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Trends in Prices of Insulin Marketed in the US

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Trends in Prices of Insulin Marketed in the US

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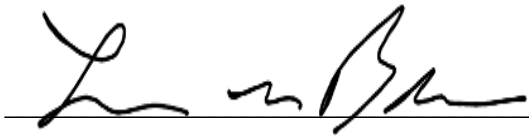

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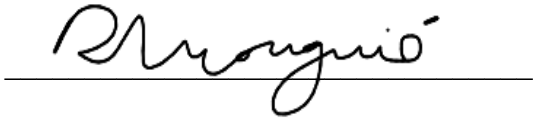

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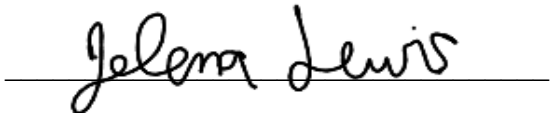

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ABSTRACT

Trends in Prices of Insulin Marketed in the US

by Hana A. Althobaiti

INTRODUCTION: Diabetes mellitus is one of the most prevalent and costly chronic diseases in the United States (US). The healthcare and drug cost of diabetes has risen steadily and the increase in patients' out-of-pocket drug expenditures are associated with a reduction in treatment adherence. The objectives of this study were to assess trends in insulin products prices in the period January 1983-July 2019, and to compare the price, acquisition costs and reimbursement amount of insulins available in the US.

DATA AND METHODS: Data of insulin products marketed in the US during the period January 1983-July 2019 was derived from the FDA databases, the RedBook online, Medicaid.gov, the Department of Veterans Affairs, and the Centers for Medicare & Medicaid Services. Prices were adjusted using the consumer price index (CPI). The compounded average group rate (CAGR) was calculated for each insulin product. Data was analyzed by summary descriptive statistics.

RESULTS: Human insulins had a CPI-adjusted AWP CAGR ranging 4.89%-8.89% from the first AWP effective date to July 2019 and insulin analogues had a CPI-adjusted AWP CAGR ranging 9.5%- 9.75%. The 2 follow-on (biosimilar) insulins; long-acting insulin glargine and rapid-acting insulin lispro experienced a negative adjusted CAGR (-1.20%, -33.70%, respectively). Insulin acquisition cost and reimbursement amounts showed a large variation when compared with the average wholesale (AWP) prices. The wholesale acquisition cost (WAC) was typically set at 83.33% of the AWP. Community pharmacies acquired insulins and analogues at a median of 80.27% of the AWP. Significant reductions in AWP were observed for Medicare Part D (78.80% of the AWP), and Federal Supply Schedule (FSS) /Big4 (25.89%).

CONCLUSION: Manufacturer prices of insulins and analogues increased significantly during the period of 1983- July 2019. There are significant differences in the manufacturer prices, pharmacy acquisition costs and reimbursement rates of insulins and analogues.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACA: Affordable Care Act

ATC: Anatomical Therapeutic Chemical

AWP: Average Wholesale Price

CAGR: Compound Annual Growth Rate

CMS: Centers for Medicare & Medicaid Services

CPI: Consumer Price Index

DDD: Defined Daily Dose

FDA: Food and Drug Administration

FSS: Federal Supply Schedule

NADAC: National Average Drug Acquisition Cost

NDC: National Drug Code

NPH: Neutral Protamine Hagedorn

US: United States

WAC: Wholesale Acquisition Cost

WHO: World Health Organization

1. INTRODUCTION

Diabetes mellitus is one of the most prevalent and costly chronic diseases in the United States (US). It was estimated that 9.7% of the US adult population had a diagnosis of diabetes mellitus in 2017.[1]The total health care cost of diagnosed diabetes was estimated at $327 billion in the US in 2017.[2] This cost included $237 billion in direct costs and $90 billion in indirect costs. Similar to estimates in 2007 and 2012, patients who were diagnosed with diabetes spent 2.3 times more in health care compared with those without diabetes. Between 2002 and 2011 patients with diabetes had significantly higher health expenditures than those without diabetes and the leading causes of high expenditures were hospitalization and medications.[3] Furthermore, from 2012 to 2017 the healthcare cost of diabetes increased by 26% due to the increased prevalence of diabetes and the increased cost per person with diabetes.[2]

The cost of diabetes has risen steadily in the past decades due to a combination of factors, including the increasing number of patients, the growing complexity of care, and the high prices of antidiabetic drugs.[4,5] The high prices of new antidiabetic drugs also result in formulary restrictions that restrict access to care and increase the administrative burden and the cost of providing diabetes care.[6,7] In 2011, one-fourth of patients with diabetes had high family out-of-pocket expenditures burden; the median out of pocket costs per prescription for all insulins increased from $19 in 2000 to $36 in 2010.[8] Increasing patient's out-of-pocket expenditures is associated with a significant reduction in adherence to drug therapy.[7,9-11]

Insulin is widely used today in patients with type 1 or type 2 diabetes and is arguably the most effective and predictable of all of the current antihyperglycemic agents. The cost of insulin treatment is high, and the growing number of patients with diabetes using insulin presents a financial challenge to health care payers and patients. The total cost of insulin and other antidiabetic medications increased by 45% from 2012 to 2017, and the inflation-adjusted cost of insulin increased by 110% during the same period.[2] A recent study found that the estimated expenditures per patient for insulin increased in 2013 in the US compared with oral antihyperglycemics based on a nationally represented survey.[12]

The price of insulin for government programs have also increased. The Center for Medicare and Medicaid Services (CMS) estimated that 32% of all Medicare spending could be attributed to patients with diabetes.[9] Medicare Part D spending on insulins has shown an increasing and accelerating trend. As spending on insulins has increased, so too have patient out-of-pocket costs.[13] Between 2007 and 2017, average out-of-pocket costs per insulin user among Medicare Part D enrollees increased fourfold for insulin. Comparatively, Medicare Part D spending per insulin increased by 280% over the same period.[14]

The Affordable Care Act (ACA) was passed by Congress and signed into law by President Obama in 2010. One of the main motivating reasons for this act was to provide health insurance to approximately 40 million Americans who were not covered by some insurance. It was also designed to address specific deficiencies in the healthcare system. [13] A published study in 2018 concluded that health insurance coverage among adults with

diabetes age 18–64 years increased significantly after implementation of the ACA, and medical costs to families decreased, especially among those with lower incomes. [15]

The increase in the cost of antidiabetic drugs has important clinical implications such as low adherence to these medications.[16] Adherence to antidiabetic drug therapy is vital to control blood glucose and prevent diabetic complications.[9,16] Low adherence results in an increase in diabetic complications and diabetes-related health care expenditures.[2,4,17]. Evidence from the study by Caro et al. indicated that diabetic complications were a large share of the total health costs of patients with type 2 diabetes.[18] Previous studies also indicated that poor adherence was associated with high healthcare costs of diabetes.[19-21] Lau et al. found that patients with type 2 diabetes with low adherence over one year were at a higher risk of hospitalization.[22] Furthermore, another study indicated that medication noncompliance was associated with increased all-cause mortality in patients with type 2 diabetes.[23]

Affordability of insulin has become the main problem for insulin users in the US. The availability of follow-on (biosimilar) insulins represents an opportunity to lower treatment costs since biosimilars are typically marketed at a lower price than the respective reference biological products. [24,25]A reduction in price has been noticed when biosimilars of other drugs entered into the market, so it is expected that the market introduction of biosimilar insulins will also result in a reduction in the price of insulin. [26]

In light of current evidence, finding the way to slow down the increasing rate of insulin product costs would be necessary. Prior research examined price differences of branded prescription drug prices among several OECD (Organization for Economic Co-

Operation and Development) countries and the US and factors that could affect prescription drug wholesale acquisition cost.[27,28]

To our knowledge, no study has assessed trends in insulin product prices in the US over a long period of time.

2. OBJECTIVES

The objectives of this study were to assess trends in insulin products prices in the period January 1983-July 2019, and to compare the price, acquisition costs and reimbursement amount of insulins available in the US.

3. HYPOTHESIS

We hypothesize that the prices of insulins marketed in the US increased faster than the inflation during the period of 1983- July 2019

4. MATERIAL AND METHODS

4.1. Data Sources

Data for all insulin products marketed in the US during the period 1983-July 2019 were collected from the FDA databases, the RedBook online, Medicaid.gov, the Department of Veterans Affairs, and the CMS.

Insulin products were classified using levels 2 (i.e., therapeutic subgroup) of the anatomical therapeutic chemical classification (ATC) system from the World Health Organization Collaborating Centre for Drug Statistics Methodology.[29] Defined daily dose (DDD) data for each insulin was collected from the World Health Organization Collaborating Centre for Drug Statistics Methodology. If the DDD was not available, the recommended dose was collected from the FDA-approved drug label. The maximum dose was used when the recommended dose was not included in the label. DDD is a technical unit of measurement and comparison in drug utilization studies.[30] DDD was first recommended in 1969 by WHO with the ATC classification system for comparing data on drug consumption. DDD defines as "the assumed average dose per day for a drug used in its main indication in adults". [31] It does not represent the recommend or actual dose. DDD is suitable for long-term studies to compare relative changes in drug usage and studies for costs, not for clinical consequences. Therefore, DDD is appropriate for economic studies.[32, 33]

Prices data as of July 2019 were retrieved from the RedBook online which included product name, price start date, deactivated status, deactivated date, active ingredient, manufacturer or distributor, generic or brand status, Orange Book code, code type, identifier, formulation, strength, route, package size, unit dose, average wholesale price (AWP) packaging price, and AWP unit price.[34] All AWP changes and their respective effective dates were collected from the first AWP effective date to the last available AWP effective date. AWP is reported by the manufacturers and, although it does not represent the actual acquisition cost because of the discounts and rebates that happen in the market, it has been the primary drug payment benchmark for brand name products for a long time in the US.[35,36] In most states, Medicaid uses the AWP to calculate the estimated acquisition costs used for outpatient pharmacy reimbursement.[37] However, AWP tends to be 20% or 25% higher than the WAC, implying that WAC is usually 16.7% or 20% lower than AWP. The presence of an AWP for drug products, whether supplied by the manufacturer or estimated by the price catalogs, transaction prices involving wholesalers, PBMs, pharmacies and other providers could all be specified with reference to AWP minus some % discount. The important point is that even though few if any transactions actually took place at the AWP price, the AWP serves a valuable role as a common reference point from which various discounts could be negotiated.[38] In practice, the actual transaction prices paid to the pharmacy by third-party payers for brand drugs are typically established using the AWP minus a percentage discount.[38] Even though some observers accurately called AWP "Ain‟t What‟s Paid," AWP played a critical role in facilitating efficiently millions of transactions among the various manufacturers, providers, and payers.[39] Therefore,

assessing AWP trends is useful to evaluate trends in prices and the burden of insulin costs on payers and patients.

National Average Drug Acquisition Cost (NADAC) data of insulin products in July 2019 were collected from Medicaid.gov.[40] NADAC data included national drug code (NDC), NADAC per unit, effective date, and pricing unit. NADAC is produced by the retail community pharmacy survey to give a better benchmark of estimated acquisition costs to Medicaid.[40] NADAC reflects the prices paid by retail community pharmacies to acquire prescription and over-the-counter covered outpatient drugs.[40] The NADAC is used by Medicaid for estimating the reimbursement to community pharmacies for the drug product.

Negotiate prices for insulin products used by the Federal Government were retrieved from the Department of Veterans Affairs. The VA is charged with negotiating prices, called the Federal Supply Schedule (FSS), for all federal direct healthcare payer agencies (not including Medicare and Medicaid).[41] In addition to the FSS, the VA can receive additional statutorily defined rebates through their shared purchasing power with other large agencies (the Big 4 price) and additional rebates for themselves through preferred formulary placement (national contract price). For certain drugs, the VA receives even lower prices for the Big 4 public payers: "Big 4 Price". In general, FSS contracts are multi-year (minimum of five years) and multiple award contracts, which means multiple companies supplying comparable products and services, at varying prices, are awarded contracts.[42] Pharmaceutical companies provide a discount to the federal government based on the lowest prices charged to private sector customers.[43] Big 4 prices are only available to the VA, Department of Defense, Public Health Service (Indian Health Service), and U.S. Coast

Guard customers and are based on pricing calculations outlined under the Public Law.[43] The following information was collected from the VA: NDC, package, contract number, vendor, generic name, trade name, and FSS and Big4 price.

Prices information was obtained from the CMS Medicare Part D as this data is available online to the general public from the CMS website. [44] The CMS website contains information about annual medication spending and utilization, but it does not include cost information for individual dosages. Instead, it provides total spending for each medication aggregated to the active ingredient unit, broken down by year. CMS is prohibited from publicly disclosing specific information on manufacturer rebates; thus, the data used to select Part D drugs do not reflect any manufacturers' rebates or other price concessions.[44] The average spending per dosage unit (weighted) for 2017 was collected based on the brand and generic names for insulin products.

4.2. Methods

The AWP per 30-DDD (AWP 30-DDD) was calculated and then adjusted to 2019 dollars (adjusted AWP 30-DDD) using the consumer price index (CPI) of all urban consumers from the Bureau of Labor Statistics.[45] We assumed daily use of 40 IU of insulin per day (0.4 NDC units) based on the standard established by the WHO (ATC) classification system guidelines for the defined daily dose of basal insulin.[29] Assuming use of only 1 insulin product at a time and no wasted insulin, the typical diabetic in this study would require 1200 IU (40 IU/d × 30 d/mo) of insulin per 1 month. For the inhaled insulin, insulin human inhaled KIT 1 mg/1 actuation; 3 mg/3, marketed by PFIZER U.S. PHARMACEUTICALS GROUP, 1mg inhaled insulin ≈ 3 IU of subcutaneously injected regular insulin. We assumed that the required daily dose of the inhaled insulin is equal to the maximum dose = 16 IU. Therefore, the typical diabetic in this study would require 480 IU (16 IU/d × 30 d/mo) of inhaled insulin per 1 month.

The total percentage increase and the compound annual growth rate (CAGR) were calculated from the adjusted AWP 30-DDD on the first effective date to the adjusted AWP 30-DDD in July 2019 or the last effective date when the drug discontinued. The CAGR was used to compare the year-over-year drug price growth rate over different time periods. CAGR was calculated by using the following formula:

$$CAGR = (EB/BB)^{1/N} - 1$$

Where:

EB = the adjusted AWP 30-DDD in the last effective date

BB = the adjusted AWP 30-DDD on the first effective date

n=Number of years

The NADAC per 30-DDD was calculated and then adjusted to 2019 dollars. The percentage of adjusted NADAC per 30-DDD with respect to the adjusted AWP per 30-DDD was calculated to assess the relationship between these two prices.

Prices data for all strengths and package types for each insulin were collected, then one strength and package type were selected to represent each drug. The strength closest to the DDD, and package type closest to 100-unit package type, if several were available, were included in the analysis. We excluded regular human insulin, U-500 (concentrated) (Eli Lilly and Company) due to its atypical dosage strength. Humulin R U-500 is different from all other insulin products because it contains 500 IU per 1mL of solution; other insulin products typically contain 100 IU per 1mL.

Summary descriptive statistics were computed to describe insulin product price trends. Comparisons of insulin prices from the different data sources were performed using the AWP as the reference for price comparisons. All analyses were performed using Microsoft Excel 2016.

5. RESULTS

Insulin products

During the study period (1983-July 2019), there were 86 insulin products marketed in the US; 40.4% (n=36) of the marketed insulin were available as over-the-counter (OTC) medications, and 59.6% (n=53) were available as prescribed medications. Five types of insulin are available based on their onset and duration of action. These are rapid-acting insulin (glulisine, lispro, aspart), regular or short-acting insulin (e.g., human regular), intermediate-acting insulin (NPH), long-acting insulin (detemir, glargine) and ultra-long-acting insulin (degludec). There are also premixed insulins on the market which contain rapid-acting or short-acting insulin and an intermediate-acting insulin analogue, as well as long-acting or ultra-long-acting insulin formulated with a non‑insulin drug. All animal-sourced insulins (n=12) were discontinued from the US market by April 2006. The final analytical sample included 28 insulin products with complete data.

The adjusted AWP total percentage increase and CAGR from approval to July 2019 or drug discontinuation date were positive for all insulin products except for the follow on-insulins (biosimilar), and one of the inhaled insulins (Table 1). The premixed insulin (insulin-GLP-1 receptor agonist combinations; insulin glargine/lixisenatide and insulin degludec/liraglutide had the lowest adjusted AWP CAGR (1.83%, 1.00%) among all insulin products marketed in the US during the study period.

All human insulin preparations (insulin human regular solution, insulin human isophane (NPH), and insulin human isophane (NPH)/insulin human regular) were on the

market on July 2019; they entered to the US market at lower price than other insulins (adjusted AWP 30-DDD, ranging from $79.04 to $95.27). Human insulins, not including inhalation formulations, had the adjusted AWP CAGR ranging from 4.89%-8.89% (n=6). The adjusted AWP 30-DDD for human insulins was very similar ($530.82 and $491.55, respectively) for the six products marketed by two different companies in July 2019, irrespective of short, intermediate, and combined acting insulin forms (Table1).

Human insulins also showed similar trends in the average AWPs and effective dates over the study period (Figure 1). For example, the cost of Eli Lilly's human insulins increased from $ 202.90 for 100 units/ml vial in 2011 to $ 535.32 in July 2019. Likewise, the price of Novo Nordisk's human insulins increased from $205.33 for 100 units/ml vial in 2011 to $ 495.72 in July 2019. However, Novo Nordisk and Eli Lilly had similar price trends until 2016 (Figure 1).

Table 1. Insulin prices per 30-DDD at market entry and July 1, 2019 (CPI-Adjusted)

Drug Class	RedBook First Date	RedBook First AWP 30-DDD	RedBook Last Date	RedBook Last AWP 30-DDD	AWP Increase	CPI CAGR	NADAC 30-DDD Jul 1, 2019	NADAC/ AWP Jul 1, 2019
Fast-Acting Insulins								
insulin aspart sol 100 u/1ml Novo Nordisk, Inc.	8/27/2001	$205.11	7/1/2019	$1,032.92	403.6%	9.5%	$826.25	80.0%
insulin glulisine sol 100 u/1ml Sanofi-Aventis U.S. Llc	1/24/2006	$298.79	7/1/2019	$1,013.62	239%	9.5%	$811.50	80.06%
insulin lispro sus 100 u/1ml Lilly, Eli & Company	7/24/1996	$121.44	7/1/2019	$980.60	707%	9.5%	$777.54	79.29%
** insulin lispro, recombinant sol 100 u/1ml Sanofi-Aventis U.S. Llc.	1/1/2018	$862.80	7/1/2019	$466.77	-46%	-33.7%	$374.07	80.14%
Short--Acting Insulins								
insulin human regular sol 100 u/1ml Lilly, Eli & Company	6/16/1986	$86.57	7/1/2019	$530.82	513.17%	5.6%	$432.83	81.54%
insulin human regular sol 100 u/1ml Novo Nordisk, Inc.	10/14/1991	$88.60	7/1/2019	$491.55	454.80%	6.4%	$399.51	81.28%
insulin pork regular sol 100u/1ml Lilly, Eli & Company	12/22/1986	$110.44	4/1/2006	$181.74	64.56%	2.6%	NA	NA
insulin pork regular sol 100u/ml Novo Nordisk, Inc.	9/1/1987	$96.23	2/7/2000	$207.35	115.47%	6.4%	NA	NA
Intermediate- Acting Insulins								
insulin human isophane (nph) sus 100 u/1ml Lilly, Eli & Company	6/27/1983	$95.27	7/1/2019	$530.82	457.17%	4.89%	$433.12	81.60%
insulin human isophane (nph) sus 100 u/1ml Novo Nordisk, Inc.	12/1/1987	$79.04	7/1/2019	$491.55	521.90%	5.96%	$400.27	81.43%
insulin pork isophane (nph) sus 100u/1ml Lilly, Eli & Company	12/22/1986	$110.44	4/1/2006	$181.74	64.56%	2.62%	NA	NA
insulin pork isophane (nph) sus 100u/1ml Novo Nordisk, Inc.	9/1/1987	$96.23	2/7/2000	$207.35	115.47%	6.37%	NA	NA
insulin beef zinc (lente) sus 100u/1ml Novo Nordisk, Inc.	2/12/1987	$60.80	10/20/1994	$73.21	20.41%	2.45%	NA	NA
insulin pork zinc (lente) sus 100u/1ml Novo Nordisk, Inc.	9/1/1987	$96.23	2/7/2000	$207.35	115.47%	6.37%	NA	NA

Drug Class	RedBook First Date	RedBook First AWP 30-DDD	RedBook Last Date	RedBook Last AWP 30-DDD	AWP Increase	CPI CAGR	NADAC 30-DDD Jul 1, 2019	NADAC/AWP Jul 1, 2019
Long-Acting Insulins								
insulin degludec sol 100 u/1ml Novo Nordisk, Inc.	10/23/2015	$1,139.47	7/1/2019	$1,209.97	6.19%	1.64%	$986.09	81.50%
insulin detemir sol 100 u/1ml Novo Nordisk, Inc.	2/6/2006	$321.50	7/1/2019	$1,099.98	242.14%	9.62%	$894.68	81.34%
insulin glargine recombinant sol 100 u/1ml Sanofi-Aventis U.S. Llc	5/1/2001	$186.88	7/1/2019	$1,012.22	441.64%	9.75%	$824.20	81.42%
** insulin glargine recombinant sol 100 u/1ml Lilly Usa, Llc.	11/17/2016	$801.59	7/1/2019	$776.67	-3.11%	-1.20%	$647.84	83.41%
Premixed; Intermediate-or Long-Acting Combined with Fast- or Short-Acting Insulins								
insulin degludec, liraglutide sol 100 u/1ml-3.6 mg/1ml Novo Nordisk, Inc.	11/21/2016	$2,411.42	7/1/2019	$2,474.72	2.63%	1.00%	$ 1,986.84	80.29%
insulin glargine, recombinant/lixisenatide sol 100 u/1ml-33 mcg/1ml Sanofi-Aventis U.S. Llc	12/12/2016	$1,605.93	7/1/2019	$1,681.97	4.73%	1.83%	$1,349.44	80.23%
insulin aspart protamine/insulin aspart sus 70 u/1ml-30 u/1ml Novo Nordisk, Inc.	9/11/2002	$306.03	7/1/2019	$1,329.91	334.57%	9.14%	$1,064.91	80.07%
insulin human isophane (nph)/insulin human regul sus 70 u/1ml-30 u/1ml Lilly, Eli & Company	6/26/1989	$83.46	7/1/2019	$530.82	536.02%	6.36%	$431.90	81.37%
insulin human isophane (nph)/insulin human regul sus 70 u/1ml-30 u/1ml Novo Nordisk, Inc.	10/14/1991	$88.60	7/1/2019	$491.55	454.8%	6.38%	$399.30	81.23%
insulin lispro protamine/insulin lispro sus 75 u/1ml-25 u/1ml Lilly, Eli & Company	12/11/2000	$209.23	7/1/2019	$1,016.30	385.73%	8.89%	NA	NA
insulin beef regular/insulin pork isophane (nph) sus 100u/1ml Lilly, Eli & Company	12/22/1986	$67.62	12/10/1999	$128.11	89.46%	5.05%	NA	NA
insulin beef regular/insulin pork zinc (lente) sus 100u/1ml Lilly, Eli & Company	12/22/1986	$67.62	12/10/1999	$128.11	89.46%	5.05%	NA	NA
Inhaled insulins								
insulin human inhaled aro 4 u MannKind and MannKind Cares	7/15/2016	$1,147.24	7/1/2019	$1,545.40	34.71%	10.59%	NA	NA
insulin human inhaled;insulin human inhaled KIT 1 mg/1 actuation; 3 mg/2 Pfizer	6/20/2006	$374.49	1/31/2008	$359.98	-3.87%	-2.42%	NA	NA

Acronym: sol-solution, sus-suspension, and aro-aerosol powder. * Last effective date is 7/1/2019 or discontinuation date, if it is not on the market as of 7/1/2019. ** Follow-on (Biosimilar) insulin

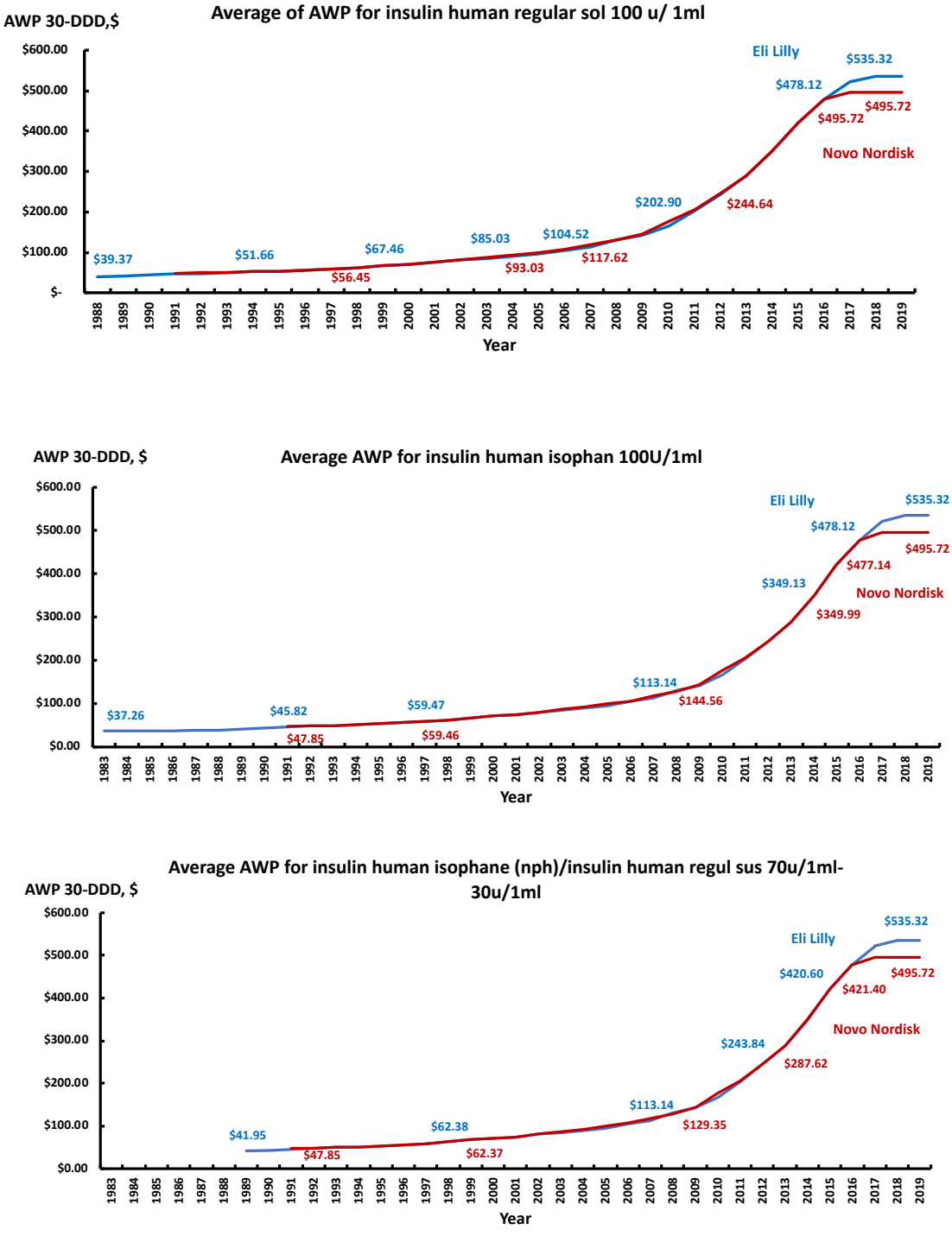

Figure 1. Trends in AWP prices for Human insulin products

AWP: Average wholesale price, DDD: Daily defined dose

All insulin analogues (insulin lispro, insulin aspart, insulin glulisine, insulin degludec, insulin glargine, and insulin detemir) remained in the market as of July 2019, and they had the highest adjusted AWP CAGR (9.5%- 9.75%) among all insulin products, excluding insulin degludec. The two fast-acting insulin analogues, insulin aspart and insulin glulisine, had similarly adjusted AWP 30-DDD ($1,032.92 and $1,013.62, respectively) for the two sponsor companies marketing these products on July 2019 (Table 1). On the contrary, the fast-acting insulin lispro had the lowest adjusted AWP 30-DDD ($980.60) among insulin analogues in July 2019 (Table 1).

The adjusted AWP 30-DDD for long-acting insulin analogues marketed by two different companies, insulin glargine and insulin detemir, was similar ($1,012.22, $1,099.98, respectively) on July 2019 (Table 1). The adjusted AWP total percentage increase and CAGR for insulin degludec were the lowest compared to other long-acting insulins (1.64% vs. 9.62%, 9.75%) (Table 1).

Fast-acting insulin and long-acting analogues also had similar upward trends in the AWP during the study period. Similarly to human insulin product prices trends, the 3 competitor companies adopted similar price increases during the study period (Figure 2). However, for fast-acting insulins, Novo Nordisk was adopted similar pricing trends than Eli Lilly until 2017 when Novo Nordisk's insulin prices increased faster than Lilly spiked up. A similar practice noticed with long-acting insulins (Figure 2).

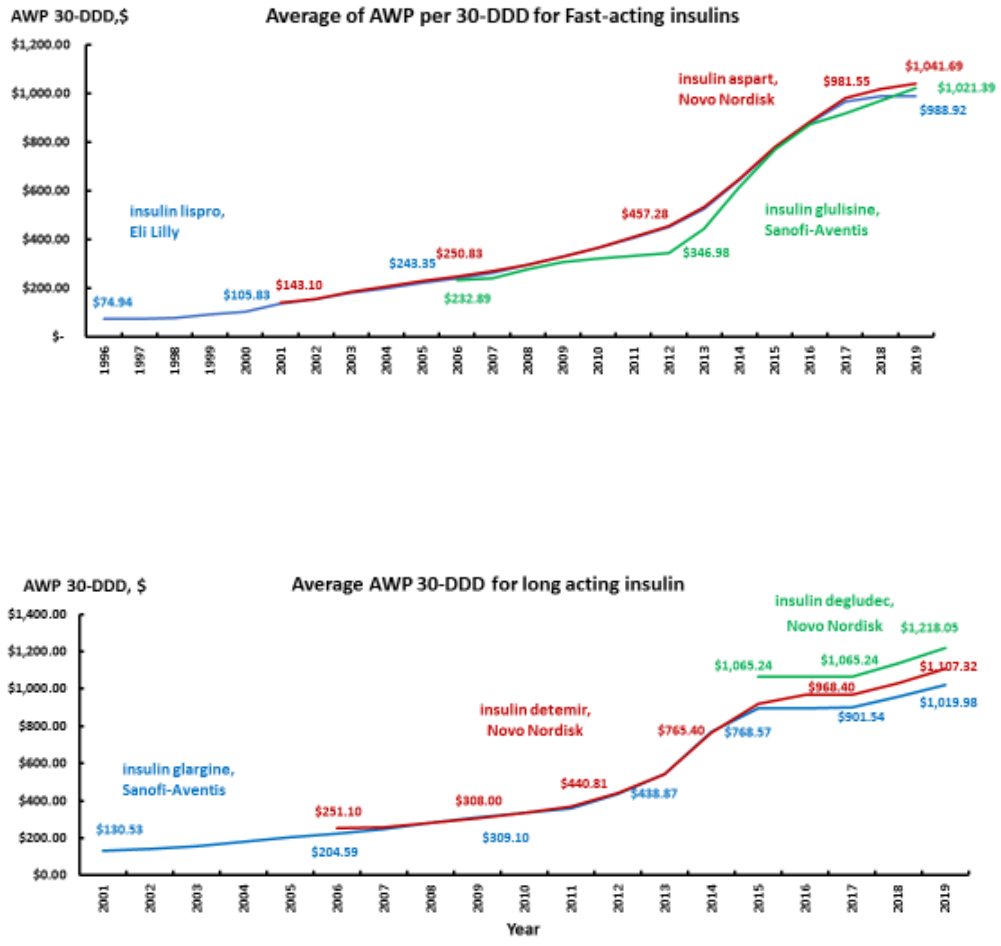

Figure 2. Trends in AWP prices for insulin analogue products and their follow-on insulins

AWP: Average wholesale price, DDD: Daily defined dose

** Follow-on (Biosimilar) insulin

The first two rapid-acting inhaled insulins marketed in the US were Exubera (approved in 2006), and Afrezza (approved in 2014). Pfizer withdrew Exubera from the market in October 2017 when it failed to gain acceptance from patients and providers. Afrezza is the only inhaled human insulin remaining in the US market in July 2019 with the adjusted AWP 30-DDD of $1,545.40 and the adjusted AWP CAGR of 10.59% from approval to July 20219.

The two follow-on (biosimilar) insulins, long-acting insulin glargine and rapid-acting insulin lispro experienced a negative adjusted CAGR (-1.20%, -33.70%, respectively) from the approval date to July 2019. However, the CAGR for all animal insulins from approval to discontinuation date was ranging from 2.6% to 6.4%.

AWP and NADAC for Insulin products

In the study period, there were 18 insulin products drugs as collected by NADAC data in July 2019 (Table 1). The average of NADAC per 30-DDD as a percentage of the AWP per 30-DDD in July 2019 was 80.47% ranging from 79.29% to 81.54% (Table 1).

Comparison of insulin prices from the different data sources

The prices of insulin products showed a significant variation in comparison with the AWP price (Table 2). The WAC was set at 83.33% of the AWP for all insulins and analogues. Community pharmacies (independent and chains) were able to acquire the insulins at a median NADAC of 80.27% of the AWP. However, pharmaceutical companies provided additional discounts to the FSS and the Big 4 that paid for insulins at a median of

25.89% of the AWP price for both FSS and Big4. The FSS and the Big 4 were able to pay 13.6% of the AWP for insulin lispro and 22.7% of the AWP for insulin glargine.

For Medicare Part D, the adjusted average price of AWP in 2017 was compared to the adjusted insulins price of Medicare part D during the same period to have a head to head comparison. Medicare Part D was able to acquire the insulins at a median of 78.8% of the AWP ranging from 54.2% to 98.7% (Table 2).

Table 2. Comparison of Insulin Prices in the US at July 1, 2019

Drug Class	First effective date	Effective Date	AWP CPI	FSS/AWP, %	Big 4/AWP, %	NADAC/ AWP, %	WAC/ AWP, %	AWP (2017)	Part D/AWP
Fast-Acting Insulins									
insulin aspart sol 100 u/1ml Novo Nordisk, Inc.	8/27/2001	7/1/2019	$ 34.43	28%	28%	80%	83%	$ 34.54	83%
insulin glulisine sol 100 u/1ml Sanofi-Aventis U.S. Llc	1/24/2006	7/1/2019	$ 33.79	30%	33%	80%	83%	$ 32.07	81%
insulin lispro sus 100 u/1ml Lilly, Eli & Company	7/24/1996	7/1/2019	$ 42.07	14%	14%	81%	83%	$ 34.27	77%
** insulin lispro, recombinant sol 100 u/1ml Sanofi-Aventis U.S. Llc.	1/1/2018	7/1/2019	$ 15.56	79%	79%	80%	83%	NA	NA
Short--Acting Insulins									
insulin human regular sol 100 u/1ml Lilly, Eli & Company	6/16/1986	7/1/2019	$ 17.69	9%	9%	82%	83%	$ 18.55	54%
insulin human regular sol 100 u/1ml Novo Nordisk, Inc.	10/14/1991	7/1/2019	$ 16.38	17%	17%	81%	83%	$ 17.31	64%
insulin pork regular sol 100u/1ml Lilly, Eli & Company	12/22/1986	4/1/2006	$ 7.14	NA	NA	NA	83%	NA	NA
insulin pork regular sol 100u/ml Novo Nordisk, Inc.	9/1/1987	2/7/2000	$ 7.14	NA	NA	NA	80%	NA	NA
Intermediate- Acting Insulins									
insulin human isophane (nph) sus 100 u/1ml Lilly, Eli & Company	6/27/1983	7/1/2019	$ 17.69	9%	9%	82%	83%	$ 18.55	54%
insulin human isophane (nph) sus 100 u/1ml Novo Nordisk, Inc.	12/1/1987	7/1/2019	$ 16.38	17%	17%	81%	83%	$ 17.31	64%
insulin pork isophane (nph) sus 100u/1ml Lilly, Eli & Company	12/22/1986	4/1/2006	$ 7.14	NA	NA	NA	83%	NA	NA
insulin pork isophane (nph) sus 100u/1ml Novo Nordisk, Inc.	9/1/1987	2/7/2000	$ 7.14	NA	NA	NA	80%	NA	NA
insulin beef zinc (lente) sus 100u/1ml Novo Nordisk, Inc.	2/12/1987	10/20/1994	$ 2.47	NA	NA	NA	80%	NA	NA
insulin pork zinc (lente) sus 100u/1ml Novo Nordisk, Inc.	9/1/1987	2/7/2000	$ 7.14	NA	NA	NA	80%	NA	NA
Long-Acting Insulins									
insulin degludec sol 100 u/1ml Novo Nordisk, Inc.	10/23/2015	7/1/2019	$ 40.33	73%	52%	80%	83%	$ 37.20	83%

Drug Class	First effective date	Effective Date	AWP CPI	FSS CPI, %	Big 4 CPI, %	NADAC, %	WAC, %	AWP CPI (2017)	Part D CPI
Long-Acting Insulins									
insulin detemir sol 100 u/1ml Novo Nordisk, Inc.	2/6/2006	7/1/2019	$ 36.67	57%	48%	80%	83%	$ 33.82	83%
insulin glargine recombinant sol 100 u/1ml Sanofi-Aventis U.S. Llc	5/1/2001	7/1/2019	$ 33.74	22.7%	22.7%	87%	83%	$ 31.70	81%
** insulin glargine recombinant sol 100 u/1ml Lilly Usa, Llc.	11/17/2016	7/1/2019	$ 25.89	64%	63%	80%	83%	$ 26.94	82%
Premixed; Intermediate-or Long-Acting Combined with Fast- or Short-Acting Insulins-or non-insulin drug									
insulin degludec, liraglutide sol 100 u/1ml-3.6 mg/1ml Novo Nordisk, Inc.	11/21/2016	7/1/2019	$ 82.49	75%	59%	80%	83%	$ 79.89	NA
insulin glargine, recombinant/lixisenatide sol 100 u/1ml-33 mcg/1ml Sanofi-Aventis U.S. Llc	12/12/2016	7/1/2019	$ 56.07	79%	57%	80%	83%	$ 53.22	NA
insulin aspart protamine/insulin aspart sus 70 u/1ml-30 u/1ml Novo Nordisk, Inc.	9/11/2002	7/1/2019	$ 44.33	26%	26%	80%	83%	$ 44.47	66%
insulin human isophane (nph)/insulin human regul sus 70 u/1ml-30 u/1ml Lilly, Eli & Company	6/26/1989	7/1/2019	$ 17.69	9%	9%	81%	83%	$ 18.55	71%
insulin human isophane (nph)/insulin human regul sus 70 u/1ml-30 u/1ml Novo Nordisk, Inc.	10/14/1991	7/1/2019	$ 16.38	17%	17%	81%	83%	$ 17.31	60%
insulin lispro protamine/insulin lispro sus 75 u/1ml-25 u/1ml Lilly, Eli & Company	12/11/2000	7/1/2019	$ 33.88	17%	NA	80%	83%	$ 35.52	80%
insulin beef regular/insulin pork isophane (nph) sus 100u/1ml Lilly, Eli & Company	12/22/1986	12/10/1999	$ 4.37	NA	NA	NA	83%	NA	NA
insulin beef regular/insulin pork zinc (lente) sus 100u/1ml Lilly, Eli & Company	12/22/1986	12/10/1999	$ 4.37	NA	NA	NA	83%	NA	NA
Inhaled insulins									
insulin human inhaled aro 4 u MannKind and MannKind Cares	7/15/2016	7/1/2019	$ 4.38	13%	NA	NA	83%	$ 3.79	98.74%
insulin human inhaled;insulin human inhaled KIT 1 mg/1 actuation; 3 mg/2 Pfizer	6/20/2006	1/31/2008	$ 12.57	NA	NA	NA	83%	NA	NA

Acronym: sol-solution, sus-suspension, and aro-aerosol powder. ** Follow-on (Biosimilar) insulin

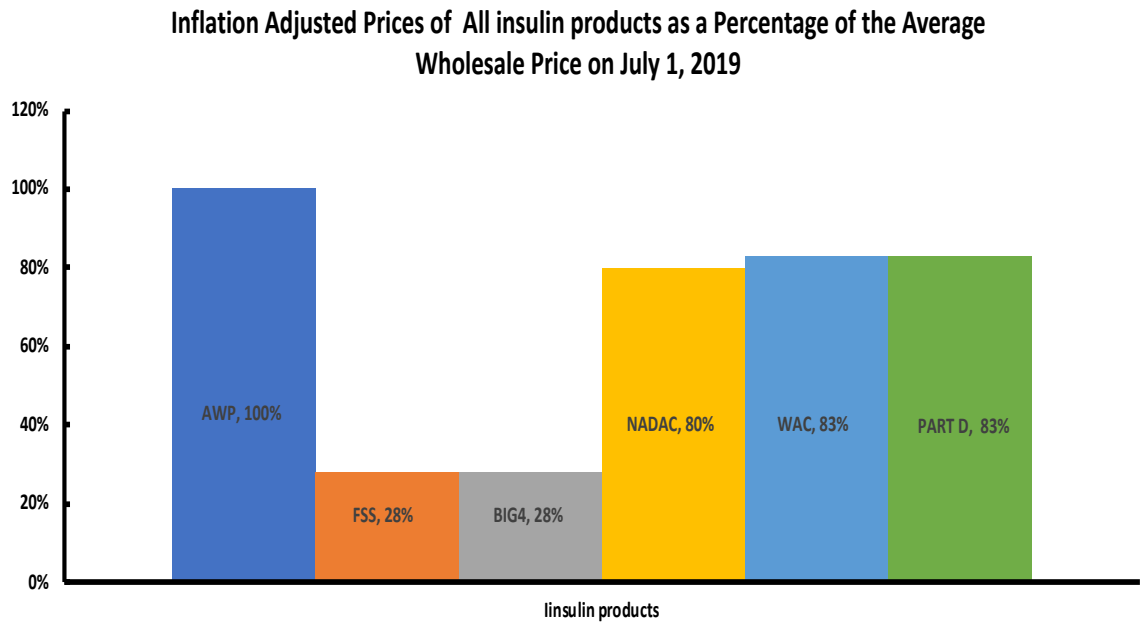

Figure 3: Comparison of Insulin Prices in the US at July 1, 2019

AWP: Average wholesale, FSS: Federal Supply Schedule, NADAC: National Average Drug Acquisition Cost, WAC: Wholesale Acquisition Cost

6. Discussion

To our knowledge, this is the first study assessing price trends for insulin products and comparing different manufacturer prices, actual transaction cost estimation, and reimbursement amounts available in the US. The study results showed that prices of insulin products increased faster than the inflation during the study period. Likewise, previous studies have found that prices for widely used brand name prescription drugs increased substantially faster than inflation over the past 14 years.[28, 46]

Additionally, the results of this study have confirmed that manufacturer listed prices (AWP and WAC) are representative of the actual transaction price paid by community pharmacy for insulin. The AWP and WAC are benchmark prices used in the US for reimbursement purposes. However, the WAC is closely related to the actual transaction price paid by community pharmacies for insulin products.

We also found that the list price of competing insulin formulations has appeared to rise in tandem, and companies do not engage in price competition at the level of the community pharmacy. The price trends of insulin products within the same pharmacological class were very similar until 2016. For instance, human insulins marketed by two different pharmaceutical companies showed very similar price trends. Prices of fast-acting insulin analogues, excluding follow on (biosimilar) insulins, also showed very similar prices and price trends. Moreover, the price of long-acting insulin analogues, insulin glargine, and insulin detemir has been the same, even though they were marketed by different pharmaceutical companies. There has been a pattern of increasing prices overtime for all

available insulin products. A previous study found that detemir has increased in price over time and in parallel with the price of insulin glargine. [47] In practice, however, competition between 2 or more brand name manufacturers selling drugs in the same class does not usually result in substantial price reductions.[48] Thus, insulins and analogues experience a similar trend in price competition. This phenomenon likely arises from limited market competition.

Of note, more than 90 years have passed since insulin was first clinically used in a patient with diabetes; and currently, there are still no generic insulin options available in the US.[49] Addressing the Challenges and Constraints of Insulin Sources and Supply (ACCISS) study reported that the global insulin market is controlled by the same three large multinational corporations that manufacture and sell insulin in the US. Eli Lilly, Novo Nordisk, and Sanofi represent 99% of the total insulin by value, 96% by total market volume, and 88% of global product registration.[50] These 3 companies control the marketplace and face no real generic competitor to drive down prices. With this level of market control and the absence of competition, there is nothing to stop the current companies from raising prices. So, the availability of generic insulin could substantially reduce overall spending and out-of-pocket costs. It would also improve patient adherence and reduce the financial burden on payers. However, the results of this study showed that the trends of insulins prices have changed during the last five years; pharmaceuticals companies stopped shadow pricing since 2015.

Additionally, we found substantial differences in the prices of insulins used in the US healthcare system. The pharmaceutical companies listed prices were higher than the estimated acquisition costs (NADAC) and also higher than the prices used for

reimbursement (Medicaid Part D, FSS, and Big 4). The prices paid by the federal government were substantially lower than the prices paid in the private sector. The FSS and the Big 4 are prices negotiated by the Federal government for federal purchases of pharmaceuticals. The FSS and the Big 4 prices are based on the lowest prices offered in the private sector, and they are used by federal agencies for reimbursement purposes. [51] Medicare Part D was able to acquire insulin products at a median slightly lower than the WAC, however the estimated Medicare Part D prices do not consider rebates obtained from manufactures by Medicare Part D plans. Medicare Part D spending on insulins has shown an increasing and accelerating trend during the past years.[14] Among all insulin products, Part D spending was highest for insulin glargine, a long-acting insulin, with $2.6 billion in Part D spending in 2017.[14]

Congress included a provision in the law that created the Medicare drug benefit program, prohibiting the Centers for Medicare & Medicaid Services from negotiating drug prices or from interfering with negotiations between individual Part D vendors and drug companies. This made prescription drugs under Part D one of the few Federal healthcare programs for which Centers for Medicare & Medicaid Services do not negotiate or set prices.[52]

Insulins are regulated as biosimilar drugs in the European Union and as chemical entities in the US.[53] For example, insulin glargine was approved by the U.S. Food and Drug Administration (FDA) on 16 December 2015 via the Food, Drug, and Cosmetic Act (FD&C Act), section 505(b)(2), new drug application (NDA) pathway system and not as a biosimilar.[54] Presently, there are three follow-on biologic insulins approved by the FDA, and two are available for sale. Those insulins were introduced to the market with a 15%

discount on the wholesale acquisition cost of the brand. [54] Despite the presence of follow-on insulins (biosimilars) in the US market, insulin prices remain high. The increased competition between insulin manufacturers might bring down the price of insulin, but most likely, not below 50% of the initial price.[55] However, the US may have a similar experience to the UK, where the first follow-on insulin glargine was recently introduced, and it has a list price that is only 15% lower than of the originator insulin product.

Increases in insulin product prices affect third-party payers, especially Medicare and the Medicaid programs that provide prescription coverage to the majority of older adults. High prices also places an economic burden on patients due to increasing out-of-pocket costs, which negatively affect adherence to drug therapy.[56] Non-adherence to therapy negatively impacts clinical outcomes, increases the risks of diabetic complications and related-hospitalizations,[12,16] and leads to increased total health care expenditures.[57, 58] Therefore, providers, pharmacies, and health plans should discuss the cost of insulin preparations with diabetic patients to help understand the advantages, disadvantages, and financial implications of potential insulin preparations. Taking cost into consideration during the prescription process can push providers and patients to decide to follow more cost-conscious treatment routes, instead of which form of insulin is best suited for a patient's medical needs. Furthermore, there is a need for more transparency throughout the insulin supply chain. List price for insulins could more closely reflect net price, and rebates based on list price could be minimized. The current payment system should rely less on rebates, discounts, and fees based on list price. The FDA also should continue to streamline the process to bring more biosimilar insulins to market.

This study has some potential limitations. We assessed the price of insulin products marketed in the US. Thus, the results do not apply to other antidiabetic medications. The AWP is reported by the manufacturer and does not represent the final net acquisition cost paid for drugs in the US since discounts and rebates are not deducted from the AWP. The NADAC is reported by community pharmacies and does not include rebates that pharmaceutical companies pay to Medicaid, managed care organizations, health care organizations, and other payers. Additionally, annual trends in insulin utilization, changes in insulin coverage by public and private insurers, and changes in insulin utilization guidelines are not readily available for the study period 1980- July 2019. Our insulin price trends analysis did not control for these variables, which may affect our analysis.

7. Conclusion

Prices of insulin products increased significantly, regardless of the presence of biosimilar competition between 1983 and July 2019. This study found substantial differences in insulin manufacturer prices, acquisition cost estimations, and reimbursement prices in the public and private US healthcare system. Pharmaceutical companies' listed prices were higher than the pharmacy estimated acquisition costs, and the amount used for reimbursement. The prices paid by the federal government were substantially lower than the prices paid in the private sector.

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Appendix 1a. insulin products marketed in the US in July 2019

Class	Active Ingredient	Proprietary Name	Applicant Holder	Mkt.Status	Approval Date
Fast-Acting insulin	insulin aspart	Fiasp	Novo Nordisk Inc	RX	Sep 29, 2017
	insulin aspart	Fiasp Flextouch	Novo Nordisk Inc	RX	Sep 29, 2017
	insulin aspart	Fiasp Penfill	Novo Nordisk Inc	RX	Sep 24, 2018
	insulin aspart recombinant	Novolog	Novo Nordisk Inc	RX	Jun 7, 2000
	insulin aspart recombinant	Novolog Flexpen	Novo Nordisk Inc	RX	Jan 19, 2001
	insulin aspart recombinant	Novolog Penfill	Novo Nordisk Inc	RX	Jun 7, 2000
	insulin glulisine recombinant	Apidra	Sanofi Aventis Us Llc	RX	Apr 16, 2004
	insulin glulisine recombinant	Apidra Solostar	Sanofi Aventis Us Llc	RX	Feb 24, 2009
	insulin lispro	Admelog**	Sanofi-Aventis Us Llc	RX	Oct 19, 2018
	insulin lispro	Admelog**	Sanofi-Aventis Us Llc	RX	Dec 11, 2017
	insulin lispro	Admelog Solostar**	Sanofi-Aventis Us Llc	RX	Dec 11, 2017
	insulin lispro recombinant	Humalog	Eli Lilly And Co	RX	Jun 14, 1996
	insulin lispro recombinant	Humalog Kwikpen	Eli Lilly And Co	RX	Sep 6, 2007
	insulin lispro recombinant	Humalog Kwikpen	Eli Lilly And Co	RX	May 26, 2015
Short-acting insulin	insulin human	Humulin R	Eli Lilly And Co	RX	Mar 31, 1994
	insulin human	Humulin R Kwikpen	Eli Lilly And Co	RX	Dec 29, 2015
	insulin recombinant human	Humulin R	Eli Lilly And Co	OTC	Oct 28, 1982
	insulin recombinant human	Humulin R Pen	Eli Lilly And Co	OTC	Aug 6, 1998
	insulin recombinant human	Novolin R	Novo Nordisk Inc	OTC	Jun 25, 1991
Intermediate- Acting insulin	insulin aspart protamine recombinant; insulin aspart recombinant	Novolog Mix 70/30	Novo Nordisk Inc	RX	Nov 1, 2001
	insulin aspart protamine recombinant; insulin aspart recombinant	Novolog Mix 70/30 Flexpen	Novo Nordisk Inc	RX	May 3, 2002
	insulin susp isophane recombinant human	Humulin N	Eli Lilly And Co	RX	Oct 28, 1982
	insulin susp isophane recombinant human	Novolin N	Novo Nordisk Inc	RX	Jul 1, 1991

Appendix 1b. insulin products marketed in the US in July 2019

Class	Active Ingredient	Proprietary Name	Applicant Holder	Mkt.Status	Approval Date
Long-Acting insulin	insulin degludec	Tresiba	Novo Nordisk Inc	RX	Sep 25, 2015
	insulin degludec	Tresiba	Novo Nordisk Inc	RX	Sep 25, 2015
	insulin degludec	Tresiba	Novo Nordisk Inc	RX	Nov 21, 2018
	insulin detemir recombinant	Levemir	Novo Nordisk Inc	RX	Jun 16, 2005
	insulin detemir recombinant	Levemir Flextouch	Novo Nordisk Inc	RX	Oct 31, 2013
	insulin glargine	Basaglar**	Eli Lilly And Co	RX	Dec 16, 2015
	insulin glargine recombinant	Lantus	Sanofi Aventis Us Llc	RX	Apr 20, 2000
	insulin glargine recombinant	Lantus Solostar	Sanofi Aventis Us Llc	RX	Apr 27, 2007
	insulin glargine recombinant	Toujeo Max Solostar	Sanofi Us Services Inc	RX	Mar 26, 2018
	insulin glargine recombinant	Toujeo Solostar	Sanofi Us Services Inc	RX	Feb 25, 2015
Premixed; Intermediate- or Long-Acting Combined with Fast- or Short-Acting insulin –or non-insulin drug	insulin degludec; liraglutide	Xultophy 100/3.6	Novo Nordisk Inc	RX	Nov 21, 2016
	insulin glargine; lixisenatide	Soliqua 100/33	Sanofi-Aventis Us Llc	RX	Nov 21, 2016
	insulin lispro protamine recombinant; insulin lispro recombinant	Humalog Mix 50/50	Eli Lilly And Co	RX	Dec 22, 1999
	insulin lispro protamine recombinant; insulin lispro recombinant	Humalog Mix 50/50 Kwikpen	Eli Lilly And Co	RX	Sep 6, 2007
	insulin lispro protamine recombinant; insulin lispro recombinant	Humalog Mix 75/25	Eli Lilly And Co	RX	Dec 22, 1999
	insulin lispro protamine recombinant; insulin lispro recombinant	Humalog Mix 75/25 Kwikpen	Eli Lilly And Co	RX	Sep 6, 2007
	insulin recombinant human; insulin susp isophane recombinant human	Humulin 70/30	Eli Lilly And Co	OTC	Apr 25, 1989
	insulin recombinant human; insulin susp isophane recombinant human	Humulin 70/30 Pen	Eli Lilly And Co	OTC	Aug 6, 1998
	insulin recombinant human; insulin susp isophane recombinant human	Novolin 70/30	Novo Nordisk Inc	OTC	Jun 25, 1991
Inhaled insulins	insulin recombinant human	Afrezza	Mannkind Corp	RX	Jun 27, 2014
	insulin recombinant human	Afrezza	Mannkind Corp	RX	Jun 27, 2014
	insulin recombinant human	Afrezza	Mannkind Corp	RX	Apr 17, 2015

** Follow-on (biosimilar) insulin