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November 2015

The Impact of Biosimilar Competition

Introduction

This document sets out to describe the effects on price, volume and market share following the arrival and presence of biosimilar competition in the European Economic Area (EEA). The document consists of a set of indicators and guidance on how to interpret these indicators. It has been prepared as a set of indicators to monitor the impact of biosimilars in the European markets. It was prepared by IMS Health at the request of the European Commission services with initial contributions from EFPIA, EGA, and EuropaBio.

EMA has a central role in setting the rules for biosimilar submissions, approving applications, establishing approved indications and monitoring adverse events, and if necessary issue safety warning. We have when appropriate quoted their information and statements.

This first report will be based on full year 2014 data; the objective thereafter is to annually publish the previous year's updated indicators.

Contents

Definitions

The report uses some basic terms defined as follows:

- **Accessible category**: products within the same ATC4 code including the following three product categories:
  - **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.
  - **Non-Referenced Medicinal Product:** Original 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 or may have been referenced but the referencing biosimilar has not been launched.
  - **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 category:** products within the same ATC4 code as the accessible category products, and 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.
- **Total market:** includes both the Accessible and the Non-accessible product markets.

The **Key Performance Indicators (KPI)** used in the report focus on price and volume trends:

- Launch date: date of first recorded sales of Biosimilar Medicinal Product in the country.

Price indicators:

- **Price:** the price level used is gross ex-mnf price, which values the product at the level that the manufacturer sells out without taking into account rebates or discounts.
- **Price evolution:** price per treatment day in 2014 versus pre-EMA approval.

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 + reference product volume, (ii) accessible market volume and (iii) total market volume
- **Volume evolution:** number of treatment days measured in 2014 versus pre-EMA approval.
- **Volume per capita:** number of treatment days consumed in 2014 normalised by population size.

Caveats

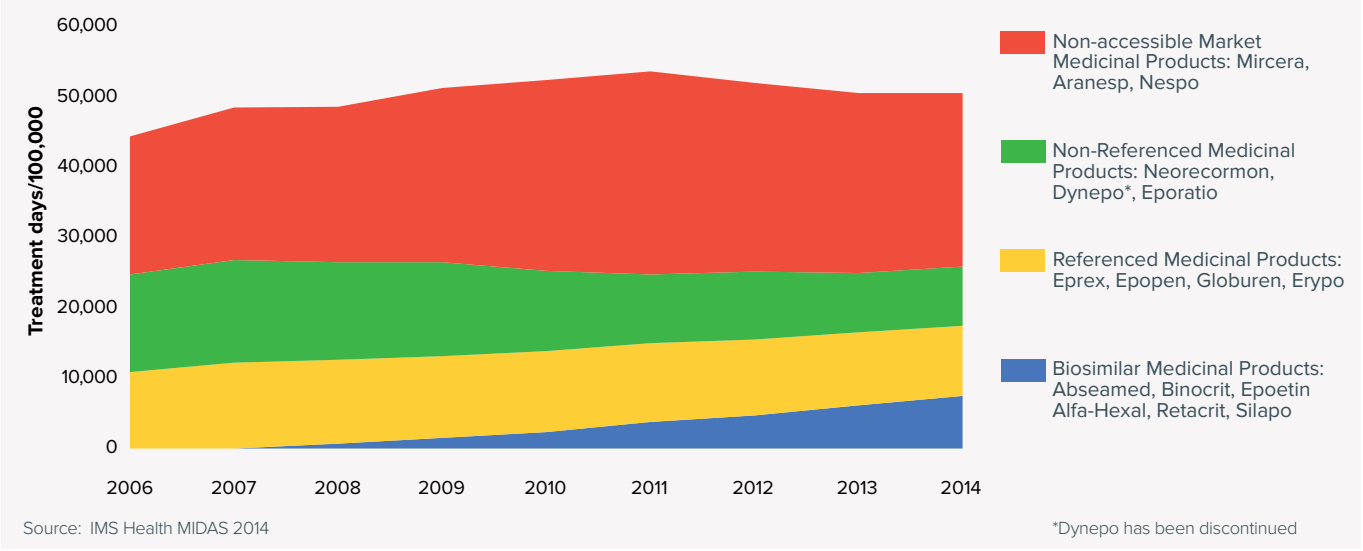
The indicators are intended to give a broad overview of the uptake and the implications on price and volume evolution after introduction of biosimilar medicines. There are differences in perspective between payers, providers, and different types of manufacturers. In focusing on the payers there are a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

- **Pricing and discounts:** the report is based on publically available 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 IMS Health 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 reference products and are inferred to have similar efficacy.
- **Volume estimates:** the pack volumes reported is based on IMS Health 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.

EPO

Epoetin (Epo) is a form of human erythropoietin produced by recombinant technology and having 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 hemoglobin, the molecule within red blood cells that transports oxygen.

Epoetin volume development



Source: IMS Health MIDAS 2014

*Dynepo has been discontinued

The average for EEA is not representative for any individual country which is illustrated in the next section.

Summary of EMA information for approved indications for Epoetin products

		Classification				Indications					Patient Type		Frequency*	Route**	
Molecule	Product	Reference product	Biosimilar	Non-reference	Non-accessible	Anemia for Chemo-therapy patients	Anemia for patients with Chronic Kidney Disease	Preventing Anaemia in premature babies	Autologuos Blood Transfusion	Reduction of allogenic transfusion exposure in Orthopedic surgery	Adult	Paediatric		Subcutaneous	Intravenous
Epoetin alfa	Eprex	●				●	●		●	●	●	●	3x a week	●	●
	Epopen	●				●	●		●	●	●	●	3x a week	●	●
	Erypo	●				●	●		●	●	●	●	3x a week	●	●
	Globuren	●				●	●		●	●	●	●	3x a week	●	●
	Abseamed		●			●	●		●	●	●	●	3x a week	●	●
	Epoetin Alfa Hexal		●			●	●		●	●	●	●	3x a week	●	●
	Binocrit		●			●	●		●	●	●	●	3x a week	●	●
Epoetin beta	NeoRecormon			●		●	●	●	●	●	●	●	3x a week	●	●
Epoetin zeta	Retacrit		●			●	●		●		●	●	3x a week	●	●
	Silapo		●			●	●		●		●	●	3x a week	●	●
Epoetin theta	Eporatio			●		●	●				●		3x a week	●	●
Methoxy polyethylene glycol-epoetin beta	Mircera				●	●					●		Every 2 weeks	●	●
Darbepoetin alfa	Aranesp				●	●	●				●	●	Weekly	●	●
	Nespo				●	●	●				●	●	Weekly	●	●

*Anemia 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.

Additional information about Epoetin

In June 2008 **The European Medicines Agency** (EMA) recommended updating the product information for Epoetin-containing medicines with a new warning for their use in cancer patients stating that blood transfusion should be the preferred method of correcting anaemia. It also advised that prescribers take into account patients' individual circumstances and preferences when making the decision to use Epoetins. The Committee for Medicinal Products for Human Use (CHMP) made clear that the new information does not apply to the use of Epoetins for patients with chronic renal failure. (EMA website)

Selected KPIs to illustrate volume share, price evolution, and volume evolution in the EEA countries:

	Market share TD (2014)			Price per TD (2014/Year before biosimilar entrance)			Volume TD (2014/Year before biosimilar entrance)			TD per capita	First Recorded Sales of Biosimilar
	Biosimilar vs Reference product	Biosimilar vs Accessible market	Biosimilar vs Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market		
AU	78%	30%	19%	-21%	-37%	-36%	20%	-9%	-28%	0.68	2008
BE	0%	0%	0%	-16%	-20%	-12%	-37%	-38%	-52%	0.52	2014
BU	100%	84%	49%	N/A	-70%	-51%	286%	57%	166%	0.26	2011
CZ	96%	26%	17%	-59%	-40%	-44%	115%	75%	165%	0.12	2011
DK*	95%	37%	1%	-6%	-12%	-15%	-87%	-88%	45%	0.98	2010
FI	100%	44%	8%	-4%	-29%	-18%	1160%	-50%	-1%	0.33	2008
FR	29%	18%	7%	-37%	-39%	-28%	29%	-17%	5%	0.91	2009
DE	72%	56%	21%	-61%	-55%	-45%	11%	-31%	-25%	0.30	2007
GR(R)*	86%	78%	70%	-35%	-49%	-47%	-25%	-58%	-69%	0.02	2008
HU	75%	47%	32%	7%	-30%	-20%	4%	-39%	-33%	0.28	2009
IE	91%	6%	2%	-33%	-26%	-18%	-51%	-53%	-25%	0.38	2008
IT	37%	29%	19%	-12%	-13%	-2%	159%	87%	49%	1.17	2008
NL*	35%	11%	3%	-44%	-33%	-23%	198%	113%	125%	0.29	2009
NO	88%	61%	7%	-24%	-29%	-22%	47%	-60%	-8%	0.21	2008
PL	83%	24%	19%	-80%	-57%	-49%	8255%	133%	112%	0.06	2009
PT*	80%	21%	13%	-59%	-75%	-51%	95%	72%	-7%	0.41	2010
RO	36%	12%	8%	-43%	-40%	-42%	446%	268%	457%	0.23	2009
SK	100%	70%	48%	-60%	-67%	-61%	125%	32%	84%	0.52	2010
SL	30%	14%	7%	-54%	-46%	-47%	-7%	-26%	9%	0.53	2009
ES	43%	31%	20%	-30%	-24%	-16%	31%	-4%	-10%	0.63	2008
SE	89%	57%	22%	-16%	-25%	-41%	30%	-32%	9%	0.55	2008
UK	7%	4%	1%	-25%	-18%	-13%	141%	-13%	37%	0.28	2009
EU	43%	29%	15%	-28%	-33%	-27%	65%	7%	16%	0.50	

* The following data history is used: NL (2009-2014), DK (2007-2014), PT (2010-2014), only retail panel is available for Greece.
**Caveats may apply - refer to page 2 for the details.

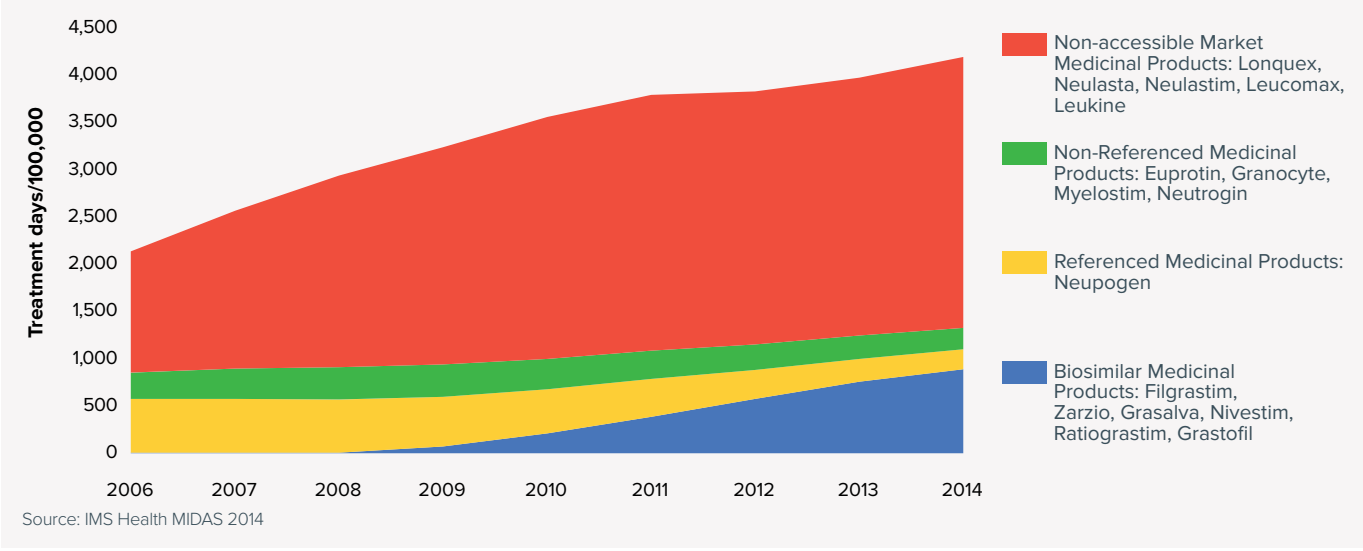
Prices per treatment days (total market) has been reduced in all markets but to a different degree ((-2%)-(-61%)) due to a combination of factors; the level of competition, to what extent Non Accessible Market products (largely differentiated by fewer injections) have been accepted, but also the price development of reference and biosimilar medicinal products.

The volume development shows that markets with already high usage were greatly reduced following the 2011 safety alert and countries with low usage increased partly based on lower prices.

G-CSF

Granulocyte-colony stimulating factor (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 with certain cancer patients to accelerate recovery from neutropenia after chemotherapy, allowing higher-intensity treatment regimens.

G-CSF volume development



Source: IMS Health MIDAS 2014

The average for EEA is not representative for any individual country which is illustrated in the next section.

Summary of EMA information for approved indications of G-CSF

		Classification				Indications					
Molecule	Product	Reference product	Biosimilar	Non-reference Product	Non-accessible Product	Cytotoxic Chemotherapy associated with Febrile induced Neutropenia	Neutropenia induced by Acute Myeloid Leukemia	Bone Marrow Trans-plantation induced Neutropenia	Mobilisation of Peripheral Blood Progenitor Cells (PBPCs)	Severe Chronic Neutropenia (SCN) with diagnosis of congenital, cyclic, or idiopathic Neutropenia	Neutropenia prevention and treatment in patients with HIV
Filgrastim	Neupogen	●				●	●	●	●	●	●
	Zarzio		●			●	●	●	●	●	●
	Grasalva		●			●		●	●	●	●
	Nivestim		●			●		●	●	●	●
	Ratiograstim		●			●		●	●	●	●
	Grastofil		●			●		●	●	●	●
Lenograstim	Euprotin			●		●		●	●		
	Granocyte			●		●		●	●		
	Myelostim			●		●		●	●		
	Neutrogin			●		●		●	●		
Lipegfilgrastim	Lonquex				●	●					
Pegfilgrastim	Neulasta				●	●					
	Neulastim				●	●					
Molgramostim	Leucomax				●	●	●	●	●		
Sargramostim	Leukine				●	●	●	●	●		

Additional information about G-CSF

Subcutaneous injection is 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. GM-CSF (Granulocyte macrophage colony-stimulating factor) Sargramostim and Molgramostim are given daily, most often as a subcutaneous injection (under the skin), but can also be given directly into a vein (intravenous, IV).

Selected KPIs to illustrate volume share, price evolution, and volume evolution in the EEA countries:

	Market share TD (2014)			Price per TD (2014/Year before biosimilar entrance)			Volume TD (2014/Year before biosimilar entrance)			TD per capita	First Recorded Sales of Biosimilar
	Biosimilar vs Reference product	Biosimilar vs Accessible market	Biosimilar vs Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market		
AU	80%	80%	14%	34%	-3%	-41%	56%	40%	131%	0.11	2008
BE	2%	2%	0%	-31%	-24%	-16%	-6%	-16%	101%	0.06	2009
BU	85%	80%	18%		-52%	-72%	344%	184%	1161%	0.01	2009
CZ	99%	99%	60%	-26%		-30%	11%	11%	55%	0.01	2010
DK*	70%	69%	8%	-7%	-2%	-33%	-6%	-11%	204%	0.06	2009
FI	97%	96%	16%	-12%	-3%	-15%	48%	47%	75%	0.07	2009
FR	81%	43%	12%	-25%	-14%	-22%	183%	63%	63%	0.07	2009
DE	71%	59%	12%	-6%	-27%	-29%	43%	20%	127%	0.05	2008
GR(R)*	97%	92%	68%	-52%	-22%	-46%	-48%	-65%	-95%	0.00	2009
HU	100%	100%	68%	-7%		-29%	232%	223%	59%	0.03	2009
IE	25%	22%	3%	-22%	0%	-17%	-5%	-2%	70%	0.07	2009
IT	81%	65%	25%	-19%	-4%	-30%	137%	43%	90%	0.04	2009
NL*	39%	38%	3%	-29%	3%	-30%	3%	2%	50%	0.04	2009
NO	84%	84%	8%	4%		-26%	46%	46%	145%	0.05	2009
PL	80%	79%	26%	-44%	-56%	-44%	108%	92%	474%	0.04	2009
PT*	89%	88%	48%	-88%	-15%	-51%	27%	18%	-49%	0.02	2010
RO	100%	100%	45%			-59%	680%	680%	1621%	0.02	2009
SK	97%	97%	26%	-66%		-71%	305%	305%	734%	0.04	2009
SL	61%	61%	12%	-70%		-47%	73%	73%	272%	0.05	2009
ES	77%	76%	57%	-41%	1%	-29%	47%	33%	0%	0.02	2009
SE	92%	92%	54%	-14%	-9%	-35%	215%	179%	70%	0.03	2009
UK	96%	79%	41%	1%	-8%	-8%	103%	82%	136%	0.03	2008
EU	81%	67%	21%	-19%	-10%	-28%	96%	59%	101%	0.04	

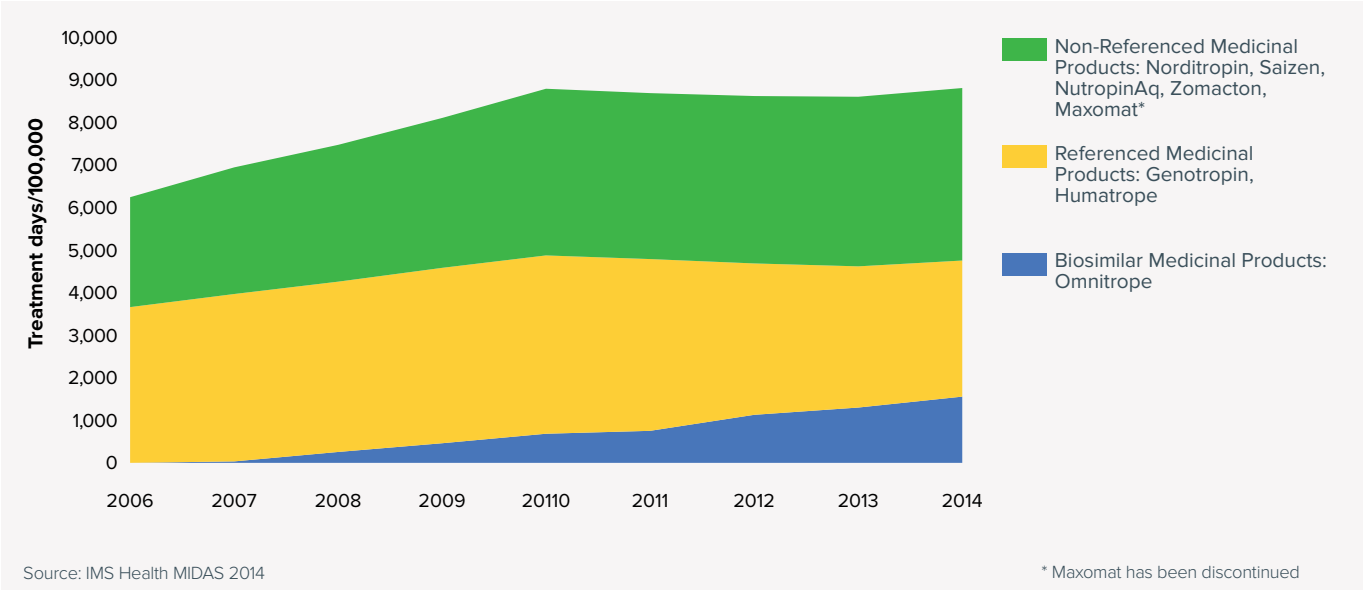
* The following data history is used: NL (2009-2014), DK (2007-2014), PT (2010-2014), only retail panel is available for Greece. The volume has likely shifted to retail in the period.
**Caveats may apply - refer to page 2 for the details.

Price changes per treatment days (total market) vary considerably across the different EEA countries, this ranges between (-72%) and (-8%).

HGH

Human Growth Hormone (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.

GH volume development



Source: IMS Health MIDAS 2014

* Maxomat has been discontinued

The average for EEA is not representative for any individual country which is illustrated in the next section.

Summary of EMA information for approved indication and administration frequency details for HGH products

		Classification			Indications							
Molecule	Product	Reference product	Biosimilar Product	Non-reference Product	Pediatric Growth Hormone Deficiency	Adult GHD	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
Somatropin	Genotropin	●			●	●	●	●	●	●	●	
	Humatrope	●			●	●	●	●	●		●	●
	Omnitrope		●		●	●	●	●	●	●		
	Norditropin			●	●	●	●	●	●			
	Saizen			●	●	●	●	●	●			
	NutropinAq			●	●	●	●	●				
	Zomacton			●	●		●					

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.

Selected KPIs to illustrate volume share, price evolution, and volume evolution in the EEA countries:

	Market share TD (2014)			Price per TD (2014/Year before biosimilar entrance)			Volume TD (2014/Year before biosimilar entrance)			TD per capita	First Recorded Sales of Biosimilar
	Biosimilar vs Reference product	Biosimilar vs Accessible market	Biosimilar vs Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market		
AU	27%	15%	15%	0%	-2%	-5%	32%	41%	41%	0.04	2008
BE	16%	8%	8%	-4%	-12%	-11%	21%	44%	44%	0.10	2009
BU	12%	12%	12%	-5%	64%	-7%	29%	13%	13%	0.01	2012
CZ	13%	0%	0%	-19%	-21%	-21%	46%	82%	82%	0.11	2010
DK*	92%	36%	36%	0%	-8%	-9%	31%	35%	35%	0.14	2011
FI	31%	8%	8%	-34%	-56%	-49%	-17%	44%	44%	0.09	2008
FR	28%	14%	14%	-9%	-8%	-10%	34%	39%	39%	0.14	2007
DE	23%	11%	6%	9%	9%	7%	3%	23%	23%	0.08	2006
GR(R)*	0%	0%	0%	-21%	0%	-21%	160%	160%	160%	0.00	
HU	6%	3%	3%	-1%	-23%	-12%	-8%	12%	12%	0.05	2012
IE	0%	0%	0%	-10%	25%	7%	26%	29%	29%	0.06	
IT	22%	9%	9%	-10%	-6%	-10%	43%	48%	48%	0.10	2007
NL*	28%	14%	14%	-29%	-19%	-28%	21%	44%	44%	0.11	2008
NO	15%	6%	6%	-26%	-29%	-28%	-7%	39%	39%	0.16	2011
PL	99%	99%	99%	-21%	17%	-39%	62%	62%	62%	0.07	2008
PT*	0%	0%	0%	-4%	-22%	-14%	56%	21%	21%	0.04	2014
RO	61%	28%	28%	-4%	-29%	-28%	70%	40%	40%	0.06	2008
SK	0%	0%	0%	-42%	-49%	-48%	144%	98%	98%	0.08	2013
SL	8%	4%	4%	-31%	-45%	-39%	36%	10%	10%	0.06	2010
ES	28%	20%	20%	-19%	-16%	-18%	40%	27%	27%	0.12	2007
SE	29%	19%	19%	-25%	-30%	-28%	-11%	-6%	-6%	0.14	2007
UK	14%	8%	8%	-25%	-4%	-15%	28%	53%	53%	0.06	2007
EU	33%	18%	18%	-7%	-7%	-13%	33%	19%	44%	0.09	

* The following data history is used: NL (2009-2014), DK (2007-2014), PT (2010-2014), only retail panel is available for Greece.
**Caveats may apply - refer to page 2 for the details.

Price changes per treatment days (total market) vary considerably across the different EEA countries, this ranges between (-49%) and 7%.

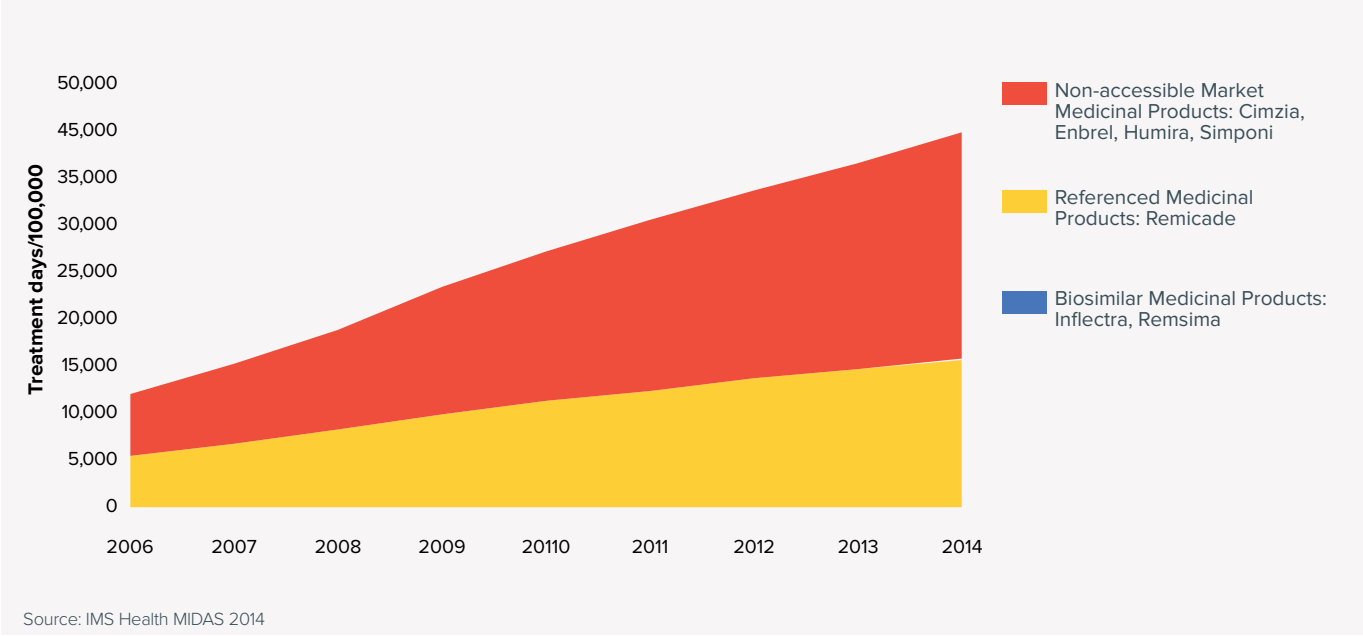
Anti-TNF

Anti-TNF (Anti-tumour necrosis factor) 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, joints 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.

Infliximab first loss of exclusivity was in Norway and Finland in Q4 2013. In the majority of countries in the EEA loss of exclusivity occurred only in February 2015. The total sales in Norway and Finland 2014 equates to 170 TD/100,000 in Europe.

Anti-TNF volume development



Source: IMS Health MIDAS 2014

The average for EEA is not representative for any individual country which is illustrated in the next section.

Additional information about Anti-TNF

Summary of EMA information for approved indications of Anti-TNF products

	Humira	Remicade	Remsima	Inflectra	Enbrel	Simponi	Cimzia
Rheumatoid Arthritis	●	●	●	●	●	●	●
Juvenile idiopathic Arthritis	●				●		
Psoriatic Arthritis	●	●	●	●	●	●	●
Axial Spondyloarthritis, comprising: **Ankylosing Spondylitis (AS)** **Axial Spondyloarthritis without radiographic evidence of AS**	● ●	●	●	●	● ●	● ●	● ●
Crohn Disease	●	●	●	●			
Paediatric Crohn Disease	●	●	●	●			
Ulcerative Colitis	●	●	●	●		●	
Paediatric Ulcerative Colitis		●	●	●			
Psoraisis	●	●	●	●	●		
Paediatric Plaque Psoraisis	●				●		
Hidradenitis suppurativa	●						

Indications have been added over time expanding the potential patient population.

Summary of EMA information for administration frequency details for Anti-TNF products

		Classification				Frequency	Route	
Molecule	**Product**	**Reference product**	**Biosimilar Product**	**Non-reference Product**	**Non-accessible Product**		**Subcutaneous**	**Intravenous**
Infliximab	Remsima		●			Every 8 weeks		●
	Inflectra		●			Every 8 weeks		●
	Remicade	●				Every 8 weeks		●
Etanercept	Enbrel				●	Twice weekly	●	
Adalimumab	Humira				●	Every 2 weeks	●	
Certolizumab Pegol	Cimzia				●	Every 4 weeks	●	
Golimumab	Simponi				●	Monthly	●	

Selected KPIs to illustrate volume share, price evolution, and volume evolution in the EEA countries:

	Market share TD (2014)			Price per TD (2014/Year before biosimilar entrance)			Volume TD (2014/Year before biosimilar entrance)			TD per capita	First Recorded Sales of Biosimilar
	Biosimilar vs Reference product	Biosimilar vs Accessible market	Biosimilar vs Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market		
AU										0.16	
BE										0.86	
BU										0.13	2014
CZ	3%	3%	2%	-7%	-7%	-4%	26%	26%	24%	0.27	2014
DK*										0.83	2015
FI	3%	3%	1%			0%	10%	10%	10%	0.71	2013
FR										0.57	2015
DE										0.45	2015
GR(R)*										0.00	
HU	7%	7%	2%			3%	-3%	-3%	6%	0.30	2014
IE	2%	2%	1%		-1%	-1%	22%	22%	14%	1.11	2014
IT										0.31	2015
NL*										0.98	2015
NO	19%	19%	8%	-3%	-10%	-1%	13%	13%	12%	1.21	2013
PL	11%	11%	3%	-24%	-26%	-4%	12%	12%	16%	0.04	2014
PT*	2%	2%	1%	-12%	-12%	-5%	16%	16%	12%	0.30	2013
RO	2%	2%	1%			6%	-24%	-24%	-7%	0.17	2014
SK	1%	1%	1%	-2%	-2%	-4%	42%	42%	34%	0.60	2014
SL										0.41	
ES										0.44	2015
SE										0.80	2015
UK										0.56	2015
EU	1%	1%	0%	-1%	-1%	0%	8%	8%	9%	0.44	

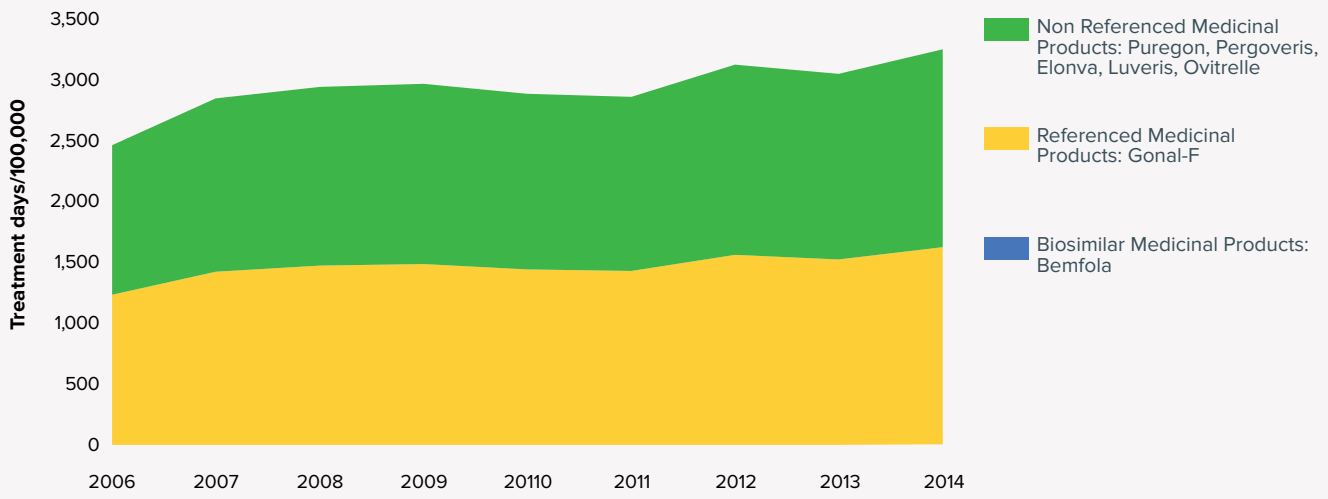
* The following data history is used: NL (2009-2014), DK (2007-2014), PT (2010-2014), only retail panel is available for Greece.
**Caveats may apply - refer to page 2 for the details.

Price changes per treatment days (total market) vary considerably across the different EEA countries, this ranges between (-5%) and 6%.

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 recombinant preparations were considered.

Fertility volume development



Source: IMS Health MIDAS 2014

The average for EEA is not representative for any individual country which is illustrated in the next section.

Additional information about fertility medicines:

Summary of information for approved indications for Fertility products

		Classification			Indications					Frequency	Route	
Molecule	Product	Reference product	Biosimilar	Non-reference	Infertility	Hypogonad-ism	Anovulation	Ovulation Induction	Reproductive Techniques Assisted		Subcutaneous	Intravenous
Genotropin	Gonal-F Bemfola	●	●		● ●	●	● ●		●	Daily Daily	●	●
Follitropin alfa/lutropin alfa	Pergoveris			●	●					Daily	●	●
Follitropin beta	Puregon			●	●	●				Patient specific	●	●
Corifollitropin alfa	Elonva			●						Patient specific	●	
Lutropin alfa	Luveris			●	●			●		Daily	●	●
Choriogonadotropin alfa	Ovitrelle			●			●	●	●	Patient specific	●	

Selected KPIs to illustrate volume share, price evolution, and volume evolution in the EEA countries:

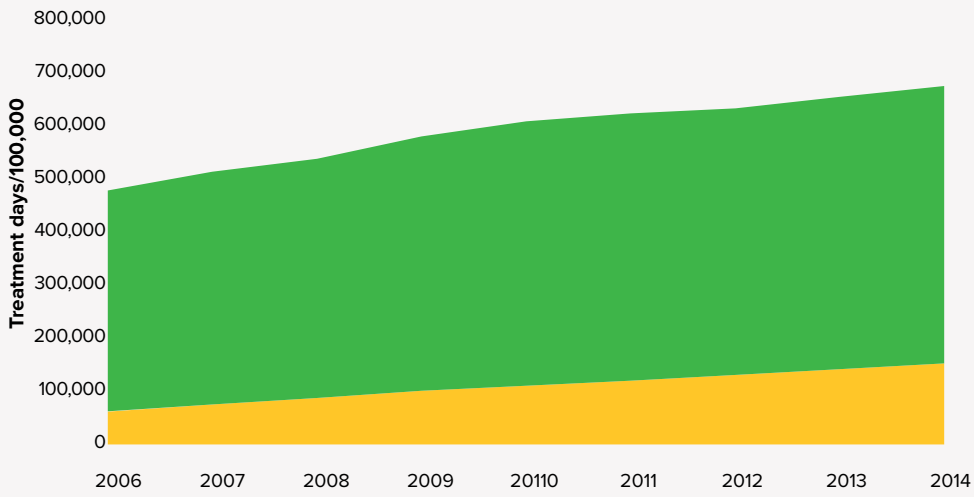
	Market share TD (2014)			Price per TD (2014/Year before biosimilar entrance)			Volume TD (2014/Year before biosimilar entrance)			TD per capita	First Recorded Sales of Biosimilar
	Biosimilar vs Reference product	Biosimilar vs Accessible market	Biosimilar vs Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market	Biosimilar and Reference product	Biosimilar Accessible market	Total market		
AU	8%	1%	0%	-1%	0%	-6%	4%	41%	40%	0.07	2014
BE										0.14	
BU										0.14	
CZ										0.16	
DK*	1%	0%	0%	-1%	-5%	-4%	14%	3%	14%	0.14	2014
FI	1%	0%	0%	-4%	-4%	-3%	7%	0%	2%	0.11	2014
FR										0.12	
DE	1%	1%	1%	0%	0%	-1%	13%	7%	11%	0.11	2014
GR(R)*										0.27	
HU										0.12	
IE										0.22	
IT										0.18	
NL*										0.15	
NO										0.10	2014
PL										0.07	
PT*										0.09	
RO										0.03	
SK										0.07	
SL										0.12	
ES										0.10	
SE	2%	1%	1%	-2%	-3%	-3%	-4%	-8%	-7%	0.12	2014
UK										0.04	
EU	0%	0%	0%	-1%	-1%	0%	4%	2%	4%	0.10	

* The following data history is used: NL (2009-2014), DK (2007-2014), PT (2010-2014), only retail panel is available for Greece.
**Caveats may apply - refer to page 2 for the details.

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.

Insulins volume development



Source: IMS Health MIDAS 2014

The European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) announced on 27 June 2014 that it had recommended granting of marketing authorization for a biosimilar insulin glargine product Abasaglar (formerly Abasria).

In 2015, Eli Lilly and Boehringer Ingelheim launched Abasaglar in the Czech Republic, Slovakia, Germany, Sweden, Poland and the UK.

Additional information about insulins

Summary of information for approved indications for Insulin products

		Classification			Indications	Frequency*	Mode of action	Route	
Molecule	Product	Reference product	Biosimilar	Non-reference	Diabetes Mellitus			Subcutaneous	Intravenous
Insulin Glargine	Abasaglar (previously Abasria)		●		●	Daily	Long-acting	●	
	Lantus	●			●	Daily	Long-acting	●	
Insulin Degludec	Tresiba			●	●	Daily	Long-acting	●	
Insulin Detemir	Levemir			●	●	Twice a day	Long-acting	●	
Insulin Aspart	Novorapid			●	●	Twice / 5x a day	Short-acting	●	
	Novomix			●	●	Twice / 5x a day	Short-acting	●	
Insulin Degludec / Insulin Aspart	Ryzodeg			●	●	Daily	Short-acting / Long-acting	●	
Insulin Glulisine	Apidra			●	●	Twice / 5x a day	Short-acting	●	
Insulin Human	Actraphane			●	●	Once / twice a day	Short-acting / Long-acting	●	
	Actrapid			●	●	Twice / 5x a day	Short-acting	●	
	Insulatard			●	●	Once / twice a day	Long-acting	●	
	Insuman			●	●	Twice / 5x a day	Short-acting	●	●
	Mixtard			●	●	Once / twice a day	Short-acting / Long-acting	●	
	Monotard			●	●	Once / twice a day	Intermediate -acting	●	
	Protaphane			●	●	Once / twice a day	Long-acting	●	
	Ultratard			●	●	Once / twice a day	Long-acting	●	
Insulin Lispro	Liprolog			●	●	Twice / 5x a day	Short-acting	●	●
Insulin Degludec / Liraglutide	Xultophy			●	●	Daily	Long-acting	●	

* Regular insulin is a short-acting insulin and is generally injected subcutaneously 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 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- (e.g. human isophane insulin = NPH insulin), and long-acting preparations (insulins with action profiles significantly longer than NPH insulin), and are used alone or as free mixtures or premixed preparations of rapid/short-acting insulin and intermediate/long-acting (biphasic) insulin in various proportions.

Appendices

1 EMA list of approved Biosimilars

Medicine Name	Active Substance	Atc code	Marketing Authorisation Holder	Authorisation date
Omnitrope	somatropin	H01AC01	Sandoz GmbH	12/04/2006
Valtropin*	somatropin	H01AC01	BioPartners GmbH	24/04/2006
Abseamed	epoetin alfa	B03XA01	Medice Arzneimittel Pütter GmbH & Co. KG	28/08/2007
Binocrit	epoetin alfa	B03XA01	Sandoz GmbH	28/08/2007
Epoetin Alfa Hexal	epoetin alfa	B03XA01	Hexal AG	28/08/2007
Retacrit	epoetin zeta	B03XA01	Hospira UK Limited	18/12/2007
Silapo	epoetin zeta	B03XA01	Stada Arzneimittel AG	18/12/2007
Accofil	filgrastim	L03AA02	Accord Healthcare Ltd	18/09/2014
Biograstim	filgrastim	L03AA02	AbZ-Pharma GmbH	15/09/2008
Ratiograstim	filgrastim	L03AA02	Ratiopharm GmbH	15/09/2008
Filgrastim Ratiopharm*	filgrastim	L03AA02	Ratiopharm GmbH	15/09/2008
Tevagrastim	filgrastim	L03AA02	Teva GmbH	15/09/2008
Filgrastim Hexal	filgrastim	L03AA02	Hexal AG	06/02/2009
Zarzio	filgrastim	L03AA02	Sandoz GmbH	06/02/2009
Nivestim	filgrastim	L03AA02	Hospira UK Ltd.	08/06/2010
Grastofil	filgrastim	L03AA02	Apotex Europe BV	18/10/2013
Bemfola	follitropin alfa	G03GA05	Finox Biotech AG	27/03/2014
Ovaleap	follitropin alfa	G03GA05	Teva Pharma B.V.	27/09/2013
Inflectra	infliximab	L04AB02	Hospira UK Limited	10/09/2013
Remsima	infliximab	L04AB02	Celltrion Healthcare Hungary Kft.	10/09/2013
Abasaglar (previously Abasria)	insulin glargine	A10AE04	Eli Lilly Regional Operations GmbH	09/09/2014

* Valtropin and Filgrastim Ratiopharm are no longer marketed in the EU

2 Methodology

- The volumes have been converted by IMS Health into daily doses using WHO DDDs. 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.
- Volume share is calculated as the volume in DDD versus the relevant market (reference market, accessible market, total market).
- Prices are calculated as a volume weighted ex-manufacturing price average.
- Price evolution is calculated as the present price for the relevant market versus the price for the same relevant market before EMA approval of biosimilars.
- Volume evolution is calculated as the present total volume versus the total volume before introduction of biosimilars.

		Methodology
Market share TD (2014)	Biosimilar vs Reference product	TD Biosimilars as % of TD Reference products in 2014
	Biosimilar vs Accessible market	TD Biosimilars as % of TD Accessible market in 2014
	Biosimilar vs Total market	TD Biosimilars as % of TD Total market in 2014
Price per TD	Biosimilar and Reference product	Δ in Price per TD for Biosimilar Reference products 2014/the year before biosimilar entrance
	Biosimilar Accessible market	Δ in Price per TD for Biosimilar Accessible market 2014/the year before biosimilar entrance
	Total market	Δ in Price per TD for Total market 2014/the year before biosimilar entrance
Volume TD	Biosimilar and Reference product	Δ in TD for Biosimilars and Reference products 2014/the year before biosimilar entrance
	Biosimilar Accessible market	Δ in TD for Biosimilar Accessible market 2014/the year before biosimilar entrance
	Total market	Δ in TD for Total market 2014/the year before biosimilar entrance
TD per capita		No. Of Treatment Days per capita in 2014
First recorded sales		The year first sales of biosimilar were recorded

3. IMS Health source of volume data

Volume information is based on channel audits for retail and non-retail channels, covering the majority of volume consumed in a country market, though may exclude some direct sales made from manufacturer to dispensing locations. IMS Health source of volume data collection route and sample varies by country; data can be collected at various points within the pharmaceutical supply chain.

Note: Points of collection

Sell-in data represents the supply of products from wholesalers to pharmacies.

Sell-out data represents the demand for products from the pharmacies to patients.

Hospital consumption data measures dispensing of products by hospital pharmacies within the hospital wards.

The table below is a matrix to identify these points of collection by country.

	AU	BE	BU	CZ	DK*	FI	FR	DE	GR (R)	HU	IE	IT	NL*	NO	PL	PT*	RO	SK	SL	ES	SE	UK
Retail	In	In	In	In	In	In	Out	Out	Out	In	In	In	In	In	In	In	Out	In		Out	Out	Out
Hospital	C	C	In	In	In	In	C	C		In	In	C	In	In	In	C	In	In		C	In	C
Combined																			In			

Data type key: In (Sell-In), Out (Sell-Out) & C (Consumption)

4. IMS Health source and treatment of price data

Sales data is collected in terms of the number of Pack Units sold and are then multiplied by the Pack Price to produce the sales values. Pricing information is based on a variety of sources including list price, wholesaler transactions, government price list and industry publications, but does not reflect rebates and discounts which in some countries and channels may be significant. Country volumes may also be impacted by unknown parallel exports or imports which cannot be identified or adjusted for. Inclusion of VAT and taxes varies per country.

Table below to show the price source reference within each EU country:

EU Geography		
Country	**Sector (Data Type)**	**Price Source**
Austria	Hospital (Consumption),Retail (Sell-In)	Hospital & Retail - List price - Arzneimittelverzeichnis or Taxe (Apotheker-Verlag)
Belgium	Hospital (Consumption),Retail (Sell-In)	Hospital - List price - Association Général de l'Industrie du Médicament (AGIM), Retail - List price - Association Pharmaceutique Belge (APB)
Bulgaria	Hospital (Sell-In),Retail (Sell-In)	Hospital & Retail - Average invoiced pack price
Czech Rep.	Hospital (Sell-In),Retail (Sell-In)	Hospital & Retail - Average invoiced pack price
Denmark	Retail (Sell-In),Hospital (Sell-In)	Hospital & Retail - Average invoiced pack price
Finland	Hospital (Sell-In),Retail (Sell-In)	List price - Wholesalers, based on official published prices of Finnish Pharmacy Association
France	Hospital (Consumption),Retail (Sell-Out)	Hospital - List price - Journal Officiel, manufacturer hospital price lists, Retail - List price - Journal Officiel, wholesaler catalogues, average transaction prices
Germany	Hospital (Consumption),Retail (Sell-Out)	Hospital - Estimated transaction price reflecting the average level of rebates and discounts, Pharmascope - List price - ABDATA (Pharmacist Association), sourced from IFA (German Health Institute)
Greece	Retail (Sell-Out)	Retail - List price - Ministry of Development
Hungary	Hospital (Sell-In),Retail (Sell-In)	Hospital & Retail - List price - National Health Fund, National Institute of Pharmacy
Ireland	Hospital (Sell-In),Retail (Sell-In)	Hospital & Retail - List price - Irish prescription drug databases
Italy	DPC (Consumption),Hospital (Consumption), Retail (Sell-In)	DPC & Retail - List price - CFO - Farmadati, Gazzetta Ufficiale della Repubblica Italiana, Hospital - List price - 45% public level retail list price
Netherlands	Hospital (Sell-In),Retail (Sell-In)	Hospital & Retail - List price - Wholesaler price list
Norway	Hospital (Sell-In),Retail (Sell-In)	Hospital & Retail - Average invoiced pack price
Poland	Hospital (Sell-In),Retail (Sell-In)	Hospital & Retail - Average invoiced pack price
Portugal	Hospital (Consumption),Retail (Sell-In)	Hospital - Average invoiced pack price, Retail - List price - Manufacturer published price list
Romania	Hospital (Sell-In),Retail (Sell-Out)	Hospital - Average invoiced pack price, Retail - Canamed, average transaction price if no Canamed Price
Slovakia	Hospital (Sell-In),Retail (Sell-In)	Hospital & Retail - Average invoiced pack price
Slovenia	Combined (Sell-In),Hospital (Consumption)	Hospital & Retail - Average invoiced pack price
Spain	Hospital (Consumption), Retail (Sell-Out)	Hospital & Retail - List price - Manufacturer price list, Base de Datos del Medicamento (BOT)
Sweden	Retail (Sell-Out),Hospital (Sell-In)	Hospital & Retail - List price - Apoteket AB, The Dental and Pharmaceutical Benefits Agency, The Drug Benefit Board, The LFN
Switzerland	Hospital (Sell-In),Retail (Sell-In)	Hospital & Retail - List price - Wholesalers, manufacturers
UK	Hospital (Consumption),Retail (Sell-Out)	Hospital & Retail - List price - Chemist and Druggist, Drug Tariff

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