated how the introduction of Prilosec OTC blocked the uptake of generic omeprazole and slowed its market-driven deflation. The theory is that insurers may be less likely to add a prescription version of a drug to their formularies when an over the counter version is available.

We were able to test this theory for esomeprazole.^{cxxvi} We purchased all Medicare Part D public-use CMS Prescription Drug Plan Formulary files going back to the start of 2014.^{cxxvii} We then looked at the number of plans that included the 20mg strength of generic Nexium on Tiers 1 through 4 in Medicare Part D in Q4 2015 - the first quarter when esomeprazole was available multi-source.^{cxxviii}

We found that in Q4 2015, **only 58%** of Part D plans covered generic Nexium 20mg on Tiers 1-4 of their formularies. Please note that we cannot directly link the incidence of low coverage of the generic to the efforts by AstraZeneca and Pfizer to bring the OTC to market. It could have also been driven by elevated rebates paid to keep the brand on the formulary, or the fact that there were lower-cost therapeutic alternatives available in the proton pump inhibitor category.

The fact remains that early in the life of the generic, Part D plans made coverage decisions that reduced the size of the generic Nexium market, which logically could have had negative ramifications on the development of a generic marketplace for this drug.

10.1.1 The risks of self-medication

There was also a new risk recognized with AstraZeneca's OTC strategy - the risk of self-medication. While this risk is much more difficult to quantify, over the long-term, it has the potential to be considerably more costly than the delayed development of the generic esomeprazole marketplace.

In 2015, New York Times Personal Health columnist Jane Brody published an article entitled “Over-the-Counter Medicines’ Benefits and Dangers.”^{cxxix} In the article, Ms. Brody acknowledged the obvious benefits of over the counter drugs being lower cost, and more readily accessible.

However, a 2008 study published in BMJ found that “proton pump inhibitors are being overprescribed worldwide in both primary and secondary care.” The authors bluntly concluded that “the drugs are clearly being overused” years before Nexium OTC (esomeprazole over the counter) was brought to market.^{cxxx}

By the time Nexium OTC came to market, omeprazole 20 mg was exceedingly cheap, with a NADAC of just \$0.08 per capsule. It was also available OTC both branded and generic at ~\$0.50 a tablet. Prevacid (lansoprazole) was also available as a generic both behind-the-counter and OTC, at less than \$1 per capsule. Aggressively bringing Nexium to market simply increased accessibility to a more potent version of an already-overused class of drugs.^{cxxxi}

Ms. Brody went on to list the dangers of OTC drugs:

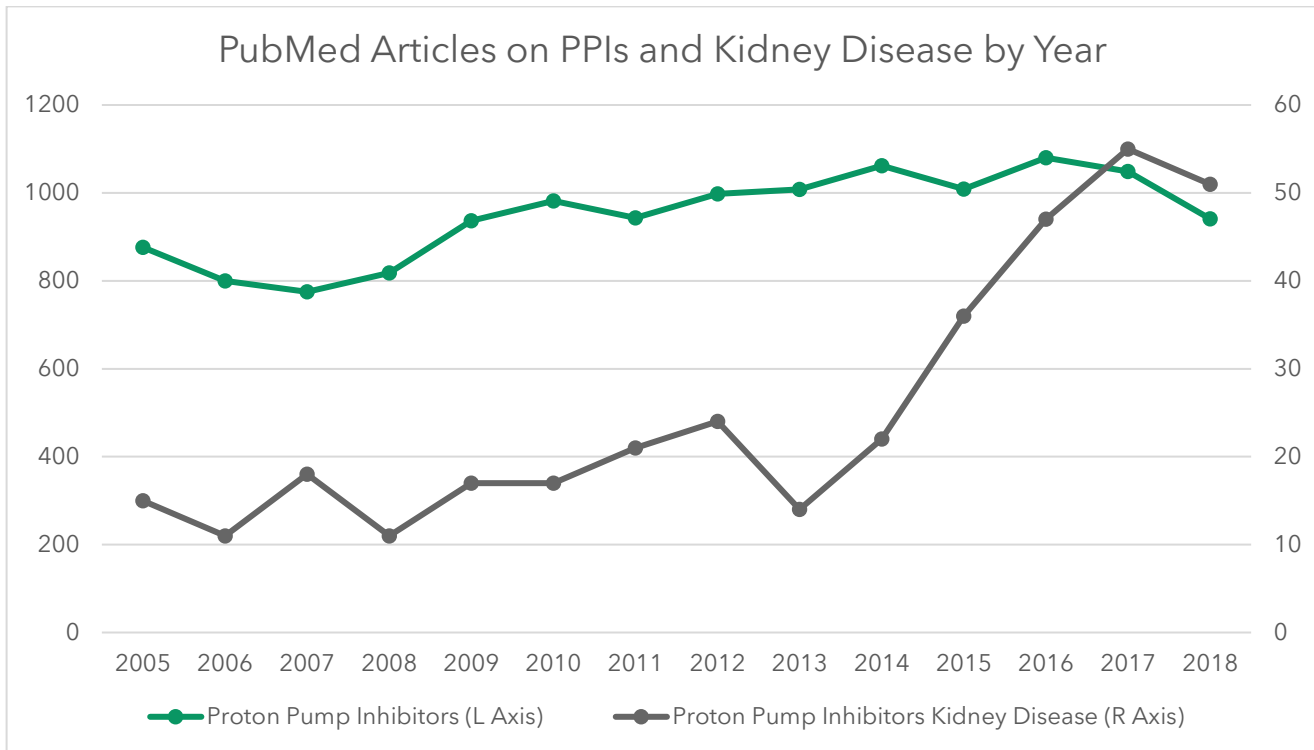
- “One in five adults who self-medicate admit to taking more than the recommended dose or using the medication more frequently than the label indicates”
- “Few (people) consult a doctor – or even a pharmacist – about the safety and wisdom of using a particular OTC drug”
- “A consumer poll taken in 2001 for the National Council on Patient Information and Education found that most people read only some of the information on product labels and thus may miss information essential to the drug’s proper use”

As more researchers have studied the adverse side effects associated with PPIs, these dangers – all of which deal with medication adherence and abuse – now seem especially concerning. A 2017 study published in *Therapeutic Advances in Drug Safety* reviewed the “existing literature of potential adverse effects with long-term PPI use in older adults” and found that “current literature has identified associations between PPI use and risk of osteoporotic-related fractures, CDI, CAP, vitamin B12 deficiency, kidney disease/injury, and dementia, particularly in older adults.”^{cxxxii}

The linkage between prolonged usage of PPIs and kidney disease has received the most scrutiny. To better quantify the academic community’s focus on this issue, we searched pubmed.gov for “Proton Pump Inhibitors Kidney Disease” and counted the number of publications each year that best matched this search criteria. We then searched pubmed.gov on only “Proton Pump Inhibitors” and counted the number of publications each year to use as a comparison set. We were curious to see if the number of publications associating PPIs with kidney disease was rising disproportionately when compared to the overall PPI publications.

The following chart shows the results of this analysis. Between 2005 and 2018, there was a 7% increase in “Proton Pump Inhibitor” articles, but a 240% increase in “Proton Pump Inhibitor Kidney Disease” articles. As a result, 5.4% of all PPI articles referenced kidney disease in 2018, up from 1.7% in 2005.

Figure 15: PubMed Articles on PPIs and Kidney Disease by Year



Source: PubMed

But the increasing focus on the connection between PPIs and kidney disease was not just isolated to academic circles. On August 2, 2017, a multidistrict litigation (MDL) was established in the New Jersey federal district court to ease the administrative burden in handling the more than 4,500 PPI lawsuits brought against drug manufacturers.^{cxxxiii cxxxiv} Pfizer acknowledged such suits in their 2018 annual report^{cxxxv}:

“A number of individual and multi-plaintiff lawsuits have been filed against Pfizer, certain of its subsidiaries and/or other pharmaceutical manufacturers in various federal and state courts alleging that the plaintiffs developed kidney-related injuries purportedly as a result of the ingestion of certain proton pump inhibitors. The cases against us involve Nexium 24HR and/or Protonix and seek compensatory and punitive damages and, in some cases, treble damages, restitution or disgorgement. In August 2017, the federal actions were ordered transferred for coordinated pre-trial proceedings to a Multi-District Litigation in the U.S. District Court for the District of New Jersey.”

Until recently, evidence of acute kidney injury (AKI) and chronic kidney disease (CKD) “has only been evaluated in a small number of studies with short follow-up periods.” This changed in April 2019 with a study published in *Pharmacotherapy* entitled, “Proton Pump Inhibitors and Risk of Acute and Chronic Kidney Disease: A Retrospective Cohort Study.” This study “examined the association between PPI use and risk of incident AKI and CKD in a large population-based health maintenance organization (HMO) cohort.” Overall, the study found the incidence rate of CKD in PPI users to be **four times** higher than the rate in non-users and the incidence rate of AKI in PPI users to be **ten times** higher than the rate in non-users. The authors concluded that “the use of PPIs is associated with an increased risk of incident AKI and CKD.” They then went on to write that, “this relationship could have a considerable public health impact; therefore, health care provider education and

deprescribing initiatives (emphasis added) will be necessary to raise awareness and reduce health care burden.^{cxxxvi}

We do not yet know how this story will end. The first bellwether trial for kidney injury lawsuits against PPI manufacturers is set for September 21, 2020.^{cxxxvii} If causality is proven, it will take years, or even decades, to better understand the cost associated with treating PPI-induced kidney disease. We will likely still be left wondering how much additional medical expense was incurred due to misuse of Nexium resulting from its over the counter availability.

“This relationship (between PPI use and kidney disease) could have a considerable public health impact; therefore, health care provider education and deprescribing initiatives will be necessary to raise awareness and reduce health care burden”

The takeaway here is not that PPIs should have never been approved for over the counter use. We are not qualified to opine on the FDA’s assessment of PPI safety for over the counter usage based on the information that was available at the time. Instead, we submit that the key takeaway is more of an economic one. With ample over the counter and prescription PPI supply already on the market in 2014, an argument could have been made that the incremental societal benefit of adding another over the counter PPI was marginal. On the flip side, with researchers starting to identify initial signs of adverse side effects of PPIs, the risk of adding a more potent over the counter PPI could potentially outweigh the marginal benefit.

Clearly, we understand that the FDA cannot rely on anecdotal evidence, speculation, or half-baked studies in evaluating over the counter applications. But at the same time, we believe that someone needs to be performing a more holistic societal cost/benefit analysis on over the counter drug applications, especially in light of the fact that patients - and the health plans that may cover their medications - typically forego consulting with physicians and pharmacists before procuring and ingesting these drugs.

Had this analysis been performed as part of the Nexium’s OTC application review, we suspect that there may have been a different outcome, or at the very least, more focus on the growing concern about the risk of long-term PPI exposure.

10.2 NEXIUM DIRECT

With Nexium’s patent expiration looming, on March 19, 2014, AstraZeneca launched a program called Nexium *Direct*, which “provide(s) eligible patients the option of having brand name NEXIUM delivered to their home.”^{cxxxviii}

Nexium *Direct* effectively acts in the same way as a copay card. It simply subsidizes a patient’s copay for Nexium. According to the website, if a patient’s copay for a 30-day supply is \$190 or less, the patient will only pay a flat \$15 using Nexium *Direct*. If the patient’s copay is greater than \$190, the patient will receive a \$175 discount. If the patient’s insurance doesn’t cover Nexium, or if the patient is uninsured, the patient can receive a \$125 contribution to the total cash price for Nexium.^{cxxxix}

When viewed from the patient’s perspective, this is actually a pretty good deal. We used GoodRx to look up the cash price of a 30-day supply of generic Nexium (esomeprazole 40 mg) in Woonsocket,

RI and found all cash prices to be more than \$15 per prescription in October 2019 - the lowest cost being \$17.48 at Stop N Shop.^{cxl}

However, when viewed from the payer's perspective, this practice starts to look much more disturbing. By subsidizing the copay to the extent where it is comparable to or less costly than the generic, Nexium is shifting the patient preference from the generic to the brand and driving up the payer's cost for its beneficiary's treatment.

Here is a hypothetical (and simplified) example to illustrate this dynamic. First, let's provide some background assumptions:

- Patient A is an employee of a small-to-mid-size *self-insured* Employer B
- Employer B hires PBM C to manage its prescription benefit
- PBM C provides Employer B with a five-tier formulary:
 - Tier 1 = preferred generics (copay = \$5)
 - Tier 2 = non-preferred generics (copay = \$15)
 - Tier 3 = preferred brands (copay = \$50)
 - Tier 4 = non-preferred brands (copay = \$100)
 - Tier 5 = specialty drugs (25% coinsurance)
- PBM C places generic Nexium (esomeprazole) on Tier 2
- PBM C places brand-name Nexium (esomeprazole) on Tier 4
- Total cost of brand-name Nexium is \$250
- Total cost of generic Nexium is \$25

In Scenario 1, Doctor D writes a prescription for brand-name Nexium. Patient A takes this prescription to a local pharmacy where he learns that his co-pay will be \$100. Pharmacist E then explains that the equivalent generic costs \$15. Due to the cost differential, Patient A switches to the generic, rather than demanding brand-name Nexium. Patient A pays \$15. With the total cost of generic Nexium being \$25, PBM C bills Employer B the \$10 balance.

In Scenario 2, Doctor D once again writes a prescription for brand-name Nexium. Instead of Patient A going to their local pharmacy, he goes to www.purplepill.com, and signs up for Nexium *Direct*. Patient A pays a subsidized copay of \$15 per prescription, equivalent to the copay of a Tier 2 generic drug, and gets the drug mailed to his door. Patient A is pleased to be able to get the brand-name drug for the generic price. The remainder of Patient A's \$100 copay (\$85) is picked up by AstraZeneca. With the cost of the brand at \$250, Employer B is likely sent a \$150 bill for the balance.

The obvious winner in Scenario 2 is AstraZeneca. It pays \$85 to get \$250 (less rebates to the PBM). It effectively manufactures demand for its off-patent drug by providing Patient A the incentive to prefer the brand over the generic. It also takes the standard retail pharmacist out of the picture (who is incentivized, and in some states legally required, to switch patients to generic drugs^{cxli}) and replaces it with a company called Eagle Pharmacy who manages direct-to-consumer mail-order programs for pharmaceutical companies to help "reduce erosion of their market share as generic competition enters the space"^{cxlii} and "ensure patients have access to your brand regardless of their insurance coverage."^{cxliii} In other words, Eagle Pharmacy helps patients navigate the challenges of receiving an off-patent brand-name drug by helping brand-name manufacturers exploit loopholes in a supply chain that is generally designed to prefer generics (when available).

Patient A also perceives himself to be a winner in this model, because he is getting a product that he perceives to be higher quality for the same price as the product he perceives to be lower quality.

The impact to PBM C is more complicated. More dispensing of brand-name Nexium means higher rebates, but lower potential to profit from “spread pricing” of the generic (a topic we will discuss in the next section). However, a 2018 STAT post written by Dr. Haider Warraich suggests that PBMs may be a net beneficiary from this tactic, as well. His op-ed, entitled “A costly PBM trick: set lower copays for expensive brand-name drugs than for generics,” discusses how PBMs “partner” with manufacturers to shift multi-source brand drugs up on formularies, thereby saving money for patients but exposing payers to higher cost drugs. His work found that \$2.1 billion could have been saved on statins between 2012 and 2014 had all brand-name Lipitor instead been dispensed as generic atorvastatin.^{cxliv}

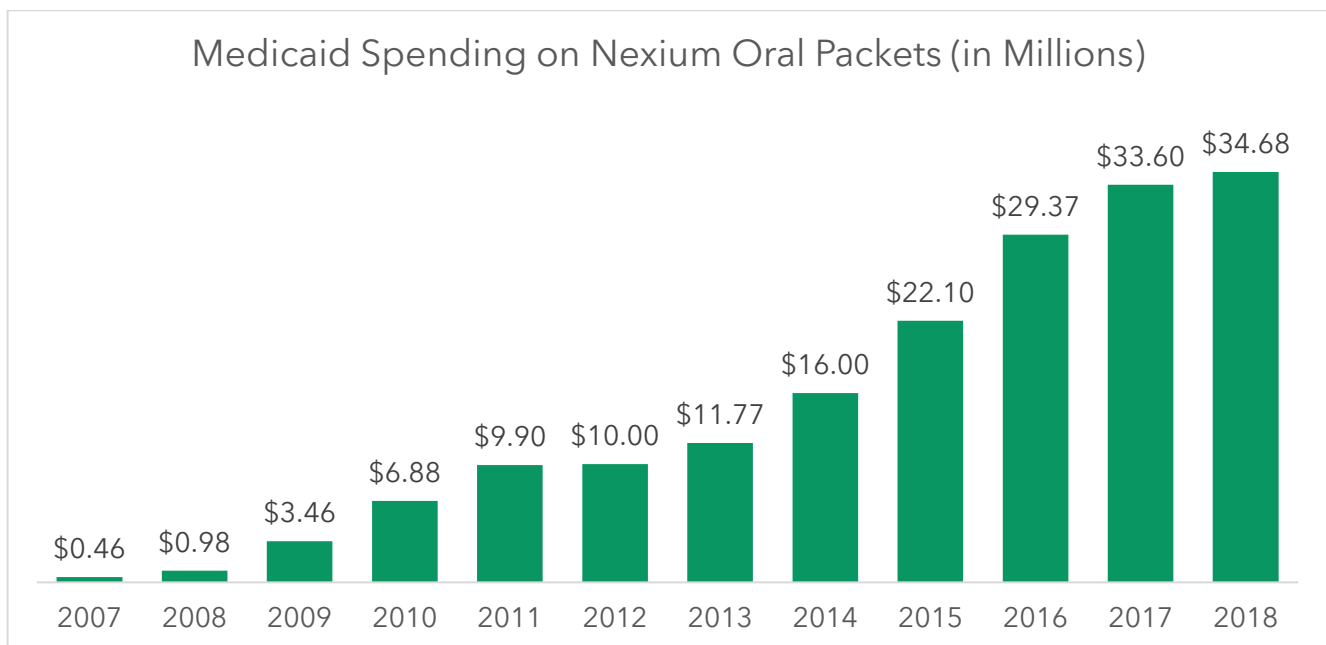
The clear loser is of course Employer B, who without even knowing it, is on the hook for \$150 when the treatment really should have only cost \$15.

10.3 NEXIUM GETS GRANULAR

In 2006, the FDA approved application number 021957 - a new dosage form (Type 3 classification) for Nexium. Nexium oral packets (i.e. granulated esomeprazole) were now approved for marketing in the U.S. in two strengths (20 mg, and 40 mg). Two years later (in 2008), the FDA approved the 10 mg strength under application number 022101. Fast-forward another three years (2011), and AstraZeneca brought two more strengths to market - 2.5 mg and 5 mg - designed for treatment of GERD and erosive esophagitis in infants and older.

Figure 16 shows Medicaid’s total spending on Nexium oral packets by year, which grew from less a million to nearly \$35 million in 2018.

Figure 16: Medicaid Spending on Nexium Oral Packets (in Millions)

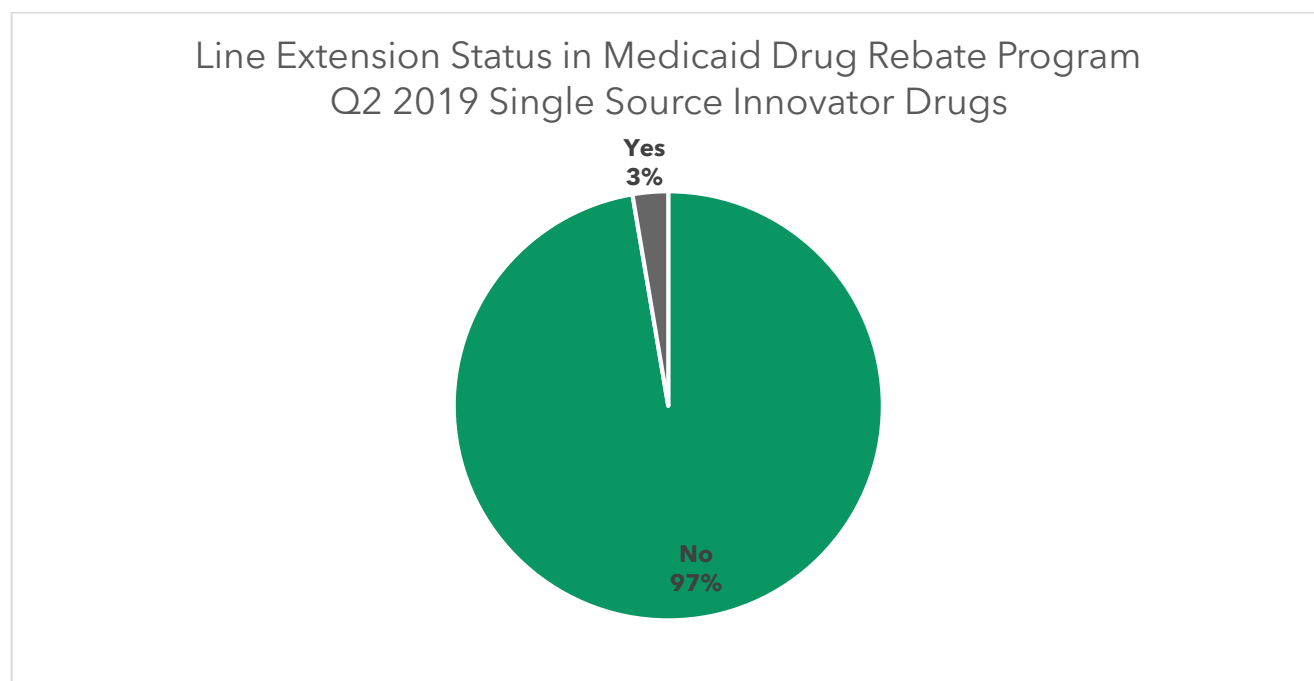


Source: 3 Axis Advisors based on data obtained from Data.Medicaid.gov

Within Medicaid, the Affordable Care Act required manufacturers to provide rebates on line extension products similar to the brand drug from which they were derived.^{cxlv} This was intended to remove the warped incentive for manufacturers to bring line extensions to market to reduce rebates paid within the Medicaid program. However, it wasn't until the Bipartisan Budget Act of 2018 (October 1, 2018) that the line extension rule was finalized, capturing drugs like Nexium oral packets.^{cxlvi} Sure enough, starting in Q4 2018, Medicaid started publicly flagging line extension drugs within the rebate program and filed Nexium oral packets within this category.^{cxlvii}

However, as shown in **Figure 17**, of a total of 4,041 single-source innovator drugs in the Medicaid Drug Rebate program in Q2 2019 (the latest quarter of data), just 108 (3%) were classified as line extensions.

Figure 17: Line Extension Status in Medicaid Drug Rebate Program Q2 2019 Single-Source Innovator Drugs



Source: [Data.Medicaid.gov](https://data.medicaid.gov)

This is in stark contrast to the percentage of drugs approved by the FDA each year with a Type 2-5 classification (**Figure 9** within the [Majority of FDA approvals are for reformulations of existing drugs](#) section), suggesting there could be considerably more work in tightening up this definition within Medicaid. Failure to adequately account for line extension drugs risks adding costs for therapies that are not innovative.

10.4 Vimovo

10.4.1 Pozen's agreement with AstraZeneca

In August 2006 - just five years after Nexium came to market - AstraZeneca entered into a global collaboration and license agreement with Pozen Inc. to "co-develop and commercialize proprietary fixed dose combinations of and commercialize a combination of the PPI esomeprazole magnesium with the NSAID naproxen."^{cxlviii}

For several years, Pozen had been developing its “PN program,” in which it completed formulation development and clinical studies for combinations of PPIs with an NSAID. The intended purpose of the treatment was to reduce, “gastrointestinal complications compared to an NSAID taken alone in patients at risk for developing NSAID associated gastric ulcers.”

Pozen initially conducted studies with lansoprazole and naproxen (called “PN 100”) and omeprazole and naproxen (called “PN 200”).^{cxlix} In April 2006, Pozen reached an agreement with the FDA on a Special Protocol Assessment (SPA) for Phase 3 clinical trials on PN 200.^{cl} Pozen also possess a U.S. patent with claims, “directed to certain compositions containing a combination of acid inhibitors, including PPIs, and NSAIDs” and “to treatment methods involving the use of such compositions.”^{cli}

Given Pozen’s progress with the FDA and its patents on the combination, it appears that AstraZeneca required Pozen to bring an esomeprazole / NSAID combination drug to market. Under terms of their agreement, AstraZeneca paid Pozen \$40 million upfront, plus up to \$160 million for “certain development and regulatory milestones” and up to \$175 million for “sales performance milestones.” Pozen would be responsible for development of filing of the New Drug Application (NDA) in the U.S. while AstraZeneca would have “full responsibility for development activities outside of the U.S. as well as all aspects of manufacturing, marketing, sales and distribution on a worldwide basis.”^{clii}

In the press release announcing the collaboration, Dr. John Patterson, Executive Director of Development for AstraZeneca said:^{cliii}

“We believe that the combination of esomeprazole and POZEN's proprietary PN technology has the potential to address one of the key unmet medical needs for patients with chronic pain; namely, good pain relief coupled to a low risk of gastrointestinal ulcers and good tolerability.”

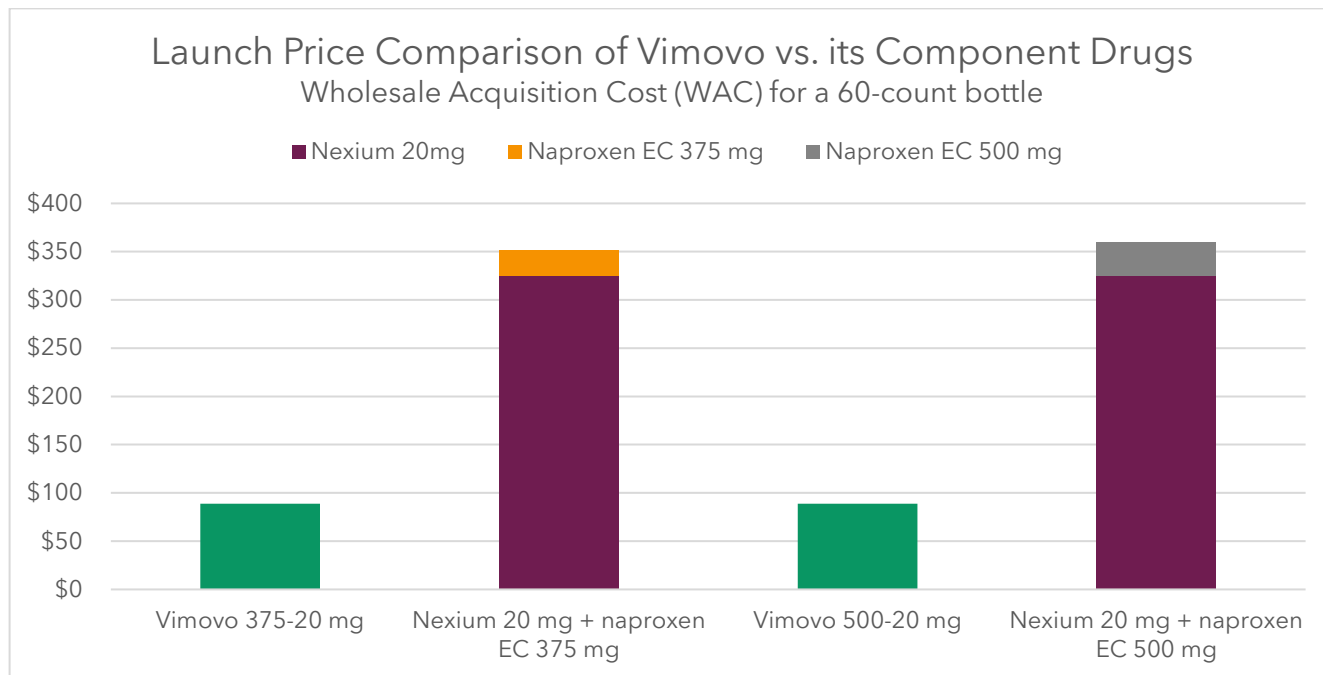
10.4.2 Vimovo’s value proposition

It turns out that Dr. Patterson was right. In 2007, Pozen/AstraZeneca conducted two Phase 3 clinical trials of the esomeprazole magnesium / naproxen combination - brand-name Vimovo - in patients at risk for developing NSAID-associated gastric ulcers, with a primary goal of reducing endoscopic gastric ulcers. In both trials, patients taking Vimovo for six-months experienced significantly fewer endoscopically confirmed ulcers (incidence rate of 4.1% and 7.1%) compared to patients on a six-month treatment course of delayed release naproxen (incidence rate of 23.1% and 24.3%).^{cliv}

It’s worth reiterating that the trials were designed to compare treatment using Vimovo with treatment using only naproxen. The trials did not compare treatment with Vimovo with a course of treatment that included equivalent dosages of naproxen and esomeprazole taken separately. Nonetheless, as the trials were designed, they proved the use case of Vimovo and cleared the path for FDA approval.

On April 30, 2010, the FDA approved Pozen’s application for Vimovo (NDA 022511).^{clv} In July 2010, AstraZeneca brought two strengths of Vimovo to market, each with a WAC of \$88.80 for a 60-count bottle. As shown in **Figure 18**, relative to its components, this price was quite attractive. At the time of Vimovo’s launch, the average WAC of a 60-count of naproxen EC 375 mg was \$26.78, while the same size bottle of the 500 mg strength carried a WAC of \$34.71. A 60-count bottle of Nexium 20 mg - only available brand name at the time - carried a WAC of \$325.10. As such, AstraZeneca’s pricing of Vimovo translated to a savings of 74.8% for the 375-20 mg and 75.3% for the 500-20 mg versus the individual pricing of their components.

Figure 18: Launch Price Comparison of Vimovo vs. its Component Drugs



Source: Medispan PriceRx

So, in this case, AstraZeneca commercialized a combination drug that was not only effective for its stated indication, but significantly more cost efficient than its component ingredients.

10.4.3 A dud of an investment

However, despite its relative value proposition, Vimovo did not do well in the United States. We dug through AstraZeneca’s annual reports and collected new revenues (after rebates and discounts) generated by AstraZeneca over the first three years that Vimovo was on the market. In 2011 – the first full year Vimovo was on the market – Vimovo generated \$21 million in net U.S. revenue.^{clvi} One year later, net U.S. revenue only stepped up to just \$25 million.^{clvii}

Meanwhile, by the end of 2012, AstraZeneca had handed over \$95 million to Pozen (\$40 million upfront plus \$55 million in regulatory milestone payments) not including any volume-related payments.^{clviii}

With hindsight as our guide, it now seems clear that AstraZeneca was looking at a situation where it sunk nearly \$100 million (and counting) for a drug that would generate between \$20-30 million a year before operating and marketing expenses. This was, in our view, a dud of an investment, which is likely what led AstraZeneca to cut its losses and look to divest Vimovo. According to Pozen’s 2014 10-K, on May 3, 2013, AstraZeneca notified Pozen that it had decided to “cease promotion and sampling of VIMOVO by the end of the third quarter of 2013 in ... the U.S. and all countries in Europe, other than Spain and Portugal.”^{clix}

10.4.4 Horizon Pharma takes over

On November 18, 2013, AstraZeneca entered into an agreement with Horizon Pharma Inc. to sell the rights to develop, commercialize, and sell Vimovo in the United States.^{clx} Horizon purchased such rights for a one-time upfront cash payment of \$35 million.^{clxi} Pozen provided its consent for the

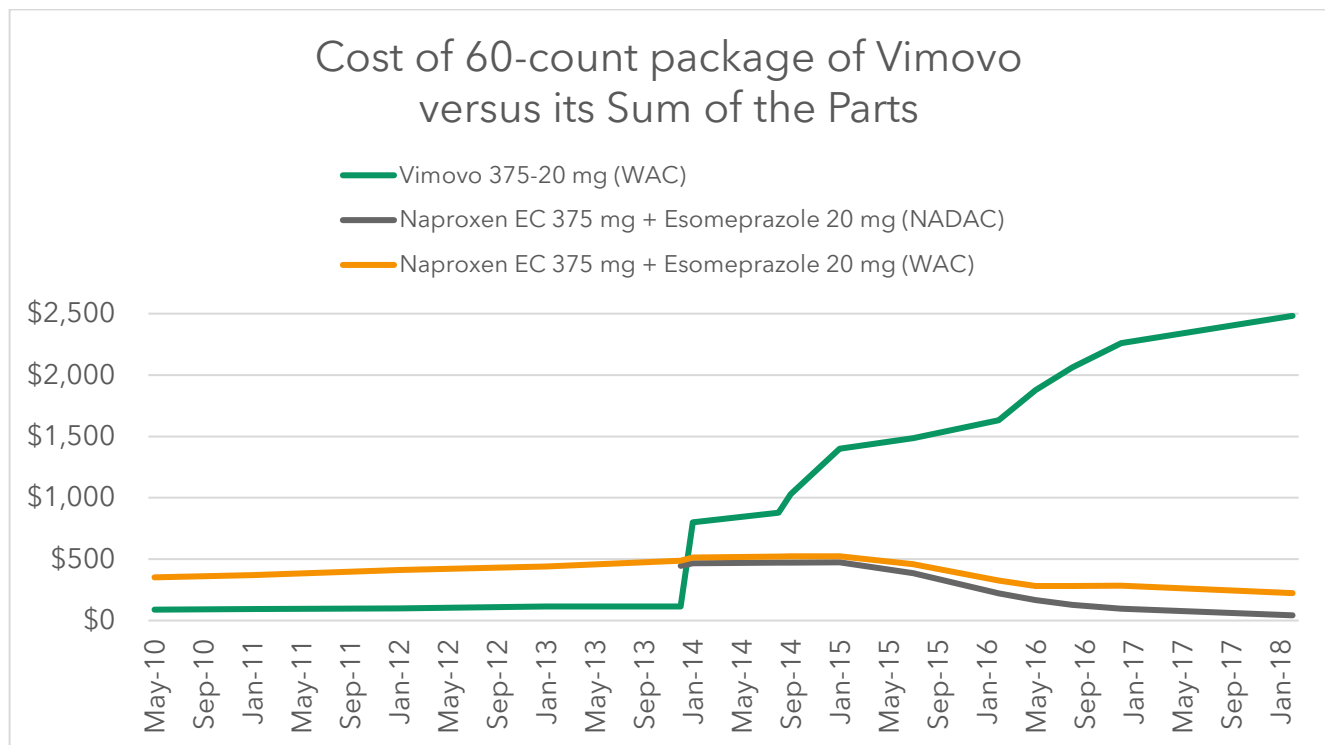
transaction and transferred rights to usage of its intellectual property over to Horizon. In return, Horizon granted Pozen a flat 10% royalty rate based on net sales of Vimovo, with a minimum royalty payment of \$5 million in 2014 and \$7.5 million in 2015 and beyond.^{clxii}

According to Horizon’s 2014 10-K, Horizon announced availability of the Horizon-labeled Vimovo on January 2, 2014, at which time it began marketing Vimovo with its 250-member primary care sales force.^{clxiii} Horizon set the price (as measured by WAC) of a 60-count bottle of its version of Vimovo WAC at \$799.20, a **597% increase** from AstraZeneca’s version available one month prior.

And that was just the beginning. As shown in **Figure 19**, over the next four years Horizon increased its WAC nine more times. The same 60-count bottle that AstraZeneca removed from the market at \$114.74 in late-2013 was \$2,482.20 in February 2018 – a **total increase of 2,063% in just over four years**.

Meanwhile, Nexium lost its patent exclusivity in 2015, ushering in cheaper esomeprazole as an alternative to brand-name Nexium and putting downward pressure on the cost of Vimovo’s component drugs. The yellow line shows the WAC of the component products, which at \$224 per 60-count was less than tenth the cost of Vimovo. We can use NADAC (the grey line) to arrive a more precise estimate of the true pharmacy invoice cost of these component drugs – which as of February 2018 was just \$43 per 60-count, or 1.7% of Horizon’s Vimovo WAC.

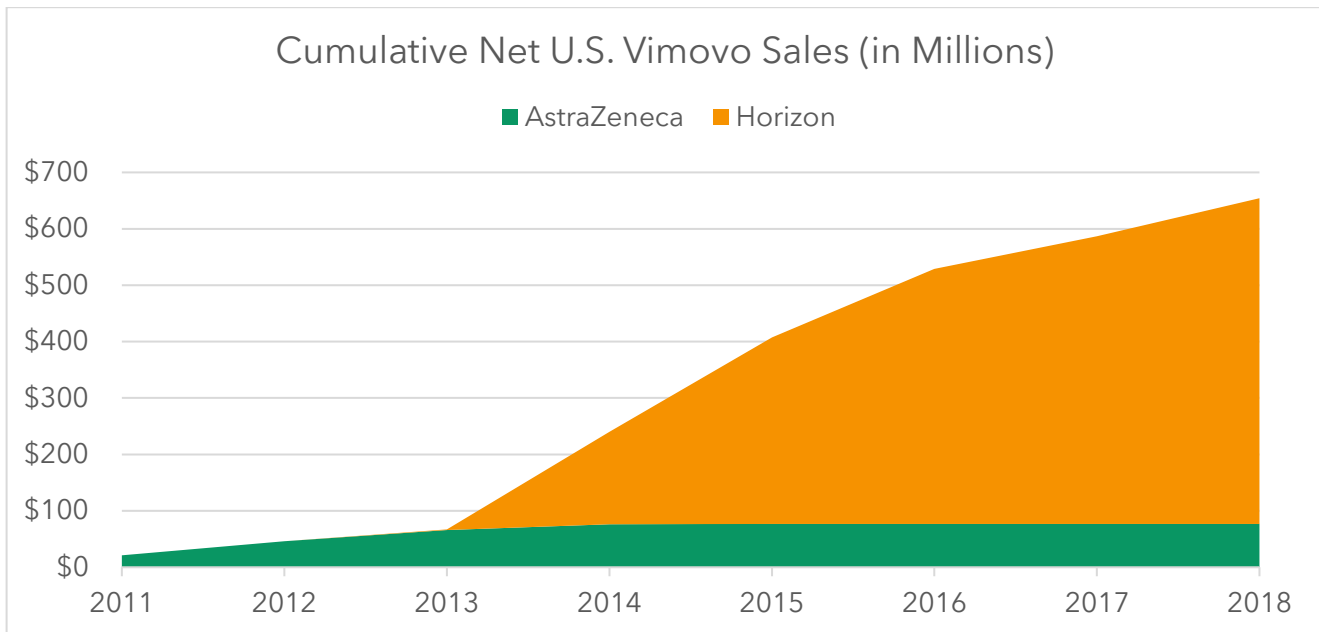
Figure 19: Cost of 60-count Package of Vimovo vs. its Sum of the Parts



Source: 3 Axis Advisors analysis – derived from data obtained from Medispan PriceRx

Recall that when Vimovo was priced reasonably, AstraZeneca never made any more than \$25 million in net revenue a year off U.S. sales of this product. This same product under Horizon’s sales strategy pulled in \$163 million in 2014 and then \$167 million in 2015, before slowing to a total \$247 million over the next three years (**Figure 20**).

Figure 20: Cumulative Net U.S. Vimovo Sales



Source: 2011-2018 AstraZeneca Annual Reports; 2013-2018 Horizon 10-Ks

10.4.5 Horizon's strategy – in its own words

The enormity of Vimovo's success under Horizon, especially when contrasted to its failure under AstraZeneca, begs the question on the details of Horizon's sales strategy. Thankfully, Horizon provides a very comprehensive overview of its marketing strategy, and its inherent risks, in its investor materials. Based on extensive reading of these materials, our summary of Horizon's Vimovo strategy is to:

- 1) Set an elevated list price for Vimovo
- 2) Market the drug to completely price insensitive physicians
- 3) Train physicians to route the prescription outside the traditional retail pharmacy channel so Horizon can control the patient co-pay
- 4) Provide patients with substantial co-pay assistance through HorizonCares to reduce their cost sensitivity
- 5) Provide rebates and discounts to PBMs to stay off commercial payer exclusion lists
- 6) Generate significant net revenue off unknowing commercial payers whose interests are not represented or protected anywhere throughout the transaction

The following subsections provide support for our assessment of the company's Vimovo strategy, primarily using Horizon's own words and data sourced directly from its 2014-2018 10-Ks (emphasis added).

10.4.5.1 Market to physicians

"In general, DUEXIS and VIMOVO also face competition from the separate use of NSAIDs for pain relief and ulcer medications to address the risk of NSAID-induced ulcers. **Use of these therapies separately**

in generic form may be less expensive than DUEXIS and VIMOVO. In addition, physicians could begin to prescribe both an NSAID and a GI protectant to be taken together but in separate pills. We expect to compete with the separate use of NSAIDs and ulcer medications primarily through DUEXIS' and VIMOVO's advantages in dosing convenience and patient compliance, and by **educating physicians** about such advantages, including through **funding we have provided for the American Gastroenterology Association** to help physicians and patients better understand and manage NSAID risks.^{clxiv}

In an effort to prevent physicians from switching from Vimovo to its generic components, Horizon was able to get the FDA to approve a labeling change in October 2016, adding the following language to the prescribing information:^{clxv}

"VIMOVO is not interchangeable with the individual components of naproxen and esomeprazole magnesium."

This language was further strengthened in June 2018 to:^{clxvi}

"Do not substitute VIMOVO with the single-ingredient products of naproxen and esomeprazole magnesium."

We unable to find any substantive clinical studies supporting these labeling changes.

10.4.5.2 Bypass the Traditional Pharmacy Channel

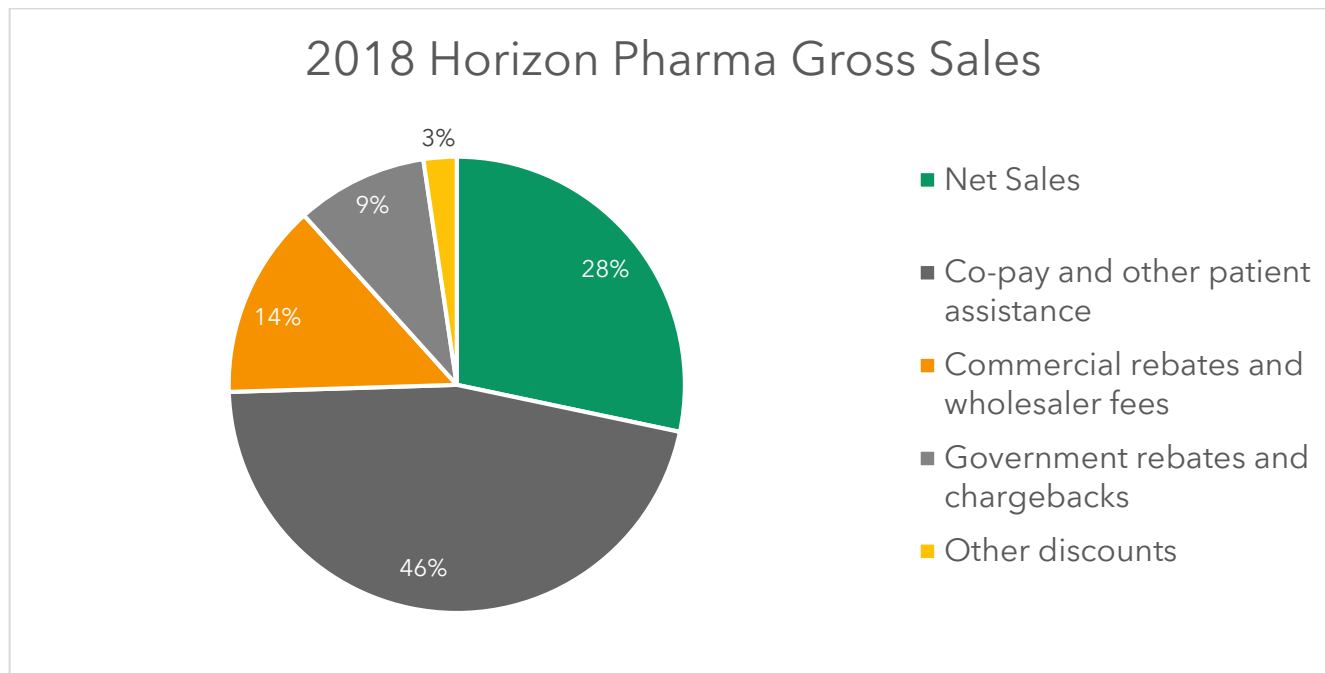
"Another key part of our commercial strategy is to **encourage physicians to have their patients agree to fill prescriptions through our Prescriptions-Made-Easy** (3AA note: this program is now called "HorizonCares"), or PME, specialty pharmacy program, which enables uninsured or commercially insured patients' enhanced access to our products by providing financial assistance to reduce eligible patients' out of pocket costs for prescriptions filled via a PME-participating mail order pharmacy. Through PME, **prescriptions for our products are filled by designated mail order specialty pharmacies**, with the product shipped directly to the patient. Because the patient out of pocket cost for our products when dispensed through the PME program may be significantly lower than such costs when our products are dispensed outside of the PME program, **prescriptions filled through our PME program are therefore less likely to be subject to the efforts of traditional pharmacies to switch a physician's intended prescription of our products to a generic or over the counter brand.** We expect that continued adoption of our PME program by physicians will be important to our ability to gain market share for our products as pressure from healthcare payors and PBMs, to use less expensive generic or over the counter brands instead of branded products increases."^{clxvii}

Horizon's HorizonCares program is, in our view, conceptually identical to AstraZenca's Nexium *Direct* program. As such, it's likely not a coincidence that the pharmacy that runs Nexium *Direct* - Eagle Pharmacy - is also a participant in HorizonCares.^{clxviii}

10.4.5.3 Offer significant copay assistance to patients

In 2018, Horizon produced just over \$4 billion in gross revenue. Of this, \$1.9 billion (46%) was used to subsidize patient copays and coinsurance (**Figure 21**). Overall, Horizon provided patient, commercial, and government discounts totaling 72% of its gross revenue in 2018.^{clxix}

Figure 21: 2018 Horizon Pharma Gross Sales



Source: 2018 Horizon 10-K

10.4.5.4 Pay PBMs to secure formulary placement

“We have evolved our commercial strategy to **enter into business arrangements with pharmacy benefit managers, or PBMs, and other payers to secure formulary status** and reimbursement of our medicines. The business arrangements with the PBMs generally require us to **pay administrative fees and rebates to the PBMs and other payers** for qualifying prescriptions.”^{clxx}

Of note, in 2015, CVS/Caremark and Express Scripts added both Vimovo and Duexis to their exclusion lists. But the success of the HorizonCares direct-to-patient program more than offset this setback; in 2015, Vimovo sales volume actually increased by 14% year-over-year despite two of the largest PBMs excluding the drug.^{clxxi} By the start of 2017, Horizon had reached agreements with both CVS Caremark and Express Scripts to remove Vimovo (and Duexis) from their exclusion lists.^{clxxii}

10.4.6 Is this legal?

Clearly, Horizon has proven that its strategy is highly lucrative. However, there could be debate on whether it is legal.

In February 2016, Horizon disclosed to shareholders that it had received a subpoena in late 2015 from then-U.S. attorney for the Southern District of New York, Preet Bharara, seeking a litany of documents related to the Horizon’s patient assistance programs, as well as other information detailing the company’s sales and marketing strategies.^{clxxiii} Those strategies were highlighted extensively by Bloomberg in 2018, where the tactics of drug manufacturer consultants Todd Smith and Benjamin Bove were exposed in detail. The duo were specialists in assisting manufacturers like Horizon to take advantage of the dynamics of the drug supply chain to boost sales. They helped

Horizon with Duexis and Vimovo, Kaleo with famed naloxone autoinjector Evzio, Novum Pharma with Alcantin A, and Iroko Pharmaceuticals with Indocin. Strategies typically involved simplifying insurance coverage barriers for prescribers, boosting rebates, limiting pharmacy distribution, and minimizing patient out-of-pocket expenses. In the Bloomberg feature, University of Minnesota professor of pharmaceutical economics Stephen Schondelmeyer explained, “It’s totally a wrong way to frame the issue to say it’s free to the patient ... It’s ripping people off.”^{clxxiv}

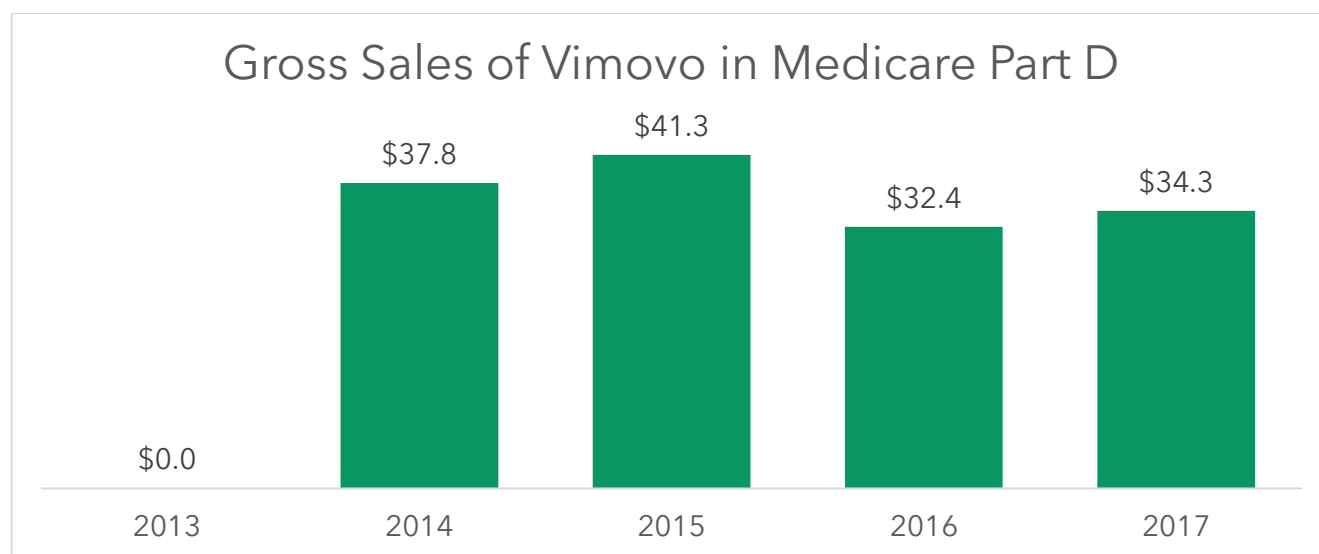
While the investigation into Horizon’s practices has continued into 2019, we found it interesting that the company itself provided investors with this warning in its 2018 10-K:^{clxxv}

“The HorizonCares program may implicate certain federal and state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, tortious interference with patient contracts and statutory or common law fraud.”

10.4.7 A commercial strategy... that somehow resulted in \$150 million in Part D sales

In its company filings, Horizon makes it very clear that government programs will not permit the copay discounting practices it employs within its HorizonCares program. As such, we were surprised when we found nearly \$150 million in spending within Medicare Part D between 2014 and 2017 – an average of \$36 million a year (**Figure 22**).

Figure 22: Gross Sales of Vimovo in Medicare Part D



Source: Medicare Part D Drug Spending Dashboard – full underlying excel data

The most interesting takeaway from **Figure 22**, in our view, is not the nearly \$150 million spent between 2014 and 2017, but the absence of any money spent in 2013. Recall that in 2013, Vimovo was priced very attractively relative to its component parts, yet there was no coverage in Part D. But that equation completely flipped in 2014 with Horizon’s price increases, and only got worse in the subsequent years, as Vimovo’s skyrocketing list price diverged from the falling costs of its component ingredients. **Ironically, that’s when Medicare Part D started to pay for Vimovo.**

In short, Medicare Part D did the exact opposite of what it was supposed to do. It blocked a drug with an attractive cost/benefit and only started paying for it once its cost/benefit was egregiously poor. For further discussion on why this could be the case, please see the [Brand over generic](#) section.

10.5 RANBAXY – THE GIFT THAT KEEPS GIVING (FOR ASTRAZENECA)

Regardless of the actions AstraZeneca took to extend Nexium’s market share, Ranbaxy was still set to bring generic esomeprazole to market on May 27, 2014 (as per its settlement with AstraZeneca) under first-to-file 180-day exclusivity rights. By late 2014, generic manufacturers were expected to flood the market, competing aggressively for share of the most popular PPI on the market. AstraZeneca warned shareholders of the impact of the coming end of Nexium exclusivity in its 2013 annual report:^{clxxvi}

“We believe challenging market conditions will persist in 2014 ... The revenue impact from the loss of exclusivity will also continue to affect our performance including the anticipated Nexium U.S. first generic launch in May 2014.”

But as already discussed in “Nexium Patent Battles,” Ranbaxy was struggling with quality control issues that were putting their May 27, 2014 launch date at risk. And unsurprisingly, that day came and went, with no generic brought to market.

Four months later, there had still been no resolution on the situation. Ranbaxy had not been given the green light to start manufacturing esomeprazole, but the FDA had also not pulled its exclusivity. The effect was that other generic manufacturers remained on the sidelines, while **sales of Nexium in the U.S. continued at a rate of \$156 million per month.**^{clxxvii} AstraZeneca ended up boosting its profit outlook for 2014 “based on lack of competition for Nexium.”^{clxxviii}

The FDA did not end up fully revoking Ranbaxy’s rights to produce generic Nexium until January 27, 2015.^{clxxix} That same week, Teva announced that it received FDA approval for its version of esomeprazole.^{clxxx} A few weeks later, on February 15, 2015, generic esomeprazole finally hit the market.^{clxxxi} But the fiscal damage had been done. AstraZeneca generated \$1.9 billion of revenue in the U.S. from Nexium in 2014, down only 12% from 2013. The year Prilosec finally lost its patent, its U.S. sales were down 70% YoY.

11 NEXIUM GOES GENERIC. WHERE ARE ALL THE SAVINGS?

Section Key Takeaways

- In 2016, Medicare Part D spent over \$1 billion on brand-name Nexium, despite the generic going multi-source in 2015
- We analyzed CMS' Part D Prescription Drug Plan Formulary and Pricing Information Files and found that over 50% of all Part D plans left Nexium on Tiers 1-4 of their formularies in 2016
- Of the plans that added generic Nexium to their formularies, 58% placed it on Tier 3 - the tier generally reserved for preferred brand drugs
- The preference for brand Nexium over generic Nexium was driven by subsidies by the federal government (federal reinsurance and low-income subsidy) that covered nearly 50% of Nexium's list cost and aggregate discounts and rebates offered by AstraZeneca on Nexium in the U.S. approaching 75% in 2015
 - The design of the Part D cost-share shifts more proportionate **net** cost to the plan for inexpensive generics (omeprazole) than it does for expensive brands (Nexium)
- By 2017, increasing competition drove generic Nexium's cost down to just \$0.70 per unit. But Medicare Part D and Medicaid managed care did not realize the full benefit of this deflation, paying \$3.27 and \$3.44 per unit, respectively.
- Payers generally pay for generic drugs based on a discount to AWP, a pricing benchmark that is not competitively set and is detached from true cost
 - Between Q1 2016 and Q1 2018, 88% of all generic NDCs experienced a decline in NADAC; only 1% of the same generic NDCs experienced a decline in AWP
- There was extreme variability in what Medicaid managed care paid for generic Nexium from state to state and what Medicare Part D paid for generic Nexium from plan to plan

While we couldn't find a statement or report indicating that 180-exclusivity rights had been granted to Teva, based on our analysis of market introduction dates for generic esomeprazole, it appears such rights were effectively granted to Teva. The next manufacturer to hit the market (Mylan) didn't come to market until August 3, 2015. The floodgates opened at this point, with five new ANDA versions of generic esomeprazole hitting the market by the end of 2015, and one more ANDA entering the market in 2016 (see **Table 3** on next page).

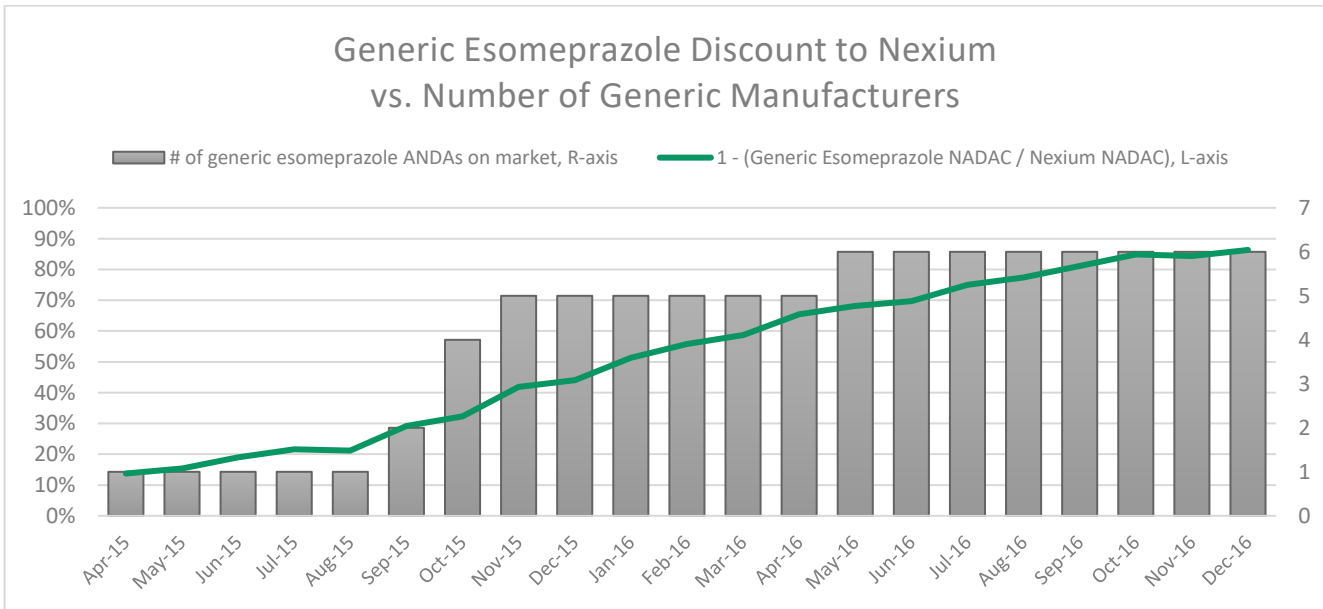
Table 3: Esomeprazole Marketing Start Dates, Labelers, and Application Numbers (2015-2016)

Marketing Start Date	Labeler	Application Type/Number
3/19/2001	AstraZeneca	NDA 021153
2/17/2015	Teva Pharmaceuticals Inc.	ANDA 078003
8/3/2015	Mylan	ANDA 078936
9/21/2015	Camber Pharmaceuticals	ANDA 202784
9/25/2015	Dr. Reddy's Laboratories Inc.	ANDA 078279
10/19/2015	Torrent Pharmaceuticals	ANDA 203636
4/21/2016	Aurobindo	ANDA 205606

Source: MediSpan PriceRx

An FDA study of IMS retail sales data spanning 1999-2004 found that generic drugs with six "manufacturers" cost, on average, 74% less than the brand.^{clxxxii} This wasn't too far off from what occurred for esomeprazole, as we show in **Figure 23**. We entered 2016 with five esomeprazole ANDAs available on the market and a 42% generic discount to the brand (based on NADAC). By the end of the year, the discount was up to 86%, despite only one new ANDA available on the market. The overall average generic discount in 2016 was 72%.

Figure 23: Generic Esomeprazole Discount to Nexium vs. # of Generic Manufacturers



Source: 3 Axis Advisors analysis using data from Medispan PriceRx

Now let's see how much savings materialized in Medicare Part D due to the considerable deflation in generic esomeprazole.

To do this, we looked at NADAC unit costs for Nexium in 2014 (before patent expiration) vs. esomeprazole (after patent expiration) and compared that to Part D unit costs in 2014 for Nexium vs. Part D unit costs in 2016 for all esomeprazole products. Had Part D plans aggressively excluded all brand-name Nexium from formularies in 2016 and passed through all savings associated with generic deflation, the unit costs based on NADAC and Part D should be similar. However, as shown in **Table 4** (on next page), this was not the case. Our NADAC analysis shows that there were savings of up to 70% available, and Medicare Part D collectively only realized 23% of these savings. With nearly 270 million dosage units of esomeprazole, Part D plans collectively left **nearly \$1 billion** of list price savings on the table in 2016.^{clxxxiii}

Table 4: 2014 to 2016 Savings on Generic Esomeprazole - NADAC vs. Medicare Part D

	NADAC	Medicare Part D
2014	\$7.75 (Nexium)	\$7.81 (Nexium)
2016	\$2.31 (Esomeprazole)	\$6.00 (Nexium & Esomeprazole)
Savings %	70%	23%

Source: CMS.gov, Data.Medicaid.gov, 3 Axis Advisors

There are two drivers behind Part D’s elevated cost for esomeprazole in 2016:

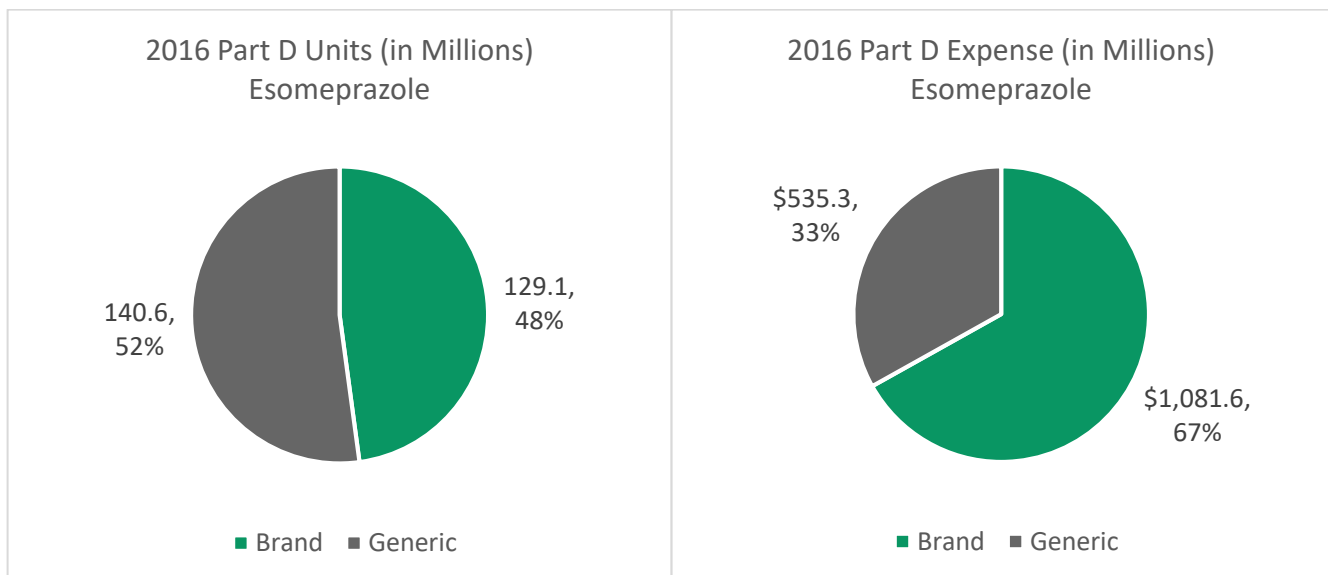
1. Plans did not aggressively switch their formularies from brand-name Nexium to generic esomeprazole
2. Plans overpriced generic esomeprazole relative to its market-based acquisition cost

The remainder of this section delves into these two drivers of elevated cost in Medicare Part D and provides evidence that some of the same dynamics are occurring in Medicaid managed care programs.

11.1 BRAND OVER GENERIC

The primary driver of the elevated Medicare Part D unit costs on esomeprazole (brand and generic, combined) in 2016 was that 48% of all esomeprazole was still dispensed as brand-name Nexium. In other words, despite there being robust generic esomeprazole competition, leading to rapidly falling generic acquisition cost, somehow Part D Plans only collectively switched 52% of volume to the generic. The 48% of volume dispensed as brand-name Nexium comprised 67% of overall expense on the esomeprazole molecule (**Figure 24**).

Figure 24: 2016 Medicare Part D Esomeprazole Units and Expense



Source: CMS.gov

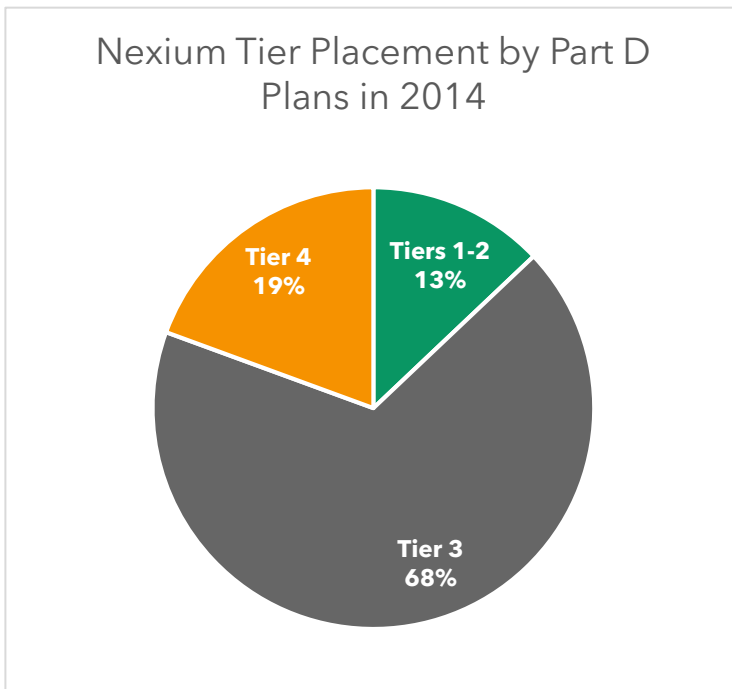
11.1.1 Plans kept Nexium on formulary

As mentioned at the start of this report, the fact that Part D spent more than \$1 billion on Nexium in 2016, despite there being robust multi-source generic competition, was the impetus for this study.

We once again dug into CMS' Part D Prescription Drug Plan Formulary and Pricing Information Files to help explain this expense. It turns out that, unsurprisingly, formulary placement decisions drive Part D expense.^{clxxxiv}

To start, we counted the number of Part D "unique plans"^{clxxxv} that placed Nexium on Tiers 1-4 of their formularies in 2014 - a total of 3,658. Of these plans that chose to cover Nexium, 2,475 (68%) placed Nexium on Tier 3 (commonly referred to as "preferred brands"). Only 710 plans placed Nexium on Tier 4 - "non-preferred brands." Tier 3 carries a lower beneficiary cost share than Tier 4 - for plans that assign copays to both tiers (as opposed to coinsurance), the Tier 3 copay could be half as much as Tier 4. An even more shocking finding is that 473 (13%) of all unique plans placed Nexium on Tiers 1 or 2, tiers normally reserved for inexpensive generic drugs (**Figure 25**).

Figure 25: Nexium Tier Placement by Part D Plans in 2014



Source: 3 Axis Advisors analysis using data from CMS.gov

This finding is alone quite interesting. With two inexpensive generic PPI options in 2014 (omeprazole = \$0.29 per unit; pantoprazole = \$0.32 per unit), we would not expect that plans (purportedly) trying to manage formularies to reduce Part D expense would collectively offer such favorable placement to Nexium. Clearly, favorable formulary placement before patent expiration was a key tailwind helping Nexium surpass \$2.6 billion in Part D sales in 2014.

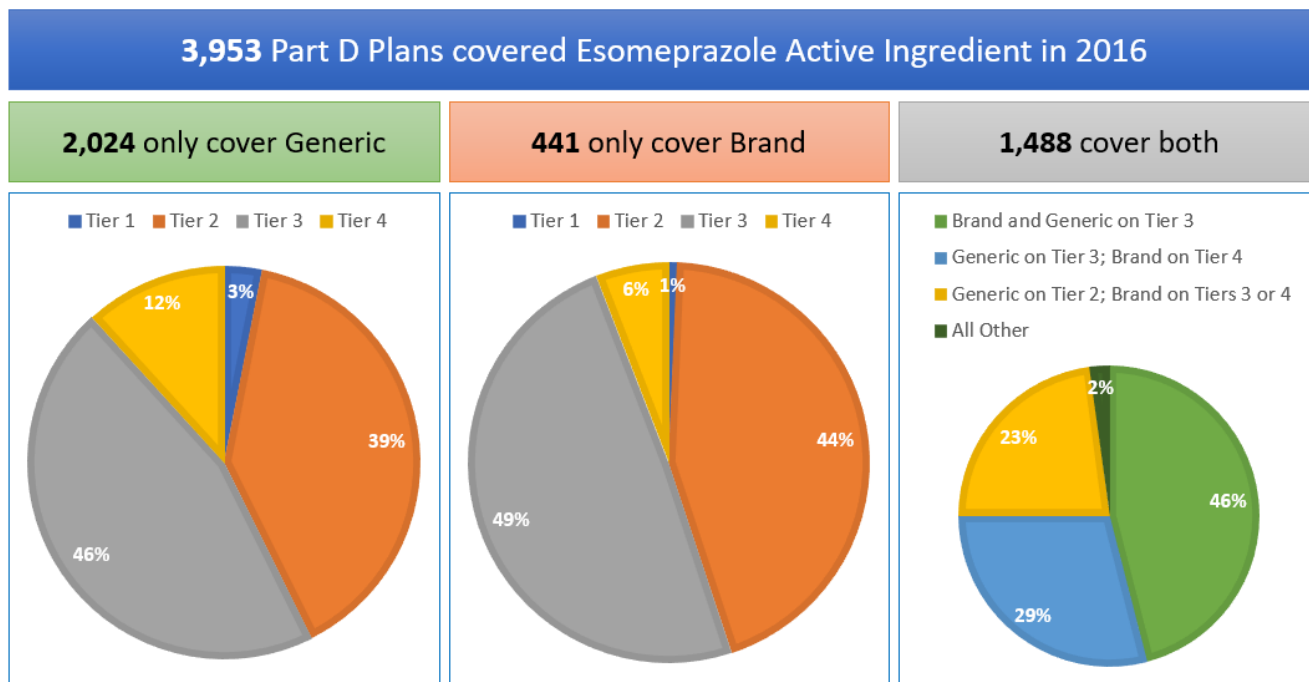
We then replicated the same analysis for 2016, when generic esomeprazole was available. If plans were aggressively working to reduce Part D cost, we would expect Nexium to be all but expunged from Part D plan formularies. This was not the case. We found 1,929 plans still decided to cover Nexium, and 1,046 (54%) of these plans still had Nexium on Tier 3.

We then found that 3,512 plans covered generic esomeprazole in 2016, a positive sign that at least more plans covered the generic than the brand. However, 2,039 (58%) of these plans placed the **generic** on Tier 3 - the Tier typically reserved for preferred brands.

In 2016, 58% of Medicare Part D plans placed generic esomeprazole on Tier 3 - the tier typically reserved for preferred brands.

When we combine the analysis for both brand Nexium and generic esomeprazole, we found that 3,953 plans covered the esomeprazole active ingredient in 2016. As shown in **Figure 26**, of these plans, 2,024 covered only the generic, 441 covered only the brand, and 1,488 covered both the generic and the brand. Of the plans that covered both, 46% placed both the brand and the generic on Tier 3, removing the financial incentive for the patient to prefer the generic over the brand.

Figure 26: 2016 Medicare Part D Plan Coverage of Nexium and Esomeprazole



Source: 3 Axis Advisors analysis based on data from CMS.gov

11.1.2 Assessing the role of reinsurance, rebates, and low-income subsidy (LIS)

In June 2015, the Medicare Payment Advisory Commission (MedPac) laid out several hypothetical Part D plan bidding strategies to illustrate how plans can maximize expected profit by underestimating catastrophic benefits.^{clxxxvi} In short, federal reinsurance covering 80% of all “unanticipated” costs when a beneficiary enters the catastrophic phase of the benefit provides the plan with very little incentive to actively manage the benefit to keep beneficiaries out of the catastrophic coverage phase.

In fact, it could be argued that - because of rebates - the health plan actually has the financial incentive to push beneficiaries as far (and quickly) into catastrophic as possible. This is because the Plan is only responsible for 15% of a claim’s list cost in catastrophic, but still collects (and retains, up to risk corridors) the full manufacturer rebate on catastrophic claims.

While we will not cover the many details of the low-income subsidy (LIS), in short, it works to reduce or eliminate all beneficiary cost-share within Part D. Making the beneficiary completely insensitive to cost could have the unintended consequence of allowing plans with a high number of LIS enrollees to place higher cost drugs (i.e. brand over generic) on their formularies to accelerate plan members’ progress through the cost-share into catastrophic coverage, where taxpayers end up footing a majority of the bill.

While a full analysis of such hypotheses is outside the scope of this work, we at the very least wanted to understand how the costs were split between “payers” for Nexium in 2016. In other words, of the \$1 billion in pre-rebate expense, how much was truly paid by Part D plans versus other payers (e.g. beneficiaries, federal government, manufacturer discounts)? Conceptually, the lower a plan’s share, the less a plan will work to control costs, especially if it can offset some portion (or all) of its share with manufacturer rebates.

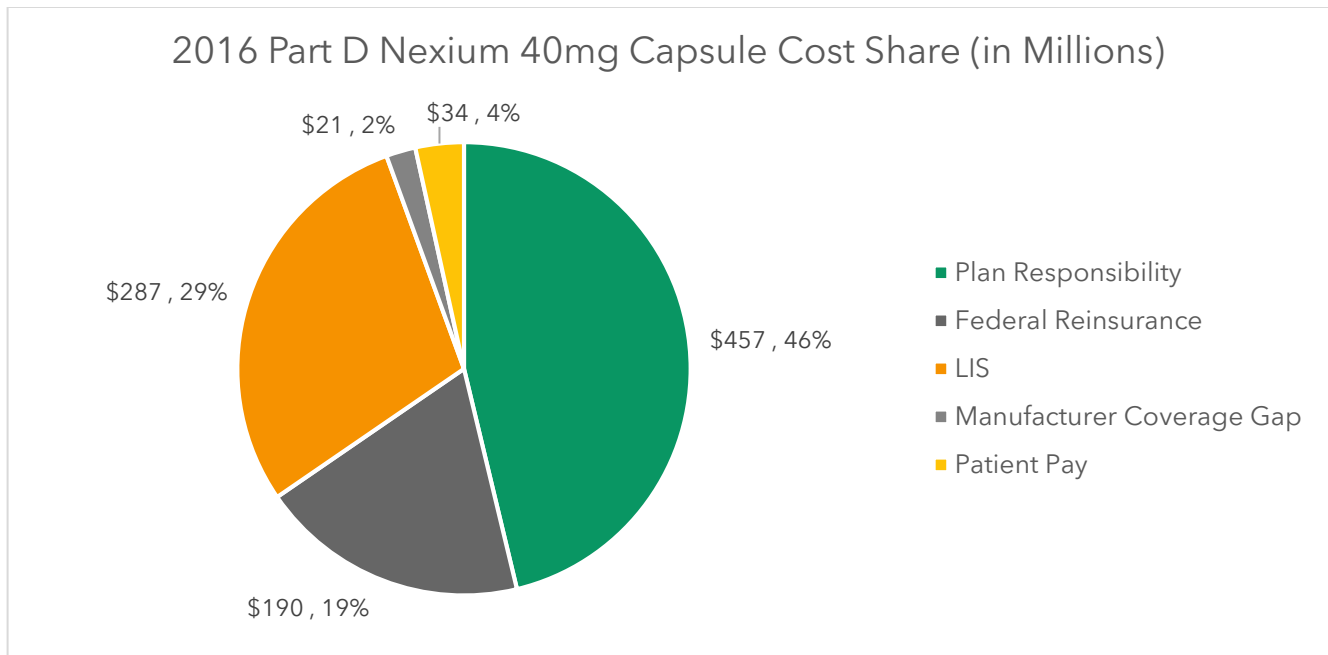
To perform this analysis, we received assistance from Mariana Social, Ge Bai and Gerard Anderson from the Johns Hopkins Drug Access and Affordability Initiative (JHDAAI) at Johns Hopkins University. JHDAAI has access to the 2016 Medicare Part D Event (PDE) database, which is required to calculate the cost-sharing breakdown in Part D drug spending. To conduct the analysis, we first sent JHU a list of all Nexium 40 mg Capsule NDCs listed in MediSpan’s database. JHU queried the PDE database on the following fields for each NDCs:

- 1) Total Part D drug cost (“tot_rx_cst_amt”)
- 2) Cost above the catastrophic threshold (“gdc_abv_oopt_amt”)
- 3) Amount paid for the PDE by Part D low income subsidy (“lics_amt”)
- 4) Amount Paid by the patient (“ptnt_pay_amt”)
- 5) Gap discount amount (“RPTD_GAP_DSCNT_NUM”)

Figure 27 shows our estimate of the cost share breakdown for Nexium 40 mg capsules in 2016 based on the data we collected. Please note that we assumed that Federal Reinsurance was 80% of the total cost above the catastrophic threshold.

If the assumptions underlying this analysis are accurate, this work suggests that plans only ultimately had to foot the bill for 46% of the total Part D cost of Nexium (before receiving rebates), while 48% of the expense was covered by the combination of the LIS and federal reinsurance.

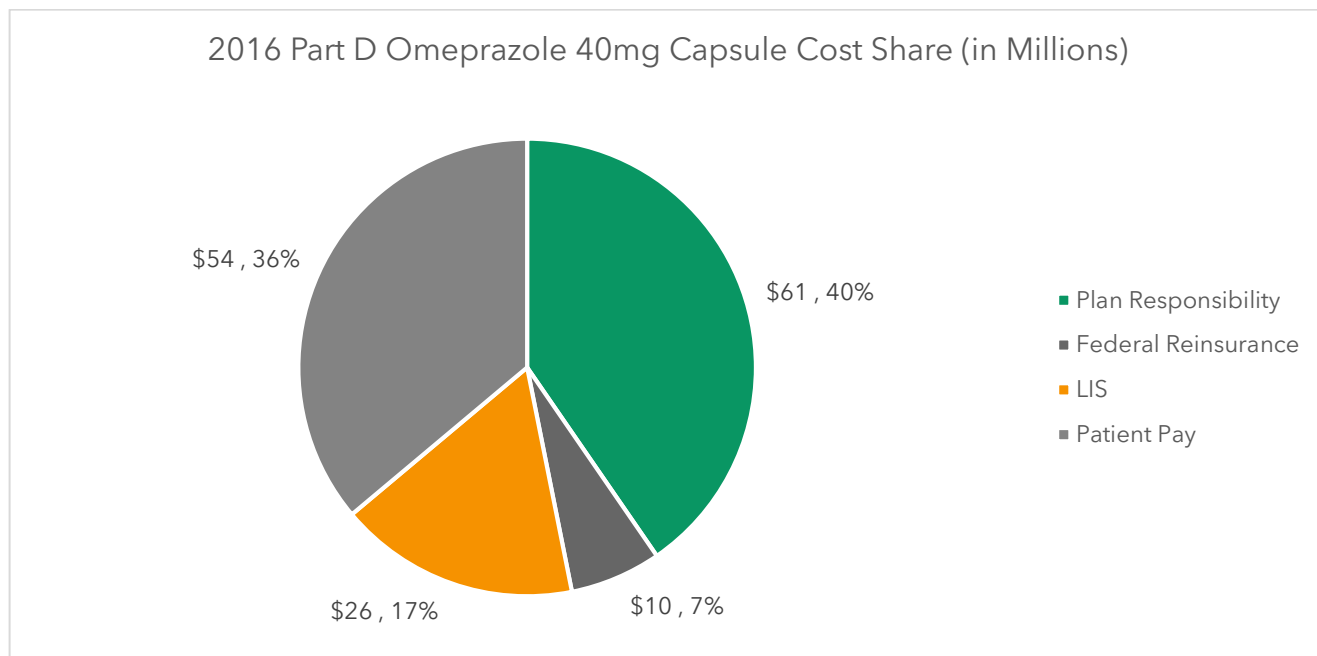
Figure 27: 2016 Part D Nexium 40mg Capsule Cost Share



Source: 3 Axis Advisors analysis based on aggregated Medicare Part D PDE data from Johns Hopkins University

Before leaving this topic, we ran the same analysis for generic omeprazole 40 mg capsules, the cheapest drug in the proton pump inhibitor class. We estimate that the plan was only responsible for just around 40% of the drug's cost (**Figure 28**). But in the case of omeprazole, the patient now shoulders 36% of the entire cost while LIS and federal reinsurance together pay only 24% of the cost. In short, high-priced brand Nexium receives considerably more federal subsidies than low-priced generic omeprazole, which could lead to a warped incentive to prefer Nexium viz-a-viz omeprazole.

Figure 28: 2016 Part D Omeprazole 40mg Capsule Cost Share

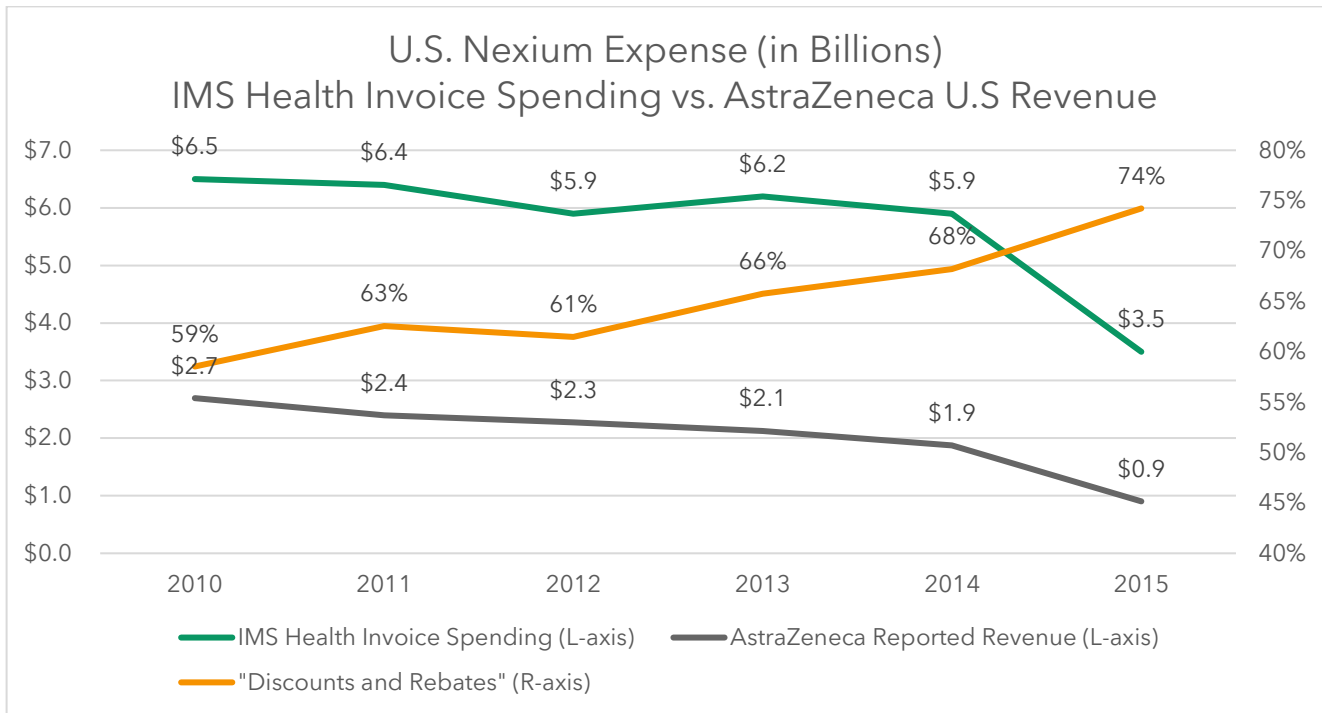


Source: 3 Axis Advisors analysis based on aggregated Medicare Part D PDE data from Johns Hopkins University

But this of course depends on rebates that plans are collecting on Nexium. If rebates were immaterial, the argument could be made that plans may at worst be indifferent to the dispensing of Nexium over omeprazole. On the other hand, if rebates were sizable, a much stronger argument can be made that plans have the incentive to dispense Nexium - or really any higher-cost drug - at great expense to federal taxpayers.

The fact that rebates are not publicly available for individual drugs severely limits our ability to advance this discussion. But we were able to estimate rebates on Nexium by combining gross invoice spending data reported publicly by IMS Health (now IQVIA) with AstraZeneca's reported U.S. Nexium revenue (reported in each AstraZeneca annual report). **Figure 29** (on next page) shows the two measures of Nexium spending for each year. If we divide the two, we get what we believe is as good of a view as we can assemble from public data into the rebates and price concessions offered on Nexium. **Over this period, those discounts increased from 59% in 2010 to 74% in 2015.** While we do not have enough information to calculate the 2016 discounts and rebates percentage, the magnitude of the 2015 number - especially when compared to the plan cost share (~40% of list cost) - helps provide a bit of additional color on why the majority of Part D plans decided to keep Nexium on their formularies in 2016.

Figure 29: U.S. Gross and Net Nexium Expense and Estimated Nexium Discounts/Rebates

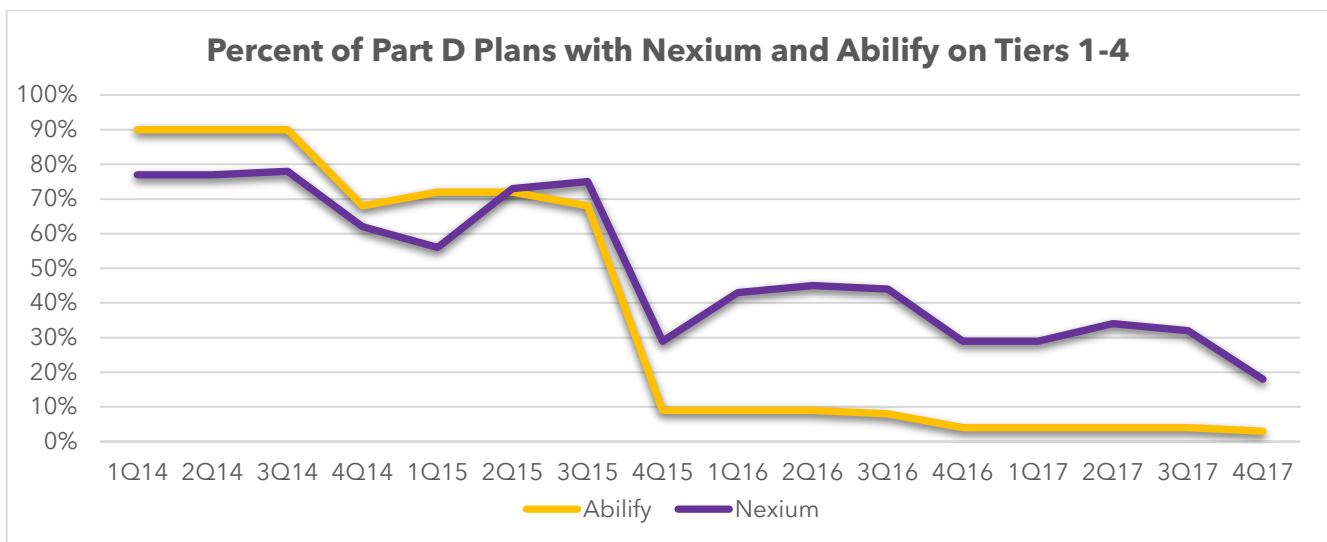


Source: 3 Axis Advisors analysis based on data from AstraZeneca 10-Ks (2010-2015) and IMS

11.1.3 Case study: Comparing Nexium to Abilify

Before closing out this subsection, we did a quick comparison of Nexium with another blockbuster drug that also went generic in 2015 - Abilify (aripiprazole). As shown in the following chart, our CMS formulary data analysis suggests that Part D plans almost completely removed brand Abilify from the market in 2016 - on average, it only was covered on 8% of all Part D plans. This is in stark contrast to Nexium, which was still covered by 40% of Part D plans (Figure 30).

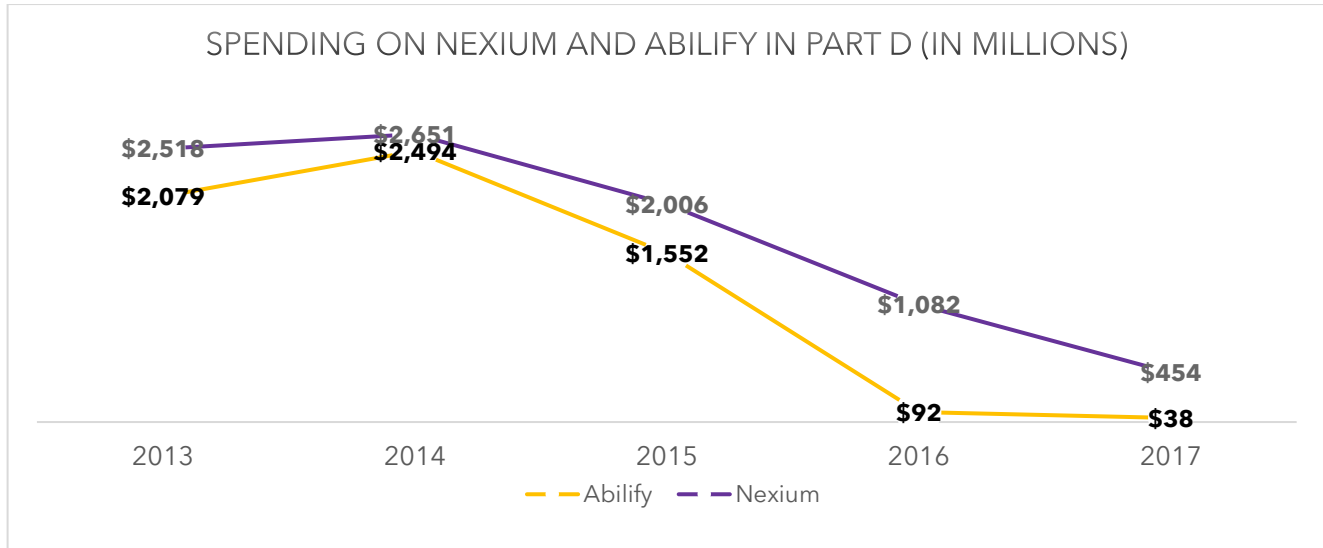
Figure 30: Percent of Part D Plans with Nexium and Abilify on Tiers 1-4



Source: 3 Axis Advisors analysis based on data from CMS.gov

Given the different coverage decisions made by Part D plans, it should come as no surprise that spending on Abilify also collapsed, while Nexium has remained stubbornly high (Figure 31). While Abilify’s manufacturer, Otsuka, does not provide enough detail on its U.S. Abilify sales to estimate discounts and rebates, we expect that if we were able to obtain this data, the discrepancy in rebates would likely be the key variable driving Part D plan coverage decisions and expense.

Figure 31: Spending on Nexium and Abilify in Part D

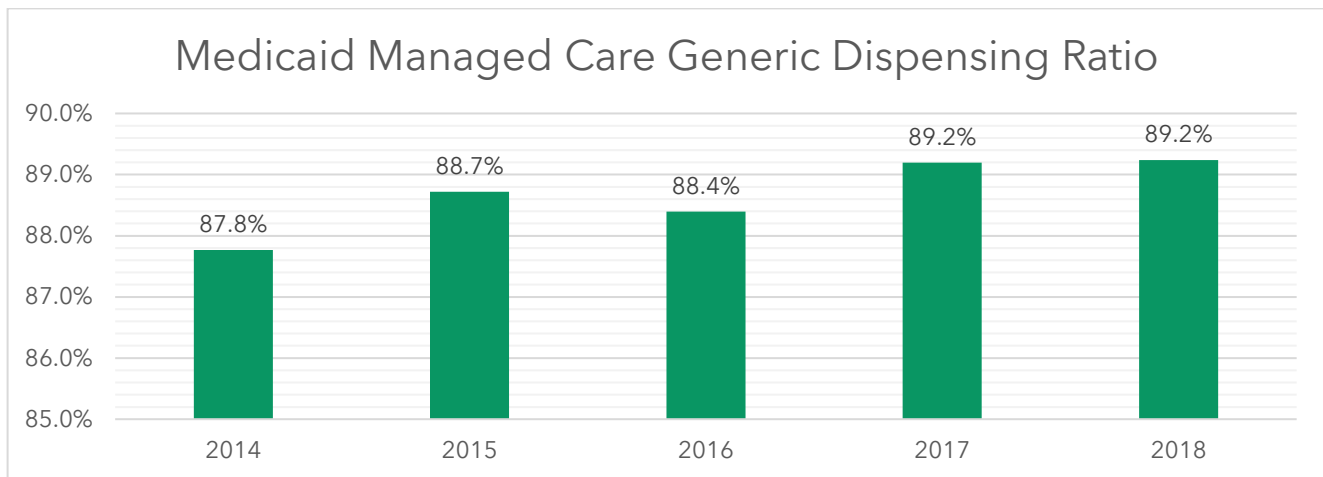


Source: CMS.gov

11.2 DISTORTIONS IN GENERIC UNIT COSTS

Despite the incentives to dispense brand-name drugs in Part D, PBMs are overall doing a good job delivering on a commonly accepted key performance indicator called Generic Dispensing Ratio, or GDR. GDR is the number of generic fills divided by the total number of prescriptions.^{clxxxvii} Figure 32 shows that PBMs have impressively driven the GDR in Medicaid managed care up to nearly 90%.

Figure 32: Medicaid Managed Care Generic Dispensing Ratio (GDR)



Source: 3 Axis Advisors analysis based on data from Data.Medicaid.gov and Medispan PriceRx

According to a study published in September 2010 in the Journal of Managed Care and Specialty Pharmacy, “Higher GDRs are considered important because they consistently produce lower prescription drug costs.”^{clxxxviii} This study arrived at this conclusion by analyzing gross pharmacy expenditures dispensed between 2007 and 2009 to a collection of 14 million commercial insurance beneficiaries. It found that a “1 percentage point increase in GDR was associated with a 2.5% reduction in gross pharmacy costs.”

But the study has two clear limitations. First, gross costs ignore rebates, which can be a substantial number. This is especially pronounced in Medicaid, which according to MACStats by MACPAC, collected rebates of \$34.9 billion, or 54.5% of total gross drug spending, in FY17.

With rebates this substantive, they must be factored into any analysis attempting to correlate cost savings with GDR. After factoring in rebates, brands sometimes carry a lower net cost than generics, especially in Medicaid. Magellan Rx Management discusses this within its 2018 Medicaid Pharmacy Trend Report, in which it speaks to the savings of “brand-over-generic” programs (emphasis added).

“At patent expiration, the launch of a generic is a welcomed event by commercial plans as a way to lower reimbursement and overall drug cost. **In Medicaid, the launch of a generic can have the exact opposite effect.** When generics first enter the market, they typically launch at a price point that is discounted to the brand’s full price but have a federal rebate at 13% AMP (Average Manufacturer Price). The net cost of a brand drug can be markedly less than the generic at this time. Factors affecting the availability of this new generic can cause the net cost of the generic to remain relatively high for periods lasting from six months to multiple years. **In 2017, brand-over-generic programs accounted for \$188 million in savings** at an average cost of \$90 per claim.”

As such, in our view, GDR is a flawed proxy for cost savings not only in Medicaid, but for any payer that is generating sizable rebates.

Even for payers that are not receiving rebates, GDR is, in our view, still misleading. This is because there can be a sizable disconnect between the price PBMs charge payers for generic drugs and their actual cost. Simply put, a PBM is able to arbitrage the difference between the contractual price set with its client and the market-clearing acquisition cost for a generic drug claim. This creates pricing distortions that undermine the savings associated with generic drugs. Generic Nexium (esomeprazole) is a prime example of this dynamic.

In a world without brand-name drug rebates and generic pricing distortions GDR would be an appropriate measure of drug cost savings. But, in our view, these two factors completely undermine GDR’s usefulness for payers looking to control drug costs.

The remainder of this section describes how generic prices are set, using esomeprazole as a case study. We then go on to evaluate and explain pricing distortions on esomeprazole in Medicare Part D and Medicaid managed care, and contrast such distortions with omeprazole, a more mature generic drug. We conclude this subsection with a discussion on the incentives that we believe are driving generic pricing distortions.

11.2.1 10% cheaper

When a generic is initially brought to market, it typically does not start out much cheaper than the brand. This was the case with esomeprazole, which was brought to market by Teva in February 2015 with the prices shown in **Table 5** (on next page). We have also presented the same benchmark costs

for brand-name Nexium for comparison. Note that the NADAC listed below corresponds to April 2015, as that is the first month a NADAC was available for generic esomeprazole.

Table 5: Launch Pricing for Nexium versus generic esomeprazole

	Nexium (AstraZeneca)	esomeprazole (Teva)
Average Wholesale Price (AWP)	\$9.47	\$8.52
Wholesale Acquisition Cost (WAC)	\$7.89	\$6.82
National Average Drug Acquisition Cost (NADAC)	\$7.64	\$6.59

Source: Medispan PriceRx

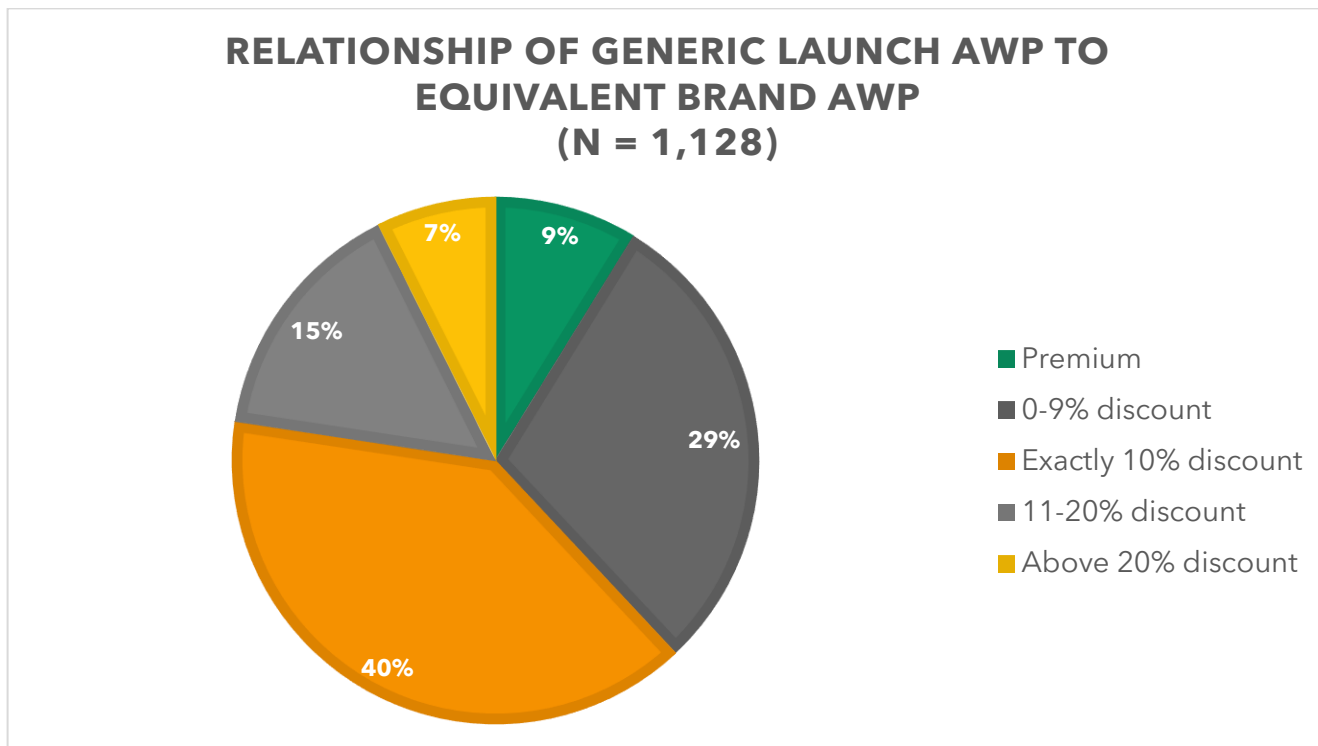
It is critical to note that out of the three benchmark prices shown above, two are either directly or indirectly set by the manufacturer - Average Wholesale Price (AWP) and Wholesale Acquisition Cost (WAC). NADAC, which is based on monthly surveys of retail pharmacy invoice acquisition costs (pre-wholesaler rebates), is the only benchmark cost that directly reflects supply and demand market forces for the drug. Without any competition on single source generics or brand-name drugs, NADAC will trend closely with the manufacturer’s WAC. Myers and Stauffer, the firm that compiles the NADAC survey on behalf of CMS publishes “NADAC Equivalence Metrics” each quarter. Their latest publication found that for “single source legend drugs,” NADAC runs at a constant 4% median discount to WAC^{clxxxix} - exactly where Teva’s esomeprazole and AstraZeneca’s Nexium were in early 2015.

The next important observation is that Teva set its AWP at a 10% discount to Nexium.

We are not sure where the 10% generic launch discount came from, but it appears to have become an industry standard of sorts. We analyzed 1,128 brand-name drugs that went off patent between January 2006 and February 2019. For each brand-name drug, we found all equivalent generic National Drug Codes (NDCs) that shared the same active ingredient, strength, and dosage form.^{exc} We then identified the first generic NDC brought to market approved under an abbreviated new drug application (ANDA) and compared its launch AWP with the AWP of its equivalent brand the month prior to its launch.

As shown in **Figure 33** (on next page), we found that of the 1,128 “first-to-market” generics, 444 (or 40%) were priced at exactly a 10% discount to the equivalent brand.

Figure 33: Relationship of Generic Launch AWP to Equivalent Brand AWP



Source: 3 Axis Advisors analysis based on data from Medispan PriceRx

11.2.2 Unchanging AWP

Average Wholesale Price (AWP) is the most important benchmark price for generic drugs from a payer's perspective. This is because contracts between payers and PBMs generally price the payer's basket of generic drugs based on a discount to the aggregate AWP for that basket of drugs.^{cxci cxcii} So, the higher the aggregate AWP, the more money the PBM collects for generic drugs.

When a generic drug is only available from one manufacturer, as was the case with esomeprazole throughout most of 2015, AWP has some relation to the actual cost of the generic drug (i.e. the NADAC) simply because there is no competition in the generic market to challenge the manufacturer-specified list price. But the relevance of AWP changes dramatically as more manufacturers come to market. In other words, the fundamentals of supply and demand dictates the drug's NADAC while AWP continues to be set directly or indirectly by the manufacturer.

This is illustrated very well with generic esomeprazole. **Table 6** shows the launch AWP for each NDC brought to market between February 2015 and the end of 2016, alongside the current AWP. The NDCs are ordered chronologically, from first entry to last. The first key observation is that as manufacturers brought competing versions of esomeprazole to market, they did not bring their versions to market with lower AWP. To illustrate, Mylan brought NDCs to market on 5/31/2016 that had AWP of only one penny per unit lower than those initially launched by Teva more than a year earlier. Instead, there appear to be two "clusters" of AWP - one around \$8.52 per unit and the other around \$9.02. The second key observation is that if we fast forward to June 2019, no manufacturer had lowered the AWP of any of these NDCs. They all remain stuck in the past, roughly 10% lower than the AWP of brand-name Nexium on Teva's launch day.

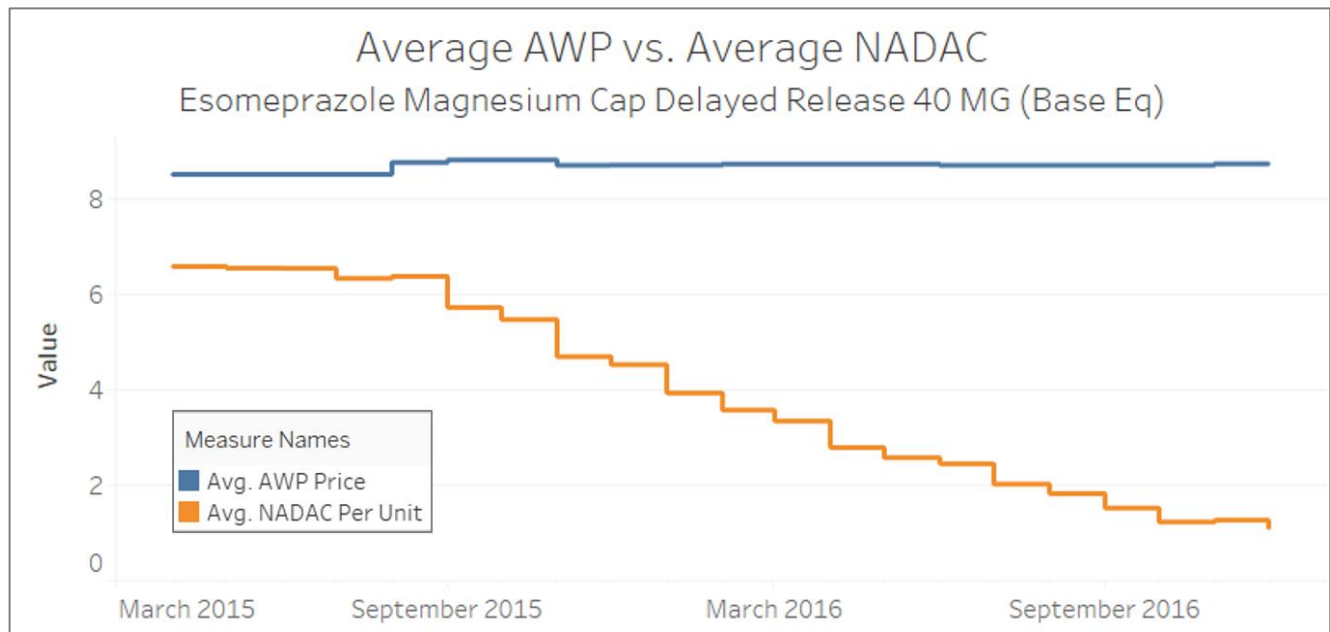
Table 6: Pricing per Unit of Generic Esomeprazole NDCs brought to market in 2015 and 2016

ANDA Number	Labeler	Marketing Start Date	NDC	Launch AWP	June 2019 AWP
078003	TEVA PHARMACEUTICALS USA	2/17/2015	00093645156	\$8.52	\$8.52
078003	TEVA PHARMACEUTICALS USA	2/17/2015	00093645198	\$8.52	\$8.52
078936	MYLAN	8/3/2015	00378235110	\$9.02	\$9.02
078936	MYLAN	8/3/2015	00378235193	\$9.02	\$9.02
202784	CAMBER PHARMACEUTICALS	9/21/2015	31722057310	\$8.52	\$8.52
202784	CAMBER PHARMACEUTICALS	9/21/2015	31722057330	\$8.52	\$8.52
202784	CAMBER PHARMACEUTICALS	9/21/2015	31722057390	\$8.52	\$8.52
078279	DR.REDDY'S LABORATORIES, INC.	9/25/2015	55111049330	\$9.02	\$9.02
203636	TORRENT PHARMACEUTICALS	10/19/2015	13668015510	\$8.52	\$8.52
203636	TORRENT PHARMACEUTICALS	10/19/2015	13668015530	\$8.52	\$8.52
203636	TORRENT PHARMACEUTICALS	10/19/2015	13668015590	\$8.52	\$8.52
078936	MYLAN	12/7/2015	00378235177	\$9.02	\$9.02
078279	DR.REDDY'S LABORATORIES, INC.	12/10/2015	43598051030	\$9.02	\$9.02
078279	DR.REDDY'S LABORATORIES, INC.	1/27/2016	43598051090	\$9.02	\$9.02
205606	AUROBINDO PHARMA	4/21/2016	65862078430	\$9.02	\$9.02
205606	AUROBINDO PHARMA	4/21/2016	65862078490	\$9.02	\$9.02
078279	DR.REDDY'S LABORATORIES, INC.	4/28/2016	43598051010	\$8.75	\$8.75
078936	MYLAN	5/31/2016	42292001001	\$8.51	\$8.51
078936	MYLAN	5/31/2016	42292001016	\$8.51	\$8.51

Source: Medispan PriceRx

Putting it all together, as shown in **Figure 34**, between April 2015 and December 2016, increasing competition drove esomeprazole’s NADAC per unit down 83% (\$6.59 to \$1.11). Against this backdrop, esomeprazole’s average AWP per unit **rose** 3% (\$8.52 to \$8.74).

Figure 34: Esomeprazole 40mg Capsule Average AWP vs. Average NADAC



Source: 3 Axis Advisors analysis based on data from Medispan PriceRx

It turns out that when it comes to the relatively unchanging nature of AWP, esomeprazole is not an outlier, but broadly representative of most generic drugs. To more broadly assess this dynamic, we isolated 7,863 generic oral solid NDCs dispensed in Medicaid in both Q1 2016 and Q1 2018. We

then counted the number of NDCs that experienced an increase, a decrease, or no change in AWP between the start and the end of the period. We then replicated the same analysis for NADAC.

Table 7 shows the results of our analysis. We found that 88% of all generic oral solid NDCs declined in NADAC between Q1 2016 and Q1 2018. Conversely, AWP of only 1% of the same NDCs saw reductions, while 96% went unchanged.

Table 7: Change in Price Benchmarks between Q1 2016 and Q1 2018 for Medicaid Generic Oral Solid NDCs

	AWP	NADAC
<i>Increase</i>	3%	9%
<i>No Change</i>	96%	2%
<i>Decrease</i>	1%	88%

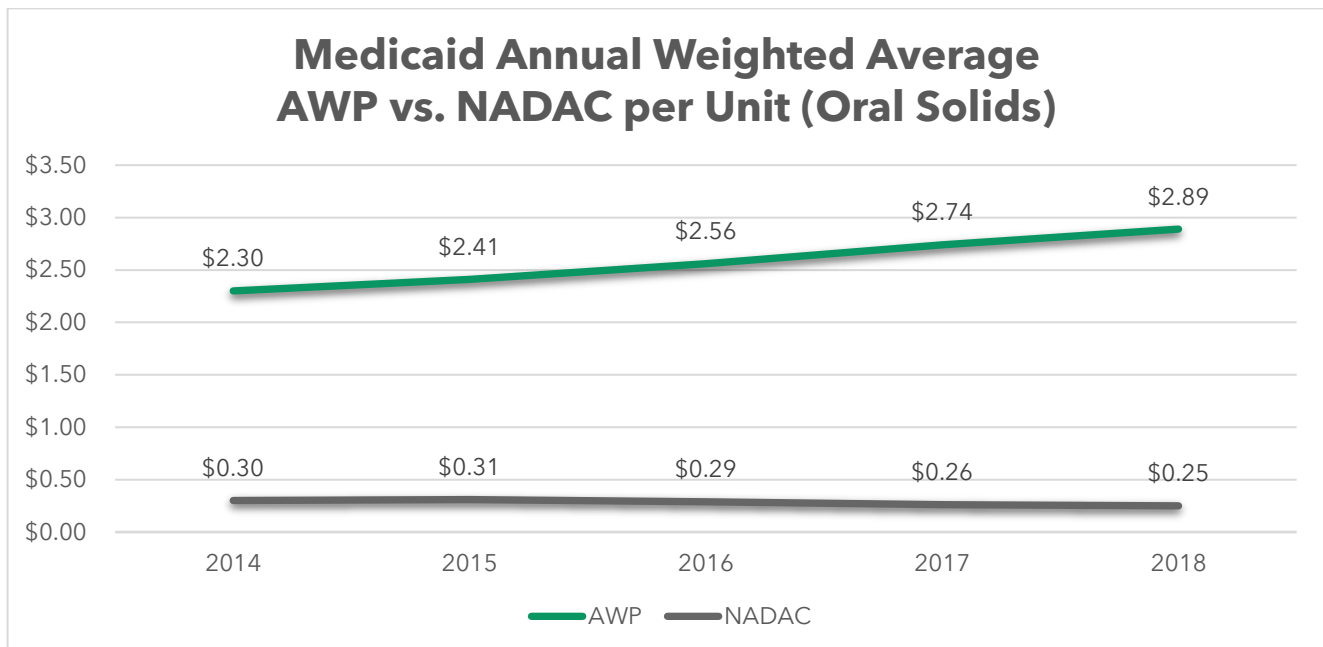
Source: 3 Axis Advisors analysis based on data from Data.Medicaid.gov and Medispan PriceRx

All told, the following factors have combined to drive aggregate AWP of generic drugs **up** during a time of material generic acquisition cost deflation:

- 1) Double digit brand-name drug AWP inflation^{cxci}
- 2) Modest discount of initial generic drug launch AWP to its equivalent brand-name drug
- 3) Clustering of manufacturer AWP around competitors^{cxci}
- 4) No downward movement of AWP with increasing competition

Our analysis of weighted average unit cost for all generic oral solids dispensed in Medicaid shows a 26% increase in unit AWP compared to a 17% decrease in unit NADACs (**Figure 35** on next page).

Figure 35: Medicaid Annual Weighted Average AWP vs. NADAC per Unit (Oral Solids)



Source: 3 Axis Advisors analysis based on data from Data.Medicaid.gov and Medispan PriceRx

11.2.3 The fallout of AWP-linked contracts – PBMs can set generic prices to optimize profit

As mentioned earlier, PBMs predominately use AWP as their basis for pricing generic drugs with their clients. They compete by offering payers steeper discounts to AWP, but all PBMs benefit from the inherent nature of aggregate generic AWP's to drift up over time. AWP is so critical to a PBM's business model that PBMs have noted that changes to this benchmark could have "a material adverse effect on ... business and results of operations." Here is the statement on AWP from the Express Scripts 2018 annual report: ^{cxcv}

"Contracts in the prescription drug industry, including our contracts with retail pharmacy networks and with PBM and specialty pharmacy clients, generally use "average wholesale price" or "AWP," which is published by a third party, as a benchmark to establish pricing for prescription drugs. In the event (i) AWP is no longer published by third parties, (ii) we adopt other pricing benchmarks for establishing prices within the industry or (iii) future changes in drug prices substantially deviate from our expectations, we can give no assurance the short- or long-term impact of such changes to industry pricing benchmarks or drug prices will not have a material adverse effect on our business and results of operations."

A generic drug is most profitable to the PBM starting when it goes multi-source. For esomeprazole, this would have been starting in late 2015, when Mylan and Camber came to market. As shown in **Figure 34** (on page 64), this is when the acquisition cost started to rapidly fall, taking the PBM's ingredient costs down with it. But as already discussed, clients locked into AWP discount contracts will not benefit from this acquisition cost decline, at least not until they renegotiate a new contract (with a steeper AWP discount) with their PBM – and even then, they could still be missing out on the savings due to drug mixes, mislabeling of drug categories, and/or if discounts don't keep pace with AWP inflation.

This, we believe, is the reason we see such disparity in pricing for drugs like esomeprazole within both Medicaid managed care and Medicare Part D. Different prices are set for different payers for the same generic drugs to optimize PBM profit and still satisfy contractual requirements to clients. Clients with better (or more recently renegotiated) contracts may receive better pricing, while clients on dated multi-year contracts may not see the benefit of much generic deflation at all.

This dynamic is explained very clearly by Decision Resources Group (DRG), a "premier provider of healthcare analytics, data and insight products and services." ^{cxcvi} DRG markets a package of "industry leading software products (that) power mission critical processes for some of the largest Plans and PBMs in the country." ^{cxcvii}

DRG Adaptive Software used to contain a module called RxPricing. While we do not know if the module has been discontinued, all information on the module has been expunged from DRG/Adaptive's website. However, we were able to find a description of the module using the Wayback Machine. ^{cxcviii} The module's description is very helpful in gaining a better understanding on how much latitude PBMs have in setting generic drug pricing for clients. Here is the company's marketing pitch for the module (emphasis added):

"We understand that the more plan sponsors you serve, the larger and more complex your pharmacy network. **Managing contracted pricing** across clients, delivery methods (retail, mail, specialty), coverage type (brand, generic, specialty), quantity, and price source are additional layers of complexity, leaving the average PBM to manage **nearly countless configurations**. We built RxPricing because we've seen first-hand that managing contractual obligations is too important to rely on an

industry-agnostic or home-built solution—and that for any modern PBM, this should not only be a core competency, but a true advantage. **RxPricing is relied upon by some of the most technology forward PBMs in the country.**

RxPricing also has a feature called “Re-Pricing Analytics.” Its description is also helpful in gaining better insight into PBM price setting practices (emphasis added, with sidebar to help translate PBM terms):

The re-pricing feature within RxPricing will help you **maximize your spread** by allowing you to create what-if scenarios and immediately see the financial impact of your changes. **Modify your MAC list** by GPI, GCN and GSN drug classification or **specify overrides at the NDC level**. Run real-time reports to calculate the current overall **effective rate** and projected overall effective rate to ensure you’re meeting your client and network guarantees.

In short, the innately distorted nature of generic AWP can be leveraged by the PBM to capture the market-driven deflationary benefits of generic drugs. In effect, the insertion of AWP into contracts undermines all benefits of competition between generic manufacturers. It allows the PBM to override market-clearing pricing for generics and set prices based on discounts to uncompetitive and stale pricing benchmarks.

11.2.4 Omeprazole pricing in Medicaid and Medicare

It is important to note that not all generic drugs have distorted pricing. Many inexpensive, mature generic drugs do not show substantive pricing distortions in federal and state programs. Over time, as PBMs increase aggregate discounts to AWP to retain clients, they must bring down pricing on existing generics to meet the more aggressive pricing guarantee. We have found that after spread has been harvested, PBMs will eventually drive down pricing of mature generics to levels below the pharmacy cost to dispense (roughly \$10 per prescription^{cxcix}).

Please note that this is simply a hypothesis we have formed through extensive analysis of Medicaid and Medicare generic pricing information. The data is not publicly available to conclusively test this hypothesis - disclosure of PBM spread profit by NDC would be required. We suspect we would find that the majority of PBM spread profit is derived from the minority of relatively new multi-source generic drugs.

Regardless, omeprazole is an example of a mature generic drug that is priced very competitively by PBMs in both Medicaid and Medicare. **Figure 36** shows the cost of omeprazole 40 mg capsules in Medicaid managed care and

DECODING PBM LINGO

“Maximize your spread”

According to CVS (in its 2018 10-K) spread is “difference between the drug price charged to the plan sponsor by a PBM and the price paid by the PBM to the dispensing provider”

“Modify your MAC list”

“MAC” stands for Maximum Allowable Cost. MAC rates are proprietary prices set by PBMs for drugs.

“Specify overrides at the NDC level”

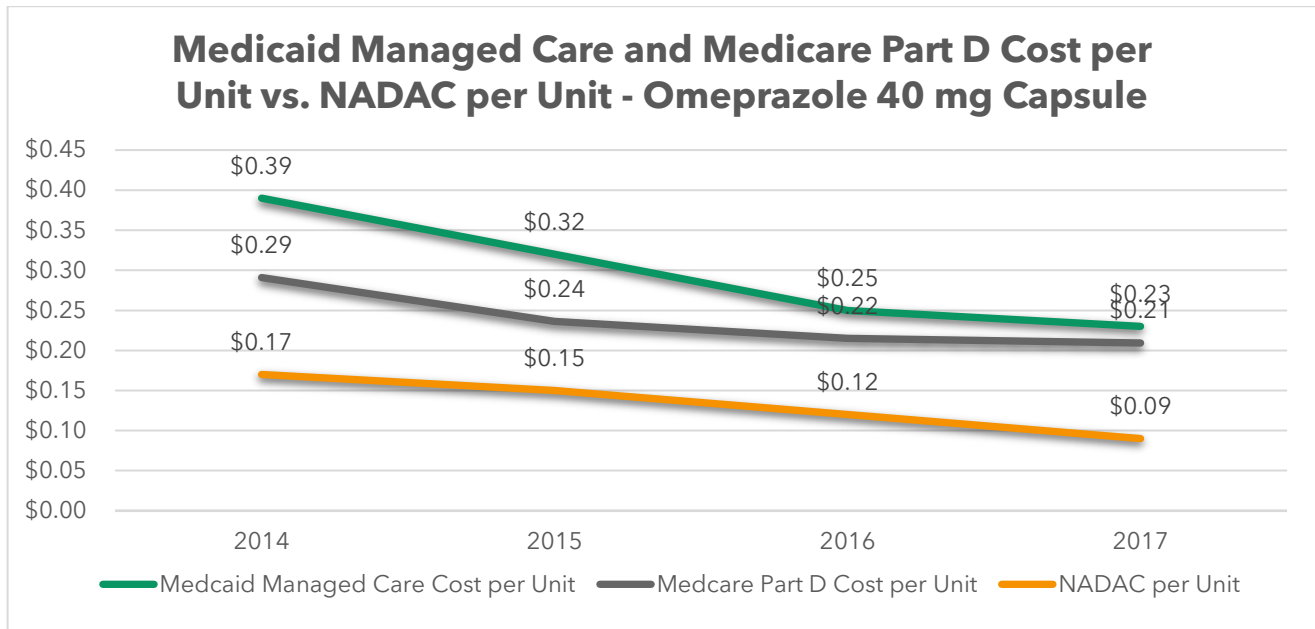
Without any regulation or oversight on MAC lists, there is nothing preventing the PBM from managing it to optimize profit. One way to do this is through “NDC overrides,” in which an NDC that is unfavorable for the PBM (one which it would lose money on) can be removed from the MAC list.

“Effective Rate”

“Effective Rate” is simply the discount to aggregate AWP. PBMs utilize both Generic Effective Rate and at times, Brand Effective Rate, in contracts.

Medicare between 2014 and 2018, compared to its NADAC per unit. The “markup” (i.e. difference between payer’s cost per unit and NADAC per unit) was only \$0.12 and \$0.14 in Medicare and Medicaid managed care, respectively. For a 30-day supply prescription, this translates to \$3.60 to \$4.20 in gross margin to be shared between the pharmacy and the PBM, considerably lower than a pharmacy’s typical cost to dispense.

Figure 36: Medicaid Managed Care and Medicare Part D Cost per Unit vs. NADAC per Unit (Omeprazole 40 mg Capsule)

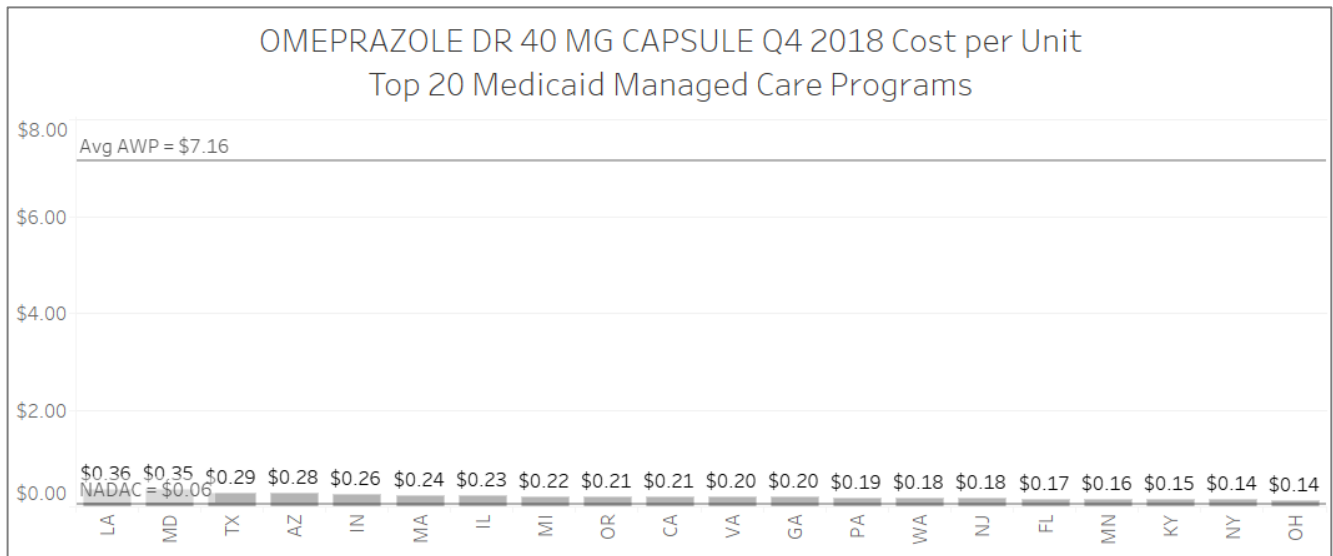


Source: 3 Axis Advisors analysis based on data from Data.Medicaid.gov and Medispan PriceRx

Of course, the figure above only presents overall weighted average costs. We need to drill deeper into both Medicaid managed care and Medicare to better understand the variability across both programs that, in our view, is driven by the quality of the payer’s contract.

Figure 37 (on next page) first presents the price reported per unit for omeprazole 40 mg tablets in the top 20 Medicaid managed care programs in Q4 2018. We have also included two reference lines on the chart - one denoting the average AWP per unit and the other denoting the NADAC per unit in Q4 2018. As shown below, there is some variation from state to state in pricing, but all states are being charged a very competitive rate for this mature drug.

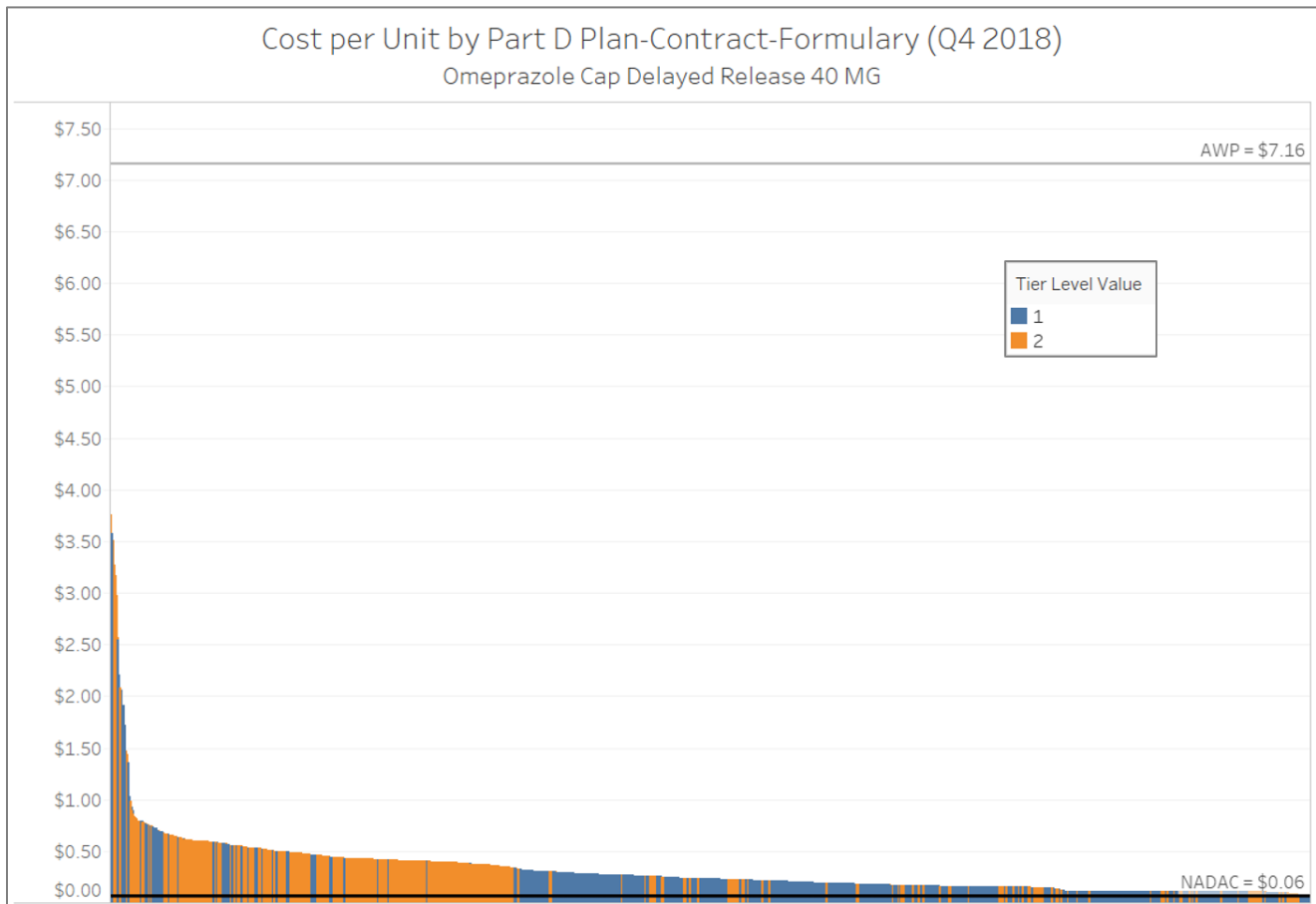
Figure 37: Cost of Omeprazole 40mg Capsules in Top 20 Medicaid Managed Care Programs (Q4 2018)



Source: 3 Axis Advisors analysis based on data from Data.Medicaid.gov and Medispan PriceRx

We then leveraged the work we performed with CMS’ Part D Prescription Drug Plan Formulary and Pricing Information Files,^{cc} from which we can calculate the cost per unit charged to each “unique plan” reported to Medicare for omeprazole 40 mg capsules. As shown in **Figure 38** (on next page), most Part D plans are getting very competitive pricing for omeprazole. However, we can also see some warning signs. There are outlier plans that reported retail costs north of \$2 per unit for this \$0.06 per unit mature generic.

Figure 38: Omeprazole 40mg Capsule Cost per Unit by Part D Plan (Q4 2018)

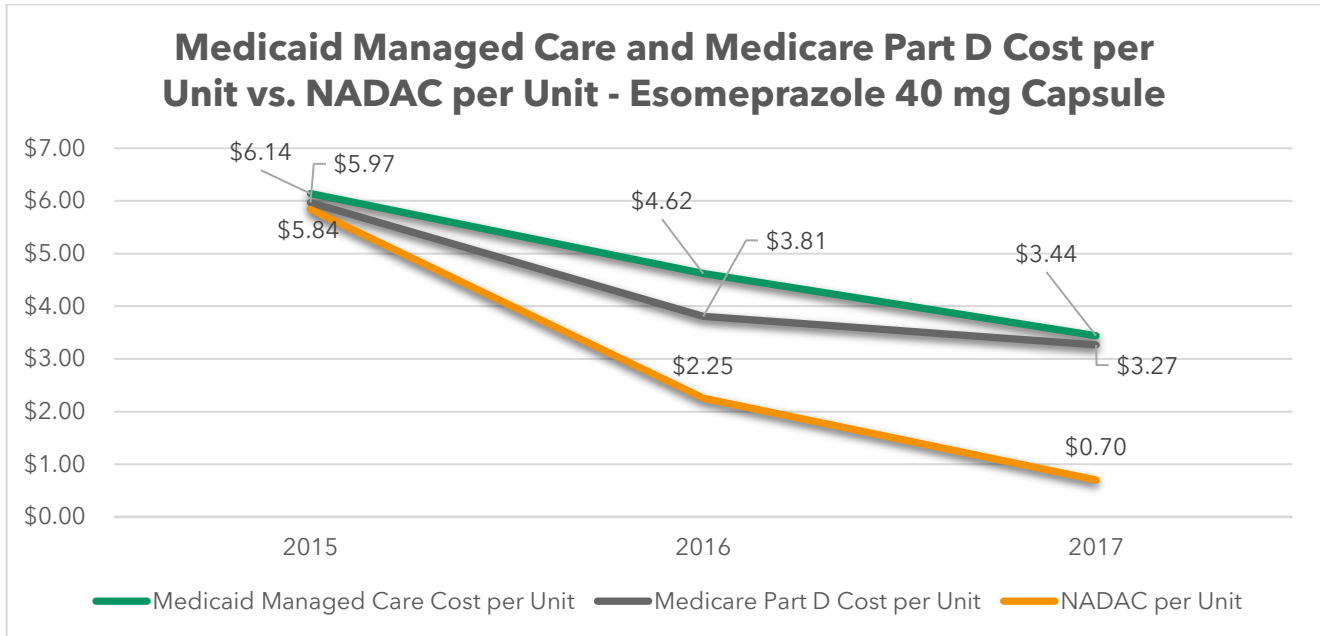


Source: 3 Axis Advisors analysis based on data from Data.Medicaid.gov, CMS.gov and Medispan PriceRx

11.2.5 Esomeprazole pricing in Medicaid and Medicare

Now let's contrast the largely efficient pricing on omeprazole with the pricing on its less mature "offspring," esomeprazole. **Figure 39** (on the next page) shows the weighted average cost of esomeprazole 40 mg capsules in Medicaid managed care and Medicare Part D. In 2017, the markup on esomeprazole was \$2.57 per unit in Medicare and \$2.74 per unit in Medicaid managed care. For a 30-day supply, that translates to \$77.10 to \$82.20 in gross margin that is essentially shared between the PBM and pharmacy provider. This amount far exceeds a pharmacy's typical cost to dispense and a PBM's cost to administer the benefit.

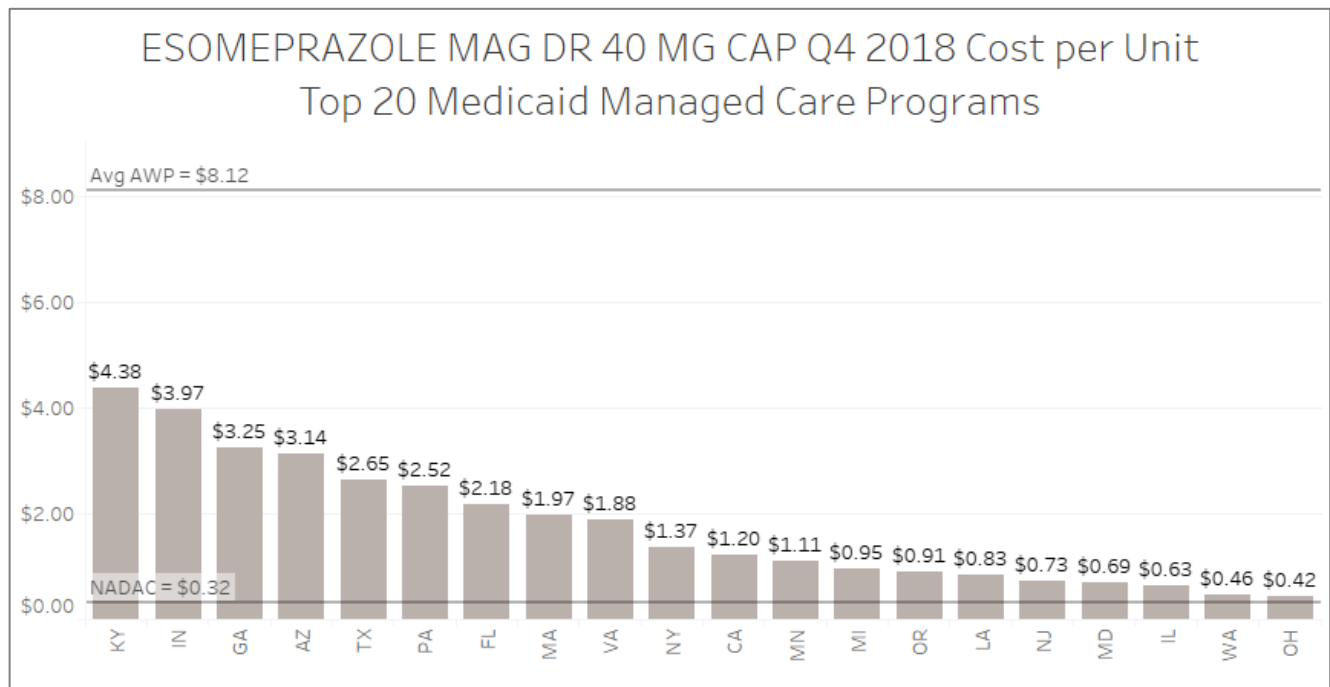
Figure 39: Medicaid MCO and Medicare Part D Cost per Unit vs. NADAC per Unit (Esomeprazole 40 mg Capsule)



Source: 3 Axis Advisors analysis based on data from Data.Medicaid.gov, CMS.gov and Medispan PriceRx

We then replicated the same drill-down analysis presented earlier for omeprazole. **Figure 40** shows the cost per unit reported by the same top 20 Medicaid managed care programs in Q4 2018 for esomeprazole 40 mg capsules. This picture paints a vastly different story – states are reporting anywhere between \$0.42 and \$4.38 per unit for a drug that cost pharmacies **at most** \$0.32 to acquire.^{cci}

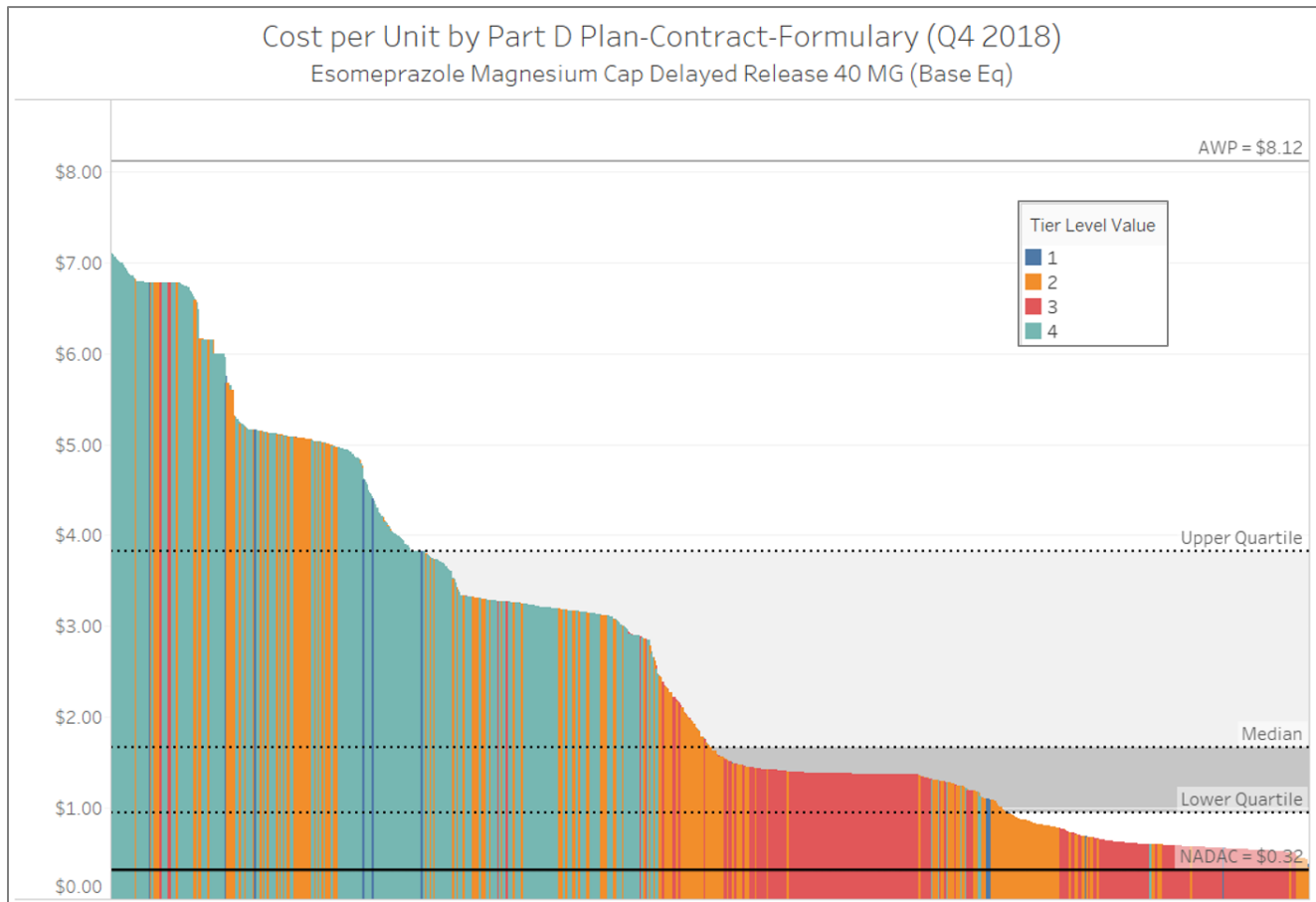
Figure 40: Cost of Esomeprazole 40 mg Capsules in Top 20 Medicaid Managed Care Programs (Q4 2018)



Source: 3 Axis Advisors analysis based on data from Data.Medicaid.gov and Medispan PriceRx

As shown in **Figure 41**, Part D shows the same wide variation in pricing across plans in Q4 2018. Plans are reporting pricing that ranges from a modest markup to NADAC, to over \$7 per unit. Quite disturbingly, plans that place the drug on Tier 4 are also pricing the drug the highest, at \$4.37 per unit, unnecessarily subjecting beneficiaries to higher cost-sharing on this inexpensive generic drug. For comparison, plans that placed this drug on Tiers 1-3 collectively priced it at \$1.73 per unit.

Figure 41: Esomeprazole 40 mg Capsule Cost per Unit by Part D Plan (Q4 2018)



Source: 3 Axis Advisors analysis based on data from Data.Medicaid.gov, CMS.gov and Medispan PriceRx

11.2.6 Incentives driving generic pricing distortions

In this subsection, we will provide a brief review of the incentives that we believe are driving pricing distortions of drugs like esomeprazole. We have divided the discussion into two sections, Medicaid managed care and Medicare Part D, as we believe the incentives in the two programs are different.

11.2.6.1 Medicaid managed care

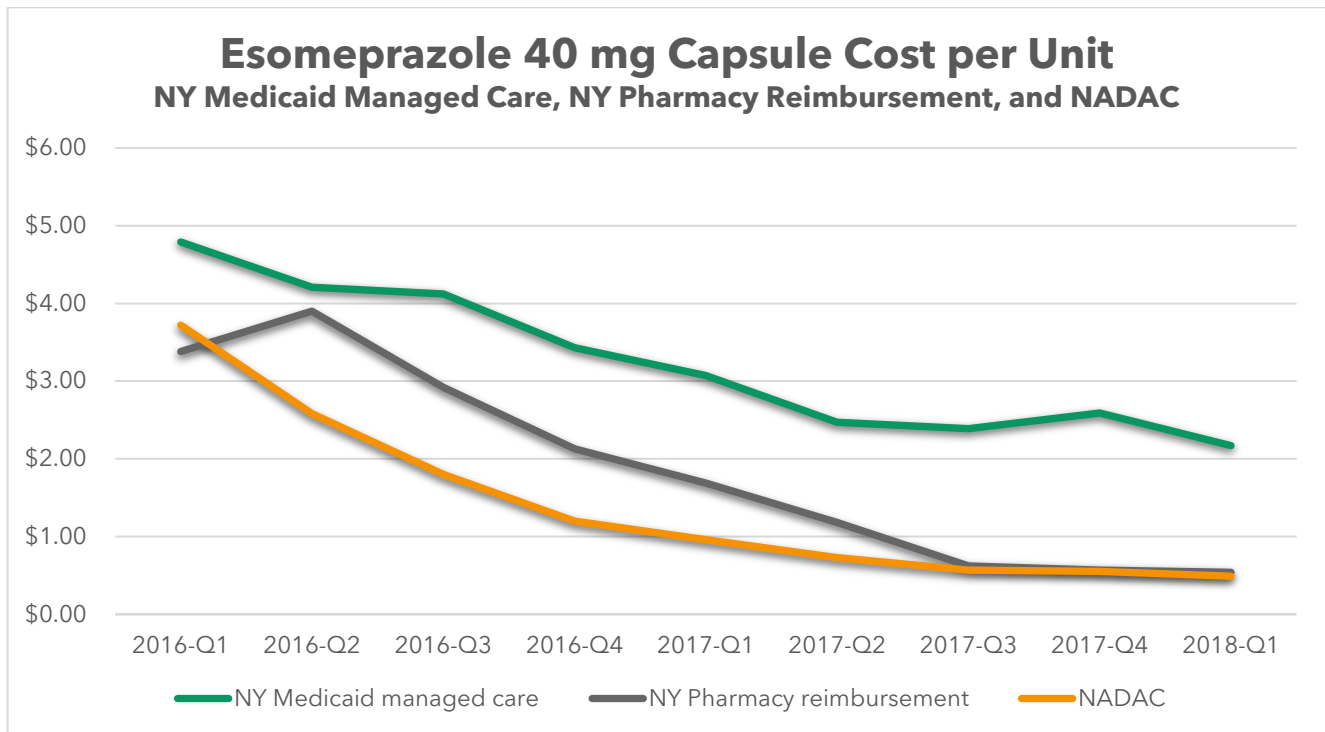
In Medicaid managed care, the primary incentive driving mispricing of generic drugs is PBM spread. According to CVS, spread is the “difference between the drug price charged to the plan sponsor by a PBM and the price paid by the PBM to the dispensing provider.”^{ccii}

States have started to investigate spread pricing in their Medicaid managed care programs. Ohio was the first to release a full audit of its program, finding \$225 million over a 12 month period - \$208 million of which taken from generic claims (31% of total generic spending).^{cciii} Earlier this year,

Kentucky released spread reported by its Medicaid managed care organizations (MCOs) and found \$124 million over a recent 12-month period.^{cciv} A few months later, Bloomberg reported that Georgia found that just one MCO (Peach State, a Centene company) reported \$30 million of spread in a recent 12-month period.^{ccv}

Our analysis suggests that esomeprazole is a spread drug. As part of a project we performed for the Pharmacists Society of the State of New York (PSSNY), we collected data from 11 pharmacies and matched their reimbursements with both NADAC and managed care cost per unit.^{ccvi} **Figure 42** shows the results of this analysis for esomeprazole 40 mg capsules - spread (the difference between the orange and red lines) increased dramatically over the study period. By the end of the 2017, the PBM/MCO was retaining all gross margin associated with this generic drug.

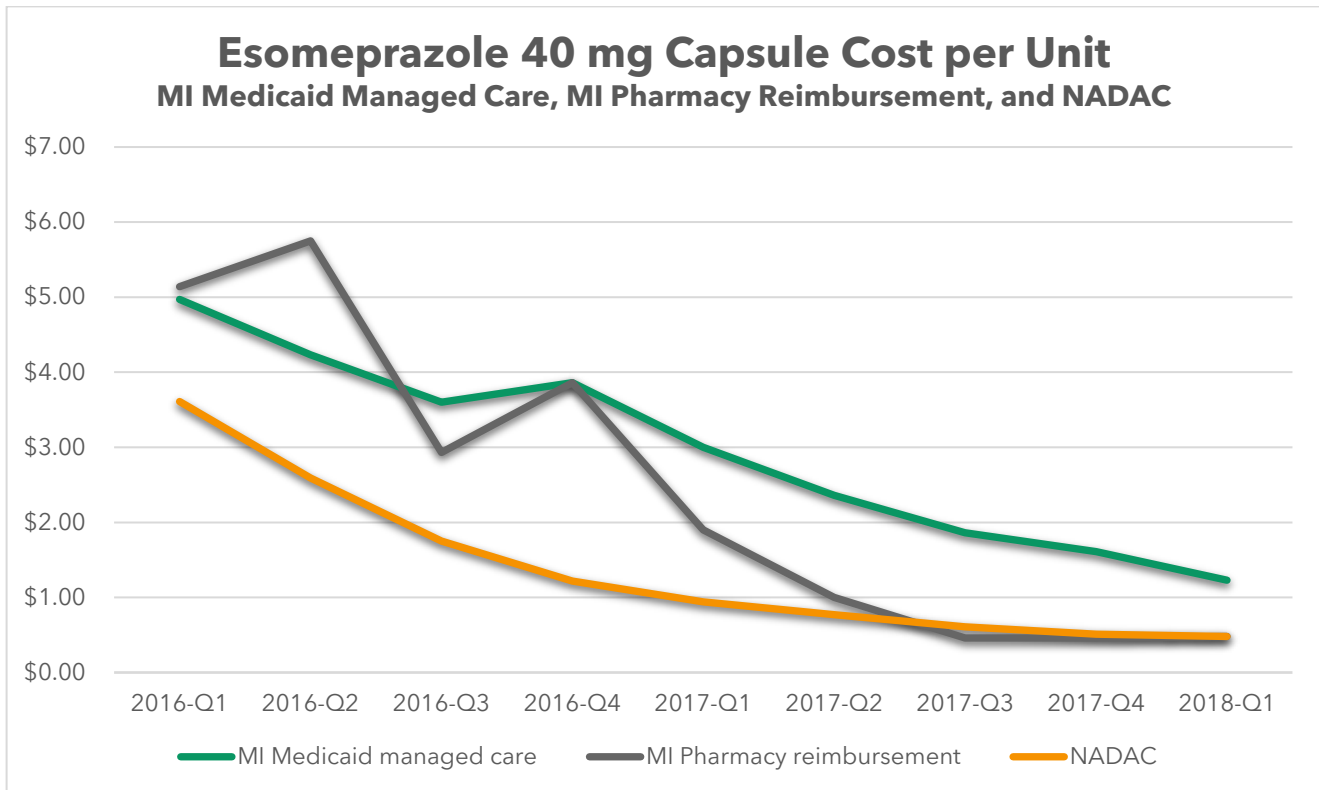
Figure 42: Esomeprazole 40 mg Cost Comparison - NY Medicaid Managed Care



Source: 3 Axis Advisors

One of the main limitations of our work in New York was the limited sample of pharmacy claims we were able to obtain. Our work in Michigan did not have that same limitation - working with SRS Pharmacy Systems, we collected de-identified, de-localized data from 451 pharmacies in Michigan.^{ccvii} **Figure 43** (on the next page) presents the same comparison for Michigan, also showing significant spread developing on this drug in 2017.

Figure 43: Esomeprazole 40 mg Cost Comparison - MI Medicaid Managed Care



Source: 3 Axis Advisors

It is also unclear the extent to which managed care organizations are incentivized to prevent this dynamic from occurring, especially as more managed care insurers merge with (or start their own) PBMs. If actuaries are using the same distorted costs set by the PBM to arrive at capitation rates, it could possibly benefit the MCO to not challenge (or even prefer) inflated generic costs, as they ultimately will help inflate the medical claims component of the medical loss ratio.

CMS recently took steps to resolve this by prohibiting spread from being included within incurred claims by managed care plans. However, we are concerned that without enforcing reference-based pricing (e.g. NADAC, AAC) within Medicaid managed care, there may not be a favorable cost impact with this change as PBMs can simply alter generic pricing to ensure that MCO capitation rates do not meaningfully decline.

There are also other mechanisms for PBMs to achieve the same results of spread pricing without directly using spread pricing in Medicaid. PBMs can put pharmacies in “effective rate” contracts, form a network consisting of multiple different payers (one of which is Medicaid managed care) and then manage the pharmacy network to an aggregate effective rate that is more aggressive (e.g. AWP minus 87%) than the aggregate effective rate of its collection of payers (e.g. AWP minus 82%). If PBMs cannot spread price in one plan (say, Medicaid) within the network, they conceptually can offset that by more aggressive spread pricing in other plans that are part of the same network (say, commercial plans) to maximize the effective rate spread.

The key takeaway is that as long as generic drugs are priced based on AWP, and the PBMs are paid based on a percentage of generic AWP, there will always be generic drug pricing distortions that can be exploited to maximize PBM and plan profitability.

11.2.6.2 Medicare Part D

We believe that we see generic pricing distortions in Part D for the same reason that we see over-dispensing of higher cost brands viz-a-viz generics - the Part D cost share structure and rebates. Ultimately, LIS and federal reinsurance work the same way for higher costs generics as they do for brand drugs - both components of Part D reduce the Part D plan share of dispensing high list-cost drugs, thereby reducing the incentive to strictly manage the formulary to reduce their utilization.

And there are rebates on generic drugs as well that could create the incentive to dispense the higher cost generics. Except unlike with brands, these rebates do not come from manufacturers, they come from network pharmacies in the form of Pharmacy Direct and Indirect Remuneration (DIR) fees.

DIR fees collectively represent the “various payments made by drug companies and pharmacies to PDPs and PBMs after the sale” and include “drug companies’ rebates, pharmacies’ fees, and other forms of price concessions.”^{ccviii} For brand-name drugs, most DIR comes in the form of manufacturer rebates, the implications of which we have already discussed in detail in the “Brand over Generic” section. However, for generic drugs, DIR is collected from pharmacies, most often as a percentage of the PBM/Plan-set ingredient cost (which as covered earlier, can be substantially higher than the drug’s acquisition cost).

Many plans incorporate a performance/outcomes component into their assessment of DIR fees. For example, one of the largest Plan Sponsor’s Part D Preferred Retail Network assesses a DIR fee of 5-7% of ingredient cost paid based on the following criteria:

- Cholesterol PDC
- Diabetes PDC
- RASA PDC
- Statin Use in Diabetes
- CMR Completion Rate (MTM)
- Formulary Compliance
- Specialty Adherence

The better the pharmacy’s performance across this collection of criteria, the lower the fee that is assessed.

However, not all plans manage a sliding DIR fee scale based on performance criteria. For example, Aetna manages its DIR by adjusting pharmacies to a generic effective rate (GER). In 2018, its Aetna/Coventry Medicare Standard Network set pharmacy payments on each generic claim at an 86% discount to AWP. If Aetna overpaid the claim at the point of sale, they simply adjusted the pharmacy retroactively (using DIR) to an AWP minus 86% payment rate. Our analysis of 2020 Part D contracts suggests that such a GER-based DIR construct is being adopted by other plan sponsors as well.

To illustrate this dynamic in action, we obtained 2018 Aetna Part D claims from nearly 1,000 community pharmacies. **Table 8** (on next page) shows the relevant statistics for the 190 claims filled for esomeprazole 40 mg capsule.

Table 8: Aetna Part D esomeprazole 40 mg capsule Pharmacy Adjudicated Payment and DIR fees

Pricing Metric	Cost per Unit	Comments
AWP	\$8.65	
Ingredient Cost Paid (Point-of-Sale)	\$4.21	51% discount to AWP
Retroactive DIR fee	(\$3.00)	Calculated to true pharmacy up to 86% discount to AWP
Net Ingredient Cost Paid	\$1.21	86% discount to AWP
Dispensing Fee Paid (Point-of-Sale)	\$0.02	
Net Reimbursement	\$1.23	
NADAC	\$0.45	
Net Reimbursement less NADAC	\$0.78	Pharmacy gross margin assuming NADAC as a proxy for acquisition cost

Source: 3 Axis Advisors analysis of 2018 pharmacy claims data

There are a few important observations in this table:

- Aetna pays a sizable premium to the pharmacy at the point of sale
 - \$4.21 per unit, which is only a 51% discount to AWP
- Aetna then retroactively takes back \$3.00 of the \$4.21 to adjust the pharmacy to an 86% discount to AWP
 - **This is effectively a 71% rebate for the PBM/plan**
- Assuming NADAC as acquisition cost, the pharmacy still makes \$0.78 per unit. However, the pharmacy’s software does not show the DIR fee at the point of sale, so the pharmacy **believes** it is making \$3.78 per unit on this claim.

Now let’s contrast this with omeprazole (**Table 9**):

Table 9: Aetna Part D omeprazole 40 mg capsule Pharmacy Adjudicated Payment and DIR fees

Pricing Metric	Cost per Unit	Comments
AWP	\$6.88	
Ingredient Cost Paid (Point-of-Sale)	\$0.22	97% discount to AWP
Retroactive DIR fee	\$0.74	Calculated to true pharmacy up to 86% discount to AWP
Net Ingredient Cost Paid	\$0.96	86% discount to AWP
Dispensing Fee Paid (Point-of-Sale)	\$0.02	
Net Reimbursement	\$0.98	
NADAC	\$0.08	
Net Reimbursement less NADAC	\$0.90	Pharmacy gross margin assuming NADAC as a proxy for acquisition cost

Source: 3 Axis Advisors analysis of 2018 pharmacy claims data

For omeprazole, Aetna set the point of sale reimbursement at just \$0.22 per unit, a 97% discount to AWP, and nearly \$4 per unit lower than esomeprazole, which again, it chose to price at just a 51% discount to AWP. As a result, Aetna, through differential pricing of two therapeutic alternatives, is providing the pharmacy the incentive to dispense a drug that inflates both Medicare Part D point of sale costs and DIR.

Interestingly, the pharmacy's net reimbursement less NADAC ends up being higher for omeprazole, but there is no way for the pharmacy to know that at the point of sale.

We must reiterate that for generic drugs, Aetna and its affiliated PBM (Caremark) completely control the point of sale ingredient cost. Aetna/Caremark can choose to set a very high ingredient cost (as was the case with esomeprazole), or a low ingredient cost (as was the case with omeprazole), incentivizing pharmacies to work with physicians to switch patients to drugs with high point of sale reimbursements. In this GER-based structure, the higher the ingredient cost, the higher the DIR fee (i.e. rebate) that goes back to Aetna/Caremark. **Higher rebates get channeled into reducing member premiums, while higher list costs are subsidized by the federal government.** This is nearly identical to the warped incentives in Part D to prefer high cost/high rebate brand-name drugs, except potentially even more pernicious given that the PBM can unilaterally set the list price so long that it meets its overall generic pricing contract guarantee to the health plan. Although, such a guarantee is becoming increasingly meaningless in a vertically integrated enterprise like CVS Health, which owns all three players involved in the claim (insurer, PBM, and pharmacy).

This is the reason why we believe modification of federal reinsurance is the most important policy change the federal government should tackle in Part D. By holding plans responsible for ingredient costs, we would expect plans to start to push back on high PBM-set ingredient costs, rather than embrace them. We believe there is a strong argument to be made for pharmacy quality incentive programs, but such programs should be tied to controllable pharmacy actions that plans want to encourage to drive better outcomes and lower costs. Most importantly, DIR fees and/or PBM/pharmacy incentives should never be set as a percentage of ingredient costs as it creates the obvious incentive for higher ingredient costs.

12 KEY LEARNINGS

After exhaustive research and analysis on Nexium, we recognize that this is only one of many cases of the U.S. drug supply chain delivering questionable value relative to cost. Billions of dollars were spent on something flagged within its initial review as no more efficacious than the medication it was designed to replace. To this end, we believe that the knowledge gained within this case study can inform a broader discourse on U.S. drug spending. Specifically, we believe enough evidence exists that demonstrates the following:

1. The approval of new drugs within the U.S. fails to adequately assess the value that new therapies provide to the healthcare system. Approving drugs based on safety and efficacy alone provides drug manufacturers with the incentive to bring to market line extensions that may be slightly more beneficial than currently available treatments, but with price tags that far exceed their incremental value. Meanwhile, in many instances, PBMs and health plans not only lack the proper incentives to block utilization on drugs like Nexium, but they have the financial incentive to actually promote their usage (i.e. rebates). In our view, **one of the primary drivers of rising U.S. drug costs are the lack of proper incentives for 1) manufacturers to exclusively focus their efforts on the development of innovative new therapies with exceptional value propositions; and 2) PBMs, health plans, and providers to discourage utilization of poor cost/benefit drugs.**
2. The use of artificial prices allows the supply chain to incentivize the use of one medication over another in ways not necessarily commensurate with a drug's relative value. Nexium offered a 75% discount off its list price to incentivize its use over its U.S. competition (brand and generic). Similarly, reliance on AWP-based payment models for generic medications obscures the savings generic medications could otherwise provide to both patients and payers. Such pricing distortions are very concerning in our view. They provide a means for the drug supply chain to disproportionately profit off the volume of drugs dispensed, creating the incentive to dispense more drugs rather than to create better outcomes. In our view, **the current design of the U.S. drug supply chain is highly reliant on sick people to generate rebates, price concessions, and pricing spreads that can then be used to help subsidize premiums for healthy people and generate excess profits for shareholders.**

We highly recommend that policymakers fix these glaring, perverse incentives embedded at the core of the U.S. prescription drug supply chain.

13 ACKNOWLEDGEMENTS

This research project started out in an innocuous manner – simply wanting to understand how \$1+ billion worth of brand-name Nexium was bought and paid for by Medicare Part D in 2016. But the journey to sufficiently answer this question ended up being much more onerous than we expected, taking nearly a year of research, analysis, writing, and editing to complete.

It goes without saying that we could not have devoted even a fraction of the time spent on this project had it not been for the financial support of **Arnold Ventures**. We are immensely grateful for organizations like Arnold Ventures, as if it were not for them, there would be little funding available for exploratory research and analysis of the U.S. prescription drug supply chain.

We would also like to thank **Waxman Strategies**, who provided invaluable support and guidance throughout as we trudged through the many months of this work. We look forward to working with Waxman to help break down this narrative into easier-to-digest issue briefs.

Additionally, we would like to thank the many pharmacies across the country who have voluntarily turned over pharmacy claims data to help us better understand the dynamics at play in the supply chain for this report and our previous work as well.

We would also like to thank the many members of the media, whose work created a general timeline for us to follow as we delved into the complexities and nuances of the entire Nexium story. If not for the important work of journalists, much of this research would not have been possible.

Lastly, we would like to thank two organizations for assisting us with data and analytical expertise required to study and understand some of the more esoteric topics in this report:

- **Johns Hopkins Drug Access and Affordability Initiative**, who assisted us with the PPI cost share split in Medicare Part D
- **American Pharmacy Cooperative Inc.**, who assisted us in understanding pharmacy DIR fees

14 ABOUT 3 AXIS ADVISORS

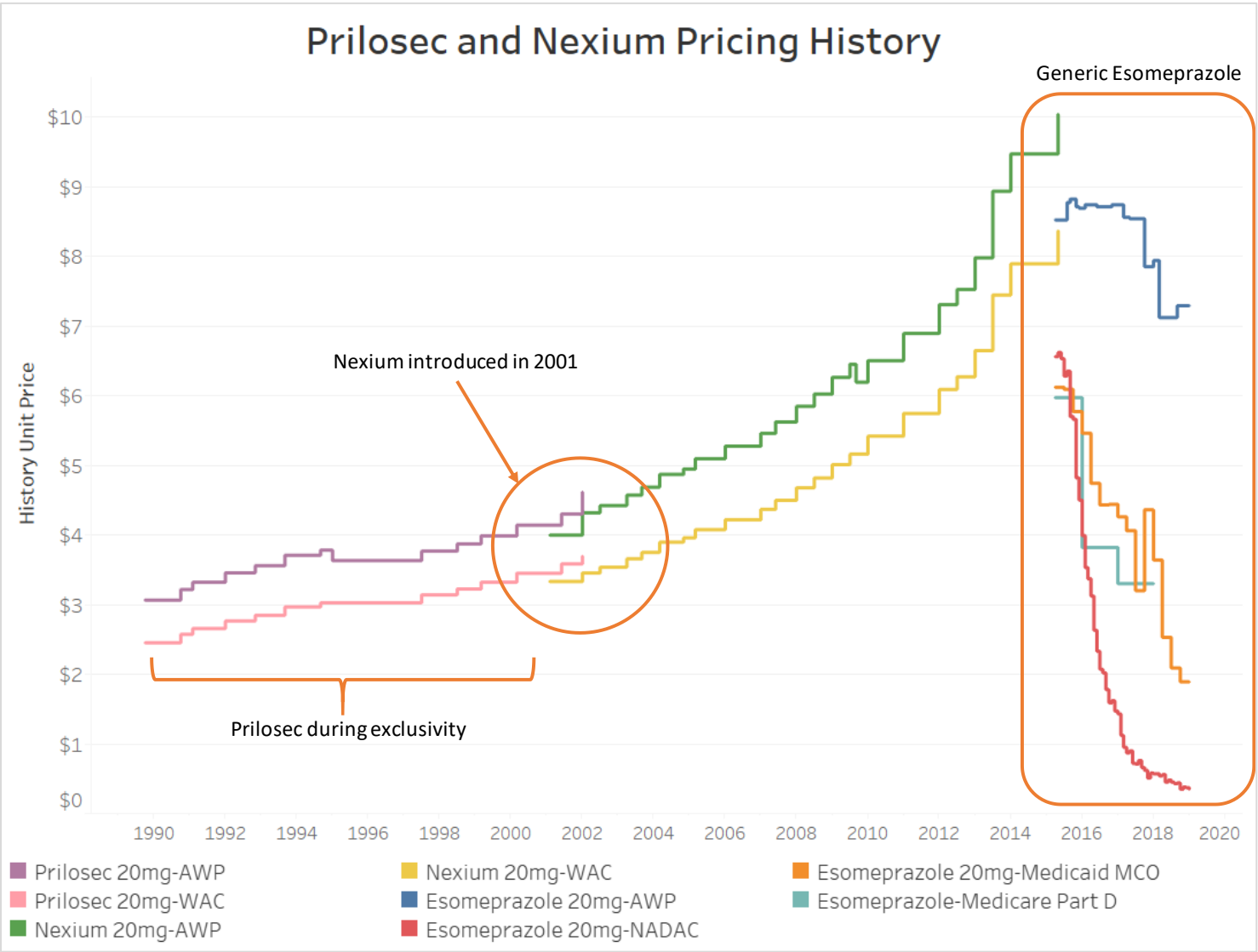
3 Axis Advisors is an elite, highly specialized consultancy that partners with private and government sector organizations to solve complex, systemic problems and propel industry reform through data-driven advocacy. With a primary focus on identifying and analyzing U.S. drug supply chain inefficiencies and cost drivers, 3 Axis Advisors offers unparalleled expertise in project design, data aggregation and analysis, government affairs and media relations.

3 Axis Advisors arms clients with independent data analysis needed to spur change and innovation within their respective industries. Co-founders Eric Pachman and Antonio Ciaccia were instrumental in exposing the drug pricing distortions and supply chain inefficiencies embedded in Ohio's Medicaid managed care program. They are also the co-founders of 46brooklyn Research, a non-profit organization dedicated to improving the transparency and accessibility of drug pricing data for the American public.

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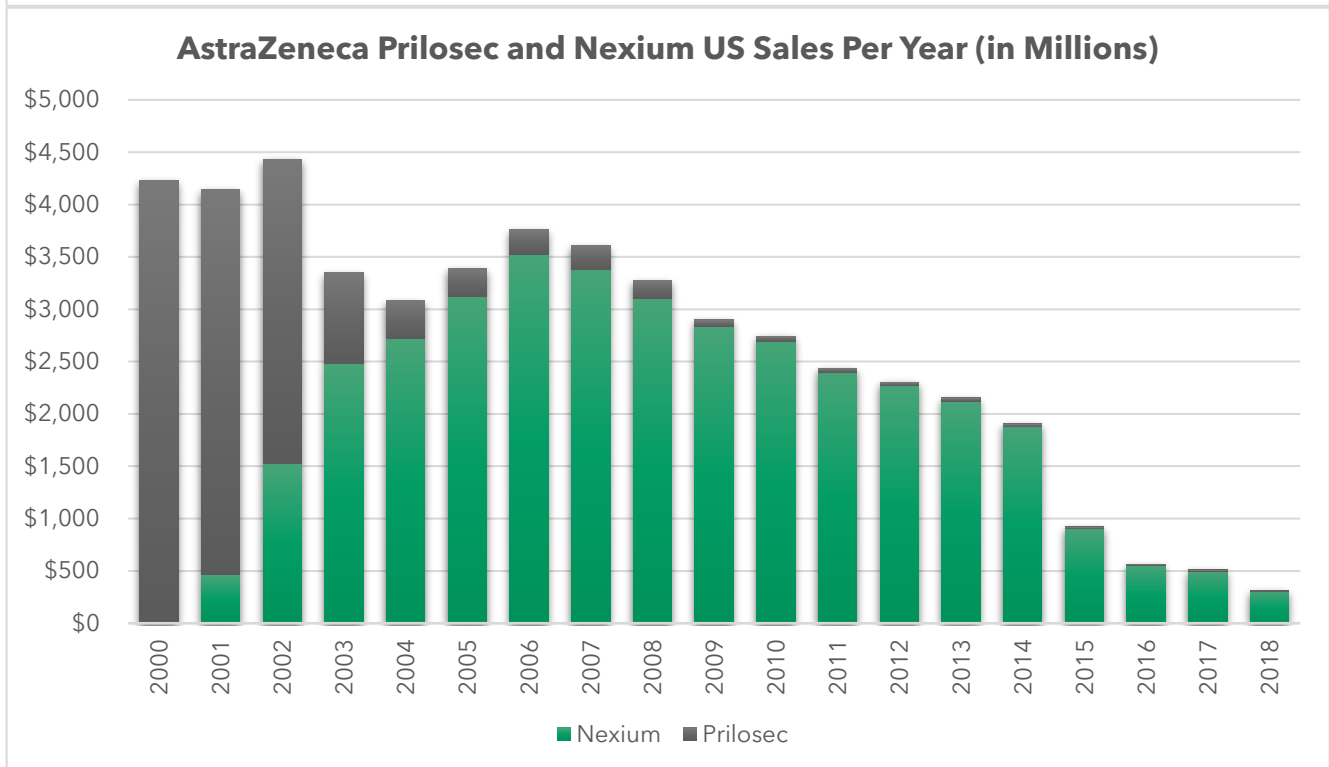
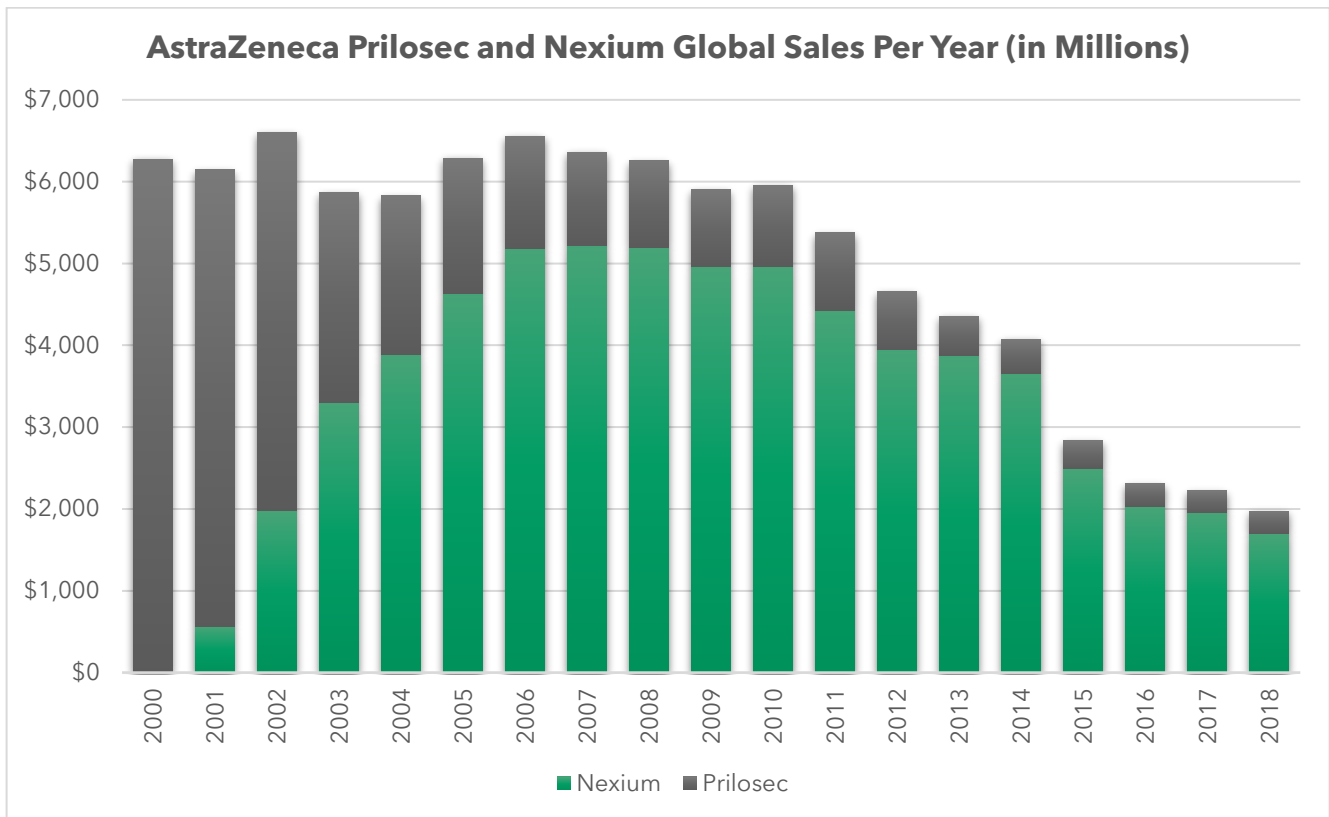
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15 APPENDIX A: PRICING HISTORY OF THE OMEPRAZOLE MOLECULE (1990 – 2018)



Source: 3 Axis Advisors, created from pricing data obtained from MediSpan PriceRx and Data.Medicaid.gov

16 APPENDIX B: ASTRAZENECA'S PRILOSEC AND NEXIUM SALES (2000-2018)



Source: AstraZeneca annual reports (2000-2018)

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