White Paper

The Impact of Biosimilar Competition in Europe

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Table of contents

Introduction

The 7th iteration of the 'Impact of Biosimilar Competition in Europe' report describes the effects on price, volume, and market share following the arrival of biosimilar competition in Europe. The report consists of observations on competitive markets, and a set of Key Performance Indicators (KPIs) to monitor the impact of biosimilars in 23 European markets.

The report has been a long-standing source of information on the status of the biosimilars market. As the report adds new therapy areas, and as new classes emerge, we have new challenges that we must adapt to. This means that we continue to refine previous definitions to make them more suitable for the current environment. These updated definitions build on the 2020 iterations, and permit improved classification of new and historic dynamics within the market.

This report has been prepared by IQVIA at the request of the European Commission services with initial contributions on defining the KPIs from EFPIA, Medicines for Europe, and EuropaBio. The observations have been developed solely by IQVIA based on the data and analyses performed. The information and views set out in this report are those of its authors and are not to be attributed to, nor necessarily reflect the views of the European Commission or any of its services. The European Medicines Agency (EMA) has a central role in setting the rules for biosimilar submissions, approving applications, establishing approved indications and monitoring adverse events, and if necessary, issuing safety warnings. We have, when appropriate, quoted their information and statements.

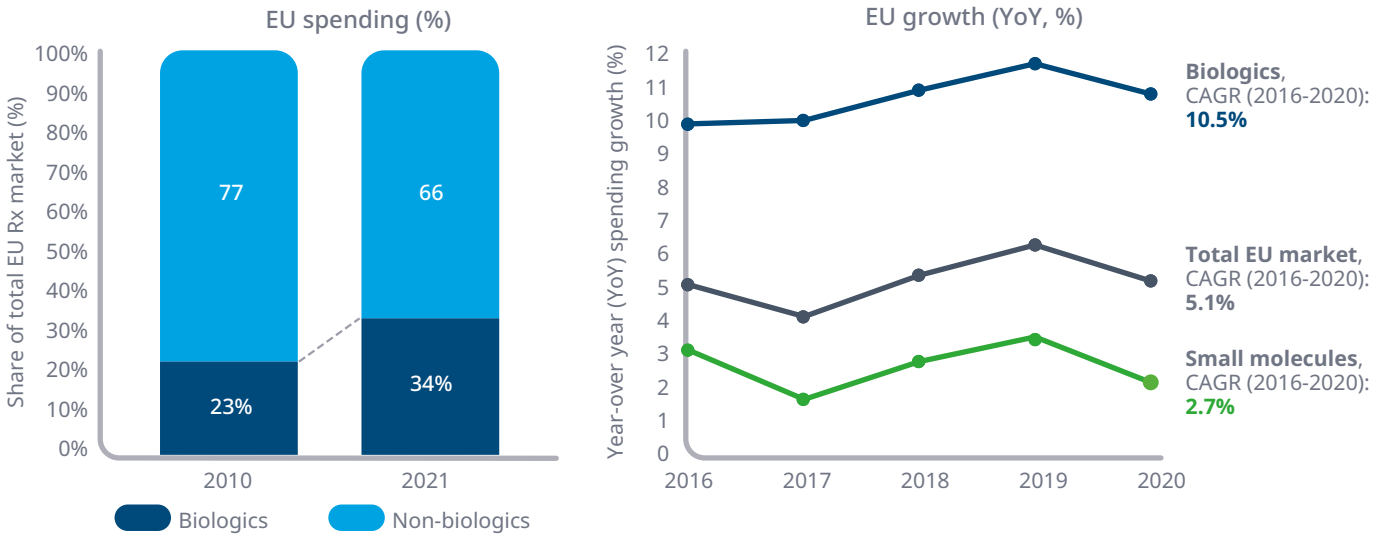
Key observations

BACKGROUND

Biologic medicines are an increasingly important component of pharmaceutical expenditure, due to their efficacy as treatments for complex conditions. Biologics represent 34% of medicine spending in Europe at list prices, reaching €78.6 billion in 2021, and growing at a 10.5% compound annual growth rate (CAGR) over the past five years. This compares to a 5.1% CAGR for the total market comprising small molecules, biologics, and biosimilar competitors. This market segment is increasingly important and continues to grow faster than non-biologic medicines as the dominant market segment for 10+ years. The importance of biologic medicines to healthcare systems continues, with new biologics accounting for ~15% of new active substances centrally approved in 2020.[1] The total European biosimilar market has reached €8.8 billion in 2021.

The accessible market (defined as the market accessible to biosimilar competition, either through approved biosimilars, or due to loss of exclusivity from the originator medicines) is between 10%–40% of the total biologics market by country. This has grown as loss of exclusivity for major molecules with high treatment volumes has occurred in recent years. In the context of this report (9 therapy classes), the accessible market is approximately 80% of the total market volume.

Exhibit 1: The importance of biologics within the European pharmaceutical market



Source: IQVIA MIDAS (Q2 2021), Rx only; Biologic molecules exclude ATC-V (vaccines, and various)

It is therefore critical to healthcare system sustainability to ensure that the impact of biosimilar competition is managed effectively in this growing segment. IQVIA's 5 observations on the impact of biosimilar competition explore this by discussing:

1. **COVID-19:** The pandemic has impacted certain segments of the biologic market
2. **Savings:** The savings from biosimilar competition reach an all-time high
3. **Access:** Development of access to biologic medicines remains challenging,
4. **Competition:** The competitive environment in Europe is changing
5. **Future:** Ensuring preparedness for the future biosimilar opportunity

[1] European Medicines Agency (EMA) European Public Assessment Reports (EPAR) list 2021 (last accessed October 2021)

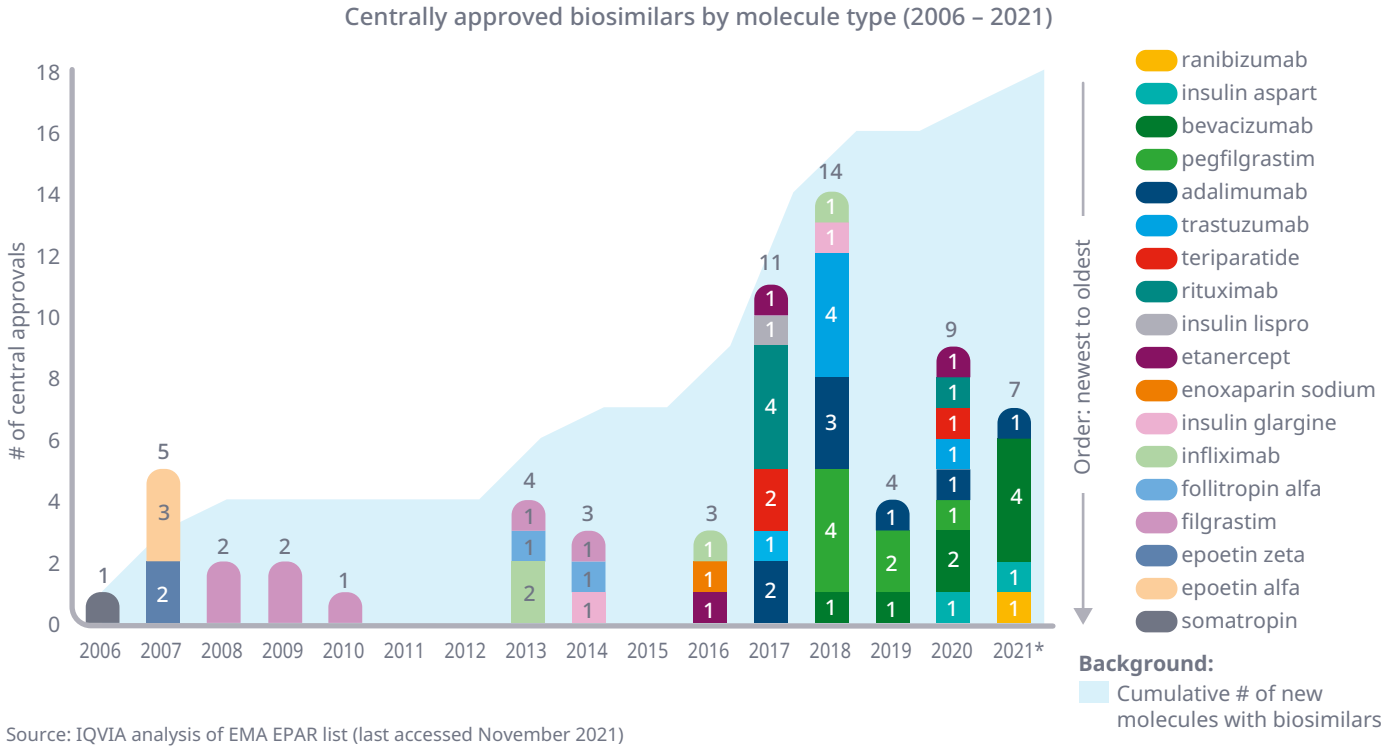
1. COVID-19: THE PANDEMIC HAS IMPACTED CERTAIN SEGMENTS OF THE BIOLOGIC MARKET

1.1. COVID-19 has not delayed the regulatory approval of new biosimilars

Since the publication of the previous report on the Impact of Biosimilar Competition (8th edition, published December 2020), the pandemic has progressed significantly. The most recent report held data for only 3 months of the pandemic (March–June 2020) and its impact on biologic prescribing was not fully available. This most recent edition covers the pandemic using IQVIA MIDAS™ data to June 2021 and provides a more complete picture of the impact to biologic medicines from both a launch, and prescribing perspective.

2020 was a particularly challenging year to launch non-COVID innovative prescription medicines. European markets saw restrictions to two key drivers of launch uptake, firstly, new and switch prescriptions, and secondly, face-to-face interactive engagement with healthcare professionals. However, from a regulatory standpoint, the EMA continued to perform well approving innovative medicines and biosimilars alike. A further 9 biosimilars were approved in 2020, and there are a further 8 products under review to add to the 7 already approved in 2021.

Exhibit 2: Centrally approved biosimilars and new molecules open to competition



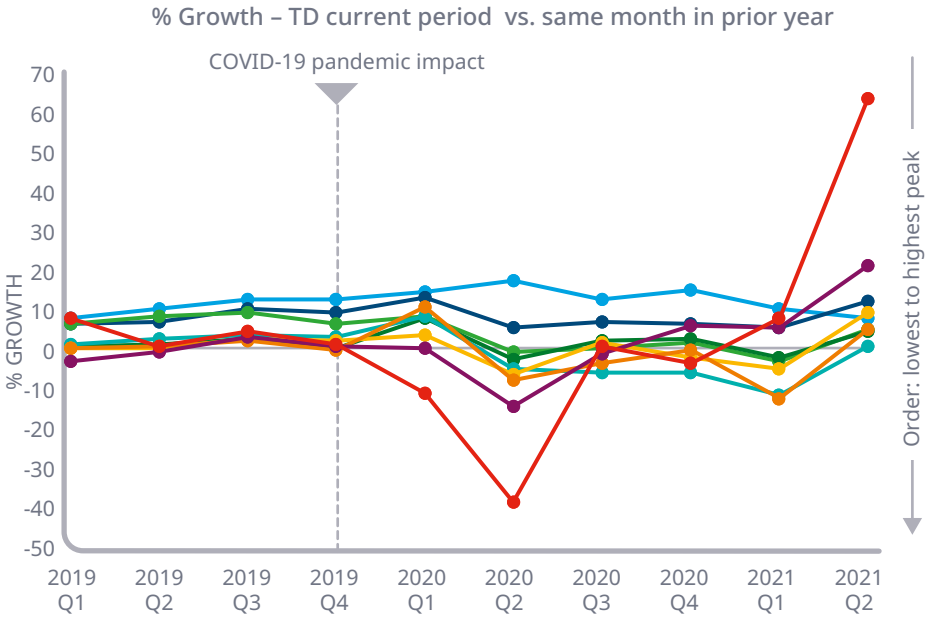
Source: IQVIA analysis of EMA EPAR list (last accessed November 2021)

1.2. COVID-19 had a negative impact on biologic prescribing

A negative impact on approvals has not been seen in biosimilars, or in new innovative medicines (so far), however, the impact on biologic prescribing is clearly visible across Europe at the peak of the COVID-19 pandemic. Comparing the growth rate to the growth year in the previous year, it is possible to see how the volume development of the critical therapy areas has been stunted. Before the pandemic, single-digit growth was present for all therapy areas (excluding: LMWHs, -3%; anti-TNFs, +12%). During the initial lockdown phase across Europe, prescribing dynamics were dramatically changed due to the prioritisation of COVID-19 patients, intensive care, and chronic conditions. This resulted in a reduction in 7 of the 9 therapy areas studied in this report, with the highest

being in non-urgent segments such as fertility (-40% at peak). It has taken 18 months for a rebound (+65% for fertility treatments in Q2 2021) to counteract the drop. At a country-level, markets saw spikes in demand for other medicines as stockpiling occurred and longer prescriptions were issue to safeguard vulnerable populations. Most concerning is the impact on oncology. As the pandemic has developed, concerns have focussed oncology with delays in surgeries, chemotherapy and fewer diagnoses being conducted.[2] While this segment has returned, the impact on the healthcare system of patients with more advanced cancers will have a knock-on impact on mortality without effective management.

Exhibit 3: Impact of COVID-19 on major therapy classes



THERAPY AREA	Q2 2020 vs. Q2 2019	Q2 2021 vs. Q2 2020
GCSF	17%	8%
Anti-TNFs	5%	12%
EPO	-1%	5%
HGH	-3%	4%
PTH (teriparatide)	-5%	0%
Oncology	-7%	9%
Insulins	-8%	5%
LMWHs	-15%	21%
Fertility	-40%	65%

Source: IQVIA MIDAS (Q2 2021), Rx only; Biologic molecules exclude ATC-V (vaccines, and various)

Despite 2020 being impacted by the COVID-19 pandemic, the volume of biosimilar prescribing has generated a record high in savings from biosimilar competition. The list price savings (excluding confidential rebates and discounts) accounted for €5.7 billion.

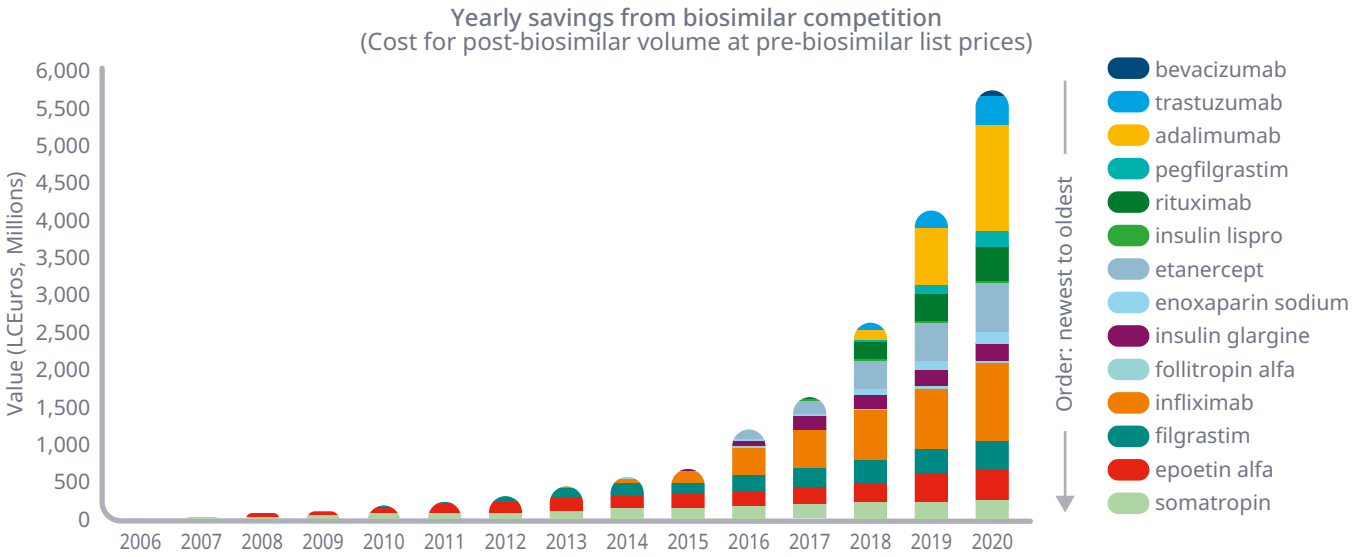
[2] IQVIA, Impact of COVID-19 on cancer treatments in EU4 + UK (published February 2021)

2. SAVINGS:
THE SAVINGS FROM BIOSIMILAR COMPETITION REACH AN ALL-TIME HIGH

2.1 Lower cost of treatment does not automatically increase access

Biosimilars and the impact they have on markets have continued to deliver significant savings to healthcare systems. Despite 2020 being impacted by the COVID-19 pandemic, the volume of biosimilar prescribing has generated a record high in savings from biosimilar competition. The list price savings (excluding confidential rebates and discounts) accounted for €5.7 billion in savings versus the pre-biosimilar cost of the originator by 2020, and this figure is likely to be even higher if it was based on net prices.

Exhibit 4: Long-term view on list price savings from biosimilar competition



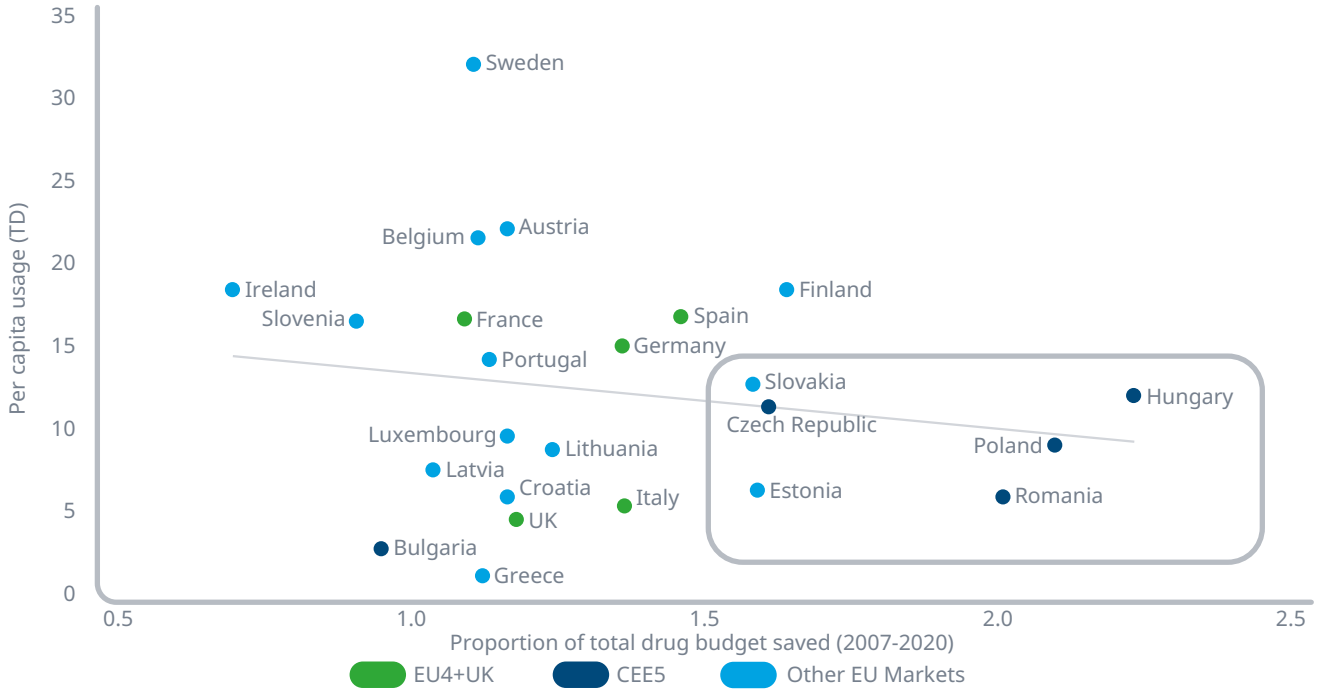
Source: IQVIA MIDAS™ data from 2006 – 2020, using Euros at constant exchange rates; 14 originator products with approved biosimilars from 2006 – 2020 (includes biosimilar and originator), covering the full European Economic Area (33 CTYs), calculated volume is in treatment days determined by WHO-DDD, and where values are unavailable via Oncology Dynamics Physician Survey (2017) DDD estimates

COVID-19 has both a direct and indirect impact on healthcare. Rising government debt, and public spending on welfare, employment wage subsidies, IT services related to the pandemic, and business loads will result in a focus on easily accessible savings opportunities in a challenging economic environment. Ensuring biosimilar competition takes place in a timely manner could be at risk, taking second place to driving uptake. However, a short-term perspective will result in an unsustainable market in a time where system resilience is increasingly important.

2.2 Even countries with low usage have made significant savings

Savings are naturally linked to the amount of the molecule that is used within a market. Despite this, analysis of the list price level savings shows that even countries with relatively low usage have benefited from significant savings on their drug budget since the introduction of biosimilar competition. It can also be the case that high use countries are those that have the highest confidential rebates which may result in movements from countries with high per capita (Sweden, Spain, Finland, Germany). However, Central and Eastern European countries with low levels of access to biologic medicines, and have seen a reduction of 1.5%–2.5% on their total drug spend. The issue is increasing the access to biologics and biosimilars will result in an increase in total pharmaceutical expenditure due to historically low usage in innovative biologicals.

Exhibit 5: Biologic usage and the impact on the total pharmaceutical budget



Source: IQVIA MIDAS (Q2 2021), Rx only; Biologic molecules exclude ATC-V (vaccines, and various); population data sourced from OECD (last accessed November 2021)

2.3 List price savings are only part of the total savings received by payers

List price savings are the visible segment of the impact of biosimilar competition. Confidential rebates and discounts are frequently available, and largely dependent on how to the healthcare system is organised. In previous years we have estimated the potential impact that confidential discounts and rebates can have on the total drug budget.[3] These agreements remain confidential, and the scale is highly variable based on the starting price of the molecule within a market, but also the volume of patients that are treated. For many countries in Europe, the majority of the savings from biosimilar competition are found in these rebates. This puts the €5.7 billion in savings shown in exhibit 4 into context.

3. ACCESS: DEVELOPMENT OF ACCESS TO BIOLOGIC MEDICINES REMAINS CHALLENGING

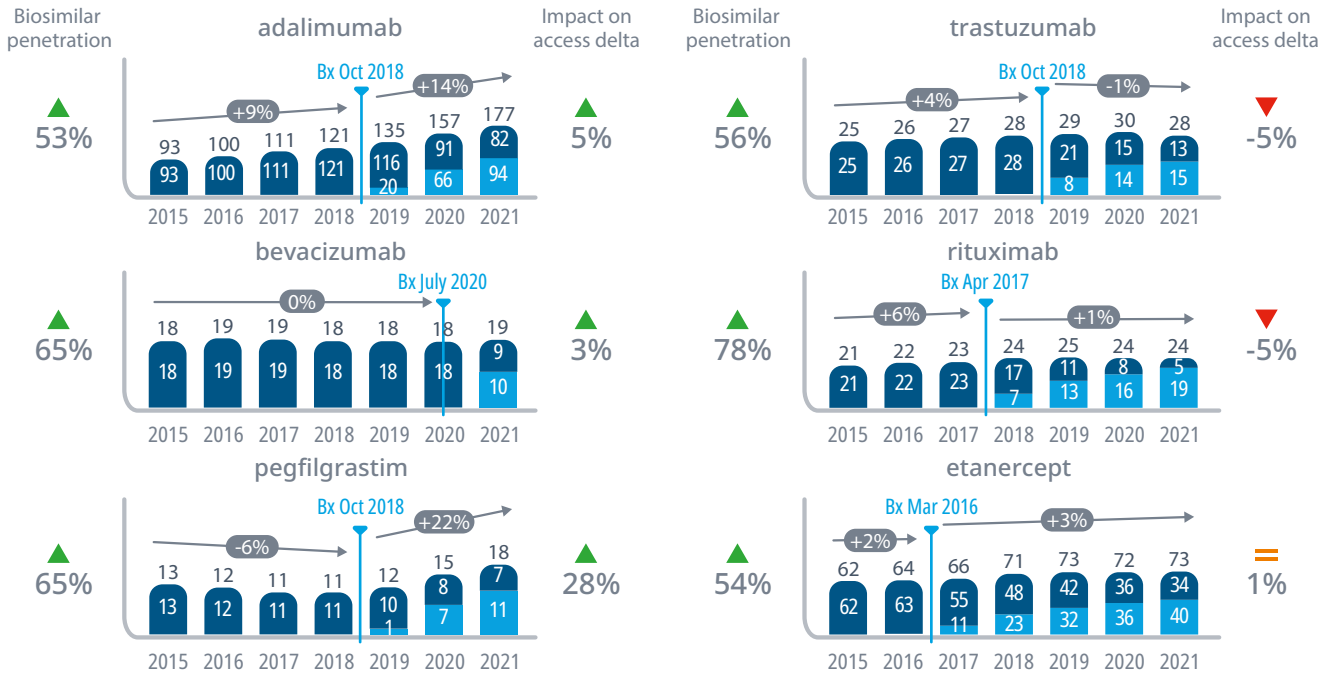
3.1 Growth in access is not occurring in all segments or markets

With increasing focus on cost pressures, pharmaceutical expenditure, and fewer patients visiting critical points of care, access to biologic medicines continues to be an issue. The core proposition of biosimilar medicines is to generate savings in the system, but also increase access to the high cost, complex biologic molecules from which they are based.

Access to biologic medicines has seen growth in some molecules (e.g., Pegfilgrastim). However, access to the molecule has not seen significant changes for several years which highlights that in many instances there were patients unable to access the treatment. In many cases, the overall impact on treatment volumes has fallen (trastuzumab, rituximab) or remained low (etanercept, bevacizumab). Adalimumab is the exception to this rule, and its growth pre-biosimilar entry has increased upon biosimilar entry resulting in delta of +5%. Molecules with flat access can have negative impact from COVID-19 but also it is often the case that the impact on the total class can be relatively limited while certain molecules cannibalise market share from others.

[3] IQVIA, The Impact of Biosimilar Competition in Europe reports (2019, page 5; 2020, page 3)

Exhibit 6: Patient access to molecules with biosimilar competition



Source: IQVIA MIDAS (Q2 2021)

3.2 Growth in access can be limited by historic usage of protected brands

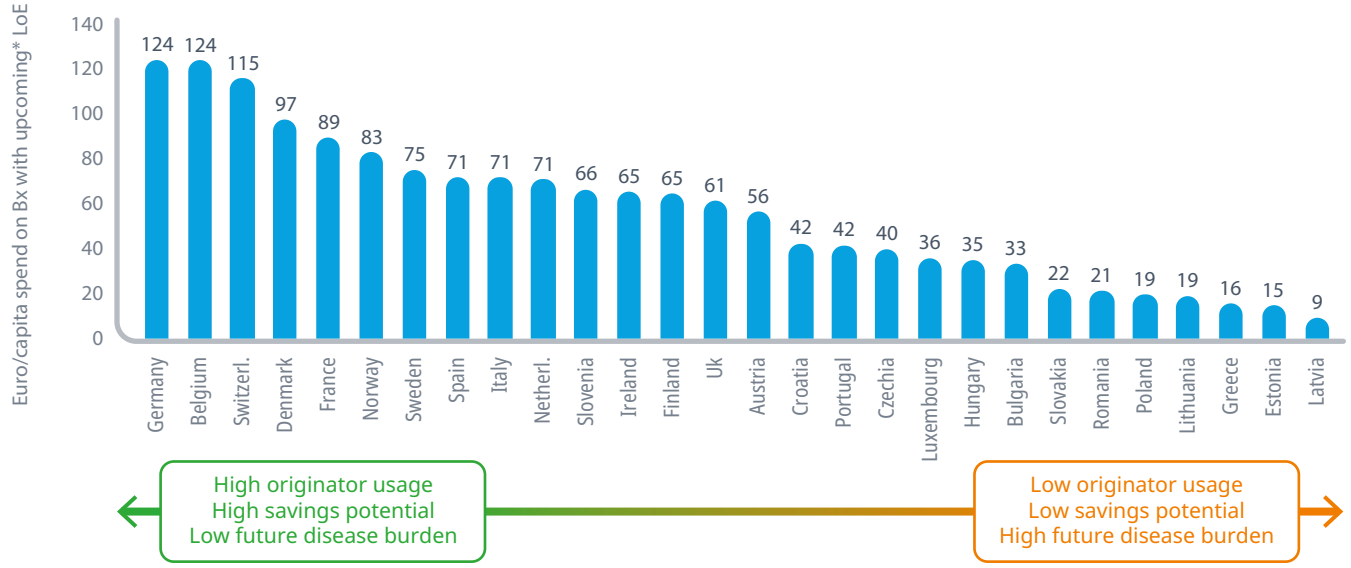
Despite significant list price reductions, subsequent confidential rebates, and increasing competition to markets not all European countries have been either willing or able to increase access to biologic medicines in the available therapy classes. On a per capita basis, central and eastern European markets lag western European countries, with treatment guidelines, and approaches to biosimilars being considered as limited factors.[4] One additional consideration is the usage of the protected brand prior to loss of exclusivity.

The per capita spending on the protected molecule prior to loss of exclusivity is a critical factor in being able to generate savings, and therefore being able to increase patient access to biologic therapies. A certain level of spending is needed to make future savings, and many markets fail to meet that level further compounding issues. This creates an issue where regardless of price countries are unable to increase access and provide improved treatments to patients. Price reductions of up to 80% have been recorded in some markets, but with patient volumes and a lack of usage in the originator the system is unable to function properly.

Access to biologic medicines has seen growth in some molecules (e.g., Pegfilgrastim). However, access to the molecule has not seen significant changes for several years which highlights that in many instances there were patients unable to access the treatment.

[4] IQVIA Institute, Spotlight on biosimilars: Optimising the Sustainability of Healthcare Systems, published June 2021

Exhibit 7: Protected brand spend on biologics with an upcoming loss of exclusivity



Notes: Includes the sales of branded biologic molecules with an upcoming loss of exclusivity date in the future, *between 2022-2030 using IQVIA MIDAS data from June MAT 2021

4. COMPETITION: THE COMPETITIVE ENVIRONMENT IN EUROPE IS CHANGING

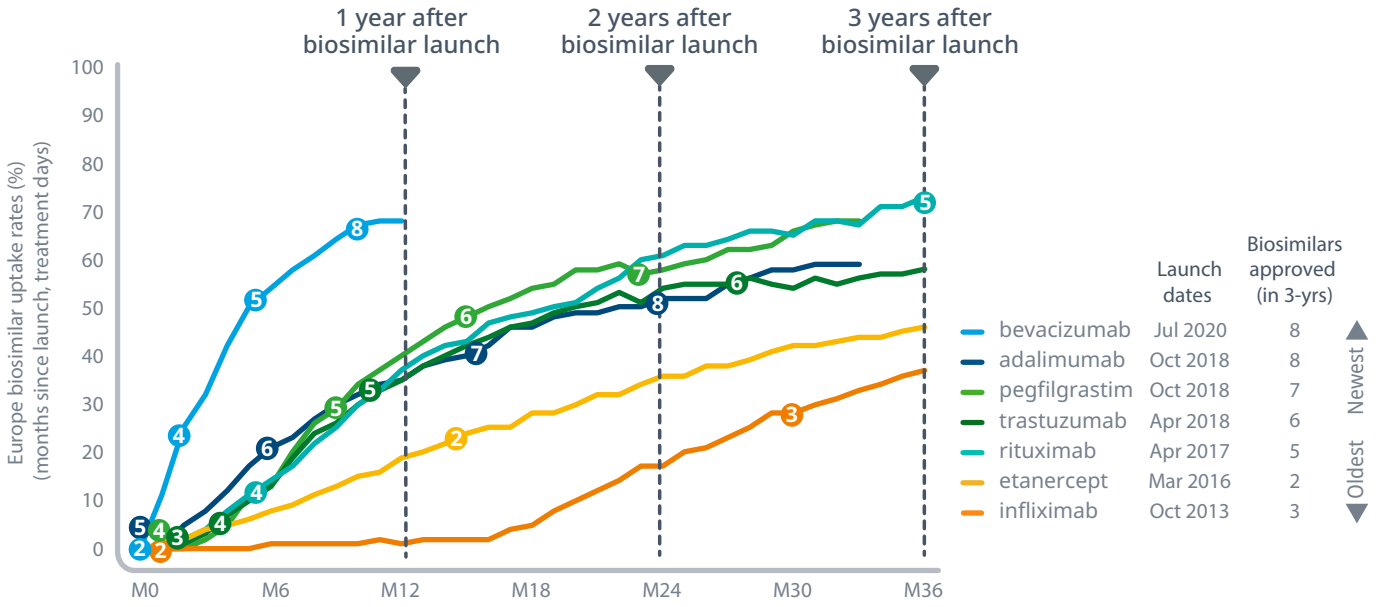
4.1 Competition in the newer therapy classes is increasingly fierce

New molecules which have experienced loss of exclusivity (LoE) see increasingly rapid biosimilar penetration rates. Biosimilars launched in the past year have reached 50% penetration of the originator within less than 1-year, while previous molecules took over 2-years to reach an equivalent position, and older products have lower penetration rates due to the preparations for biosimilar competition by both payers and biosimilar manufacturers who have learnt from over 15 years of biosimilar competition.

In addition, the number of competitors present within the market upon LoE is markedly higher for new molecules. Biosimilar manufacturers are increasingly prepared for LoE opportunities, and creating increasingly crowded and competitive marketplaces within European countries. Those who have the right system in place will able to benefit most, as older methods such as single-winner tendering approaches are being left behind in favour of multiple players.

Biosimilars launched in the past year have reached 50% penetration of the origionator within less than 1-year, while previous molecules took over 2-years.

Exhibit 8: Increasing biosimilar uptake and competition within markets



Source: IQVIA MIDAS (Q2 2021); EMA EPAR list of approved biosimilar medicines and marketing authorization dates (last accessed November 2021), number of competitors represents the number approved within the market during the first 36 months post-launch

4.2 Different types of companies are launching biosimilars

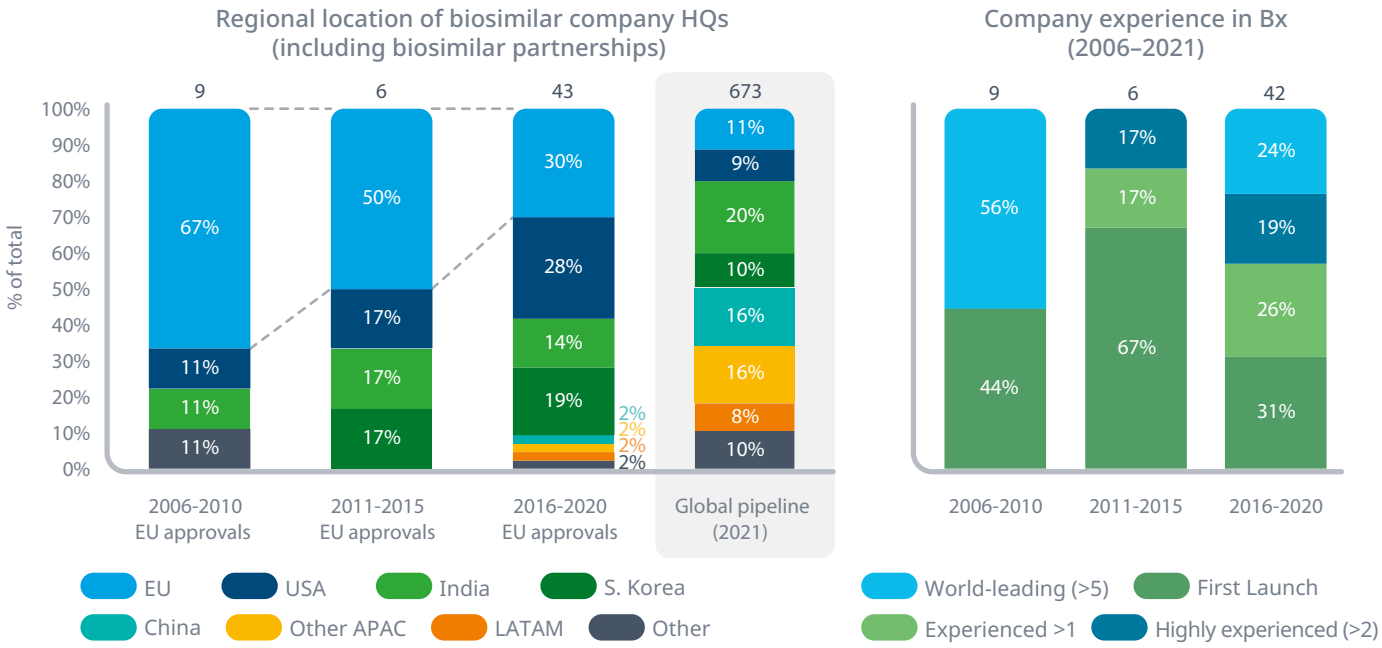
Throughout the pandemic, the issue of international trade and supply of medicines became a focus area for all stakeholders. The trends in the geographic location, and type of manufacturer active in the European marketplace have implications for the success of the market.

The source of biosimilar development has historically been based on large multi-national generics manufacturers-turned biosimilar manufacturers, or specialists in the biosimilar development space. Over the past 5-years the market has accelerated, and with this comes a growth in the number of companies developing lower cost biosimilar medicines for use locally, or internationally. The commoditisation, barriers to entry, and financial incentive for manufacturers make this an attractive proposition and this can be seen clearly within the types of companies turning to biosimilar development.

The European biosimilar market has benefited from research by a broad spectrum of companies from across the globe, willing and able to develop complex biologic molecules. The history of the market has been European dominated, with the leading generics manufacturers like Sandoz, Ratiopharm and Hexal leading the first wave of biosimilar development, alongside global players like Teva and Cipla. This trend is changing as other regions enter the biosimilar space, resulting in growth internationally and the emergence of new players that are preparing to launch their first biosimilar molecule.

This raises questions about how to ensure effective competition from new players. While many of these molecules from ex-EU could be in development for local markets (e.g., Brazil or India), those with robust manufacturing standards and commercial capabilities will be planning a European launch. The regulatory and development processes are not directly interchangeable between regions, and to maximise competition alignment is critical. Rebates and discounts can act as an opaque barrier to entry for naïve international manufacturers who do not realise the true price paid by payers for a given product, which can result in delays to access (as seen in the case of the low-molecular-weight-heparins class). New manufacturers also provide the opportunity for new strategic approaches to biosimilars, and have implications for the future of the market.

Exhibit 9: Composition of biosimilar manufacturers



Source: IQVIA MIDAS data (Q2 2021); and IQVIA Pipeline Intelligence analysis 2021

The high upfront investment and production costs coupled with pricing pressures and limited access are raising the bar for biosimilar developers. An increasing number of pharmaceutical companies decided to not launch biosimilars or continue their development plans putting sustainability of the biosimilars marketplace as a critical issue for all stakeholders. Europe may become more dependant on importation on medicines in a time where supply security is considered high priority at a European level.

5. FUTURE: ENSURING PREPAREDNESS FOR THE FUTURE BIOSIMILAR OPPORTUNITY

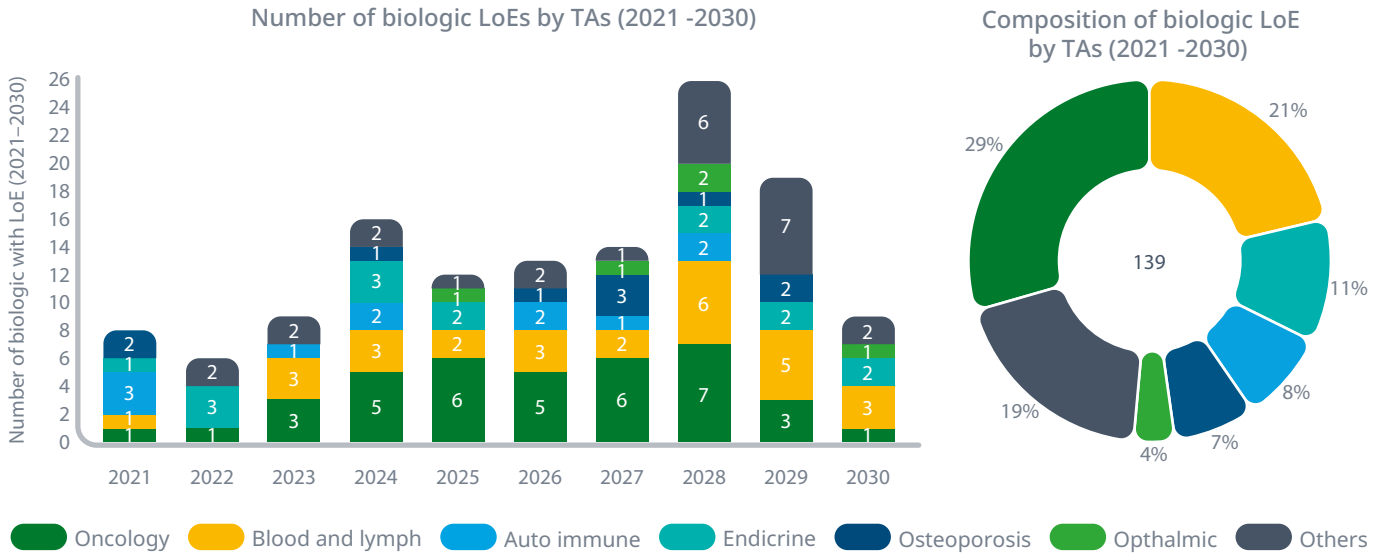
5.1 A high volume of molecules will become open to biosimilar competition

Previous iterations of the 'Impact of Biosimilar Competition in Europe' report have shown the size of the opportunity available to biosimilar competition in the future, which peaks around 2027–2028 at €8 billion upon PD-1 inhibitors losing exclusivity. It is important to consider which therapy areas this represents as physician awareness of biosimilars is a major hurdle to successful implementation. Over the next 10-years, the majority of biologic LoEs will be oncology biologics (29%), followed by biologics to treat blood and lymphatic conditions (21%).

Ensuring physicians are aware of biosimilars in these areas will be critical to success, but more importantly, having a sustainable purchasing policy in place that can manage the biosimilars that enter the markets will be critical. Many markets struggle to leverage competition in the therapy areas and molecules that are currently available in European markets, and this influx has the potential to overwhelm systems who will miss opportunities and create knock-on implications for patients.

55% of the LoE opportunity comes from just 10% (13) molecules, which are concentrated in the oncology space. This provides large opportunities to make savings and increase access to previously high-cost cancer medications.

Exhibit 10: Forecast number of biologic LoEs by therapy area

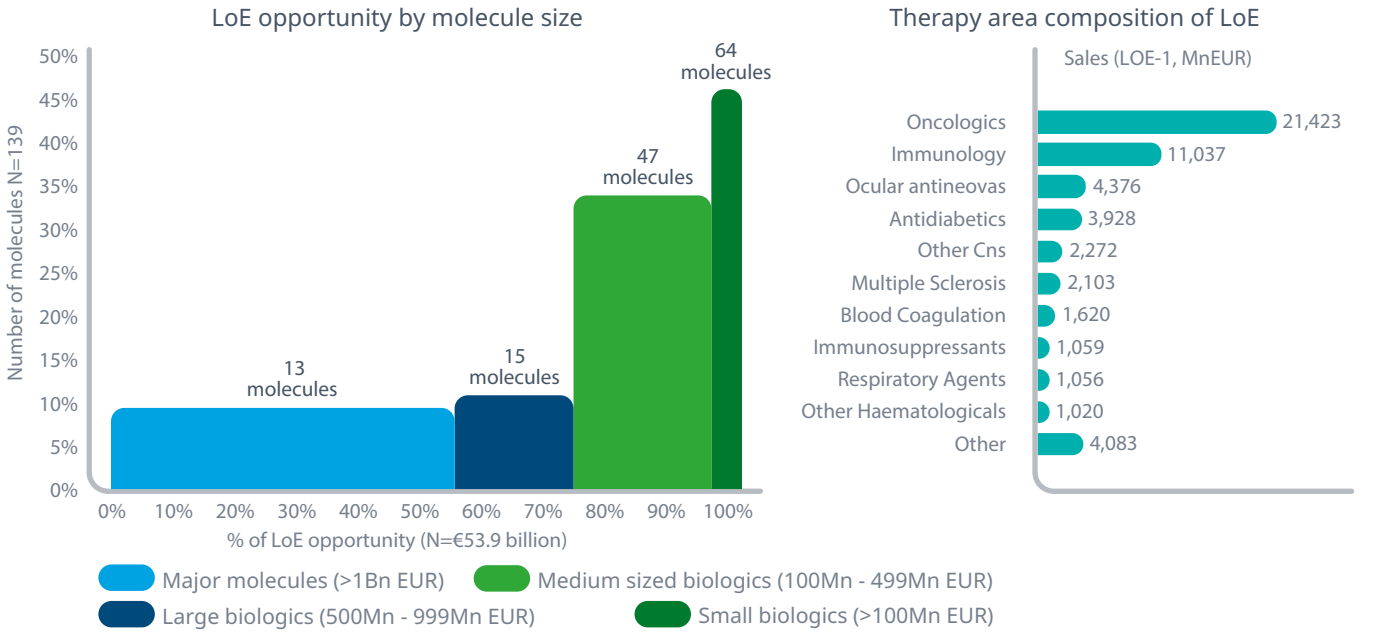


Source: IQVIA Forecast Link analysis (Q2 2021)

5.2 Future opportunity is concentrated but still larger than previous years

55% of the LoE opportunity (based on forecast sales values) comes from just 10% (13) molecules, which are concentrated in the oncology space. This provides large opportunities to make savings and increase access to previously high-cost cancer medications, however, the issues will be two-fold. Firstly, how to manage the biosimilar introductions in other areas, and to ensure that biosimilar manufacturers are incentivised to take these smaller opportunities. Secondly, the 'major molecules' and the 'large molecules' are only 20% of all biologics losing exclusivity but are twice as many as Europe has experienced since the introduction of biosimilars in 2006 (18 total in 2021).

Exhibit 11: Forecast biosimilar opportunity by molecule size and therapy area



Source: IQVIA Forecast Link analysis (Q2 2021)

Methodology

The indicators are intended to give a broad overview of the uptake and the implications on price and volume evolution after introduction of biosimilar medicines. There are differences in perspective between payers, providers, and different types of manufacturers. In focusing on the payer perspective, there are caveats that should be considered when interpreting the results.

- **Pricing and discounts:**
  The report is based on publicly available list prices. Discounting occurs, especially in contracting with hospitals and in countries using tenders for biological drug procurement, which can lead to larger price fluctuations than is visible through the reported IQVIA data

- **Approved indications and efficacy:**
  Not all products in a specific product group in the accessible, non-accessible or total market have the same approved indications and can have differences in efficacy and individual patient outcomes. Biosimilars normally receive the same indications as the referenced products and are expected to have the same safety and efficacy.

- **Volume estimates:**
  The pack volumes reported are based on IQVIA collected data which may have been unknowingly impacted by issues such as parallel exporting. The volumes have been converted to daily doses using the published World Health Organization (WHO) defined daily doses (DDD) which can introduce bias. Consumption measures are therefore not adjusted for clinical practice guidelines, patient characteristics, indications for which the molecule is used, or other factors that may result in different volumes utilised on a per patient Treatment Day basis.

- **Long-term vs. one-off use:**
  Hospital-only vs. retail: no distinction is made in this report between biologicals for long term (repeat use) and one-off use, nor between hospital-only and retail products, although competitive conditions and scope for biosimilar uptake are likely to differ in the various scenarios.

- **Protection expiry:**
  The intellectual property for biologicals can involve multiple patents, patent timelines, data exclusivity, and litigation for each individual product and therefore it is difficult to give an exact date for protection expiry for biologicals. It should be noted that these results are estimates as determined from IQVIA MIDAS® and ARK Patent Intelligence where available, and historical products are cross-referenced to public sources.

Other definitions found within the report include:

- **Launch date:**
  Date of first recorded sales of Biosimilar Medicinal Product in the country. Products can be approved in Europe prior to this date but it is not recorded as such.

- **Price indicators:**
  Price: the price level used is gross ex-manufacturer price (list price), which values the product at the level that the manufacturer sells out, without considering rebates or discounts. Price evolution: price per Treatment Day (TD) in 2021 (June MAT) versus year before biosimilar entry.

- **Volume indicators:**

  Volume: volume is measured in Treatment Days (also known as Defined Daily Dose) which is a measure of the average dose prescribed as defined by the WHO.

  Biosimilar market share: number of biosimilar treatment days as a share of (i) biosimilar + referenced product(s) volume, (ii) accessible market volume and (iii) total market volume.

  Volume evolution: number of Treatment Days in 2021 (June MAT) versus year before biosimilar entry.

  Volume per capita 2021 (June MAT): number of Treatment Days consumed in 2021 (June MAT) normalised by population size (World Bank data).

  Volume per capita year before biosimilar entrance: number of Treatment Days consumed the year before the entrance of biosimilars, normalised by population size.

Amendments in 2021

Previously unavailable data has been included for the first time in 2021, due to an improved methodology.

In 2021, the non-accessible market is defined primarily according to the protection status of the product according to IQVIA MIDAS and ARK Patent intelligence. This means that products that are not protected, or no longer protected (according to IQVIA MIDAS and ARK Patent intelligence) fall into the 'non-referenced' category rather than the 'non-accessible' category. Previously, products are often classified as non-accessible if the molecule is not subject to biosimilar competition, or could never be. Defining the non-accessible market by protection status allows an improved view on the maturity of the market and improved visibility to innovation and loss of exclusivity, however it is important to note that in some cases, non-referenced molecules will never be referenced by biosimilars. Notable changes are included in the market development for each therapy area.

The following terms are used throughout this segment of the report:

TOTAL MARKET: Products within the same ATC code	**ACCESSIBLE MARKET**	**Referenced Medicinal Product:** Original product, granted market exclusivity at the start of its life, exclusivity has now expired, and the product has been categorised as referenced by having a biosimilar with an EMA-approved marketing authorisation available on a European market.	
		Non-Referenced Medicinal Product: Original, or second generation product, granted market exclusivity at the start of its life, exclusivity has now expired, and the product has never been categorised as a Referenced Medicinal product by a biosimilar receiving centrally-approved marketing authorisation.	
		Biosimilar Medicinal Product: Product, granted regulatory approval, demonstrating similarity to the Reference Medicinal Product in terms of quality characteristics, biological activity, safety and efficacy.	
	NON-ACCESSIBLE MARKET	**Non-accessible category:** products within the same ATC4 code as the accessible category products. These are typically second-generation products; this category may include products with different dosing schedules and / or route of administration to those in the accessible category, and have valid protection status.	

Country and therapy area KPIs

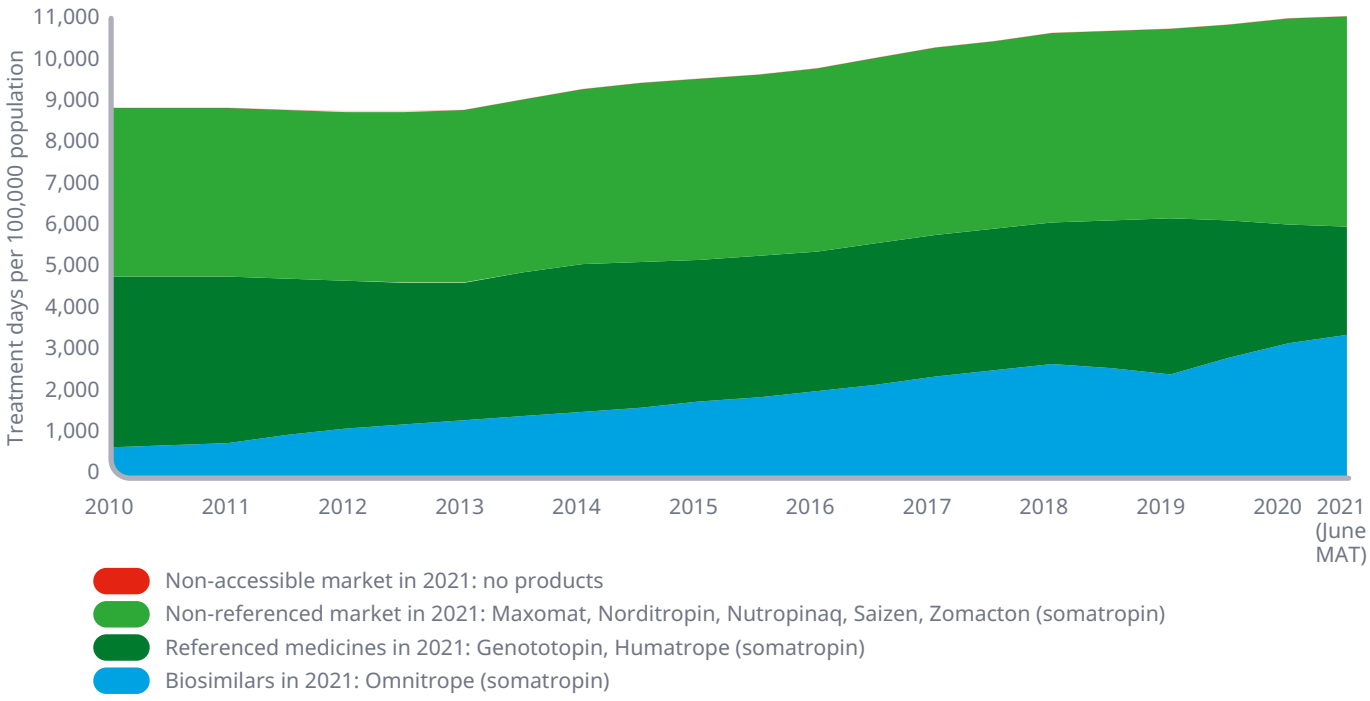
Human growth hormone (HGH)

HGH also known as somatropin, is a peptide hormone that stimulates growth, cell reproduction and regeneration in humans. It is used to treat growth disorders in children and growth hormone deficiency in adults.

HGH MARKET DEVELOPMENT

According to IQVIA MIDAS and ARK Patent Intelligence insights protection has expired for Humatrope (somatropin). The figure below reflects the existence of 2nd-generation products that are not classified as biosimilars, nor have protection status, and as such are not able to be classified within the 'referenced medicines' category. Products for mescasermin (another molecule within the same ATC4 class, H4C0) have been excluded from the analysis because despite being a competing product in the growth hormone area, this molecule works further down the response pathway from somatropin. Therefore, from a medical practice setting, they are different. This means that the total market is ~5% smaller than in the 2020 report, where both molecules in the H4C0 ATC4 class were included.

HGH market development



ADDITIONAL INFORMATION ABOUT HGH MEDICINES

Subcutaneous injection is typically used to administer Human Growth Hormone treatment. The dosage of administration should be individualised for each patient, with a weight-based regimen. The duration of treatment, usually a period of several years, will depend on maximum achievable therapeutic benefit.

HGH approved indications

NAMING		CLASSIFICATION												INDICATIONS								
MOLECULE	PRODUCT	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2021	2021 (JUNE MAT)	PEDIATRIC GROWTH HORMONE DEFICIENCY	ADULT GROWTH HORMONE DEFICIENCY	TURNER SYNDROME	GROWTH FAILURE DUE TO CHRONIC RENAL INSUFFICIENCY (CRI)	SGA - SMALL FOR GESTATIONAL AGE	PWS - PRADER-WILLI SYNDROME	IDIOPATHIC SHORT STATURE	SHOX - SHORT-STATURE HOMEBOX-CONTAINING GENE DEFICIENCY	NOONAN SYNDROME
SOMATROPIN	GENOTROPIN HUMATROPE* OMNITROPE NORDITROPIN NUTROPINAQ SAIZEN ZOMACTON	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

● Non-accessible market ● Non-referenced market ● Referenced medicines ● Biosimilars

* Note: The biosimilar for Humatrope (Valtropin) has been withdrawn from the market, however Humatrope is still categorized as a referenced medicine.

Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countries

		AT	BE	BG	CH	CZ	DE	DK	ES	FI	FR	HU	IT	NL	NO	PL	PT	RO	SE	SI	SK	UK	EU
MARKET SHARE TD (2021, JUNE MAT)	Biosimilar vs Referenced product	34%	33%	49%	34%	21%	50%	99%	44%	62%	47%	27%	48%	60%	10%	99%	47%	65%	56%	17%	0%	63%	56%
	Biosimilar vs Accessible market	10%	21%	49%	6%	8%	24%	82%	27%	15%	18%	11%	25%	37%	1%	99%	26%	43%	38%	9%	0%	33%	31%
	Biosimilar vs Total market	10%	21%	49%	6%	8%	24%	82%	27%	15%	18%	11%	25%	37%	1%	99%	26%	43%	38%	9%	0%	33%	31%
PRICE PER TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-11%	-27%	-24%	-37%	-14%	-8%	-13%	-18%	-31%	-15%	-8%	-13%	-46%	-10%	14%	-51%	-21%	-25%	-36%	-19%	-40%	-25%
	Biosimilar Accessible market	-6%	-29%	-24%	-31%	-22%	-3%	-17%	-18%	-40%	-15%	-5%	-11%	-41%	-1%	13%	-40%	-17%	-27%	-35%	-7%	-23%	-21%
	Total market	-6%	-29%	-24%	-31%	-22%	-3%	-17%	-18%	-40%	-15%	-5%	-11%	-41%	-1%	13%	-40%	-17%	-27%	-35%	-7%	-23%	-21%
VOLUME TD (2021, JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	8%	35%	34%	-32%	51%	-4%	148%	20%	23%	-19%	-14%	35%	64%	-68%	145%	42%	118%	-9%	59%	17%	38%	24%
	Biosimilar Accessible market	111%	28%	31%	33%	66%	-1%	-5%	37%	72%	7%	18%	3%	19%	27%	145%	6%	17%	-16%	47%	28%	59%	21%
	Total market	111%	28%	31%	33%	66%	-1%	-5%	37%	72%	7%	18%	3%	19%	27%	145%	6%	17%	-16%	47%	28%	59%	21%
	TD per capita	0.08	0.13	0.03	0.09	0.16	0.08	0.14	0.19	0.12	0.15	0.06	0.11	0.13	0.17	0.11	0.05	0.05	0.12	0.09	0.08	0.08	0.11
	TD/capita (Yr before BS entrance)	0.04	0.10	0.02	0.07	0.10	0.08	0.15	0.14	0.07	0.14	0.05	0.10	0.11	0.14	0.05	0.04	0.04	0.14	0.06	0.06	0.05	0.09
	First Recorded sales of Biosimilars	2010	2010	2012	2010	2010	2010	2011	2010	2010	2010	2012	2010	2010	2011	2010	2014	2010	2010	2010	2013	2010	2010

* Only retail panel data is available for Greece

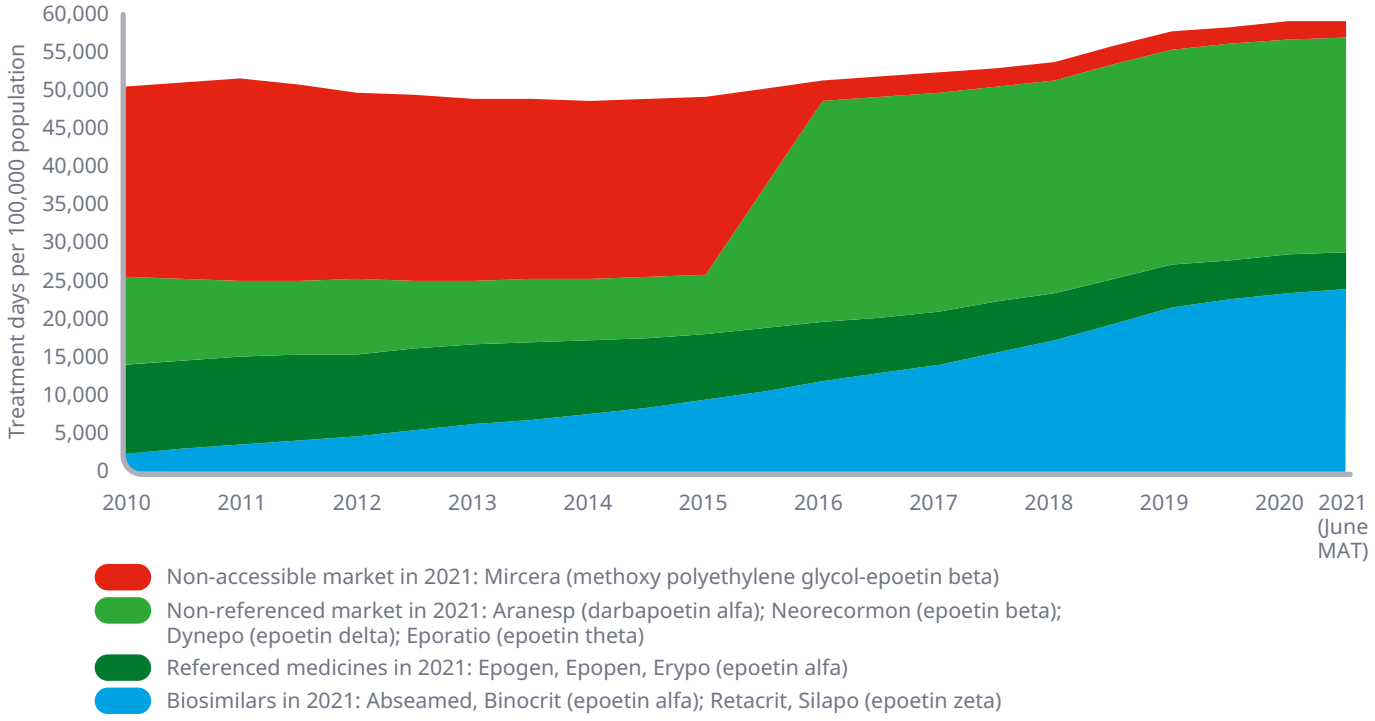
Epoetin (EPO)

EPO is a form of human erythropoietin produced by recombinant technology, with the same amino acid sequence and mechanism of action as endogenous erythropoietin. Its major functions are to promote the differentiation and development of red blood cells and to initiate the production of haemoglobin, the molecule within red blood cells that transports oxygen.

EPO MARKET DEVELOPMENT

According to IQVIA MIDAS and ARK Patent Intelligence insights protection expired for a significant molecule in this class, Aranesp (darbepoetin alfa). The figure below reflects this shift from the molecule from a non-accessible product, to one that is now open to biosimilar competition but is yet to be referenced.

EPO market development



EPO approved indications

NAMING		CLASSIFICATION												INDICATIONS					DOSING/ADMINISTRATION	
MOLECULE	PRODUCT	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021 (JUNE MAT)	ANEMIA FOR CHEMOTHERAPY PATIENTS	ANEMIA FOR PATIENTS WITH CKD*	PREVENTING ANEMIA IN PREMATURE BABIES	ANEMIA IN ADULTS WITH MDS	REDUCTION OF ALLOGENIC TRANSFUSION EXPOSURE IN ORTHAPEDIC SURGERY	PATIENT TYPE** (ADULT OR PEDIATRIC)	FREQUENCY
DARBEPOETIN ALFA	ARANESP	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●	Both	3 x per week
EPOETIN ALFA	ABSEAMED BINOCRIT EPOGEN EPOPEN ERYPO	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ●		● ● ● ●	● ● ● ●	Both	3 x per week
EPOETIN BETA	NEORECORMON	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	Both	3 x per week
EPOETIN DELTA	DYNEPO***	●	●	●	●									●	●	●			Both	3 x per week
EPOETIN THETA	EPORATIO	●	●	●	●	●	●	●	●	●	●	●	●	●	●				Adult	3 x per week
EPOETIN ZETA	RETACRIT SILAPO	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●				Both	3 x per week
METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA	MIRCERA	●	●	●	●	●	●	●	●	●	●	●	●		●				Adult	Every 2 weeks

● Non-accessible market ● Non-referenced market ● Referenced medicines ● Biosimilars

* Anaemia for patients with Chronic kidney disease

** Subcutaneous injection is typically used for chemotherapy patients. Intravenous injection is typically used for patients with kidney problems and for patients who are going to donate their own blood.

*** Dynepo has been discontinued.

Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countries

		AT	BE	BG	CH	CZ	DE	DK	ES	FI	FR	*GR	HU	IE	IT	NL	NO	PL	PT	RO	SE	SI	SK	UK	EU
MARKET SHARE TD (2021, JUNE MAT)	Biosimilar vs Referenced product	79%	14%	100%	27%	93%	89%	36%	90%	100%	76%	93%	100%	100%	89%	24%	100%	100%	97%	98%	98%	77%	100%	11%	87%
	Biosimilar vs Accessible market	23%	2%	63%	1%	33%	60%	0%	52%	19%	25%	87%	34%	6%	76%	2%	9%	19%	25%	55%	12%	21%	58%	3%	46%
	Biosimilar vs Total market	23%	2%	57%	1%	25%	56%	0%	51%	16%	25%	86%	33%	6%	76%	2%	7%	19%	25%	52%	12%	19%	56%	3%	45%
PRICE PER TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-23%	-7%	19%	-43%	-62%	-26%	-10%	-75%	-30%	-32%	-49%	-68%	-24%	-12%	-34%	41%	-43%	-83%	-49%	36%	-43%	-54%	3%	-28%
	Biosimilar Accessible market	-34%	2%	-2%	-39%	-53%	-21%	-25%	-51%	-32%	-34%	-49%	-26%	-29%	-9%	-20%	2%	3%	-73%	-42%	-40%	-46%	-47%	2%	-26%
	Total market	-35%	-11%	-12%	-36%	-47%	-27%	-18%	-49%	-29%	-31%	-48%	-21%	-24%	-9%	-27%	1%	0%	-69%	-39%	-32%	-44%	-46%	1%	-26%
VOLUME TD (2021, JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	45%	9%	58%	-42%	364%	173%	0%	113%	843%	49%	-51%	32%	127%	153%	-67%	492%	1250%	232%	-10%	-11%	-16%	288%	63%	107%
	Biosimilar Accessible market	113%	309%	56%	254%	239%	166%	271%	100%	302%	128%	-63%	131%	121%	100%	113%	933%	715%	208%	-60%	229%	73%	96%	226%	115%
	Total market	22%	52%	36%	22%	211%	46%	-4%	4%	39%	6%	-82%	2%	4%	25%	-15%	34%	360%	1%	-65%	41%	22%	7%	49%	15%
	TD per capita	0.76	0.78	0.36	0.39	0.29	0.43	0.47	0.73	0.46	0.99	0.05	0.37	0.40	1.25	0.43	0.27	0.10	0.45	0.12	0.62	0.61	0.50	0.38	0.63
	TD/capita (Yr before BS entrance)	0.62	0.52	0.27	0.32	0.09	0.29	0.49	0.70	0.33	0.93	0.28	0.37	0.39	1.00	0.51	0.20	0.02	0.44	0.34	0.44	0.51	0.47	0.25	0.55
	First Recorded sales of Biosimilars	2010	2014	2011	2010	2011	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010

* Only retail panel data is available for Greece

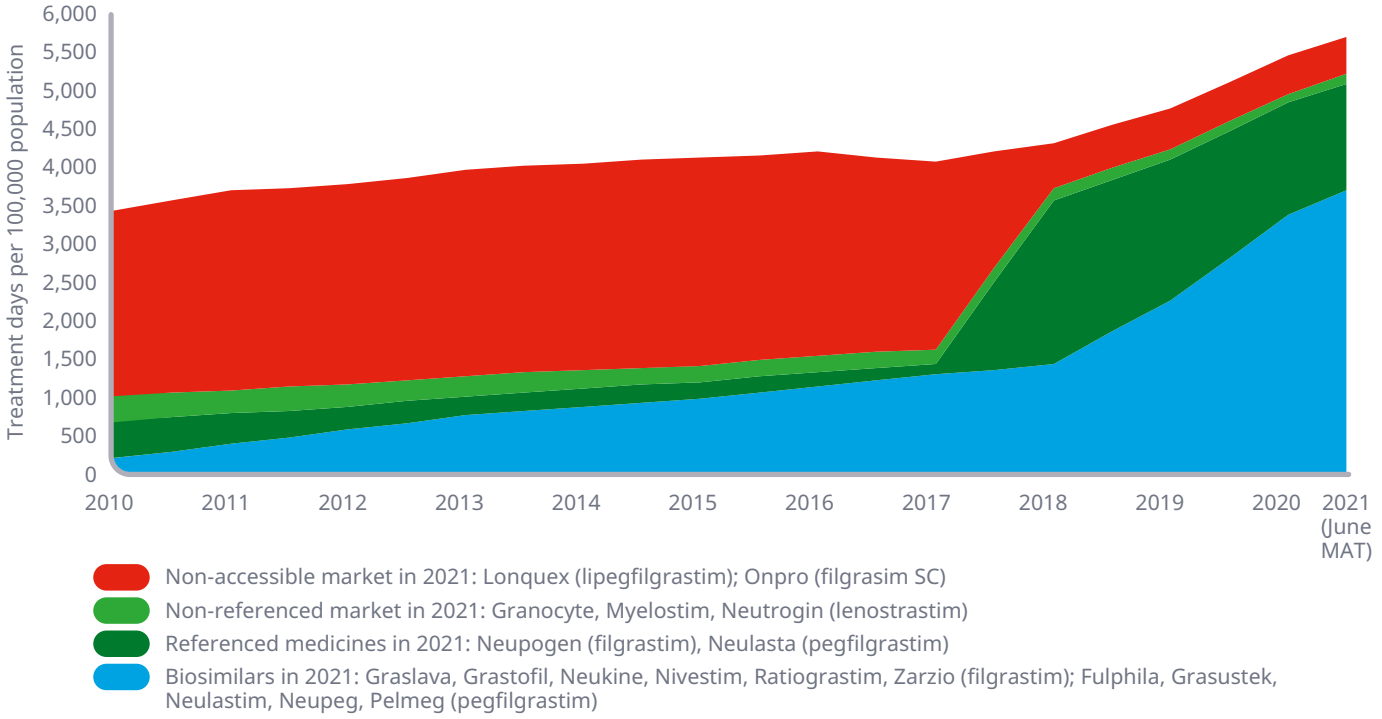
Granulocyte-colony stimulating factor (GCSF)

G-CSF is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. G-CSF is used prophylactically with certain cancer patients accelerate recovery from neutropenia after chemotherapy, allowing higher-intensity treatment regimens.

GCSF MARKET DEVELOPMENT

According to IQVIA MIDAS and ARK Patent Intelligence insights protection expired for a significant molecule in this class, Neulasta (pegfilgrastim). The figure below reflects this shift from the molecule as a non-accessible product with protection, to one that is now open to biosimilar competition and has been referenced within the same year by a significant number of biosimilars. Lenograstim products (Granocyte, Myelostim, Neutrogin) are not protected according to IQVIA MIDAS and ARK Patent Intelligence, meaning they are classified as 'non-referenced' products in 2021, according to the definition outlined on page 13.

GCSF market development



ADDITIONAL INFORMATION ABOUT G-GCSF MEDICINES

Subcutaneous injection typically used to administer G-CSF daily for 5-7 days, starting 72hrs after completion of chemotherapy or bone marrow transplantation, with the exception of pegfilgrastim and lipegfilgrastim which are long acting G-CSF and therefore administered once only at least 24 hrs after completion of each chemotherapy cycle.

GSCF approved indications

NAMING		CLASSIFICATION												INDICATIONS					
MOLECULE	PRODUCT	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2221 (JUNE MAT)	CYTOTOXIC CHEMOTERAPY ASSOCIATED WITH FEBRILE INDUCED NEUTROPENIA	NEUTROPENIA INDUCED BY ACUTE MYELOID LEUKEMIA	BONE MARROW TRANSPLANTATION FOR NON MYELOID MALIGNANCY INDUCED NEUTROPENIA	MOBILISATION OF PERIPHERAL BLOOD PROGENITOR CELLS (PBPCS)	SEVERE CHRONIC NEUTROPENIA (SCN) WITH DIAGNOIS OF CONGENITAL, CYCLIC, OR IDIOPATHIC NEUTROPENIA	NEUTROPENIA PREVENTION AND TREATMENT IN PATIENTS WITH HIV
FILGRASTIM	GRANULOKINE GRASALVA GRASTOFIL NEUKINE NEUPOGEN NIVESTIM RATIOGRASTIM ZARZIO FILGRASTIM HEXAL	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ● ● ●	● ● ●	● ● ● ● ● ● ● ● ●	● ● ● ● ● ● ● ● ●	● ● ● ● ● ● ● ● ●	● ● ● ● ● ● ● ● ●
LENOGRASTIM	GRANOCYTE MYELOSTIM NEUTROGIN	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●		● ● ●	● ● ●		
LIPEGFILGRASTIM	LONQUEX					●	●	●	●	●	●	●	●	●					
PEGFILGRASTIM	NEULASTA ONPRO NEULASTIM NEUPEG PELMEG FULPHILA CEGFILA GRASUSTEK NYVEPRIA	●	●	●	●	●	●	●	●	● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ●	● ● ● ● ● ● ● ● ●					

● Non-accessible market ● Non-referenced market ● Referenced medicines ● Biosimilars

Notes: Tevagrastim = Grasalva in IQVIA MIDAS; Accofil = Neukine in IQVIA MIDAS; Ziextenzo = Neulastim in IQVIA MIDAS; Pelgraz is Neupeg in MIDAS.

Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countries

		AT	BE	BG	CH	CZ	DE	DK	ES	FI	FR	*GR	HU	IE	IT	NL	NO	PL	PT	RO	SE	SI	SK	UK	EU
MARKET SHARE TD (2021, JUNE MAT)	Biosimilar vs Referenced product	58%	18%	46%	37%	98%	45%	100%	92%	51%	76%	95%	99%	14%	86%	70%	98%	94%	94%	92%	97%	40%	83%	85%	71%
	Biosimilar vs Accessible market	58%	18%	46%	36%	98%	44%	99%	91%	51%	72%	95%	99%	14%	85%	70%	98%	94%	93%	92%	97%	40%	83%	82%	70%
	Biosimilar vs Total market	48%	12%	31%	36%	78%	39%	99%	91%	39%	71%	94%	99%	12%	78%	55%	98%	85%	93%	92%	94%	37%	72%	78%	64%
PRICE PER TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-61%	-64%	-58%	-54%	-75%	-57%	-57%	-42%	-71%	-66%	-60%	-78%	-58%	-46%	-68%	-32%	-89%	-94%	-79%	-55%	-83%	-69%	-18%	-60%
	Biosimilar Accessible market	-61%	-64%	-61%	-54%	-75%	-57%	-57%	-43%	-71%	-67%	-63%	-78%	-58%	-50%	-68%	-32%	-89%	-94%	-79%	-55%	-83%	-69%	-25%	-63%
	Total market	-57%	-48%	-55%	-22%	-66%	-41%	-24%	-32%	-53%	-42%	-56%	-74%	-19%	-24%	-42%	-9%	-83%	-87%	-62%	-44%	-75%	-58%	17%	-46%
VOLUME TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	605%	1434%	1580%	490%	1029%	682%	1226%	89%	932%	1690%	62%	492%	1089%	372%	911%	2758%	926%	250%	958%	508%	1230%	1344%	583%	676%
	Biosimilar Accessible market	588%	1392%	1442%	457%	1029%	463%	1178%	79%	915%	581%	27%	480%	995%	149%	895%	2758%	706%	222%	958%	487%	1230%	1344%	326%	439%
	Total market	97%	186%	1245%	45%	532%	77%	62%	-37%	65%	83%	-28%	45%	64%	18%	-8%	185%	304%	-23%	121%	67%	314%	196%	49%	69%
	TD per capita	0.12	0.12	0.05	0.04	0.05	0.06	0.08	0.02	0.11	0.11	0.01	0.07	0.10	0.04	0.03	0.09	0.06	0.03	0.04	0.04	0.08	0.08	0.03	0.06
	TD/capita (Yr before BS entrance)	0.06	0.04	0.00	0.03	0.01	0.03	0.05	0.04	0.07	0.06	0.02	0.05	0.06	0.03	0.04	0.03	0.02	0.04	0.02	0.03	0.02	0.03	0.02	0.04
	First Recorded sales of Biosimilars	2010	2011	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010	2010

* Only retail panel data is available for Greece

Anti-tumour necrosis factor (ANTI-TNF)

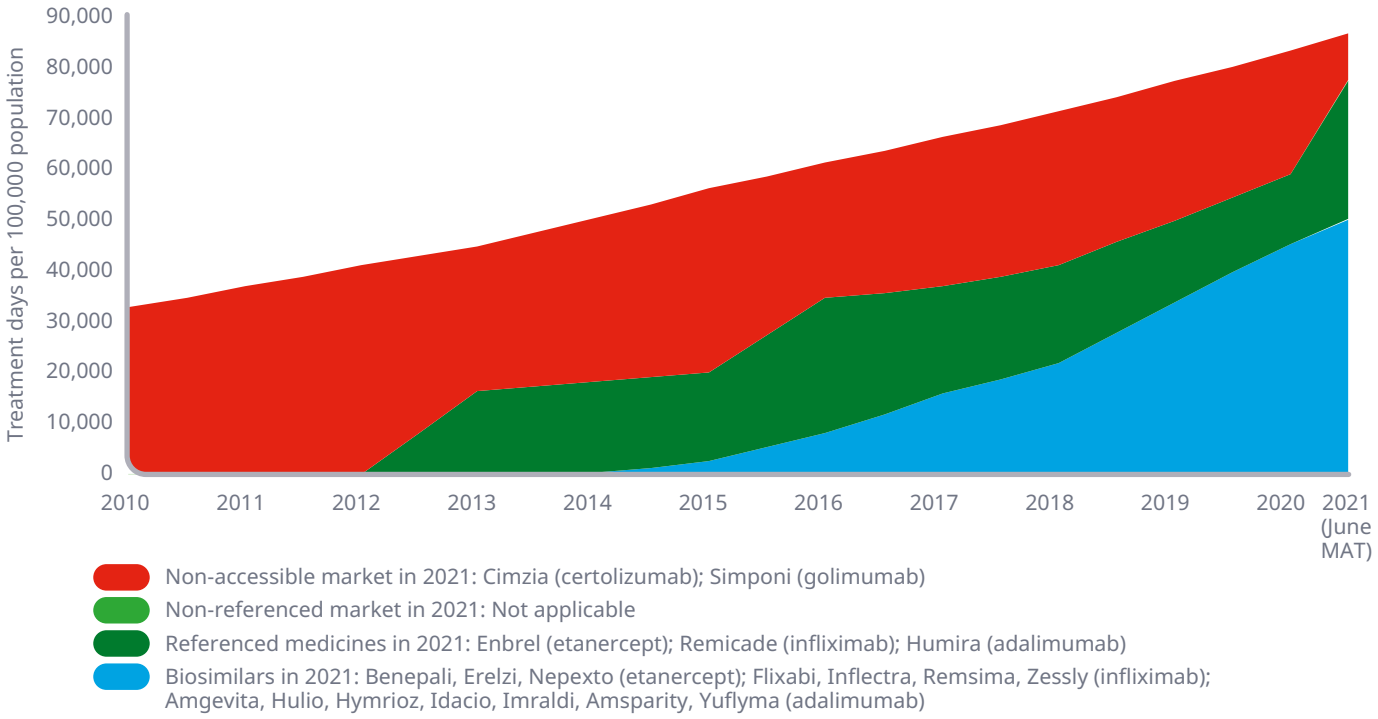
Anti-TNF drugs are a class of drugs that are used to treat inflammatory conditions such as Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Juvenile Arthritis, Crohn's Disease, Ulcerative Colitis, Psoriasis and Hidradinitis Suppurativa. These drugs are able to reduce inflammation and stop disease progression.

TNF is a chemical produced by the immune system that causes inflammation in the body. In healthy individuals, excess TNF in the blood is blocked naturally, but in those who have conditions like RA, higher levels of TNF in the blood lead to more inflammation, joint destruction and persistent symptoms. Anti-TNF agents can alter the disease's effect on the body by controlling inflammation in joints, gastrointestinal tract and skin.

ANTI-TNF MARKET DEVELOPMENT

Humira citrate free has moved from the non-accessible category to the referenced medicines category in 2021. This is because an adalimumab biosimilar with high concentration, low-volume and a citrate-free formulation (Celltrion's Yuflyma) was approved in Europe in February 2021, with some sales already observed in Germany by June 2021.

ANTI-TNF market development



ADDITIONAL INFORMATION ABOUT ANTI-TNF MEDICINES

In this section we report insights from biosimilars on the market in Europe for three anti-TNF molecules: infliximab, etanercept and adalimumab. The EU approved the first infliximab biosimilars in September 2013, the first etanercept biosimilar in January 2016 and the first adalimumab biosimilar in March 2017. The EMA has also approved several rituximab biosimilars, however these have been considered separately in the Oncology section of the report. The market shares and price/volume evolution figures refer to the total Anti-TNF market, therefore, include all products within each category. This means, for example, in markets where only infliximab biosimilars have launched, the "biosimilar versus referenced product" market share will still represent the biosimilar market share of all the biosimilars and referenced products on the market.

ANTI-TNF approved indications

NAMING		CLASSIFICATION												INDICATIONS											DOSING	
MOLECULE	PRODUCT	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021 (JUNE MAT)	RA	JIA	PSA	AS	AS WITHOUT RADIOGRAPHIC EVIDENCE	CD (ADULT / PEDIATRIC)	UC (ADULT / PEDIATRIC)	PSO (ADULT/ PEDIATRIC)	HS	UV (ADULT/PAEDIATRIC)	FREQUENCY	ROUTE (SUBQ / IV)	CITRATE FREE (Y/N)
ADALIMUMAB	HUMIRA	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🟢	●	●	●	●	●	●	●	●	●	●	Every 2 weeks	SC	N
	HUMIRA (citrate free)							🔴	🔴	🔴	🔴	🔴	🟢	●	●	●	●	●	●	●	●	●	●		SC	Y
	AMGEVITA								🔵	🔵	🔵	🔵	🔵	●	●	●	●	●	●	●	●	●	●		SC	Y
	HULIO									🔵	🔵	🔵	🔵	●	●	●	●	●	●	●	●	●	●		SC	Y
	HYRIMOZ									🔵	🔵	🔵	🔵	●	●	●	●	●	●	●	●	●	●		SC	N
	IMRALDI									🔵	🔵	🔵	🔵	●	●	●	●	●	●	●	●	●	●		SC	N
	IDACIO										🔵	🔵	🔵	●	●	●	●	●	●	●	●	●	●		SC	N
	AMSPARITY											🔵	🔵	●	●	●	●	●	●	●	●	●	●		SC	Y
	YUFLYMA												🔵	●	●	●	●	●	●	●	●	●	●		SC	Y
CERTOLIZUMAB PEGOL	CIMZIA	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	●		●	●				*●			Monthly	SC	n/a
ETANERCEPT	ENBREL	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🟢	🟢	🟢	●	●	●	●				●			Once or twice weekly	SC	n/a
	BENEPALI							🔵	🔵	🔵	🔵	🔵	🔵	●	●	●	●				●				SC	n/a
	ERELZI								🔵	🔵	🔵	🔵	🔵	●	●	●	●				●				SC	n/a
	NEPEXTO											🔵	🔵													
GOLIMUMAB	SIMPONI	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	●		●	●			*●				Monthly	SC	n/a
INFLIXIMAB	REMICADE**	🔴	🔴	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	●		●	●		●	●	*●			Every 8 weeks	IV	n/a
	REMSIMA				🔵	🔵	🔵	🔵	🔵	🔵	🔵	🔵	🔵	●		●	●		●	●	*●				BOTH	n/a
	INFLECTRA					🔵	🔵	🔵	🔵	🔵	🔵	🔵	🔵	●		●	●		●	●	*●					n/a
	FLIXABI							🔵	🔵	🔵	🔵	🔵	🔵	●		●	●		●	●	*●				IV	n/a
	ZESSLY									🔵	🔵	🔵	🔵	●		●	●		●	●	*●					n/a

🔴 Non-accessible market 🟢 Non-referenced market 🟢 Referenced medicines 🔵 Biosimilars

*Adult only

**Protection expired earlier in some markets, resulting in the appearance of biosimilars prior to the formal EU protection expiry. Notes: RA = rheumatoid arthritis, JIA = Juvenile idiopathic arthritis; PsA = Psoriatic arthritis; AS = Ankylosing spondylitis; CD = Crohn's disease; UC = ulcerative colitis; PPs = plaque psoriasis; HS = Hidradenitis Suppurativa; Uv = Uveitis

Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countries

		AT	BE	BG	CH	CZ	DE	DK	ES	FI	FR	*GR	HU	IE	IT	NL	NO	PL	PT	RO	SE	SI	SK	UK	EU
MARKET SHARE TD (2021, JUNE MAT)	Biosimilar vs Referenced product	38%	33%	15%	27%	50%	69%	96%	59%	65%	54%	18%	67%	64%	74%	63%	82%	91%	64%	28%	71%	49%	20%	86%	60%
	Biosimilar vs Accessible market	38%	33%	15%	27%	50%	69%	96%	59%	65%	54%	18%	67%	64%	74%	63%	82%	91%	64%	28%	71%	49%	20%	86%	60%
	Biosimilar vs Total market	31%	30%	13%	21%	44%	60%	88%	53%	55%	48%	11%	58%	59%	63%	60%	76%	75%	59%	25%	66%	44%	18%	80%	54%
PRICE PER TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-42%	-24%	0%	14%	-19%	7%	10%	-1%	-23%	-26%	-18%	18%	-2%	40%	-8%	17%	-64%	-46%	-4%	-33%	-49%	-31%	46%	-7%
	Biosimilar Accessible market	-42%	-24%	0%	15%	-19%	7%	10%	-1%	-23%	-26%	-18%	18%	-2%	40%	-8%	17%	-64%	-46%	-4%	-33%	-49%	-31%	46%	-7%
	Total market	-50%	-42%	-22%	-18%	-33%	-34%	-25%	-28%	-39%	-44%	-15%	-16%	-30%	-15%	-35%	-11%	-70%	-63%	-37%	-52%	-58%	-46%	-5%	-36%
VOLUME TD (2021, JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	627%	241%	50%	169%	598%	369%	311%	309%	608%	262%	-1%	238%	745%	281%	277%	652%	990%	624%	207%	366%	327%	137%	390%	508%
	Biosimilar Accessible market	627%	241%	150%	169%	598%	369%	311%	309%	608%	262%	-1%	238%	745%	281%	277%	652%	990%	624%	207%	366%	327%	137%	390%	508%
	Total market	303%	65%	303%	49%	219%	64%	88%	72%	135%	76%	0%	33%	138%	34%	53%	126%	174%	142%	27%	86%	67%	34%	67%	97%
	TD per capita	1.17	1.56	0.46	1.20	0.72	0.80	1.67	0.97	1.61	1.08	0.01	0.43	2.21	0.49	1.48	2.51	0.12	0.69	0.26	1.66	0.78	0.65	1.04	0.81
	TD/capita (Yr before BS entrance)	0.29	0.94	0.11	0.80	0.23	0.49	0.89	0.56	0.69	0.61	0.01	0.32	0.93	0.37	0.97	1.11	0.04	0.28	0.21	0.89	0.47	0.49	0.62	0.41
	First Recorded sales of Biosimilars	2015	2015	2014	2016	2013	2015	2015	2015	2015	2015	2019	2014	2014	2015	2015	2013	2014	2013	2014	2015	2015	2014	2015	2013

* Only retail panel data is available for Greece

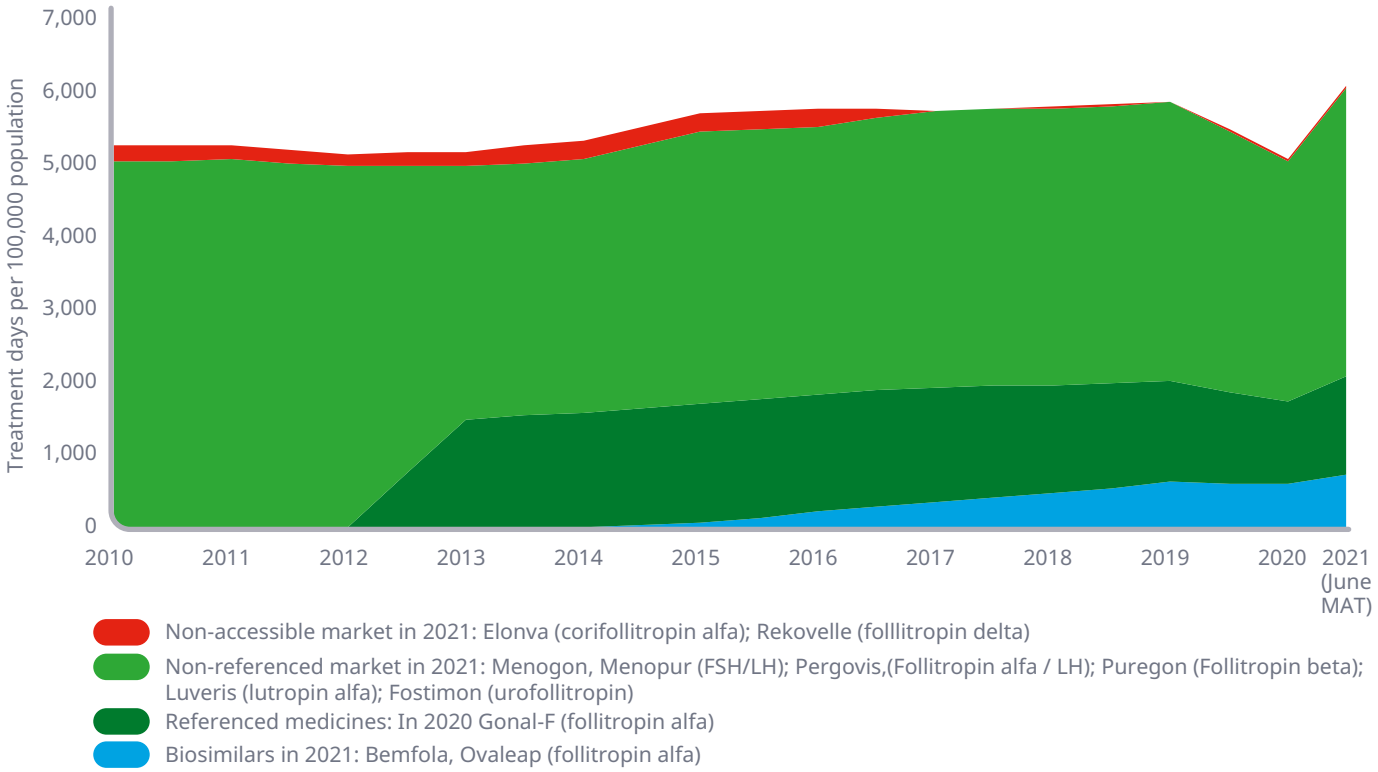
Fertility (FOLLITROPIN ALFA)

Gonadotropin preparations are drugs that mimic the physiological effects of gonadotropins, used therapeutically primarily as fertility medication for ovarian hyperstimulation and reversal of an ovulation. For the purpose of this report, only Follicle-Stimulating Hormones (FSH) and Luteinizing Hormone (LH) preparations were considered.

FERTILITY MARKET DEVELOPMENT

Puregon, Fostimon, Menogon, Menopur are classified as 'non-referenced' products in 2021, according to the definition outlined on page 13 to reflect that they are not protected according to IQVIA MIDAS and ARK Patent intelligence and despite being a second-generation product have now been on the market for a significant number of years and are part of the accessible market for biosimilar competition. Such products may be unlikely to have a biosimilar directly manufactured for them given their age, current price erosion, chemical similarity, previous regulatory schemes, and total opportunity size. A significant decline in treatment volume in 2020 is not a trend break in reporting, but the impact of the COVID-19 pandemic on prescriptions in this area and is therefore an accurate assessment of the market dynamics.

Fertility market development



Fertility approved indications

NAMING		CLASSIFICATION											INDICATIONS					DOSING/ADMINISTRATION	
MOLECULE	PRODUCT	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021 (JUNE MAT)	INFERTILITY	HYPOGONADISM	ANOVULATION	OVULATION INDUCTION	REPRODUCTIVE TECHNIQUES, ASSISTED	ROUTE (SUBQ/IV/IM)	FREQUENCY
CORIFOLLITROPIN ALFA	ELONVA	●	●	●	●	●	●	●	●	●	●	●	●	●					SC	Patient specific
FOLLICLE-STIMULATING HORMONE / LUTEINISING HORMONE	MENOGON MENOPUR	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●		●		● ●	SC/IM SC	Daily Daily
FOLLITROPIN ALFA	GONAL-F BEMFOLA OVALEAP	●	●	●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ●		● ● ●	All All All	Daily Daily Daily
FOLLITROPIN ALFA / LUTEINISING HORMONE	PERGOVERIS	●	●	●	●	●	●	●	●	●	●	●	●	●					All	Daily
FOLLITROPIN BETA	PUREGON	●	●	●	●	●	●	●	●	●	●	●	●	●	●				SC	Patient specific
FOLLITROPIN DELTA	REKOVELLE	●	●	●	●	●	●	●	●	●	●	●	●	●			●	●	SC	Daily
LUTROPIN ALFA	LUVERIS	●	●	●	●	●	●	●	●	●	●	●	●	●			●		All	Daily
UROFOLLITROPIN	FOSTIMON	●	●	●	●	●	●	●	●	●	●	●	●	●			●		IM	Daily

● Non-accessible market ● Non-referenced market ● Referenced medicines ● Biosimilars

Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countries

		AT	BE	BG	CH	CZ	DE	DK	ES	FI	FR	*GR	HU	IE	IT	NL	NO	PL	PT	RO	SE	SI	SK	UK	EU
MARKET SHARE TD (2021, JUNE MAT)	Biosimilar vs Referenced product	1%	51%	0%	8%	25%	44%	30%	51%	25%	34%	29%	93%	0%	33%	0%	34%	46%	39%	5%	25%	31%	64%	22%	35%
	Biosimilar vs Accessible market	0%	13%	0%	1%	11%	14%	9%	16%	9%	14%	6%	44%	0%	9%	0%	13%	12%	11%	1%	11%	17%	22%	7%	12%
	Biosimilar vs Total market	0%	13%	0%	1%	11%	14%	9%	16%	9%	14%	6%	43%	0%	9%	0%	13%	12%	11%	1%	11%	17%	22%	7%	12%
PRICE PER TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-18%	-6%	-18%	-10%	-13%	-10%	-18%	-26%	-27%	-25%	-21%	-24%	-12%	-8%	-16%	0%	-5%	-23%	-14%	-5%	-24%	-17%	16%	-18%
	Biosimilar Accessible market	-4%	11%	7%	2%	13%	15%	9%	1%	-8%	-6%	17%	23%	4%	3%	-2%	21%	-12%	16%	29%	-6%	2%	72%	9%	4%
	Total market	0%	9%	19%	2%	13%	11%	-1%	-11%	-13%	-11%	13%	13%	3%	-2%	2%	19%	-9%	16%	29%	-6%	1%	69%	9%	0%
VOLUME TD (2021, JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	163%	78%	72%	-1%	98%	34%	59%	27%	127%	46%	27%	40%	143%	-26%	13%	199%	78%	62%	96%	76%	76%	74%	-6%	37%
	Biosimilar Accessible market	21%	20%	-66%	4%	67%	24%	52%	15%	45%	23%	10%	3%	69%	0%	-5%	58%	17%	50%	80%	20%	1%	-25%	-15%	21%
	Total market	23%	20%	-66%	4%	67%	16%	40%	2%	39%	18%	9%	-3%	69%	-4%	-3%	59%	14%	48%	80%	20%	1%	-25%	-15%	16%
	TD per capita	0.02	0.07	0.00	0.09	0.10	0.04	0.14	0.08	0.06	0.11	0.04	0.07	0.15	0.07	0.07	0.10	0.02	0.05	0.03	0.10	0.06	0.03	0.02	0.07
	TD/capita (Yr before BS entrance)	0.01	0.06	0.01	0.08	0.06	0.04	0.10	0.08	0.04	0.09	0.03	0.07	0.09	0.08	0.07	0.06	0.02	0.03	0.02	0.08	0.06	0.04	0.02	0.06
	First Recorded sales of Biosimilars	2014	2015	2016	2018	2015	2014	2014	2015	2014	2015	2016	2015	2016	2015	2016	2014	2015	2015	2017	2014	2015	2016	2015	2014

* Only retail panel data is available for Greece

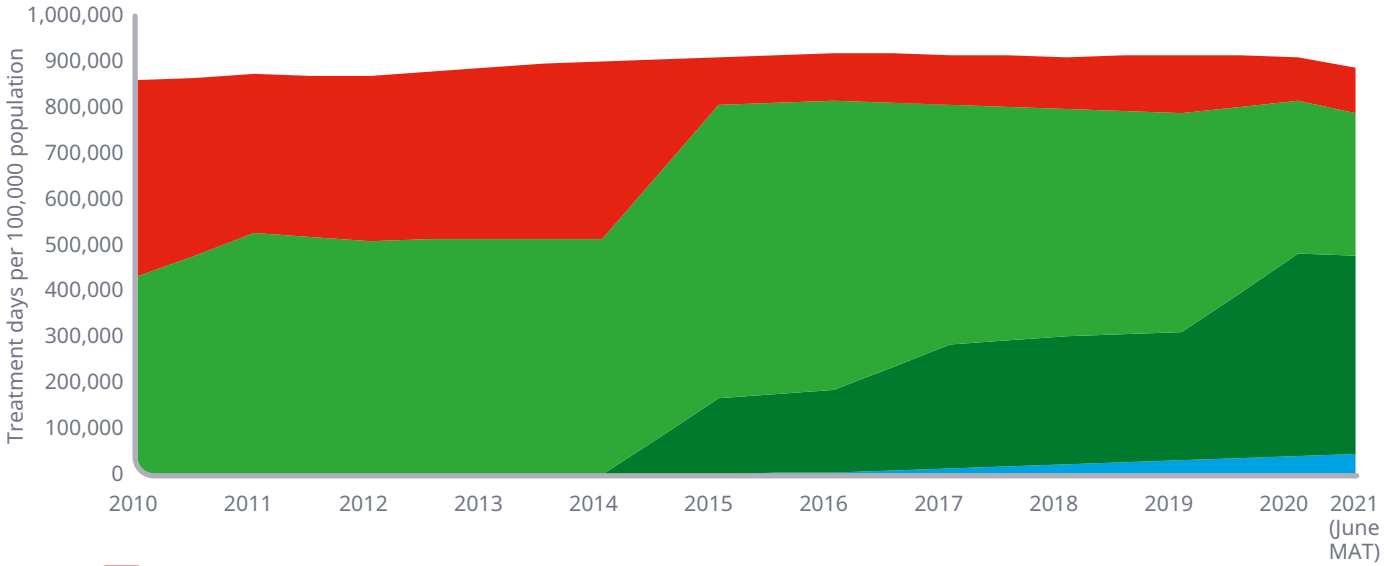
Insulins

Recombinant human insulin is a form of insulin made from recombinant DNA that is identical to human insulin; used to treat diabetics who are allergic to preparations made from beef or pork insulin.

INSULIN MARKET DEVELOPMENT

Products for human insulin are classified as 'non-referenced' products in 2021, according to the definition outlined on page 13 to reflect that they are not protected according to IQVIA MIDAS and ARK Patent intelligence. Such products may be unlikely to have a biosimilar directly manufactured for them given their age, current price erosion, chemical similarity, previous regulatory schemes, and total opportunity size. A small decline in treatment volume in 2020 is not a trend break in reporting, but the impact of the COVID-19 pandemic on prescriptions in this area and is therefore an accurate assessment of the market dynamics.

Insulin market development



- Non-accessible market in 2021: Ryzodeg (insulin aspart / combinations); Tresiba, Xultophy (insulin degludec / combinations); Toujeo (insulin glargine)
- Non-referenced market in 2021: Novomix (insulin aspart / proatmine); Levemir (insulin detemir); Apidera (insulin glusine); Actrapid, Humulin, Protaphane (insulin human); Humalog/Liprolog Mix (insulin lispro/insulin lispro protamine)
- Referenced medicines in 2021: Novorapid (insulin aspart), Lantus (insulin glargine); Humalog / Liprolog (insulin lispro)
- Biosimilars in 2021: Insulin aspart SNFI, Kirsty (insulin aspart); Abasaglar, Semglee (insulin glargine); Ademlog (insulin lispro SNFI.)

ADDITIONAL INFORMATION ABOUT INSULIN MEDICINES

Insulin preparations differ mainly by their kinetic/pharmacodynamic profiles. They are usually classified as rapid- (faster acting than soluble human insulin), short- (e.g. soluble human insulin), intermediate- (NPH /Neutral Protamine Hagedorn insulin, e.g. human isophane insulin), and long-acting preparations (insulins with action profiles significantly longer than NPH insulin). They are used alone or as free mixtures or premixed preparations of rapid/short-acting insulin and intermediate/long-acting (biphasic) insulin in various proportions.

Regular insulin is a short-acting insulin and is generally injected subcutaneously (SubQ) 2-5 times daily within 30-60 minutes before a meal. In conventional regimen the total daily insulin dose is administered as a mixture of rapid/short-acting and intermediate-acting insulins in 1-2 injections. In intensive regimen the total daily dose is administered as 3 or more injections or by continuous subcutaneous infusion to cover basal and pre-meal bolus insulin requirements.

Insulin approved indications

NAMING		CLASSIFICATION												INDICATIONS	DOSING/ADMINISTRATION	
MOLECULE	PRODUCT	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021 (JUNE MAT)	DIABETES MELLITUS	FREQUENCY	MODE OF ACTION
INSULIN ASPART	NOVORAPID INSULIN ASPART SANOFI KIRSTY	●	●	●	●	●	●	●	●	●	●	● ●	● ● ●	● ● ●	before every meal	Fast-acting
INSULIN ASPART#INSULIN ASPART PROTAMINE	NOVOMIX	●	●	●	●	●	●	●	●	●	●	●	●	●	before every meal	Fast-acting
INSULIN ASPART#INSULIN DEGLUDEC	RYZODEG				●	●	●	●	●	●	●	●	●	●	daily	Fast-acting
INSULIN DEGLUDEC	TRESIBA				●	●	●	●	●	●	●	●	●	●	daily	Long-acting
INSULIN DEGLUDEC / LIRAGLUTIDE	XULTOPHY					●	●	●	●	●	●	●	●	●	daily	Long-acting
INSULIN DETEMIR	LEVEMIR	●	●	●	●	●	●	●	●	●	●	●	●	●	twice a day	Long-acting
INSULIN GLARGINE	LANTUS TOUJEO ABASAGLAR SEMGLEE	● ●	● ●	● ●	● ●	● ●	● ● ●	● ● ●	● ● ●	● ● ● ●	● ● ● ●	● ● ● ●	● ● ● ●	● ● ● ●	daily daily daily daily	Long-acting Long-acting Long-acting Long-acting
INSULIN GLARGINE / LIXISENATIDE	SOLIQUA								●	●	●	●	●	●	daily	Long-acting
INSULIN GLULISINE	APIDRA	●	●	●	●	●	●	●	●	●	●	●	●	●	before every meal	Fast-acting
INSULIN HUMAN*	ACTRAPID HUMULIN PROTAPHANE	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	before every meal once/twice a day once/twice a day	Short-acting Short-acting Intermediate-acting
INSULIN LISPRO	HUMALOG/LIPROLOG ADEMLOG/ INSULIN LISPRO SANOFI	●	●	●	●	●	●	●	● ●	● ●	● ●	● ●	● ●	● ●	before every meal before every meal	Fast-acting Fast-acting
INSULIN LISPRO#INSULIN LISPRO PROTAMINE	HUMALOG /LIPROLOG MIX	●	●	●	●	●	●	●	●	●	●	●	●	●	determined by physician	Fast-acting

● Non-accessible market ● Non-referenced market ● Referenced medicines ● Biosimilars

* Only the top 3 products by sales are shown in the table

Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countries

		AT	BE	BG	CH	CZ	DE	DK	ES	FI	FR	*GR	HU	IE	IT	NL	NO	PL	PT	RO	SE	SI	SK	UK	EU
MARKET SHARE TD (2021, JUNE MAT)	Biosimilar vs Referenced product	0%	1%	3%	0%	3%	8%	9%	9%	6%	11%	9%	3%	0%	12%	19%	1%	19%	12%	3%	20%	3%	19%	4%	10%
	Biosimilar vs Accessible market	0%	1%	1%	0%	2%	5%	6%	7%	4%	9%	7%	1%	0%	11%	14%	1%	5%	5%	2%	13%	1%	8%	2%	6%
	Biosimilar vs Total market	0%	1%	1%	0%	1%	4%	5%	6%	4%	8%	5%	1%	0%	9%	12%	1%	5%	5%	2%	12%	1%	7%	2%	6%
PRICE PER TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-21%	-27%	-24%	-19%	-29%	-9%	-24%	-31%	-33%	-34%	-21%	-25%	-33%	-27%	-35%	-25%	-46%	-22%	-15%	-34%	-39%	-26%	-25%	-25%
	Biosimilar Accessible market	6%	-4%	9%	-1%	20%	15%	-11%	-5%	-12%	-12%	2%	15%	-8%	-3%	-7%	17%	2%	5%	18%	5%	-8%	13%	5%	6%
	Total market	6%	0%	17%	10%	28%	6%	-5%	-5%	-17%	-2%	27%	44%	-5%	18%	-8%	38%	0%	2%	20%	5%	10%	18%	0%	5%
VOLUME TD (2021, JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	302%	195%	287%	270%	991%	637%	295%	160%	153%	140%	114%	435%	227%	178%	505%	677%	2143%	114%	170%	631%	347%	503%	525%	483%
	Biosimilar Accessible market	-13%	1%	-4%	0%	22%	4%	-5%	11%	37%	7%	-17%	-4%	14%	-8%	31%	4%	-1%	3%	18%	15%	-11%	12%	36%	17%
	Total market	-10%	5%	-7%	-2%	22%	-8%	-7%	-7%	-4%	9%	-4%	-3%	10%	-6%	-3%	4%	-9%	-1%	18%	-10%	-8%	-3%	3%	-3%
	TD per capita	6.62	8.65	8.78	4.98	11.56	11.56	7.27	8.04	11.27	7.56	8.53	10.55	5.72	5.73	10.32	7.67	9.17	7.39	7.85	10.41	10.92	8.26	9.72	8.72
	TD/capita (Yr before BS entrance)	7.33	8.22	9.39	5.06	9.48	12.51	7.82	8.69	11.71	6.97	8.88	10.86	5.20	6.07	10.60	7.36	10.08	7.46	6.67	11.54	11.86	8.47	9.44	8.95
	First Recorded sales of Biosimilars	2017	2016	2015	2015	2015	2015	2015	2015	2015	2016	2016	2015	2016	2016	2015	2015	2015	2016	2016	2015	2016	2015	2015	2015

* Only retail panel data is available for Greece

Oncology

Monoclonal Antibody Antineoplastic agents use monoclonal antibodies (mAb) to bind monospecifically to certain cells or proteins to treat cancer. The objective is that this treatment will stimulate the patient's immune system to attack those cells.

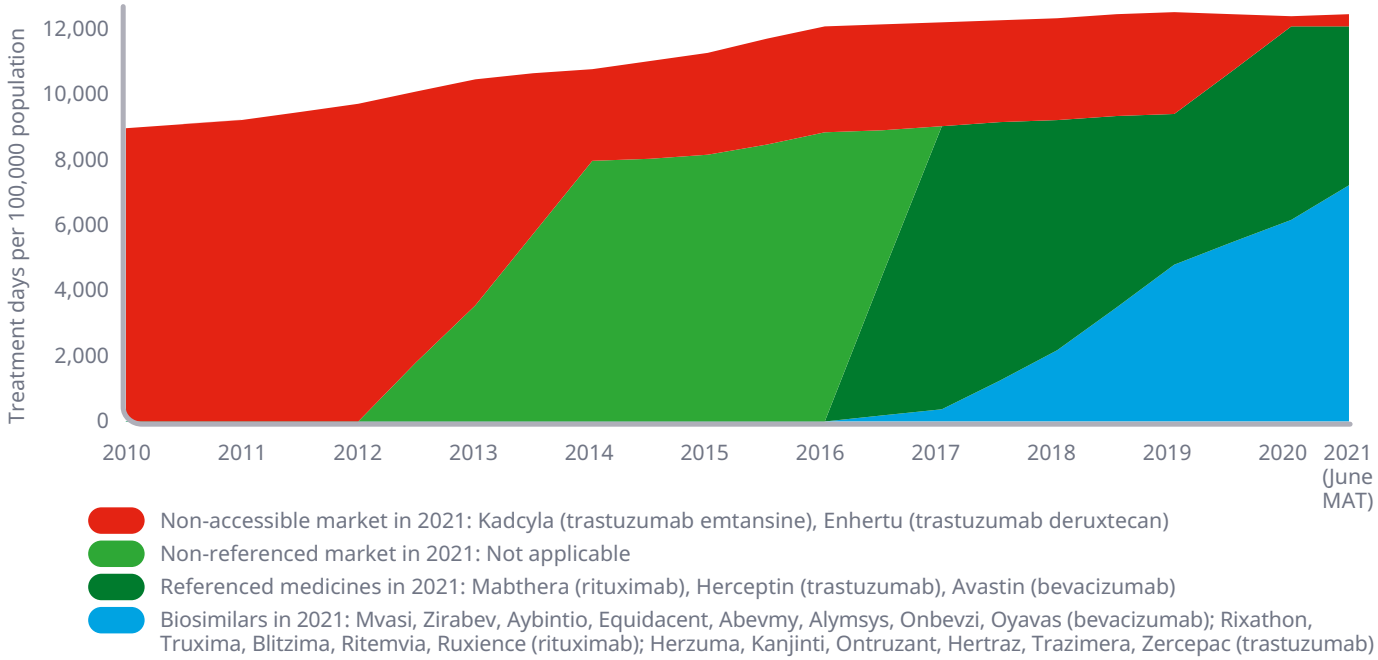
In this market the non-accessible products are classified by identifying products which have a similar mechanism of action, and are used for similar indications to rituximab. There are both IV and SC forms of Mabthera available, but because the biosimilar is only available in IV form, Mabthera IV is classified as the referenced product, and Mabthera SC is classified as a non-referenced product.

ONCOLOGY MARKET DEVELOPMENT

This market is a representation of the total oncology market, as the number of products in this class is vast, with the majority being new innovative meicines that would be classified in the non-accessible category. The approach is therefore to focus on products which are open, or approaching biosimilar competition. This therefore will continue to change in the future and impact the KPIs.

Protection for Mabthera and Herceptin expired a number of years prior to biosimilar entry. This chart reflects theperiod in which these products were 'non-referenced'. In contrast, Avastin had approved biosimilars in Europe before protection expiry. There are no recorded sales, but this is recorded, and Avastin is classified accurately as 'non-accessible' until its protection status expires.

Oncology market development



Oncology approved indications

NAMING		CLASSIFICATION												INDICATIONS								DOSING	
MOLECULE	PRODUCT	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021 (JUNE MAT)	FL, DLBC (NON-GL)	CLL	MC	BC	METASTATIC GC	RCC	NSCLC	EOC	PPC	ROUTE (SUBQ / IV)	FREQUENCY
BEVACIZUMAB*	AVASTIN MVASI ZIRABEV AYBINTIO EQUIDACENT ABEVMY ALYMSYS ONBEVZI OYAVAS	●	●	●	●	●	●	●	●	● ●	● ●	● ● ● ● ●	● ● ● ● ● ● ● ● ●			● ● ● ● ● ● ● ●	● ● ● ● ● ● ● ●		● ● ● ● ● ● ● ●	● ● ● ● ● ● ● ●	● ● ● ● ● ● ● ●	● ● ● ● ● ● ● ●	IV IV IV IV IV IV IV IV IV	2 - 3 week cycles (indication/ combination dependant)
RITUXIMAB**	MABTHERA RIXATHON TRUXIMA BLITZIMA RITEMVIA RUXIENCE	●	●	●	●	●	●	●	● ●	● ● ● ●	● ● ● ●	● ● ● ●	● ● ● ● ● ●	● ● ● ● ● ●	● ● ● ●								SC/IV IV IV IV IV IV	3 week cycles
TRASTUZUMAB	HERCEPTIN HERZUMA KANJINTI ONTRUZANT HERTRAZ TRAZIMERA ZERCEPAC	●	●	●	●	●	●	●	● ●	● ● ● ●	● ● ● ● ●	● ● ● ● ●	● ● ● ● ● ●				● ● ● ● ● ●	● ● ● ● ● ●					SC/IV IV IV IV IV IV IV	3 week cycles
TRASTUZUMAB EMTANSINE	KADCYLA				●	●	●	●	●	●	●	●	●				●						IV	3 week cycles
TRASTUZUMAB DERUXTECAN	ENHERTU											●	●				●						IV	3 week cycles

● Non-accessible market ● Non-referenced market ● Referenced medicines ● Biosimilars

OGIVRI is coded as HERTRAZ in IQVIA MIDAS

"** Indicatied for non-conology indications such as rheumatoid arthritis, Granulomatosis with polyangiitis and microscopic polyangiitis Pemphigus vulgaris.";
FL = follicular lymphoma, DLBC = Diffuse large B-cell lymphoma, CLL = Chronic lymphocytic leukemia; MC = metastatic carcinoma or the colon or rectum, GC = gastic cancer, RCC = renal cell carcinoma, NSCLC = non-small cell lung cancer, EOC = epithelial ovarian cancer, PPC = Primary peritoneal cancer

Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countries

		AT	BE	BG	CH	CZ	DE	DK	ES	FI	FR	HU	IE	IT	NL	NO	PL	PT	RO	SE	SI	SK	UK	EU
MARKET SHARE TD (2021, JUNE MAT)	Biosimilar vs Referenced product	87%	12%	9%	17%	26%	67%	94%	60%	60%	64%	40%	37%	67%	89%	85%	45%	40%	53%	75%	41%	43%	64%	60%
	Biosimilar vs Accessible market	87%	12%	9%	17%	26%	67%	94%	60%	60%	64%	40%	37%	67%	89%	85%	45%	40%	53%	75%	41%	43%	64%	60%
	Biosimilar vs Total market	84%	11%	9%	16%	26%	65%	91%	58%	59%	61%	39%	36%	66%	88%	83%	44%	39%	42%	72%	40%	42%	62%	58%
PRICE PER TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-3%	-19%	-11%	-9%	-18%	-44%	-12%	-12%	-5%	-24%	-3%	-10%	-11%	-17%	-2%	-55%	-24%	-3%	-5%	-32%	-17%	1%	-23%
	Biosimilar Accessible market	-3%	-19%	-12%	-9%	-18%	-44%	-12%	-12%	-5%	-25%	-3%	-14%	-11%	-18%	5%	-55%	-23%	-3%	-5%	-32%	-17%	6%	-23%
	Total market	-2%	-25%	-14%	-12%	-19%	-40%	-12%	-13%	-8%	-19%	-10%	-16%	-13%	-22%	5%	-46%	-22%	35%	-2%	-34%	-21%	10%	-21%
VOLUME TD (2021, JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	103%	113%	109%	34%	30%	385%	100%	216%	54%	120%	81%	394%	130%	554%	189%	25%	204%	-14%	15%	23%	48%	259%	474%
	Biosimilar Accessible market	52%	113%	109%	34%	30%	20%	52%	57%	54%	66%	81%	23%	15%	63%	50%	25%	54%	-14%	15%	23%	48%	-14%	44%
	Total market	-3%	57%	22%	2%	-3%	-14%	12%	22%	18%	15%	4%	-2%	-17%	27%	25%	10%	21%	-62%	0%	4%	-17%	-16%	4%
	TD per capita	0.16	0.25	0.13	0.17	0.10	0.09	0.17	0.16	0.18	0.18	0.12	0.14	0.12	0.16	0.16	0.07	0.11	0.01	0.13	0.12	0.09	0.11	0.12
	TD/capita (Yr before BS entrance)	0.17	0.16	0.11	0.16	0.10	0.11	0.15	0.13	0.15	0.16	0.12	0.15	0.14	0.13	0.13	0.06	0.09	0.04	0.13	0.11	0.11	0.13	0.12
	First Recorded sales of Biosimilars	2017	2018	2018	2018	2018	2017	2017	2017	2018	2017	2018	2017	2017	2017	2017	2018	2017	2018	2018	2018	2018	2017	2017

* Only retail panel data is available for Greece

Low-molecular-weight heparin (LMWH)

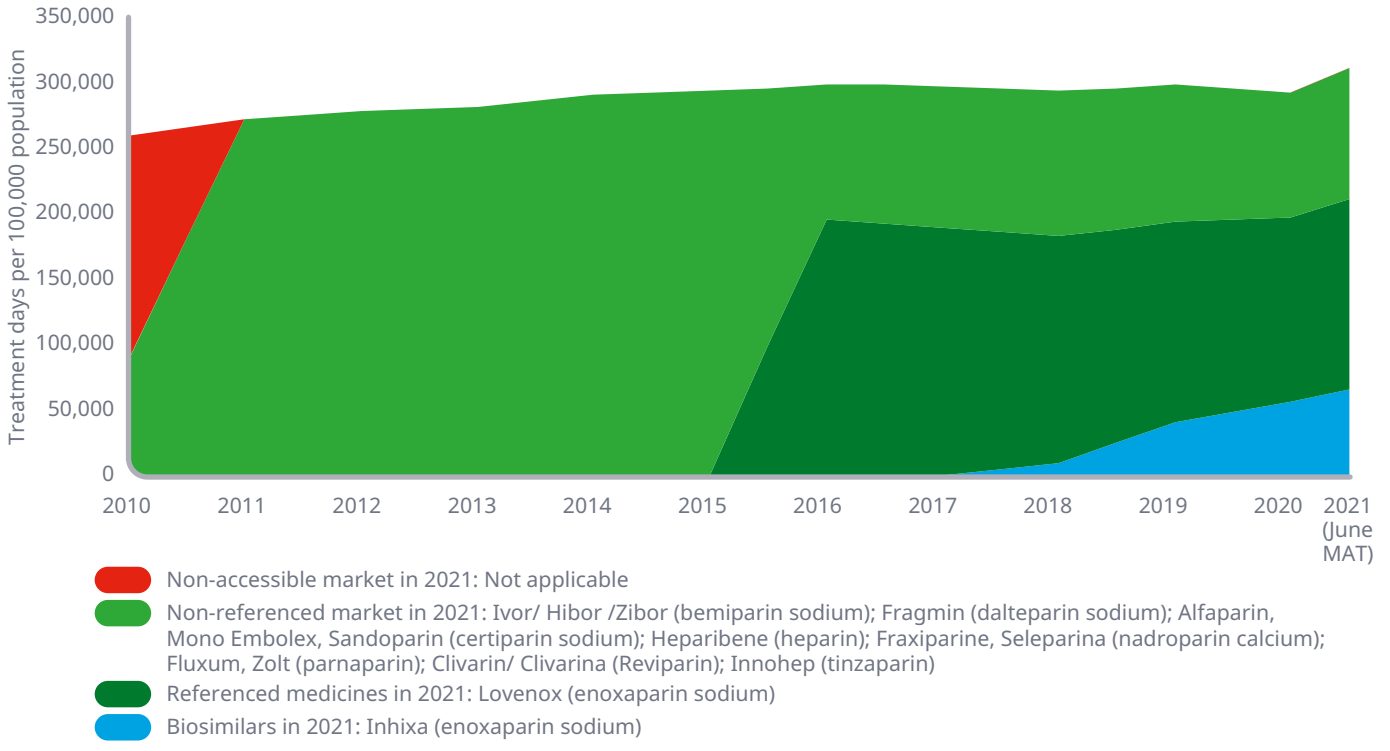
Low-Molecular-Weight Heparin (LMWH) is a class of anticoagulant medications. They are used in the prevention of blood clots, treatment of venous thromboembolism (deep vein thrombosis and pulmonary embolism) and in the treatment of myocardial infarction. LMWH is obtained by fractionation of polymeric heparin. Many LMWH products are on the market, each similar in structure but created using different initial chemical procedures e.g. Enoxaparin is created using alkaline beta-eliminative cleavage of the benzyl ester of heparin.

Two enoxaparin sodium biosimilars (Inhixa and Thorinane) were authorised by the EMA in 09/2016, however Thorinane is now withdrawn meaning that Inhixa is the only remaining biosimilar in 2021.

LMWH MARKET DEVELOPMENT

Products for molecules in this class (bemiparin sodium, certoparin sodium, dalteparin sodium , heparin, nadroparin calcium, parnaparin, reviparin and tinzaparin) are classified as 'non-referenced' products in 2021, according to the definition outlined on page 13 to reflect that they are not protected according to IQVIA MIDAS and ARK Patent intelligence. Such products may be unlikely to have a biosimilar directly manufactured for them given their age, current price erosion, chemical similarity, previous regulatory schemes, and total opportunity size. An increase in treatment volume in 2020 is not a trend break in reporting, but the impact of the COVID-19 pandemic on prescriptions and usage of LMWHs for COVID-19 patients and is therefore an accurate assessment of the market dynamics.

LMWH market development



LMWH approved indications

NAMING		CLASSIFICATION												INDICATIONS			
MOLECULE	PRODUCT	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021 (JUNE MAT)	DEEP VEIN THROMBOSIS TREATMENT AND PROPHYLAXIS	PULMONARY EMBOLISM	ATRIAL THROMBUS	BRIDGING THERAPY PRIOR TO STARTING WARFARIN
BEMIPARIN SODIUM	IVOR/HIBOR/ZIBOR	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
CERTOPARIN SODIUM	ALFAPARIN MONO EMBOLEX SANDOPARIN	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●		
DALTEPARIN SODIUM	FRAGMIN	●	●	●	●	●	●	●	●	●	●	●	●	●			
ENOXAPARIN SODIUM	LOVENOX NEOPARIN INHIXA	● 	● 	● 	● 	● 	● 	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●	● ● ●			● ● ●
HEPARIN	HEPARIBENE	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
NADROPARIN CALCIUM	FRAXIPARINE SELEPARINA	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●		
PARNAPARIN	FLUXUM ZOLTAR	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●		
REVIPARIN	CLIVARIN CLIVARINA	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●		
TINZAPARIN	INNOHEP	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●

● Non-accessible market ● Non-referenced market ● Referenced medicines ● Biosimilars

Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countries

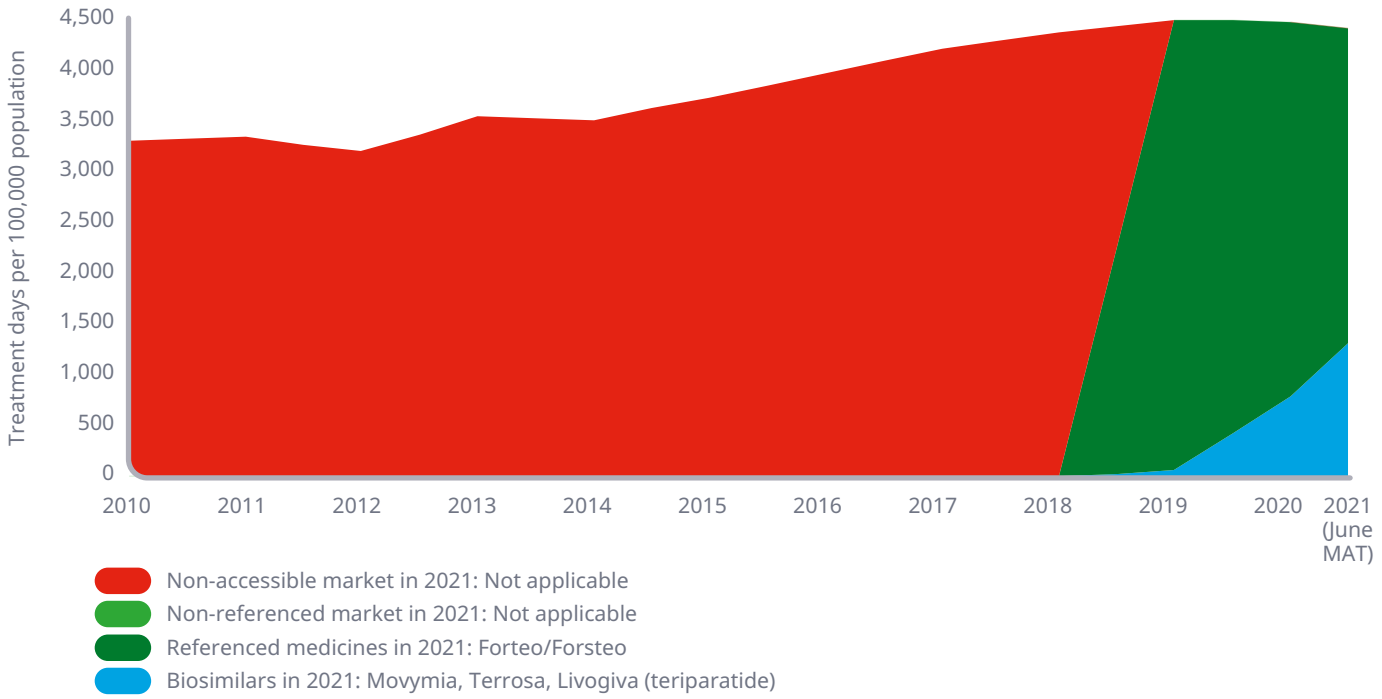
		AT	BE	BG	CH	CZ	DE	DK	ES	FI	FR	HU	IE	IT	NL	NO	PL	PT	SE	SI	SK	UK	EU
MARKET SHARE TD (2021, JUNE MAT)	Biosimilar vs Referenced product	49%	0%	0%	1%	0%	23%	86%	42%	54%	6%	0%	0%	55%	0%	0%	0%	41%	0%	0%	0%	52%	26%
	Biosimilar vs Accessible market	39%	0%	0%	1%	0%	17%	2%	33%	35%	4%	0%	0%	50%	0%	0%	0%	39%	0%	0%	0%	28%	18%
	Biosimilar vs Total market	39%	0%	0%	1%	0%	17%	2%	33%	35%	4%	0%	0%	50%	0%	0%	0%	39%	0%	0%	0%	28%	18%
PRICE PER TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-29%	-1%	0%	-1%	5%	-1%	-11%	-17%	-17%	-8%	0%	0%	-5%	0%	0%	-3%	-9%	-1%	0%	0%	-1%	-6%
	Biosimilar Accessible market	-25%	-1%	0%	1%	10%	0%	0%	-12%	-9%	-6%	0%	0%	-6%	0%	0%	-3%	-9%	1%	0%	0%	-1%	-5%
	Total market	-25%	-1%	0%	1%	10%	0%	0%	-12%	-9%	-6%	0%	0%	-6%	0%	0%	-3%	-9%	1%	0%	0%	-1%	-5%
VOLUME TD (2021, JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-18%	5%	0%	10%	15%	-17%	-8%	21%	-13%	8%	0%	0%	15%	0%	0%	51%	-6%	7%	0%	0%	7%	3%
	Biosimilar Accessible market	-16%	4%	0%	4%	5%	-17%	1%	15%	0%	4%	0%	0%	0%	0%	0%	13%	-7%	1%	0%	0%	-6%	1%
	Total market	-16%	4%	0%	4%	5%	-17%	1%	15%	0%	4%	0%	0%	0%	0%	0%	13%	-7%	1%	0%	0%	-6%	1%
	TD per capita	4.08	3.25	1.02	2.14	3.96	3.39	1.26	3.92	2.48	2.8	5.23	1.66	3.54	1.12	2.18	3.97	1.75	2.27	2.56	5.08	1.91	3.18
	TD/capita (Yr before BS entrance)	4.88	3.13	N/A	2.06	3.78	4.07	1.24	3.42	2.49	2.69	N/A	N/A	3.52	N/A	N/A	3.51	1.88	2.25	N/A	N/A	2.03	3.15
	First Recorded sales of Biosimilars	2018	2021	N/A	2020	2020	2017	2019	2018	2020	2018	N/A	N/A	2017	N/A	N/A	2019	2019	2020	N/A	N/A	2017	2017

* Only retail panel data is available for Greece

Parathyroid hormones

Teriparatide is a recombinant form of parathyroid hormone (PTH). Teriparatide is identical to a part of human PTH and intermittent use activates osteoblasts more than osteoclasts, which leads to an overall increase in bone production. This makes it an effective anabolic, i.e., bone growing, agent. It is used for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture and for glucocorticoid-induced osteoporosis in men and postmenopausal women.

PTH market development



PARATHYROID HORMONES MARKET DEVELOPMENT

The first biosimilars for teriparatide had already been centrally approved two years earlier in January 2017 (Movymia and Terrosa), and a third has now been approved in August 2020 (Livogiva). Sales for biosimilar teriparatide are now observed across Europe and this is the first year the market has been included within 'The Impact of Biosimilar Competition' report.

PTh approved indications

NAMING		CLASSIFICATION												INDICATIONS
MOLECULE	PRODUCT	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021 (JUNE MAT)	OSTEOPEROSIS (IN POST MENOPAUSAL WOMEN AND MEN AT INCREASED RISK OF FACTURE)
TERIPARATIDE	FORTEO MOVYMIA TERROSA LIVOGIVA	●	●	●	●	●	●	●	● ● ●	● ● ●	● ● ●	● ● ● ●	● ● ● ● ●	● ● ● ●

● Non-accessible market ● Non-referenced market ● Referenced medicines ● Biosimilars

Selected KPIs to illustrate volume share, price evolution, and volume evolution in selected European countriesCZ

		AT	CZ	DE	DK	ES	FI	FR	HU	IE	IT	NL	PT	RO	SE	SI	SK	UK	EU
MARKET SHARE TD (2021, JUNE MAT)	Biosimilar vs Referenced product	42%	61%	27%	20%	31%	2%	15%	86%	8%	27%	24%	15%	26%	27%	29%	97%	47%	26%
	Biosimilar vs Accessible market	42%	61%	27%	20%	31%	2%	15%	86%	8%	27%	24%	15%	26%	27%	29%	97%	47%	26%
	Biosimilar vs Total market	42%	61%	27%	20%	31%	2%	15%	86%	8%	27%	24%	15%	26%	27%	29%	97%	47%	26%
PRICE PER TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	-48%	-46%	-9%	-37%	-25%	-27%	-21%	-30%	-4%	-14%	-14%	-6%	-7%	-10%	-22%	-35%	-6%	-19%
	Biosimilar Accessible market	-48%	-46%	-9%	-37%	-25%	-27%	-21%	-30%	-4%	-14%	-14%	-6%	-7%	-10%	-22%	-35%	-6%	-19%
	Total market	-48%	-46%	-9%	-37%	-25%	-27%	-21%	-30%	-4%	-14%	-14%	-6%	-7%	-11%	-23%	-35%	-6%	-19%
VOLUME TD (2021 JUNE MAT/YR BEFORE BS ENTRY)	Biosimilar and Referenced product	55%	173%	121%	129%	99%	-13%	101%	126%	38%	56%	8%	-7%	-33%	30%	-4%	150%	93%	90%
	Biosimilar Accessible market	55%	173%	121%	129%	99%	-13%	101%	126%	38%	56%	8%	-7%	-33%	30%	-4%	150%	93%	90%
	Total market	16%	39%	10%	14%	0%	-13%	3%	11%	4%	-21%	8%	-7%	-33%	-1%	-30%	1%	-1%	-4%
	TD per capita	0.07	0.02	0.02	0.08	0.13	0.02	0.06	0.04	0.09	0.07	0.04	0.02	0.01	0.02	0.02	0.01	0.02	0.05
	TD/capita (Yr before BS entrance)	0.06	0.01	0.02	0.07	0.13	0.02	0.05	0.03	0.08	0.09	0.04	0.02	0.02	0.02	0.02	0.01	0.02	0.05
	First Recorded sales of Biosimilars	2019	2019	2019	2019	2019	2020	2019	2019	2019	2019	2020	2020	2020	2019	2019	2019	2019	2019

Appendix

Table 1: EU list of approved biosimilars (July 2021)

MEDICINE NAME	INTERNATIONAL NON-PROPRIETARY NAME (INN) / COMMON NAME	THERAPEUTIC AREA	ATC CODE	MARKETING AUTHORISATION HOLDER/COMPANY NAME	MARKETING AUTHORISATION DATE
ABEVMY	bevacizumab	Colorectal Neoplasms; Breast Neoplasms; Ovarian Neoplasms; Fallopian Tube Neoplasms; Peritoneal Neoplasms; Carcinoma, Non-Small-Cell Lung; Carcinoma, Renal Cell; Uterine Cervical Neoplasms	L01XC07	Mylan IRE Healthcare Limited	21/04/2021
ALYMSYS	bevacizumab	Colorectal Neoplasms; Breast Neoplasms; Ovarian Neoplasms; Peritoneal Neoplasms; Carcinoma, Non-Small-Cell Lung; Carcinoma, Renal Cell; Uterine Cervical Neoplasms	L01XC07	Mabxience Research SL	26/03/2021
OYAVAS	bevacizumab	Colorectal Neoplasms; Breast Neoplasms; Ovarian Neoplasms; Fallopian Tube Neoplasms; Peritoneal Neoplasms; Carcinoma, Non-Small-Cell Lung; Carcinoma, Renal Cell; Uterine Cervical Neoplasms	L01XC07	STADA Arzneimittel AG	26/03/2021
YUFLYMA	adalimumab	Arthritis, Rheumatoid; Spondylitis, Ankylosing; Psoriasis; Arthritis, Psoriatic; Colitis, Ulcerative; Crohn Disease; Arthritis, Juvenile Rheumatoid; Hidradenitis Suppurativa; Uveitis	L04AB04	Celltrion Healthcare Hungary Kft.	11/02/2021
KIRSTY (PREVIOUSLY KIXELLE)	insulin aspart	Diabetes Mellitus	A10AB05	Mylan Ireland Limited	5/02/2021
ONBEVZI	bevacizumab	Colorectal Neoplasms; Breast Neoplasms; Ovarian Neoplasms; Fallopian Tube Neoplasms; Peritoneal Neoplasms; Carcinoma, Non-Small-Cell Lung; Carcinoma, Renal Cell; Uterine Cervical Neoplasms	L01XC07	Samsung Bioepis NL B.V.	11/01/2021
NYVEPRIA	pegfilgrastim	Neutropenia	L03AA13	Pfizer Europe MA EEIG	18/11/2020
EQUIDACENT	bevacizumab	Colorectal Neoplasms; Breast Neoplasms; Ovarian Neoplasms; Carcinoma, Non-Small-Cell Lung; Carcinoma, Renal Cell	L01XC07	Centus Biotherapeutics Europe Limited	24/09/2020
LIVOGIVA	teriparatide	Osteoporosis	H05AA02	Theramex Ireland Limited	27/08/2020
AYBINTIO	bevacizumab	Colorectal Neoplasms; Breast Neoplasms; Ovarian Neoplasms; Fallopian Tube Neoplasms; Peritoneal Neoplasms; Carcinoma, Non-Small-Cell Lung; Carcinoma, Renal Cell; Uterine Cervical Neoplasms	L01XC07	Samsung Bioepis NL B.V.	19/08/2020
ZERCEPAC	trastuzumab	Breast Neoplasms; Stomach Neoplasms	L01XC03	Accord Healthcare S.L.U.	27/07/2020
INSULIN ASPART SANOFI	insulin aspart	Diabetes Mellitus	A10AB05	sanofi-aventis groupe	25/06/2020
NEPEXTO	etanercept	Arthritis, Rheumatoid; Arthritis, Juvenile Rheumatoid; Arthritis, Psoriatic; Spondylarthropathies; Spondylitis, Ankylosing; Psoriasis	L04AB01	Mylan Ireland Limited	20/05/2020
RUXIENCE	rituximab	Leukemia, Lymphocytic, Chronic, B-Cell; Arthritis, Rheumatoid; Microscopic Polyangiitis; Pemphigus	L01XC02	Pfizer Europe MA EEIG	1/04/2020
AMSPARITY	adalimumab	Arthritis, Rheumatoid; Arthritis, Juvenile Rheumatoid; Psoriasis; Arthritis, Psoriatic; Spondylitis, Ankylosing; Uveitis; Colitis, Ulcerative; Crohn Disease; Hidradenitis Suppurativa	L04AB04	Pfizer Europe MA EEIG	13/02/2020
CEGFILA (PREVIOUSLY PEGFILGRASTIM MUNDIPHARMA)	pegfilgrastim	Neutropenia	L03AA13	Mundipharma Corporation (Ireland) Limited	19/12/2019
GRASUSTEK	pegfilgrastim	Neutropenia	L03AA13	Juta Pharma GmbH	20/06/2019
IDACIO	adalimumab	Arthritis, Rheumatoid; Arthritis, Juvenile Rheumatoid; Psoriasis; Arthritis, Psoriatic; Spondylitis, Ankylosing; Uveitis; Hidradenitis Suppurativa; Colitis, Ulcerative; Crohn Disease	L04AB04	Fresenius Kabi Deutschland GmbH	2/04/2019
ZIRABEV	bevacizumab	Colorectal Neoplasms; Breast Neoplasms; Carcinoma, Non-Small-Cell Lung; Carcinoma, Renal Cell; Uterine Cervical Neoplasms	L01XC07	Pfizer Europe MA EEIG	14/02/2019
OGIVRI	trastuzumab	Stomach Neoplasms; Breast Neoplasms	L01XC03	Mylan S.A.S	12/12/2018
ZIEXTENZO	pegfilgrastim	Neutropenia	L03AA13	Sandoz GmbH	22/11/2018
PELMEG	pegfilgrastim	Neutropenia	L03AA13	Mundipharma Corporation (Ireland) Limited	20/11/2018
FULPHILA	pegfilgrastim	Neutropenia	L03AA13	Mylan S.A.S, Viatris Limited	20/11/2018
PELGRAZ	pegfilgrastim	Neutropenia	L03AA13	Accord Healthcare S.L.U.	21/09/2018
HULIO	adalimumab	Hidradenitis Suppurativa; Psoriasis; Crohn Disease; Uveitis; Arthritis, Rheumatoid; Colitis, Ulcerative; Spondylitis, Ankylosing; Arthritis, Psoriatic	L04AB04	Mylan S.A.S.	17/09/2018
HEFIYA	adalimumab	Hidradenitis Suppurativa; Spondylitis, Ankylosing; Psoriasis; Arthritis, Juvenile Rheumatoid; Uveitis	L04AB04	Sandoz GmbH	26/07/2018
TRAZIMERA	trastuzumab	Stomach Neoplasms; Breast Neoplasms	L01XC03	Pfizer Europe MA EEIG	26/07/2018
HYRIMOZ	adalimumab	Hidradenitis Suppurativa; Crohn Disease; Arthritis, Juvenile Rheumatoid; Uveitis; Arthritis, Rheumatoid; Colitis, Ulcerative; Spondylitis, Ankylosing; Skin Diseases, Papulosquamous; Arthritis, Psoriatic	L04AB04	Sandoz GmbH	26/07/2018

MEDICINE NAME	INTERNATIONAL NON-PROPRIETARY NAME (INN) / COMMON NAME	THERAPEUTIC AREA	ATC CODE	MARKETING AUTHORISATION HOLDER/COMPANY NAME	MARKETING AUTHORISATION DATE
ZESSLY	infliximab	Arthritis, Psoriatic; Psoriasis; Crohn Disease; Arthritis, Rheumatoid; Colitis, Ulcerative; Spondylitis, Ankylosing	L04AB02	Sandoz GmbH	18/05/2018
KANJINTI	trastuzumab	Stomach Neoplasms; Breast Neoplasms	L01XC03	Amgen Europe BV	16/05/2018
SEMGLEE	insulin glargine	Diabetes Mellitus	A10AE04	Mylan S.A.S	23/03/2018
HERZUMA	trastuzumab	Stomach Neoplasms; Breast Neoplasms	L01XC03	Celltrion Healthcare Hungary Kft.	8/02/2018
MVASI	bevacizumab	Carcinoma, Renal Cell; Peritoneal Neoplasms; Ovarian Neoplasms; Breast Neoplasms; Carcinoma, Non-Small-Cell Lung; Fallopian Tube Neoplasms	L01XC07	Amgen Technology (Ireland) UC	15/01/2018
ONTRUZANT	trastuzumab	Stomach Neoplasms; Breast Neoplasms	L01XC03	Samsung Bioepis NL B.V.	15/11/2017
IMRALDI	adalimumab	Hidradenitis Suppurativa; Psoriasis; Crohn Disease; Uveitis; Arthritis, Rheumatoid; Arthritis; Colitis, Ulcerative; Spondylitis, Ankylosing; Arthritis, Psoriatic	L04AB04	Samsung Bioepis NL B.V.	24/08/2017
INSULIN LISPRO SANOFI	insulin lispro	Diabetes Mellitus	A10AB04	sanofi-aventis groupe	18/07/2017
BLITZIMA	rituximab	Lymphoma, Non-Hodgkin; Leukemia, Lymphocytic, Chronic, B-Cell	L01XC02	Celltrion Healthcare Hungary Kft.	13/07/2017
ERELZI	etanercept	Arthritis, Psoriatic; Psoriasis; Arthritis, Juvenile Rheumatoid; Arthritis, Rheumatoid; Spondylitis, Ankylosing	L04AB01	Sandoz GmbH	23/06/2017
RIXIMYO	rituximab	Lymphoma, Non-Hodgkin; Arthritis, Rheumatoid; Microscopic Polyangiitis; Wegener Granulomatosis	L01XC02	Sandoz GmbH	15/06/2017
RIXATHON	rituximab	Lymphoma, Non-Hodgkin; Arthritis, Rheumatoid; Leukemia, Lymphocytic, Chronic, B-Cell; Wegener Granulomatosis; Microscopic Polyangiitis; Pemphigus	L01XC02	Sandoz GmbH	15/06/2017
AMGEVITA	adalimumab	Arthritis, Psoriatic; Colitis, Ulcerative; Arthritis, Juvenile Rheumatoid; Spondylitis, Ankylosing; Psoriasis; Crohn Disease; Arthritis, Rheumatoid	L04AB04	Amgen Europe B.V.	21/03/2017
TRUXIMA	rituximab	Lymphoma, Non-Hodgkin; Arthritis, Rheumatoid; Wegener Granulomatosis; Leukemia, Lymphocytic, Chronic, B-Cell; Microscopic Polyangiitis	L01XC02	Celltrion Healthcare Hungary Kft.	17/02/2017
MOVYMIA	teriparatide	Osteoporosis	H05AA02	STADA Arzneimittel AG	11/01/2017
TERROSA	teriparatide	Osteoporosis	H05AA02	Gedeon Richter Plc.	4/01/2017
INHIXA	enoxaparin sodium	Venous Thromboembolism	B01AB05	Techdow Pharma Netherlands B.V.	15/09/2016
FLIXABI	infliximab	Spondylitis, Ankylosing; Arthritis, Rheumatoid; Crohn Disease; Colitis, Ulcerative; Arthritis, Psoriatic; Psoriasis	L04AB02	Samsung Bioepis NL B.V.	26/05/2016
BENEPALI	etanercept	Arthritis, Psoriatic; Arthritis, Rheumatoid; Psoriasis	L04AB01	Samsung Bioepis NL B.V.	13/01/2016
ACCOFIL	filgrastim	Neutropenia	L03AA02	Accord Healthcare S.L.U.	17/09/2014
ABASAGLAR (PREVIOUSLY ABASRIA)	insulin glargine	Diabetes Mellitus	A10AE04	Eli Lilly Nederland B.V.	9/09/2014
BEMFOLA	follitropin alfa	Anovulation	G03GA05	Gedeon Richter Plc.	26/03/2014
GRASTOFIL	filgrastim	Neutropenia	L03AA02	Accord Healthcare, SLU	17/10/2013
OVALEAP	follitropin alfa	Anovulation	G03GA05	Theramex Ireland Limited	27/09/2013
REMSIMA	infliximab	Arthritis, Psoriatic; Spondylitis, Ankylosing; Colitis, Ulcerative; Psoriasis; Crohn Disease; Arthritis, Rheumatoid	L04AB02	Celltrion Healthcare Hungary Kft.	10/09/2013
INFLECTRA	infliximab	Arthritis, Psoriatic; Spondylitis, Ankylosing; Colitis, Ulcerative; Psoriasis; Crohn Disease; Arthritis, Rheumatoid	L04AB02	Pfizer Europe MA EEIG	10/09/2013
NIVESTIM	filgrastim	Neutropenia; Hematopoietic Stem Cell Transplantation; Cancer	L03AA02	Pfizer Europe MA EEIG	7/06/2010
ZARZIO	filgrastim	Neutropenia; Hematopoietic Stem Cell Transplantation; Cancer	L03AA02	Sandoz GmbH	6/02/2009
FILGRASTIM HEXAL	filgrastim	Neutropenia; Hematopoietic Stem Cell Transplantation; Cancer	L03AA02	Hexal AG	6/02/2009
TEVAGRASTIM	filgrastim	Neutropenia; Hematopoietic Stem Cell Transplantation; Cancer	L03AA02	Teva GmbH	15/09/2008
RATIOGRASTIM	filgrastim	Neutropenia; Hematopoietic Stem Cell Transplantation; Cancer	L03AA02	Ratiopharm GmbH	15/09/2008
RETACRIT	epoetin zeta	Anemia; Blood Transfusion, Autologous; Kidney Failure, Chronic; Cancer	B03XA01	Pfizer Europe MA EEIG	18/12/2007
SILAPO	epoetin zeta	Anemia; Blood Transfusion, Autologous; Cancer; Kidney Failure, Chronic	B03XA01	Stada Arzneimittel AG	18/12/2007
BINOCRIT	epoetin alfa	Anemia; Kidney Failure, Chronic	B03XA01	Sandoz GmbH	28/08/2007
ABSEAMED	epoetin alfa	Anemia; Kidney Failure, Chronic; Cancer	B03XA01	Medice Arzneimittel Pütter GmbH Co. KG	27/08/2007
EPOETIN ALFA HEXAL	epoetin alfa	Anemia; Kidney Failure, Chronic; Cancer	B03XA01	Hexal AG	27/08/2007
OMNITROPE	somatropin	Turner Syndrome; Prader-Willi Syndrome; Dwarfism, Pituitary	H01AC01	Sandoz GmbH	12/04/2006

Source: EMA website, data accessed November 2021
(https://www.ema.europa.eu/en/m edicines/download-medicine-data)

Appendix

Table 2: List of Biosimilars under review by EMA (July 2021); Source: EMA, July 2021: report accessed November 2021

COMMON NAME	THERAPEUTIC AREA	NUMBER OF APPLICATIONS	EMA APPROVED ORIGINATOR(S)	ORIGINATOR COMPANY(IES)
ADALIMUMAB	Immunosuppressant	2	Humira	AbbVie
BEVACIZUMAB	Antineoplastic medicines (anticancer)	1	Avastin	Roche
INSULIN ASPART	Diabetes	1	NovoLog	Novo Nordisk
INSULIN HUMAN (RDNA)	Diabetes	1	Actrapid/	Novo Nordisk/
PEGFILGRASTIM	Immunostimulant (neutropenia)	1	Humulin	Eli Lilly
TERIPARATIDE	Calcium homeostasis (osteoporosis)	3	Neulasta	Amgen
TRASTUZUMAB	Antineoplastic medicines (anticancer)	2	Forsteo	Eli Lilly
TRASTUZUMAB	Antineoplastic medicine (anticancer)	1	Herceptin	Roche

Source: EMA, July 2021: report accessed July 2020: https://www.ema.europa.eu/documents/report/applications-new-human-medicines-under-evaluation-chmp-july-2021_en.xlsx

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