



Top 10 Best-Selling Drugs of 2019

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Executive Summary



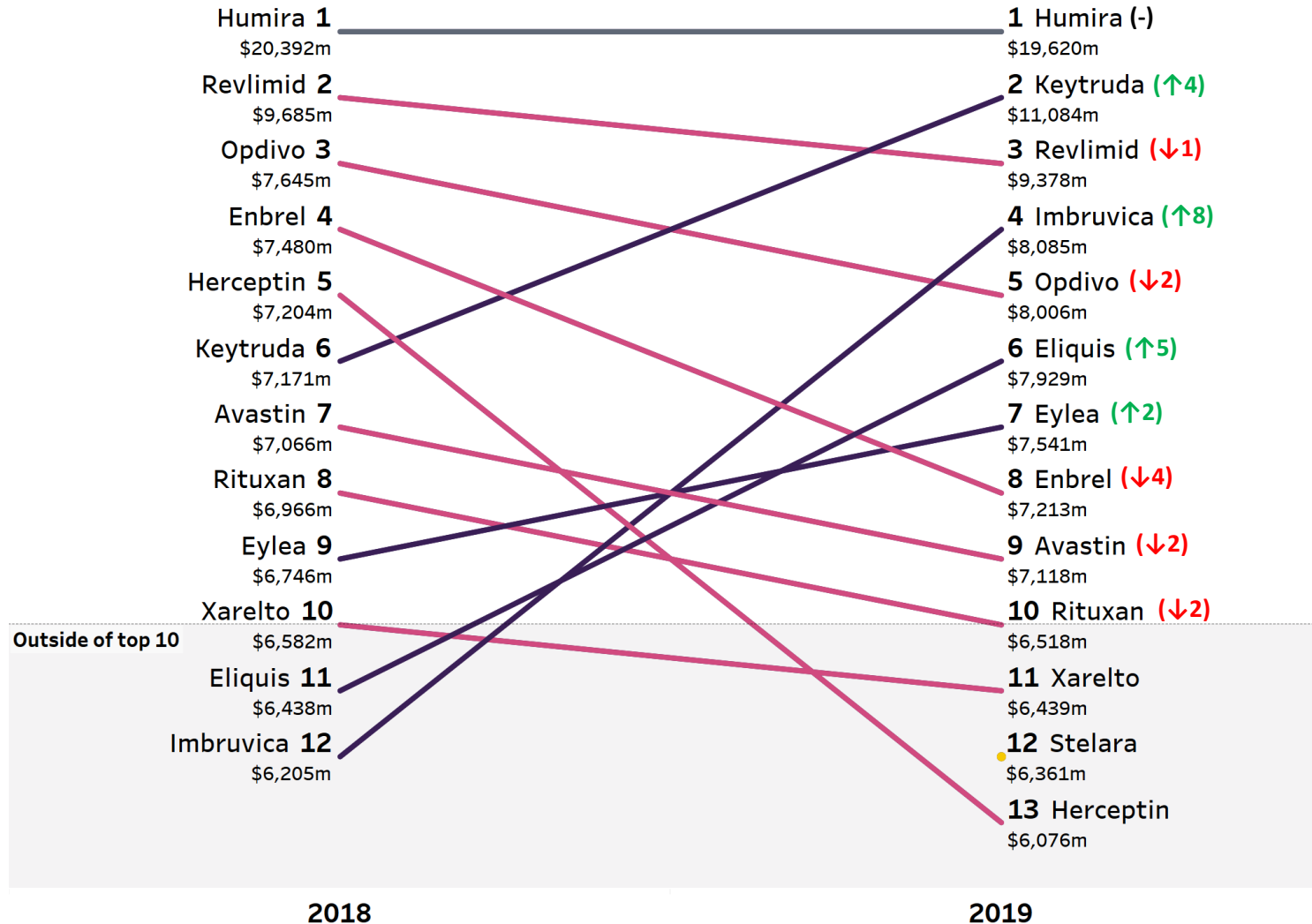
\$92bn Total Sales

1	 <p>HUMIRA[®] adalimumab</p>	<p>\$19.6bn Worth 21% of the top 10 drugs' total sales</p> <p>AbbVie (\$19.2bn), Eisai (JPY49bn)</p>	6	 <p>Eliquis[™] apixaban</p>	<p>\$7.9bn</p> <p>Bristol Myers Squibb (\$7.9bn)</p>
2	 <p>KEYTRUDA[®] (pembrolizumab) Injection 100 mg</p>	<p>\$11.1bn</p> <p>Merck & Co (\$11.1bn)</p>	7	 <p>EYLEA[®] (aflibercept) Injection For Intravitreal Injection</p>	<p>\$7.5bn</p> <p>Regeneron (\$7.5bn)</p>
3	 <p>Revlimid[®] (lenalidomide) capsules 2.5 · 5 · 10 · 15 · 20 · 25 mg</p>	<p>\$9.4bn</p> <p>Bristol Myers Squibb (\$1.3bn), Celgene (\$8.1bn)</p>	8	 <p>Enbrel[®] etanercept</p>	<p>\$7.2bn</p> <p>Amgen (\$5.2bn), Pfizer (\$1.7bn), Takeda (JPY31.3bn)</p>
4	 <p>imbruvica[®] (ibrutinib) 560, 420, 280, 140 mg tablets 140, 70 mg capsules</p>	<p>\$8.1bn</p> <p>AbbVie (\$3.4bn), Johnson & Johnson (\$4.7bn)</p>	9	 <p>AVASTIN[®] bevacizumab 100 MG/4 ML INJECTION FOR IV USE</p>	<p>\$7.1bn</p> <p>Roche (CHF7.1bn)</p>
5	 <p>OPDIVO[®] (nivolumab)</p>	<p>\$8.0bn</p> <p>Bristol Myers Squibb (\$7.2bn), Ono Pharmaceutical (JPY87.2bn)</p>	10	 <p>Rituxan[®] Rituximab</p>	<p>\$6.5bn</p> <p>Roche (CHF6.5bn)</p>

Executive Summary



Rankings of the best-selling drugs in 2018 and 2019

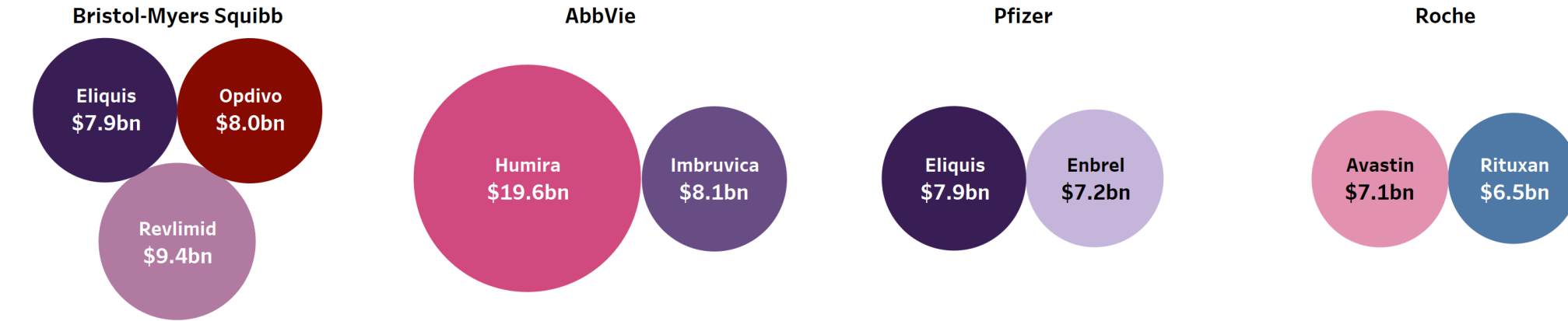


- Of the best-selling drugs in 2018, Humira is the only unchanged brand, continuing to defend its first place position in 2019.
- Four brands, Keytruda, Imbruvica, Eliquis, and Eylea, have risen in the ranking of the 10 best-selling drugs in 2019.
- Imbruvica and Eliquis have displaced Xarelto and Herceptin from the top 10 brands in 2019.
- Revlimid, Enbrel, and Rituxan showed declining sales compared to 2018 due to biosimilar/generic competition, and subsequently dropped in their sales rankings in 2019.

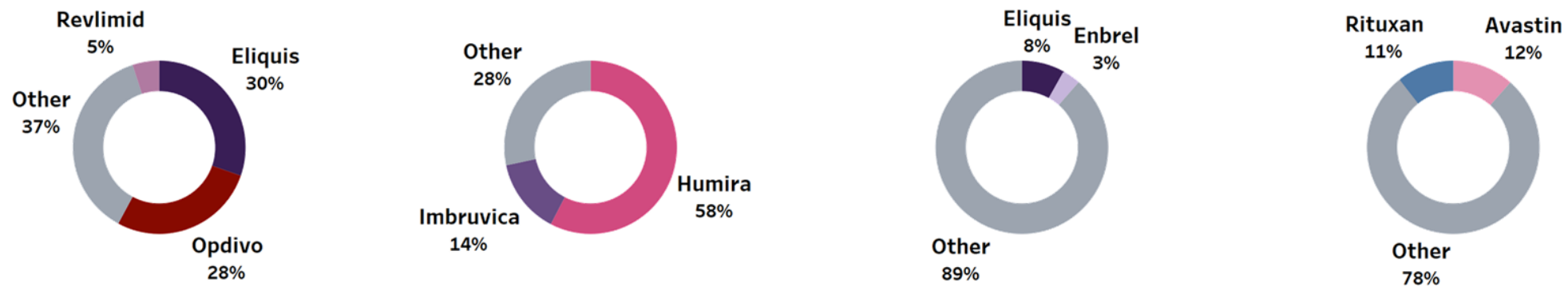
Executive Summary



Companies with multiple best-selling drugs



← Increasing total sales value of the companies' best-selling drugs



- There were four pharmaceutical companies (Bristol Myers Squibb, AbbVie, Pfizer, and Roche) with more than one best-selling drug of 2019.
- Bristol Myers Squibb had the most best-selling drugs (Eliquis, Opdivo, and Revlimid), and these contributed 63% of the company's total revenues in 2019. AbbVie's revenues in 2019 were most heavily reliant upon its top drugs (Humira and Imbruvica), which represented a combined 72% of the company's total revenues for the year.

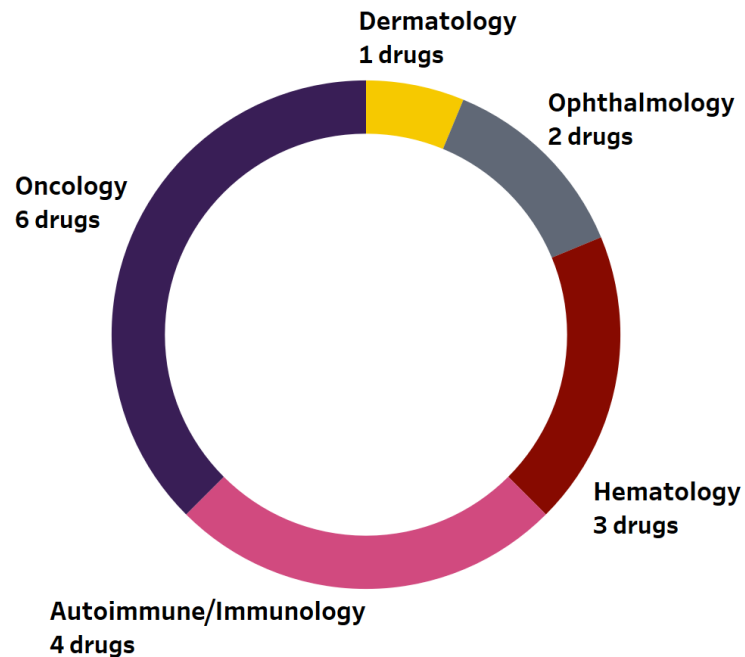
Executive Summary



Therapy Area

- Oncology
- Autoimmune/Immunology
- Hematology
- Ophthalmology
- Dermatology

Therapy areas targeted by the best-selling drugs of 2019



- The top drugs of 2019 span five different therapy areas: oncology, autoimmune/immunology, hematology, ophthalmology, and dermatology. Six of the best-selling drugs of 2019 are oncologic treatments, making oncology the most targeted field.
- Most (six) of the best-selling drugs are approved to treat a single therapy area, while Humira and Rituxan possess the broadest labels – each catering for three different therapy areas.
- There is notable overlap in the breadth of the top drugs' approved indications. There are five diseases where three of the top 10 drugs are approved. An additional 18 diseases are targeted by two of the top 10 drugs.
- Programmed cell death protein-1 (PD-1) inhibitors Keytruda and Opdivo directly compete within 12 shared oncology indications, while anti-tumor necrosis factor (TNF) inhibitors Humira and Enbrel compete within six shared autoimmune/immunology indications.

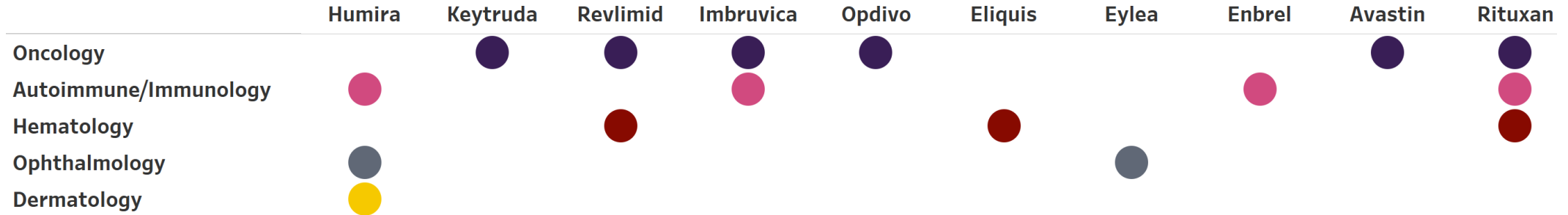
Executive Summary



Therapy Area

- Oncology
- Autoimmune/Immunology
- Hematology
- Ophthalmology
- Dermatology

Therapy areas targeted by the top drugs of 2019



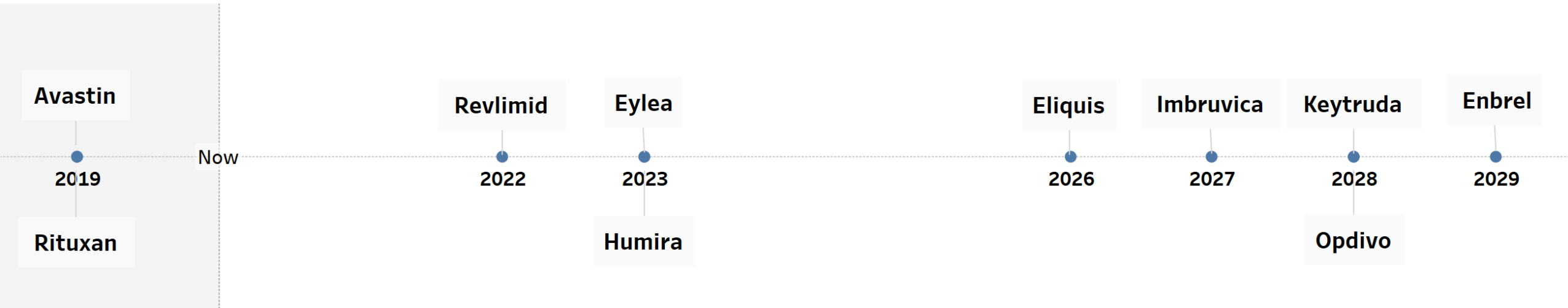
Drug type and route of administration of the top drugs of 2019

		Humira	Keytruda	Revlimid	Imbruvica	Opdivo	Eliquis	Eylea	Enbrel	Avastin	Rituxan
Biologic	Intravenous		●			●				●	●
	Subcutaneous	●							●		●
	Intravitreal							●			
Small molecule			●	●		●					

Executive Summary



Launch year of the first US biosimilar/generic for each top brand



- All best-selling brands of 2019 will face biosimilar/generic erosion in the next 10 years.
- Two top brands currently face biosimilar competition in the US market. Biosimilars for Avastin and Rituxan first launched in the US in July 2019 and November 2019, respectively. These drugs fell in their rankings from 2018 to 2019.
- By the end of 2023, Revlimid, Humira, and Eylea will become the next products to face biosimilar/generic competition in the US. Revlimid will experience volume-restricted generic competition in the US from March 2022 onwards. US biosimilar erosion of Humira's sales is anticipated to be fiercer than current international erosion, considering that there are five approved biosimilars awaiting launch successively in 2023, starting from January 2023. Eylea will likely encounter indirect biosimilar competition from Lucentis biosimilars prior to its own US patent expiry in 2023.



Summary of Trends

Summary of Trends



Global sales of the 10 best-selling drugs of 2019

- The top 10 drugs with the highest global sales in 2019 each generated revenues of at least \$6.5bn.
- The total sales value of these drugs amounted to a staggering \$92bn in 2019.
- Humira was the best-selling drug with a global sales value of \$19.6bn, which was equivalent to over a fifth (21%) of the top 10 drugs' total sales.

Changes from 2018

- Of the best-selling drugs in 2018, Humira is the only unchanged brand, continuing to defend its first place position in 2019.
- Imbruvica and Eliquis have displaced Xarelto and Herceptin from the top 10 brands in 2019.
- Four brands, Keytruda, Imbruvica, Eliquis, and Eylea, have risen in the rankings of the 10 best-selling drugs in 2019.
- Revlimid, Enbrel, and Rituxan showed declining sales compared to 2018 due to biosimilar/generic competition, and subsequently dropped in their sales rankings in 2019.

Companies

- The top 10 drugs are each marketed by at least one Big Pharma player (defined as a company with annual revenues in excess of \$15bn).
- Bristol Myers Squibb had the greatest number of the best-selling drugs in 2019 (Eliquis, Opdivo, and Revlimid), and these contributed to 63% of the company's total revenues during the year.
- AbbVie, Pfizer, and Roche also marketed multiple best-selling drugs of 2019, with two brands each.

Diseases targeted

- The top drugs of 2019 span five different therapy areas: oncology, autoimmune/immunology, hematology, ophthalmology, and dermatology.
- Six of the best-selling drugs target oncology, making it the most targeted field. The second-most targeted therapy area is the autoimmune/immunology field, which is targeted by four of the best-selling drugs.
- Six of the best-selling drugs are approved to treat a single therapy area. Keytruda, Opdivo, and Avastin are solely oncologic drugs, while Eliquis, Eylea, and Enbrel treat hematologic, ophthalmologic, and autoimmune/immunologic conditions, respectively.
- Although the broadest drugs (Humira and Rituxan) are approved to treat conditions across three different therapy areas, they are mainly used to treat select specialties.
- Colorectal cancer, mantle cell lymphoma, non-small cell lung cancer, rheumatoid arthritis, and renal cancer are the most targeted diseases, each treated by three of the top 10 drugs.
- There is notable overlap in the breadth of the top drugs' approved indications. There are five diseases each treated by three of the top 10 drugs. An additional 18 diseases are catered for by two of the top 10 drugs.
- PD-1 inhibitors Keytruda and Opdivo directly compete within 12 shared oncology indications.

Summary of Trends



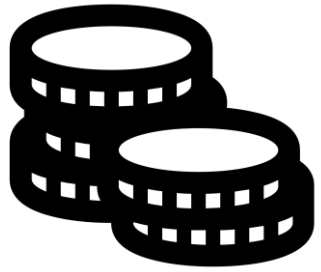
Drug type	<ul style="list-style-type: none">• Seven of the top 10 best-selling drugs are injectable biologics, the remainder being oral small molecules.• Of the biologics, three are administered intravenously, two subcutaneously, and Rituxan may be administered either intravenously or subcutaneously, using Rituxan Hycela. Eylea remains the only intravitreal injection in the top 10.
US dynamics	<ul style="list-style-type: none">• On average, US sales represented 62% of global sales for the best-selling drugs in 2019.• The US market was dominant as the largest contributor to global sales for all the top brands, with the exception of Avastin.• Inflated pricing is characteristic of the US market and intrinsic to the continued sales growth of lucrative drugs.• Most of the best-selling drugs in 2019 have undergone at least one price hike since 2018.• Opdivo experienced the most price hikes as its list price increased twice during 2018–19.• The list price of the best-selling drug, Humira, increased the most, by 7.4%.• Eylea, Avastin, and Rituxan were exceptional in having unchanged list prices from 2018.
Lifecycle stage	<ul style="list-style-type: none">• On average, global sales of the top brands grew by 11% from 2018 to 2019.• Four (Humira, Revlimid, Enbrel, and Rituxan) of the top drugs of 2019 experienced a reduction in sales from 2018 to 2019. On average, these products' global sales decreased by 4.2%. These headwinds were primarily imposed by biosimilar/generic competition.• Five of the best-selling brands in 2019 (Opdivo, Keytruda, Imbruvica, Eliquis, and Eylea) first reached the US market in the past 10 years.

Summary of Trends



US biosimilar/ generic threat

- All of the best-selling brands of 2019 will face biosimilar/generic erosion in the next 10 years.
- Two top brands currently face biosimilar competition in the US market. Biosimilars for Avastin and Rituxan first launched in the US in July 2019 and November 2019, respectively. By 2023, Revlimid, Humira, and Eylea will be the next top brands encountering biosimilar/generic competition.
- Biosimilars and generics enter with steeper price discounts as more biosimilar/generic competitors are launched, stoking competition and deepening sales erosion.
- US biosimilar erosion of Humira's sales is anticipated to be fiercer than current international erosion, considering that there are five approved biosimilars awaiting launch successively in 2023. To offset this, AbbVie is lining up Skyrizi, Rinvoq, and ABBV-3373 as Humira's successors in the autoimmune/immunology space.
- Revlimid will experience volume-restricted generic competition in the US from 2022 onwards. Celgene was publicly listed for hindering access to drug samples for generic testing, thereby obstructing competition.
- Eylea will likely encounter indirect biosimilar competition from Lucentis biosimilars prior to its own US patent expiry in 2023.
- Pharmaceutical companies are adopting numerous strategies in the face of biosimilar/generic competition, including defending intellectual property, the "rebate trap", limiting access to reference products, developing biobetters, evolving into hybrid originator/biosimilar companies, and developing successor brands.



Global Sales of the 10 Best-Selling Drugs of 2019

Global Sales of the 10 Best-Selling Drugs of 2019

The top 10 most lucrative drugs were worth approximately \$92bn

The top 10 drugs with the highest global sales in 2019 each generated revenues of at least \$6.5bn. The total sales value of these 10 drugs amounted to a staggering \$92bn in 2019. Humira (adalimumab) continued to dominate the pharmaceutical market; its global sales of \$19.6bn were equivalent to over a fifth (21%) of the top 10 drugs' total sales.

Rank (difference from 2018 rank)	Global sales, 2019	Brand (molecule)	Companies (total sales by company)
1 (-)	\$19.6bn	Humira (adalimumab)	AbbVie (\$19,169m), Eisai (JPY49,000m*)
2 (↑4)	\$11.1bn	Keytruda (pembrolizumab)	Merck & Co (\$11,084m)
3 (↓1)	\$9.4bn	Revlimid (lenalidomide)	Bristol Myers Squibb (\$1,299m), Celgene (\$8,079m)**
4 (↑8)	\$8.1bn	Imbruvica (ibrutinib)	AbbVie (\$3,411m), Johnson & Johnson (\$4,674m)
5 (↓2)	\$8.0bn	Opdivo (nivolumab)	Bristol Myers Squibb (\$7,204m), Ono Pharmaceutical (JPY87,200m*)
6 (↑5)	\$7.9bn	Eliquis (apixaban)	Bristol Myers Squibb (\$7,929m)
7 (↑2)	\$7.5bn	Eylea (aflibercept)	Regeneron (\$7,541m)
8 (↓4)	\$7.2bn	Enbrel (etanercept)	Amgen (\$5,226m), Pfizer (\$1,699m), Takeda (JPY31,300m*)
9 (↓2)	\$7.1bn	Avastin (bevacizumab)	Roche (CHF7,073m)
10 (↓2)	\$6.5bn	Rituxan (rituximab)	Roche (CHF6,477m)

*Sum of Q1–Q3 2019 sales and Q4 2019 sales.

**Celgene reported sales until its acquisition by Bristol Myers Squibb in November 2019.



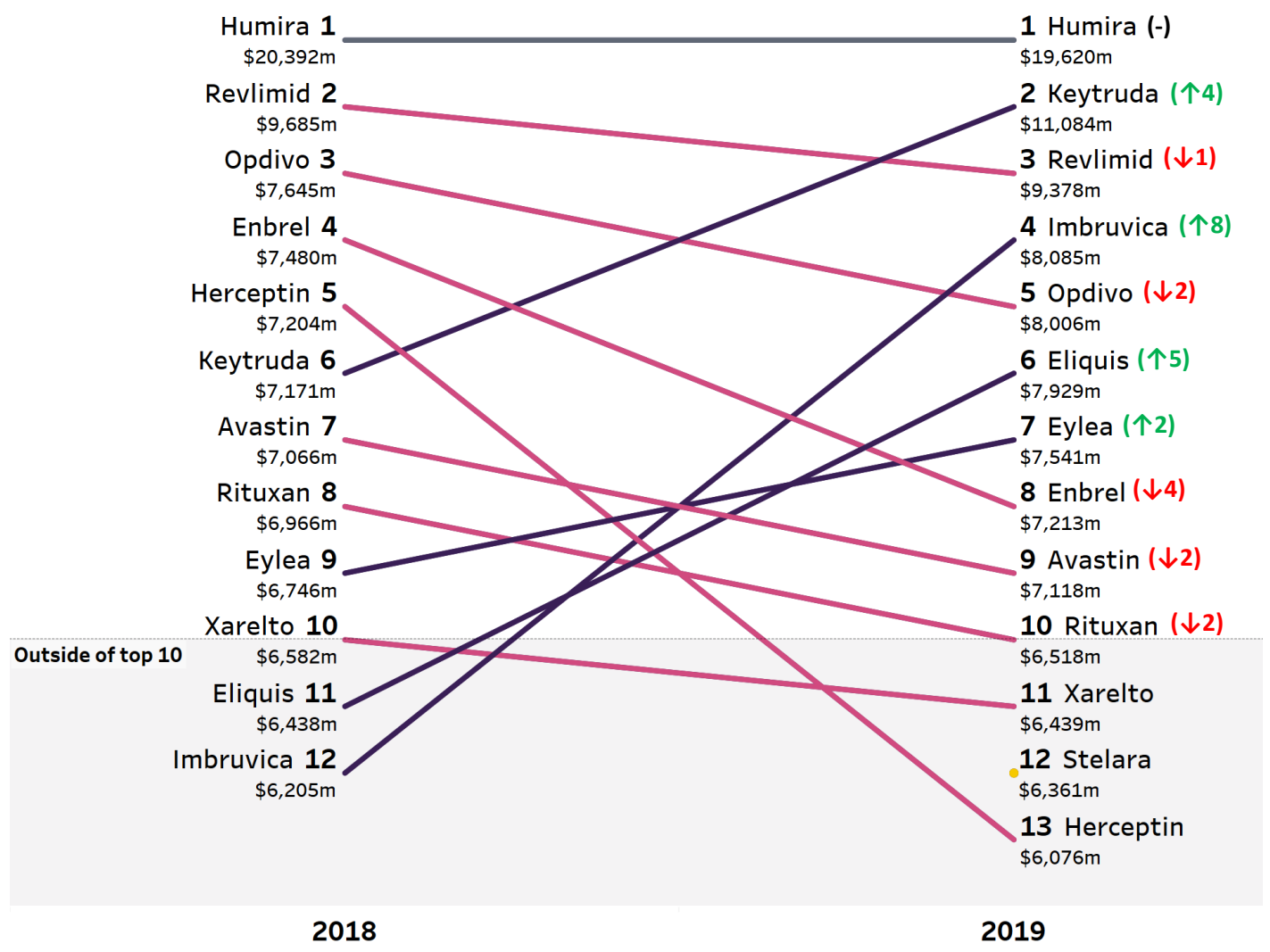
Changes From 2018





Rankings of the Best-Selling Drugs in 2018 and 2019

Of the top drugs in 2018, Humira is the only brand bearing the same rank in 2019



- Of the best-selling drugs in 2018, Humira is the only unchanged brand, continuing to defend its first place position in 2019.
- Imbruvica (ibrutinib) and Eliquis (apixaban) have displaced Xarelto (rivaroxaban) and Herceptin (trastuzumab) from the top 10 brands in 2019.
- Four brands, Keytruda (pembrolizumab), Imbruvica, Eliquis, and Eylea (afibercept), have risen in the rankings of the 10 best-selling drugs in 2019.
- Keytruda is closing the sales gap between the highest-selling and second-highest selling brands compared to Revlimid (lenalidomide) in 2018.



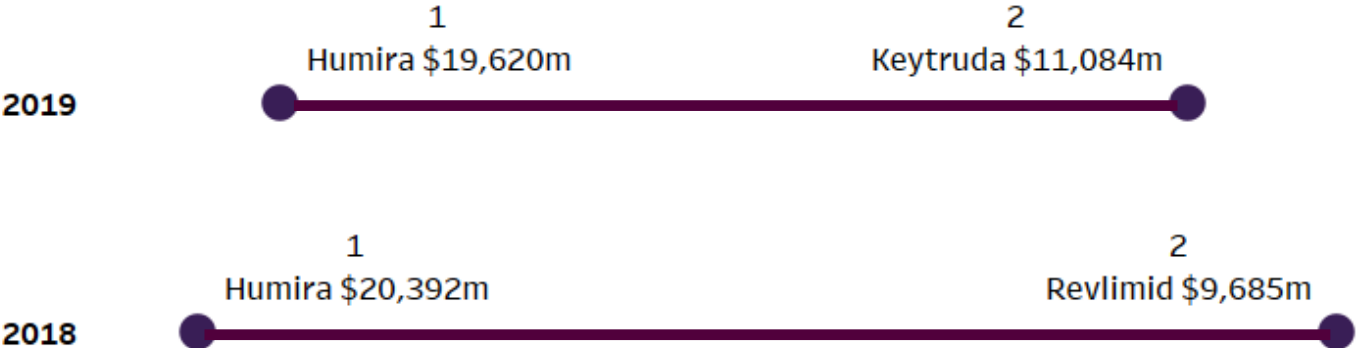
Rankings of the Best-Selling Drugs in 2018 and 2019

Imbruvica and Eliquis have displaced Xarelto and Herceptin from the 10 best-selling brands

As of 2019, Imbruvica and Eliquis have made their first entries into the top 10 best-selling drugs list. Notably, Imbruvica’s sales momentum allowed it to climb eight places, rising from 12th to become the fourth best-selling drug. Eliquis did not quite penetrate the top five; nevertheless, the brand advanced from 11th place to sixth. Of the best-selling drugs in 2018, Herceptin had the greatest fall (eight places), plummeting from fifth out of the top 10 to 13th. A slight dip in Xarelto’s sales, which totaled just shy of \$6.5bn, caused it to fall short of the top 10 in 2019.

Keytruda is closing the sales gap between the top and second-placed brand compared to Revlimid in 2018

In 2019, Keytruda rose to second place, having previously been the sixth most lucrative drug in 2018. Keytruda’s impressive global growth from \$7.2bn in 2018 to \$11.1bn in 2019 has surpassed Revlimid, which held second place in 2018 with global sales of \$9.7bn. Thus, Keytruda narrowed the sales gap between the second best-selling drug and first-placed Humira from \$10.7bn in 2018 to \$8.5bn in 2019. Nevertheless, Humira remains a behemoth brand resolutely defending its number one position despite sustaining biosimilar erosion in Europe. The second best-selling drug will likely only have a chance to match Humira’s sales after the latter encounters biosimilar erosion in the US from January 2023 onwards.





Companies



Companies Associated With the Top Drugs in 2019

Most of the top drugs benefit from the marketing experience and resources of multiple companies, including Big Pharma

Each of the top 10 drugs are marketed by at least one Big Pharma player (defined as a company with annual revenues in excess of \$15bn). Most of the top brands are marketed by multiple companies and harness their substantial pooled marketing experience and commercial resources. Success in the Asian market is mostly supported through strategic partnerships with pharmaceutical companies headquartered in the Asia-Pacific region, such as Eisai, Takeda, and Ono Pharmaceutical, which have an established presence and experience in the targeted market. Although Roche has not entered into a strategic partnership for the marketing of Avastin, it utilizes the expertise of its Japanese subsidiary, Chugai.

Rank (difference from 2018 rank)	Brand (molecule)	Originator	Marketing companies
1 (-)	Humira (adalimumab)	AstraZeneca	AbbVie (US/RoW); Eisai (Japan)
2 (↑4)	Keytruda (pembrolizumab)	Merck & Co	Merck & Co; Taiho Pharmaceutical (subsidiary of Otsuka; Japan)
3 (↓1)	Revlimid (lenalidomide)	Celgene	Bristol Myers Squibb*; BeiGene (China); GENESIS Pharma (Greece)
4 (↑8)	Imbruvica (ibrutinib)	AbbVie	AbbVie; Johnson & Johnson
5 (↓2)	Opdivo (nivolumab)	Ono Pharmaceutical	Bristol Myers Squibb (US/RoW); Ono Pharmaceutical (Japan)
6 (↑5)	Eliquis (apixaban)	Bristol Myers Squibb	Bristol Myers Squibb; Pfizer
7 (↑2)	Eylea (aflibercept)	Regeneron	Regeneron (US/RoW); Bayer; Santen (Japan)
8 (↓4)	Enbrel (etanercept)	Amgen	Amgen (US/RoW); Pfizer (EU); Takeda (Japan)
9 (↓2)	Avastin (bevacizumab)	Roche	Roche; Chugai (subsidiary of Roche; Japan)
10 (↓2)	Rituxan (rituximab)	Biogen	Roche; Biogen (US); Chugai (subsidiary of Roche; Japan); Zenyaku Kogyo (Japan)

RoW = rest of world

*Celgene was acquired by Bristol Myers Squibb in November 2019.

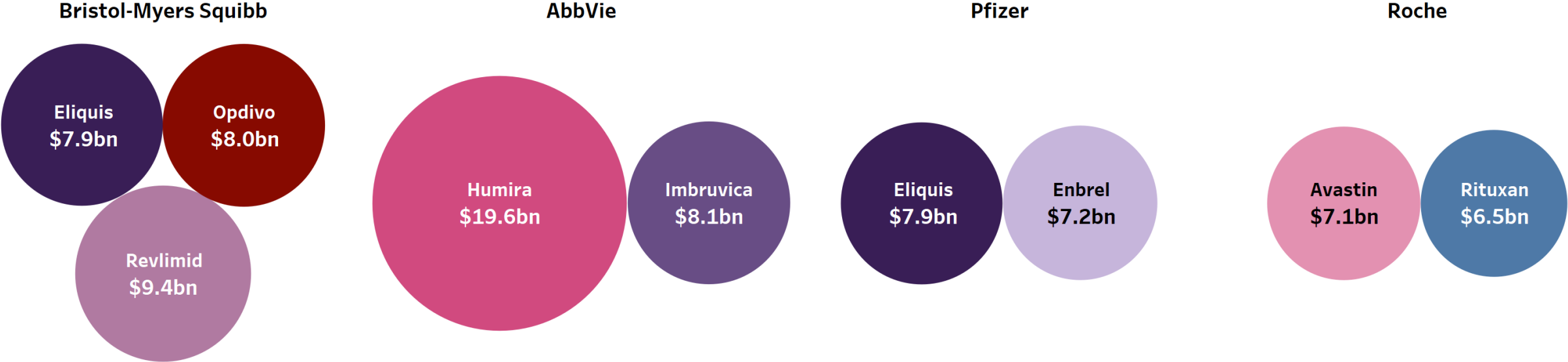


Companies With Multiple Best-Selling Drugs

Bristol Myers Squibb had the greatest number of best-selling drugs in 2019

Bristol Myers Squibb had three of the best-selling drugs in 2019 (Eliquis, Opdivo, and Revlimid). Revlimid became Bristol Myers Squibb's asset in November 2019 upon the company's acquisition of Celgene. Bristol Myers Squibb markets Eliquis in partnership with Pfizer, and global sales reported by both companies totaled \$7.9bn in 2019.

AbbVie, Pfizer, and Roche each had two of the best-selling drugs of 2019. AbbVie not only had the most lucrative drug of 2019, but also marketed Imbruvica, which had the fourth highest global sales, reaching \$8.1bn. Roche had the two smallest drugs of the top 10 in 2019, Avastin and Rituxan, with global sales of \$7.1bn and \$6.5bn, respectively.



Source: Biomedtracker; Datamonitor Healthcare; Pharmaprojects; [AbbVie, 2020](#); [Amgen, 2020](#); [Bristol Myers Squibb, 2020](#); [Celgene, 2020](#); [Eisai, 2020](#); [Johnson & Johnson, 2020](#); [Ono, 2020](#); [Pfizer, 2020](#); [Roche, 2020](#); [Takeda, 2020](#)

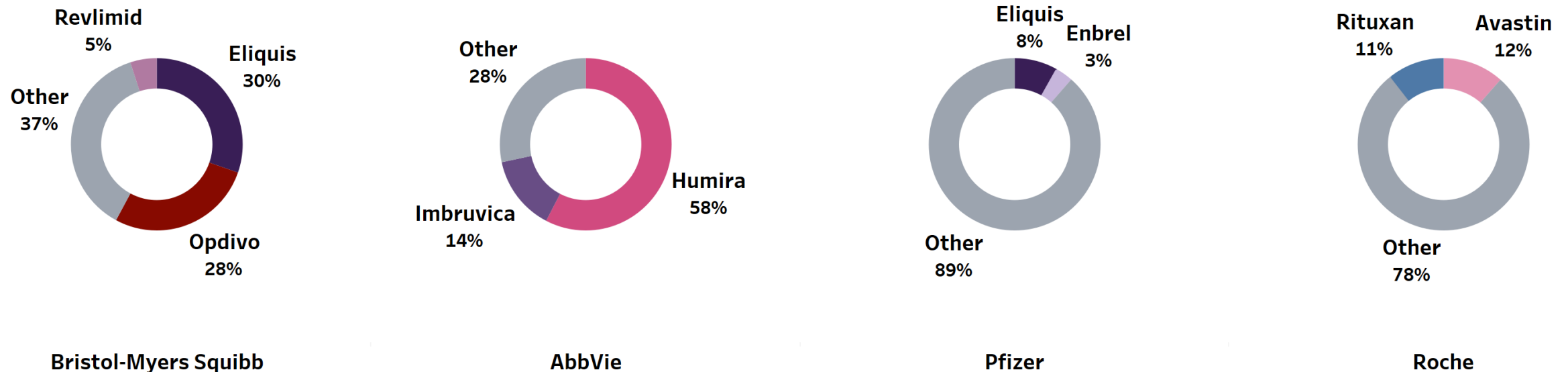


Importance of the Best-Selling Drugs to 2019 Company Revenues

Bristol Myers Squibb and AbbVie's 2019 revenues heavily relied upon their best-selling drugs

The best-selling brands contributed to 63% and 72% of Bristol Myers Squibb and AbbVie's total revenues in 2019, respectively. Humira represents the largest single revenue contributor to company revenues, as AbbVie's reported sales for Humira in 2019 represented 58% of the company's total revenues for the year. Less profoundly, the top brands only represented 11% and 22% of Pfizer and Roche's 2019 revenues, respectively. Thus, Pfizer and Roche are less reliant on their best-selling brands as they possess more diverse portfolios.

Drug sales as a proportion of company revenues





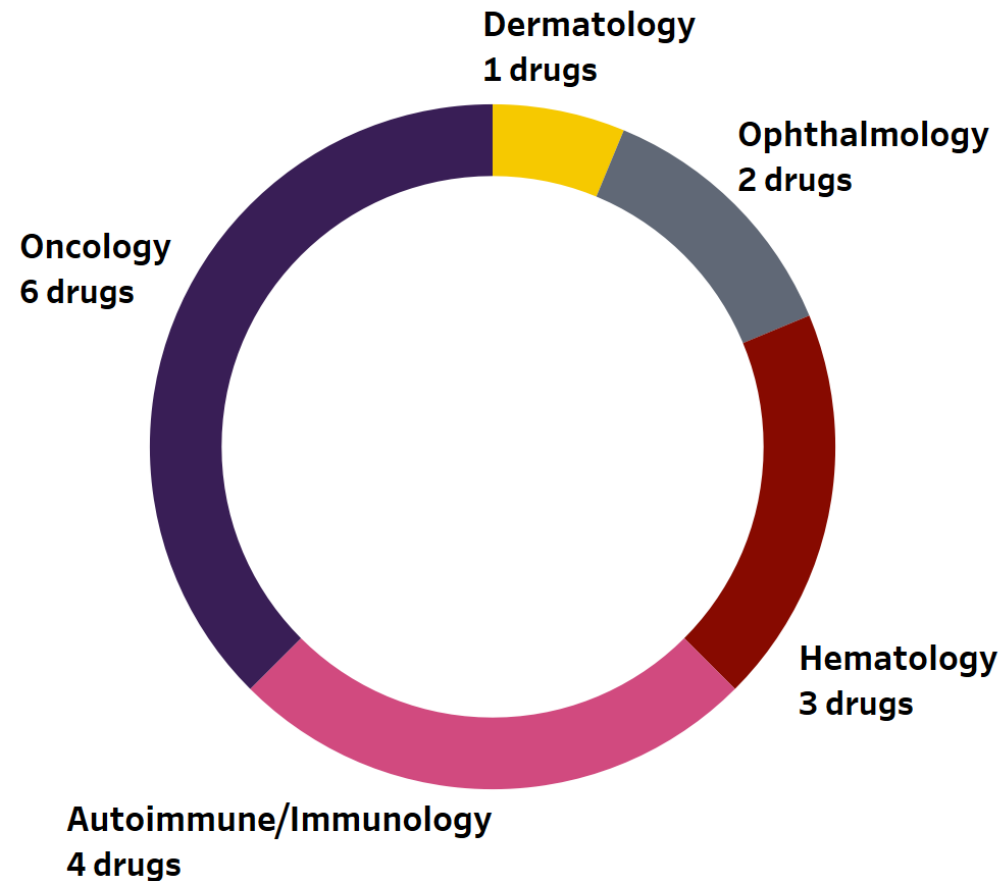
Diseases



Therapy Areas Targeted by the Best-Selling Drugs of 2019

Six of the best-selling drugs target oncology

The top drugs of 2019 span five different therapy areas: oncology, autoimmune/immunology, hematology, ophthalmology, and dermatology. Six of the best-selling drugs of 2019 are oncologic treatments, making oncology the most targeted field. The second-most targeted therapy area is the autoimmune/immunology field, which is targeted by four of the best-selling drugs.



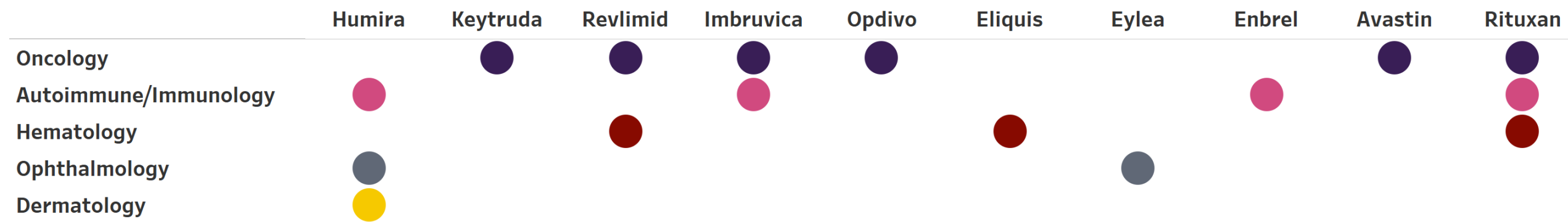


Therapy Areas Targeted by the Best-Selling Drugs of 2019

Six of the best-selling drugs are approved to treat a single therapy area

Keytruda, Opdivo, and Avastin are solely oncologic drugs, while Eliquis, Eylea, and Enbrel treat hematologic, ophthalmologic, and autoimmune/immunologic conditions, respectively.

Although the broadest drugs (Humira and Rituxan) are approved to treat conditions spanning three different therapy areas, they are mainly used to treat select specialties. The vast majority of Humira’s approved indications fall under autoimmune/immunology, the exceptions being its approvals to treat the ophthalmic condition uveitis and the dermatological condition hidradenitis suppurativa. Rituxan’s label is relatively balanced in the number of oncology and autoimmune/immunology indications it is approved for. The drug also treats the hematologic condition thrombotic thrombocytopenic purpura and received supplemental approval for this indication in February 2020 in Japan.



Accumulating approvals for multiple conditions within a therapy area facilitates greater volume-based rebates to secure better formulary positioning through payer contracts. Additionally, it is advantageous for companies to secure label expansions to build a strong reputation and familiarity with a specific physician type.



Top Diseases Targeted by the Best-Selling Drugs of 2019

CRC, MCL, NSCLC, RA, and renal cancer are the most targeted diseases

Therapy Area

- Autoimmune/Immunology
- Oncology

CRC = colorectal cancer;
 MCL = mantle cell
 lymphoma; NSCLC = non-
 small cell lung cancer; RA
 = rheumatoid arthritis

Arthritis, rheumatoid	Rituxan	Humira	Enbrel
Cancer, colorectal	Opdivo	Keytruda	Avastin
Cancer, lung, non-small cell	Opdivo	Keytruda	Avastin
Cancer, lymphoma, mantle cell	Rituxan	Revlimid	Imbruvica
Cancer, renal	Opdivo	Keytruda	Avastin
Ankylosing spondylitis	Humira	Enbrel	
Arthritis, juvenile	Humira	Enbrel	
Arthritis, psoriatic	Humira	Enbrel	
Cancer, bladder	Opdivo	Keytruda	
Cancer, cervical	Keytruda	Avastin	
Cancer, gastro-oesophageal junction	Opdivo	Keytruda	
Cancer, gastrointestinal, stomach	Opdivo	Keytruda	
Cancer, head and neck	Opdivo	Keytruda	
Cancer, leukaemia, chronic lymphocytic	Rituxan	Imbruvica	
Cancer, liver	Opdivo	Keytruda	
Cancer, lung, small cell	Opdivo	Keytruda	
Cancer, lymphoma, B-cell, diffuse large	Rituxan	Keytruda	
Cancer, lymphoma, follicular	Rituxan	Revlimid	
Cancer, lymphoma, Hodgkin's	Opdivo	Keytruda	
Cancer, melanoma	Opdivo	Keytruda	
Cancer, oesophageal	Opdivo	Keytruda	
Psoriasis	Humira	Enbrel	
Spondyloarthritis, axial	Humira	Enbrel	

- There are five diseases where three of the top 10 drugs are approved. An additional 18 diseases are treated by two of the top 10 drugs.
- PD-1 inhibitors Keytruda and Opdivo directly compete within 12 shared oncology indications, while anti-TNF inhibitors Humira and Enbrel compete within six shared autoimmune/immunology indications.














Drug Types

Drug Type and Route of Administration of the Top Drugs of 2019

Seven of the top 10 best-selling drugs are injectable biologics

In parallel with 2018, biologics account for most of the top 10 drugs of 2019. Seven of the best-selling drugs were biologics in 2019 compared to eight in 2018. Of the biologics, three are administered intravenously, two subcutaneously, and Rituxan may be administered either intravenously or subcutaneously, using Rituxan Hycela. Eylea remains the only intravitreal injection in the top 10. The remainder of the top drugs (Revlimid, Imbruvica, and Eliquis) were small molecules, boasting the convenience of oral administration.

		Humira	Keytruda	Revlimid	Imbruvica	Opdivo	Eliquis	Eylea	Enbrel	Avastin	Rituxan
Biologic	Intravenous										
	Subcutaneous										
	Intravitreal										
Small molecule	Oral										

The global outbreak of COVID-19 (coronavirus) has shaken up healthcare systems, changing priorities and limiting the capacity for the administration of drugs by a healthcare professional. Within the context of the pandemic, self-administered and oral medications are the most feasible, while intravenous infusions at healthcare centres are less accessible. More than ever, route of administration holds importance from a patient's perspective, not just as an issue of convenience or preference but of fundamental accessibility. The American College of Rheumatology has issued infusion guidance during the crisis. Recommendations include temporary interruption of therapy, increased dosing intervals, provisional use of a bridge therapy, and switching to an alternative therapy. The UK National Institute for Health and Care Excellence (NICE) recommends either switching patients from the intravenous form of a drug to the subcutaneous one or moving to a different subcutaneous treatment. Sales of intravenous drugs are being negatively impacted as a result. This turbulent climate necessitates take-home, self-administered therapies and may shape a future trend towards blockbusters possessing these attributes for greater resilience in case of uncertain times.



US Dynamics

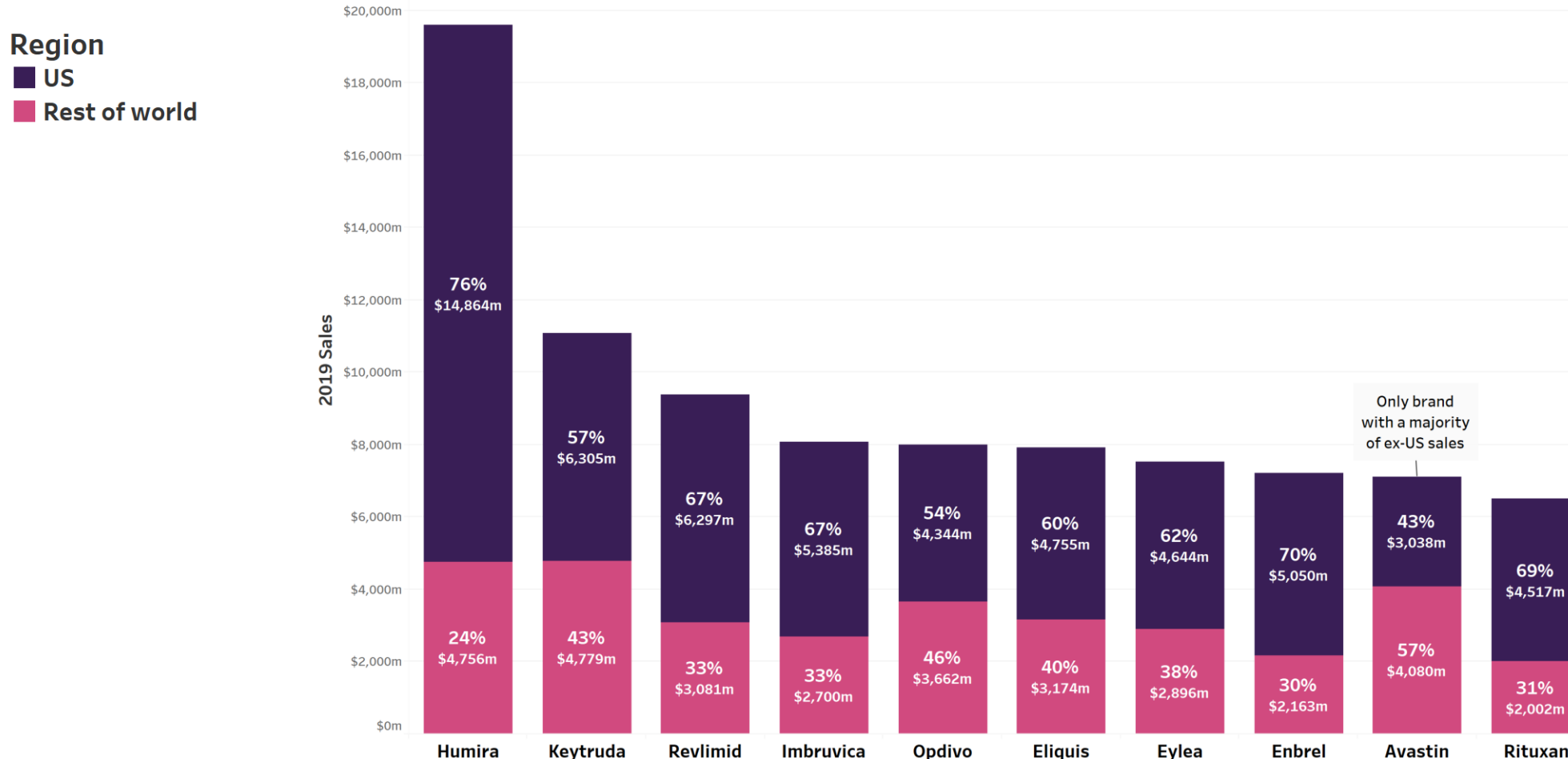




US Versus ex-US Sales of the Top Drugs

On average, US sales represented 62% of global sales for the best-selling drugs in 2019

The US market was dominant as the largest contributor to global sales for all the top brands, with the exception of Avastin. Avastin's US sales comprised 43% of its global sales in 2019 as the brand has experienced biosimilar attrition since July 2019 in the US.





US Proportion of Global Sales of the Top Drugs of 2019

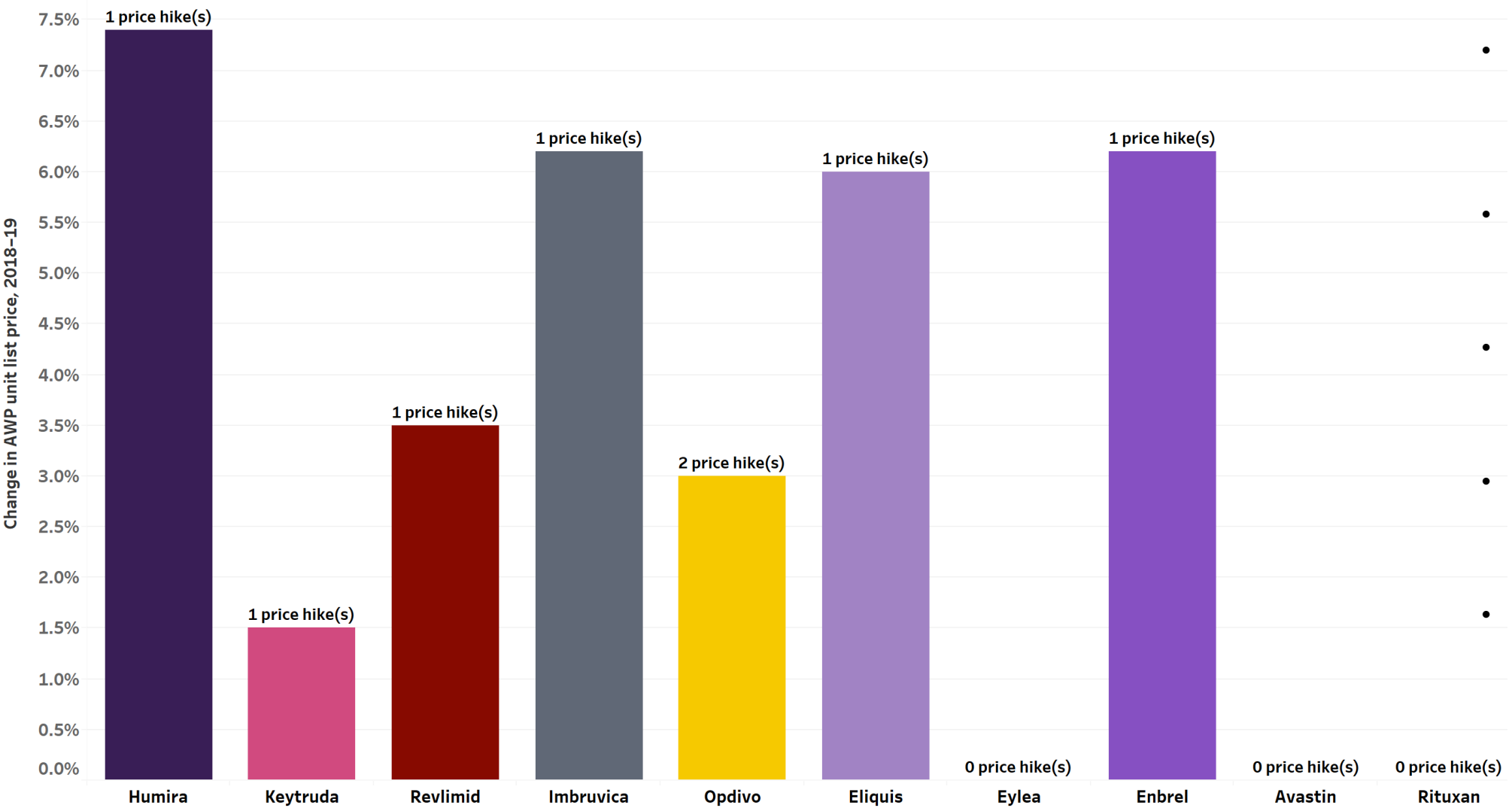
On average, US sales represented 62% of global sales for the best-selling drugs in 2019

Rank	Global sales	Brand (molecule)	US % of global sales
1	\$19.6bn	Humira (adalimumab)	75.8%
2	\$11.1bn	Keytruda (pembrolizumab)	56.9%
3	\$9.4bn	Revlimid (lenalidomide)	67.1%
4	\$8.1bn	Imbruvica (ibrutinib)	66.6%
5	\$8.0bn	Opdivo (nivolumab)	54.3%
6	\$7.9bn	Eliquis (apixaban)	60.0%
7	\$7.5bn	Eylea (aflibercept)	61.6%
8	\$7.2bn	Enbrel (etanercept)	70.0%
9	\$7.1bn	Avastin (bevacizumab)	42.7%
10	\$6.5bn	Rituxan (rituximab)	69.3%



2018–19 US Price Changes of the Best-Selling Drugs of 2019

The list prices of seven top drugs in 2019 increased from 2018 AWP = Average Wholesale price



Source: Redbook

- Inflated pricing is characteristic of the US market and intrinsic to the continued sales growth of lucrative drugs.
- Most of the best-selling drugs in 2019 have undergone at least one price hike since 2018.
- Opdivo experienced the most price hikes as its list price increased twice during 2018–19.
- The list price of the best-selling drug, Humira, increased the most, by 7.4%.
- Eylea, Avastin, and Rituxan were exceptional in having unchanged list prices from 2018.

2018–19 US Price Changes of the Best-Selling Drugs of 2019

The list prices of the top drugs in 2019 increased from 2018, bar Eylea, Avastin, and Rituxan

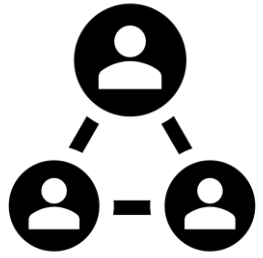


Sales rank, 2019	Global sales, 2019	Brand (molecule)	Change in US AWP unit list price, 2018–19	Number of price hikes, 2018–19
1	\$19.6bn	Humira (adalimumab)	7.4%	1
2	\$11.1bn	Keytruda (pembrolizumab)	1.5%	1
3	\$9.4bn	Revlimid (lenalidomide)	3.5%	1
4	\$8.1bn	Imbruvica (ibrutinib)	6.2%	1
5	\$8.0bn	Opdivo (nivolumab)	3.0%	2
6	\$7.9bn	Eliquis (apixaban)	6.0%	1
7	\$7.5bn	Eylea (aflibercept)	0.0%	0
8	\$7.2bn	Enbrel (etanercept)	6.2%	1
9	\$7.1bn	Avastin (bevacizumab)	0.0%	0
10	\$6.5bn	Rituxan (rituximab)	0.0%	0

Drugs were ranked by their AWP unit list price in Redbook, “1” being the most expensive.

Changes in list price were calculated using the prices that were listed for most of each year.

AWP = average wholesale price

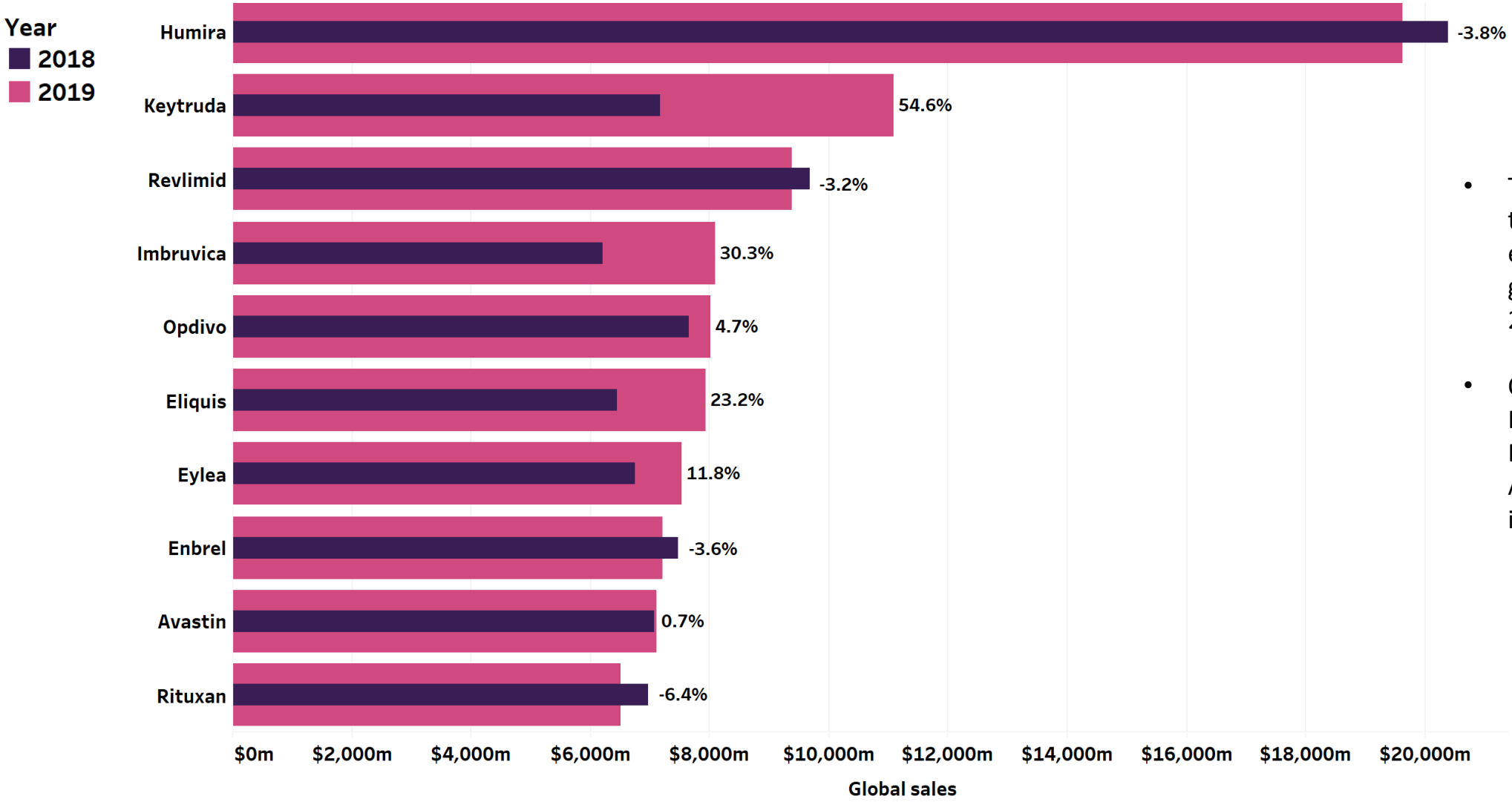


Lifecycle Stage



Global Sales of the Top Drugs of 2019 Compared to 2018

On average, global sales of the top brands grew by 11% from 2018 to 2019



- The majority of the top brands experienced sales growth from 2018 to 2019.
- On average, Keytruda, Imbruvica, Opdivo, Eliquis, Eylea, and Avastin grew by 20.9% in global sales.



2018 and 2019 Global Sales of the Best-Selling Drugs of 2019

Four of the top drugs of 2019 experienced contracted sales from 2018 to 2019

Of the top drugs of 2019, Humira, Revlimid, Enbrel, and Rituxan are on a sales decline compared to their previous sales in 2018. On average, these products' global sales decreased by 4.2%. These headwinds were primarily imposed by biosimilar/generic competition.

Rituxan's sales decreased the most (-6.4%) as it faced biosimilar competition in the US market, whereas the other declining brands still benefit from exclusivity in the US, from where most of their sales are derived. Humira is sustaining direct biosimilar erosion in Europe since patent expiration in October 2018, as well as in other countries, while Revlimid is also experiencing ex-US sales erosion. In February 2019, Alvogen and Lotus launched the first lenalidomide generics in multiple European countries, including Romania, Croatia, and Bulgaria. For Enbrel, biosimilar competition has been ongoing since 2016 in most developed European markets.

Brand (molecule)	Rank, 2019	Global sales, 2019	Rank, 2018	Global sales, 2018	Change in global sales, 2018–19
Humira (adalimumab)	1	\$19.6bn	1	\$20.4bn	-3.8%
Keytruda (pembrolizumab)	2	\$11.1bn	6	\$7.2bn	54.6%
Revlimid (lenalidomide)	3	\$9.4bn	2	\$9.7bn	-3.2%
Imbruvica (ibrutinib)	4	\$8.1bn	12	\$6.2bn	30.3%
Opdivo (nivolumab)	5	\$8.0bn	3	\$7.6bn	4.7%
Eliquis (apixaban)	6	\$7.9bn	11	\$6.4bn	23.2%
Eylea (aflibercept)	7	\$7.5bn	9	\$6.7bn	11.8%
Enbrel (etanercept)	8	\$7.2bn	4	\$7.5bn	-3.6%
Avastin (bevacizumab)	9	\$7.1bn	7	\$7.1bn	0.7%
Rituxan (rituximab)	10	\$6.5bn	8	\$7.0bn	-6.4%



US First Approval and Launch Dates of the Top Drugs of 2019

Half of the top brands first launched in the US during the past 10 years

Five of the best-selling brands in 2019 first reached the US market in the past 10 years. Opdivo (ranked fifth), Keytruda (ranked second), Imbruvica (ranked fourth), Eliquis (ranked sixth), and Eylea (ranked seventh) represent the newer brands that are part of the top 10 drugs.

First US Launch



Rank	Global sales, 2019	Brand (molecule)	Initial FDA approval date	US launch date
1	\$19.6bn	Humira (adalimumab)	Dec-02	Jan-03
2	\$11.1bn	Keytruda (pembrolizumab)	Sep-14	Jan-15
3	\$9.4bn	Revlimid (lenalidomide)	Dec-05	Dec-05
4	\$8.1bn	Imbruvica (ibrutinib)	Nov-13	Nov-13
5	\$8.0bn	Opdivo (nivolumab)	Dec-14	Jan-15
6	\$7.9bn	Eliquis (apixaban)	Dec-12	Mar-13
7	\$7.5bn	Eylea (aflibercept)	Nov-11	Nov-11
8	\$7.2bn	Enbrel (etanercept)	Nov-98	Dec-98
9	\$7.1bn	Avastin (bevacizumab)	Feb-04	Mar-04
10	\$6.5bn	Rituxan (rituximab)	Nov-97	Mar-98

FDA = US Food and Drug Administration



US Biosimilar/Generic Threat



First US Biosimilar/Generic Entries of the Top Drugs of 2019

Two of the best-selling drugs currently face biosimilar competition in the US

Two of the best-selling brands in 2019 have faced biosimilar competition in the US market since 2019. Biosimilars for Avastin and Rituxan first launched in the US in July 2019 and November 2019, respectively. All best-selling brands will face biosimilar/generic erosion within the next 10 years.

Launch year of the first US biosimilar/generic



Rank	Global sales, 2019	Brand (molecule)	First biosimilar/generic entry in the US
1	\$19.6bn	Humira (adalimumab)	2023
2	\$11.1bn	Keytruda (pembrolizumab)	2028
3	\$9.4bn	Revlimid (lenalidomide)	2022
4	\$8.1bn	Imbruvica (ibrutinib)	2027
5	\$8.0bn	Opdivo (nivolumab)	2028
6	\$7.9bn	Eliquis (apixaban)	2026
7	\$7.5bn	Eylea (afibercept)	2023
8	\$7.2bn	Enbrel (etanercept)	2029
9	\$7.1bn	Avastin (bevacizumab)	2019
10	\$6.5bn	Rituxan (rituximab)	2019

Avastin Biosimilars

Two biosimilars for Avastin have launched in the US at an average discount of 19%

Product type	Drug	Companies	Approval date	Launch date	Discount on list price
Originator	Avastin	Roche	February 2004	March 2004	
Biosimilar	Mvasi	Amgen	September 2017	July 2019	15%
Biosimilar	Zirabev	Pfizer	June 2019	January 2020	23%

Amgen's Mvasi was the first biosimilar approved for the treatment of cancer in the US in September 2017. The biosimilar entered the US market in July 2019 at 15% below Avastin's list price. Pfizer's Zirabev entered the US market in January 2020 at a 23% discount compared to Avastin.

Both biosimilars are approved to treat five types of cancer and are not indicated for Avastin's sixth indication – epithelial ovarian, fallopian tube, or primary peritoneal cancer. Approved biosimilar indications encompass:

- metastatic colorectal cancer
- unresectable/locally advanced/recurrent/metastatic non-squamous non-small cell lung cancer
- recurrent glioblastoma
- metastatic renal cell carcinoma
- persistent/recurrent/metastatic cervical cancer.

In just under half a year, Mvasi experienced strong uptake with a 17% share of the bevacizumab marketplace by the end of 2019. As of 2020, this has increased to a 33% share of the bevacizumab market.



Rituxan Biosimilars

Two biosimilars for Rituxan have launched in the US at an average discount of 17%

Product type	Drug	Companies	Approval date	Launch date	Discount on list price
Originator	Rituxan	Roche/Biogen	November 1997	March 1998	
Biosimilar	Truxima	Teva/Celltrion	November 2018	November 2019	10%
Biosimilar	Ruxience	Pfizer	July 2019	January 2020	24%

Teva and Celltrion's Truxima was the first rituximab biosimilar launched in the US in November 2019, entering at 10% below Rituxan's list price. Pfizer exceeded Truxima's price discount with Ruxience's competitive 24% discount versus Rituxan. In January 2020, Ruxience was Pfizer's fifth biosimilar to enter the US market.

Although Ruxience launched after Truxima, the former entered the market with an edge over Truxima in the breadth of its label. Ruxience was already indicated for granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA), unlike Truxima. While Truxima first received approval in November 2018, its label was narrower than the originator due to patent protection across therapeutic areas. Truxima's initial approval was limited to three non-Hodgkin's lymphoma (NHL) indications. In May 2019, the FDA approved Truxima to match all of Rituxan's oncology indications for NHL and chronic lymphocytic leukemia (CLL). Following a settlement agreement, Truxima was launched for rheumatoid arthritis (RA), GPA, and MPA in May 2020. This shifted the upper hand to Truxima, making it the only biosimilar rituximab available in the US for RA.

During Teva's Q4 2019 Earnings Call, it was highlighted that Truxima achieved 12–15% market share.



First US Biosimilar/Generic Entries of the Top Drugs of 2019

In three years' time, half of the best-selling drugs of 2019 will be encountering biosimilar/generic competition

By 2023, Revlimid, Humira, and Eylea will join Avastin and Rituxan as the next best-selling brands facing biosimilar/generic competition.

Launch year of the first US biosimilar/generic



Rank	Global sales, 2019	Brand (molecule)	First biosimilar/generic entry in the US	Notes
1	\$19.6bn	Humira (adalimumab)	January 2023	Settlement agreement with Amgen permitting launch of biosimilar Amjevita
3	\$9.4bn	Revlimid (lenalidomide)	March 2022	Settlement agreement with Natco Pharma permitting volume-limited launch of generics
7	\$7.5bn	Eylea (aflibercept)	June 2023	Patent term extension; no approved biosimilars



Biosimilar Threat to Humira

US biosimilar erosion in 2023 is anticipated to be fiercer than current international erosion

In the US, biosimilar erosion of Humira’s sales will be aggressive from the outset, given the handful of FDA-approved biosimilars waiting in the wings for successive launch during 2023. During AbbVie’s Q4 2019 earnings call, it was elucidated that sales erosion has elapsed in a step-wise manner, increasing over time as new adalimumab biosimilars enter the markets. Within the international markets that possessed biosimilars in 2019, biosimilar erosion of Humira stood at ~45–48%, of which 20–30% may be attributed to market share loss, while the rest was due to price.

US launches of adalimumab biosimilars in 2023



Amjevita
31 January



Hadlima
30 June



Cyltezo
1 July



Hyrimoz
30 September



Abrilada
20 November

Although Humira’s US composition of matter patent expired in December 2016, approved biosimilars are yet to launch in the country. Biosimilar adalimumab innovators have committed to delay US launch until 2023 in return for earlier access to the European market as part of settlement agreements with AbbVie. Amgen’s Amjevita (approved in September 2016) is set to be the first adalimumab biosimilar to launch on 31 January 2023, with a post-approval delay of six years and four months. Four other FDA-approved adalimumab biosimilars will also launch in 2023. This intensely competitive environment will likely carve a sharp sales decline, smoothing out into an early plateau.



Defense Against Biosimilar Threat to Humira

AbbVie is lining up Skyrizi and Rinvoq as Humira's successors in the autoimmune/immunology space

AbbVie expects Skyrizi (risankizumab) and Rinvoq (upadacitinib) to match or exceed Humira's commercial success by establishing their broad applicability through global clinical trial programs. Skyrizi and Rinvoq first launched in the US in July 2019 for psoriasis and September 2019 for RA, respectively. The company is pursuing investigations into Skyrizi and Rinvoq's potential to treat all core indications for which Humira is approved, as well as atopic dermatitis beyond Humira's label.

AbbVie has been conducting clinical trials to establish the superiority of these new brands over Humira in head-to-head trials, to encourage uptake and defend its market share in preparation for biosimilar erosion of Humira's US sales. Considering that 40% of Humira's sales may be attributed to RA and psoriasis, there is confidence that the immunology space represents a significant opportunity for Skyrizi and Rinvoq.



AbbVie's Phase II pipeline antibody drug conjugate, ABBV-3373, is a next-generation Humira

Earlier in the pipeline, AbbVie is also investing in ABBV-3373 to offset future biosimilar erosion. ABBV-3373 is an investigational antibody drug conjugate comprised of a novel glucocorticoid receptor modulator linked to adalimumab. It is being designed to deliver high-potency steroid, which cannot be delivered systemically, directly to activated immune cells. Thus, the drug is being developed to achieve precise drug delivery for dampened inflammation while minimizing systemic side effects associated with glucocorticoids. ABBV-3373 has already produced positive data from its first proof-of-concept Phase IIa study in RA patients who are inadequate responders to methotrexate. AbbVie reported that ABBV-3373 demonstrated statistically significant improvement on the remission primary endpoint compared to a pre-specified historical adalimumab mean.

Generic Threat to Revlimid

Revlimid will experience controlled generic competition in the US from 2022 onwards

Celgene, Revlimid's originator company, entered into settlement agreements with multiple generics manufacturers, granting volume-limited licenses for these companies to sell generic lenalidomide. The settlement with Natco Pharma permits the earliest generic launch, commencing in March 2022. Alvogen has also been granted a volume-limited license; however, the agreed generic launch date after March 2022 is confidential. Additionally, the permitted percentage volumes of generic lenalidomide have not been disclosed. From 31 January 2026, generic erosion will intensify as Natco and Alvogen will be able to sell generic lenalidomide exempt from volume limitations.



The availability of more generics will stoke competition and is associated with steeper price discounts. Generally in the US, the average manufacturer price (AMP) discounts of generics may range from 39% to over 95% compared to the branded drug's AMP. Historically, generic erosion in the US has been formidable, with cheap generics claiming 85–90% of the originator's market share within two years of their launch.



Celgene was publicly listed for restricting access to drug samples for generic testing, obstructing competition

In 2018, the FDA commissioner issued a statement condemning the tactics adopted by brand companies to create obstacles for generic developers in purchasing samples of their branded drugs. Companies may leverage Risk Evaluation and Mitigation Strategy programs and misuse them to limit access to reference products. The FDA is cracking down on this anti-competitive behavior, and has already demonstrated action regarding small molecules by listing cases publicly. Revlimid was among the inquiries that drug makers put forward to the FDA concerning the challenge in obtaining samples for lenalidomide testing.



Biosimilar Threat to Eylea

Eylea will likely face indirect biosimilar competition prior to its US patent expiry in 2023

Eylea is yet to face biosimilar competition in any markets, and there are currently no FDA-approved aflibercept biosimilars. Although its US patent is not set to expire until June 2023, Eylea will likely face indirect biosimilar competition prior to this date. Lucentis (ranibizumab; Roche/Novartis) is a key competitor of the same drug class in the retinal disorders market, as the first-to-market anti-vascular endothelial growth factor (VEGF) therapy, and its US patent expired in June 2020. Thus, the advent of ranibizumab biosimilars will result in indirect erosion of Eylea's sales prior to its own patent expiry.

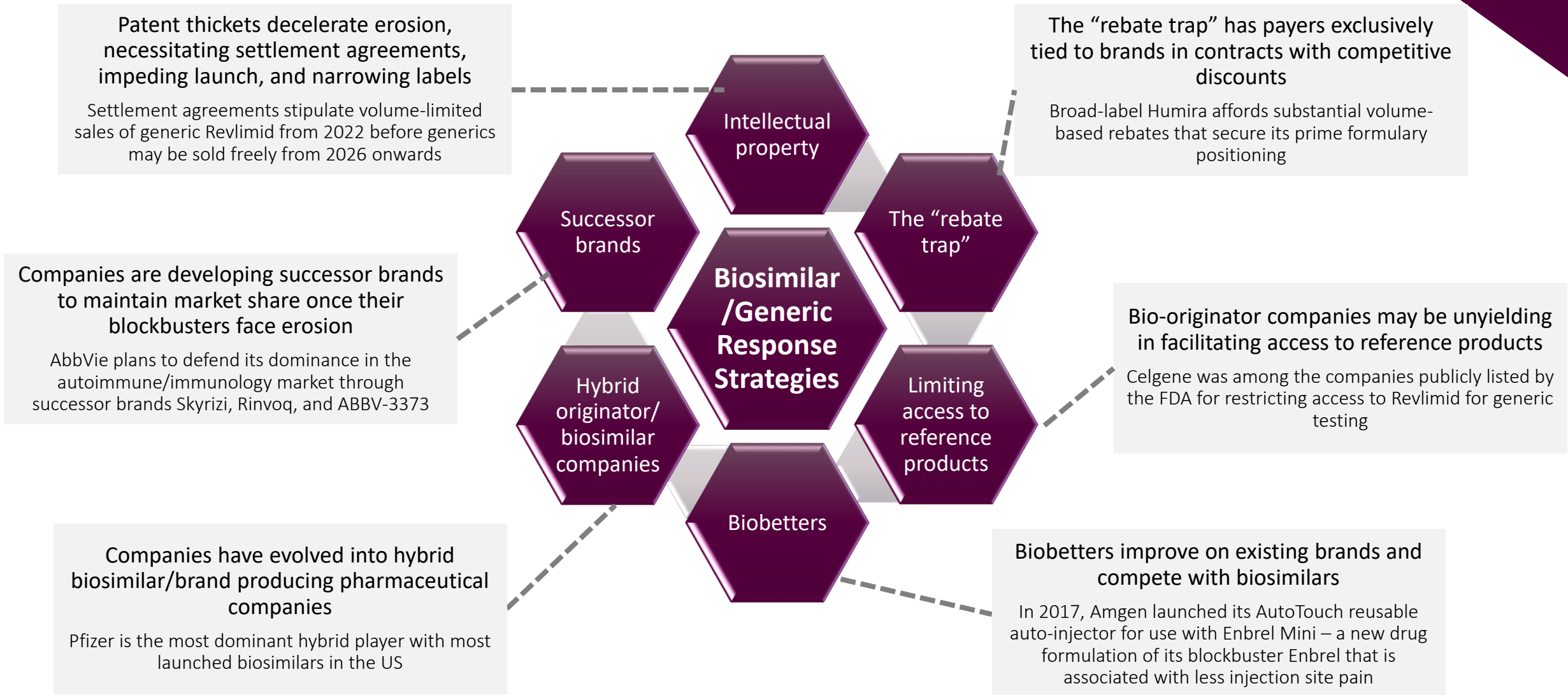
Regeneron and Bayer have encountered setbacks, unsuccessfully fulfilling their lifecycle management strategy to position Eylea as a backbone therapy

Regeneron and Bayer conducted multiple studies exploring Eylea's potential to treat retinal disorders as part of a combination regimen. These studies aimed to establish the gold-standard anti-VEGF as a backbone therapy, further entrenching its position in the treatment algorithm. Implementing this lifecycle management strategy has proved challenging, however, considering the slew of negative Phase II trials yielded.

Negative combination trial	ClinicalTrials.gov identifier	Phase	Drug regimen	Disease
RUBY	NCT02712008	II	Eylea + nesvacumab	Diabetic macular edema
ONYX	NCT02713204	II	Eylea + nesvacumab	Wet AMD
CAPELLA	NCT02418754	II	Eylea + rinucumab	Wet AMD

Wet AMD = wet age-related macular degeneration

Strategies Being Adopted in the Face of Biosimilars/Generics



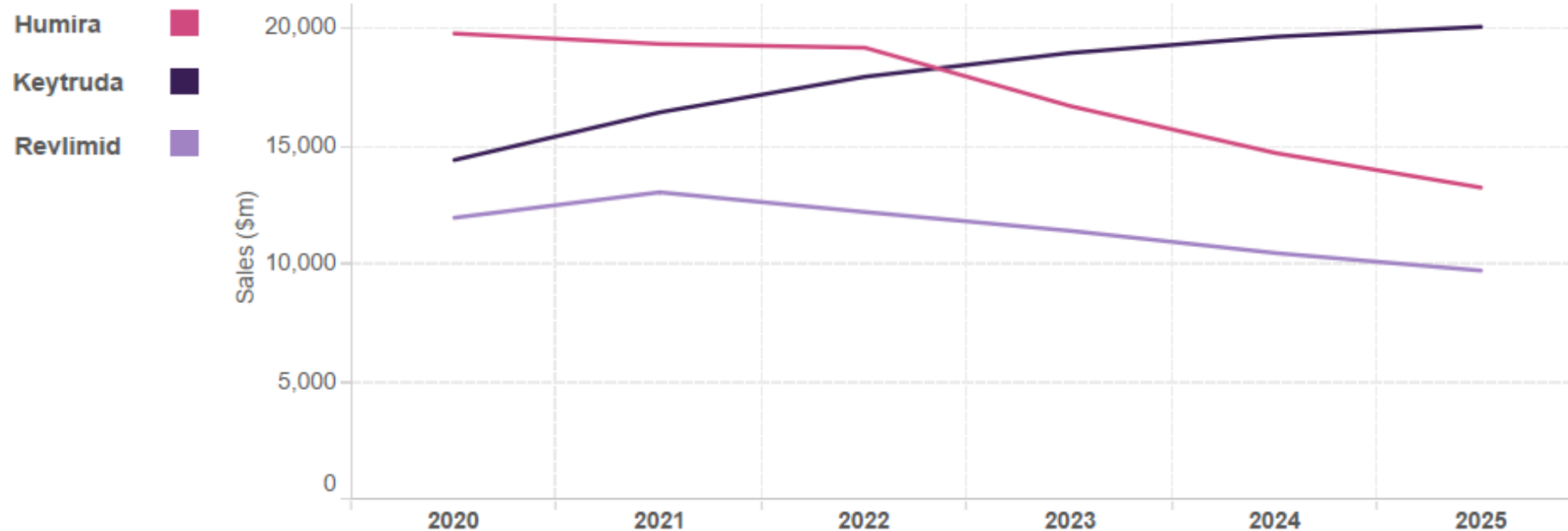


Sales Forecasts of the Top 3 Drugs



PharmaVitae Global Sales Forecasts of the Top 3 Drugs of 2019

Keytruda is forecast to supplant Humira as a \$20bn drug by 2025



- In the five-year window, Keytruda is the only drug that will continue on a positive sales trajectory, expanding to attain \$20.1bn in sales in 2025, thereby superseding Humira (worth \$19.8bn in 2020).
- Sharp declines in Humira and Revlimid’s sales projections are attributed to biosimilar and generic launches in the US in 2023 and 2022, respectively.
- PharmaVitae forecasts projected drug sales based on historical company-reported product revenues and anticipated market-moving events, supplemented by primary and secondary research.

Drug	CAGR	2020	2021	2022	2023	2024	2025
Humira	-7.7%	\$19.8bn	\$19.4bn	\$19.2bn	\$16.8bn	\$14.8bn	\$13.3bn
Keytruda	6.8%	\$14.5bn	\$16.5bn	\$18.0bn	\$19.0bn	\$19.7bn	\$20.1bn
Revlimid	-4.1%	\$12.0bn	\$13.1bn	\$12.2bn	\$11.4bn	\$10.5bn	\$9.8bn
Total		\$46.3bn	\$49.0bn	\$49.5bn	\$47.2bn	\$45.0bn	\$43.2bn

CAGR = compound annual growth rate

Appendix



Abbreviations

AWP = Average Wholesale Price

CRC = colorectal cancer

FDA = US Food and Drug Administration

MCL = mantle cell lymphoma

NSCLC = non-small cell lung cancer

PD-1 = programmed cell death protein-1

RA = rheumatoid arthritis

RoW = rest of world

TNF = tumor necrosis factor

VEGF = vascular endothelial growth factor

Wet AMD = wet age-related macular degeneration



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Stephanie Yip joined Informa Pharma Intelligence in 2017. As a Senior Analyst, she is experienced in conducting primary research involving key opinion leaders and payers, analyzing treatment landscapes, and tracking market-moving events to build robust drug forecasts. Stephanie has produced content spanning numerous therapy areas including neurology, psychiatry, immunology & inflammation, gynecology, and rare diseases. Furthermore, she has executed diverse consulting projects, delivering custom commercial intelligence to clients. Additionally, she has authored white papers covering current topics in the pharmaceutical industry, such as medical marijuana and the best-selling drugs. Prior to working at Informa Pharma Intelligence, Stephanie gained experience as an editorial assistant in scientific publishing. She graduated from Imperial College London with a Biomedical Science degree.





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