**RESEARCH ARTICLE**

# Insight into Biosimilars: Short Description, Analytical Assessment and Market

**Authors**

Klaus Zimmermann, Markus Fido, and Markus Roucka

**Affiliations**

VelaLabs GmbH

**Correspondence**

Email: k.zimmermann@vela-labs.at

**Abstract**

The World Health Organization (WHO) defines a similar biotherapeutic product, i.e. a biosimilar as a biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference product on the market (termed as originator or innovator). To ensure similar efficacy and safety, comparability studies for biosimilars should be carried out at quality, preclinical and clinical level. Glycosylation profiles of biosimilars are getting an additional critical quality attribute. The portfolio required for regulatory comparison of identity and release testing has to be assessed with a large number of analytical tests, which are presented here in detail for the example of adalimumab. Adalimumab, as one of the blockbuster drugs and the best-selling pharmaceutical product world-wide, is analyzed additionally with a competitive field presenting the marketed products or such in development. This competitive field is not surprisingly very crowded. Furthermore, general information about the currently marketed biosimilars including Mode of Action (MoA), clinical indication(s), patent situation, and market situation are shortly summarized for each of the respective originator / biosimilar molecules. As there are not only markets in developed and highly regulated countries, but also in other regions, examples for companies and products in Asia, South and Middle America, and even in Africa are highlighted as well.

## 1. Introduction

A biosimilar is a generic version of a pharmaceutical product, usually a biotechnologically produced biomolecule, and in many cases a recombinant protein. In its guidelines on the evaluation of similar biotherapeutic products, the World Health Organization (WHO) defines a similar biotherapeutic product (= biosimilar) as a "biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference product".[1]

Unlike the classical generic "small molecule" drugs, biosimilars are not completely identical to the original version of the product. Even if the amino acid sequences of biosimilars are identical to their originator molecules, however, very complex post-translational modifications may occur to finalize the maturation process in the cell itself. Also on the way to their place of destination or target activity modifications may occur. Main reasons for potential modifications are first-of-all different types of cell lines in which the target protein is expressed. Thus, biosimilars are usually produced in the same cell line as their originator molecule in order to minimize potential differences in the mature protein. Furthermore, different growth conditions for cell lines as well as complex purification steps may be also responsible for changes in the structure or glycosylation pattern. Variations in glycosylation of otherwise identical molecules may have consequences for the pharmacokinetic profile of the respective drug. Therefore, development of biosimilars require more complex monitoring measures and thorough approval procedures than small molecules.

The aim of the present review is to give a short general overview about biosimilars and to present basic facts including market data about the most important therapeutic products. As analytical assessment of biosimilars is an important aspect for regulatory approval, this topic will be discussed in more detail and an example for the variety of assays required for testing of adalimumab will be presented.

## 2. Biosimilars – Scientific Literature

Interesting parties, which are not familiar with the subject biosimilars and try to get a first scientifically sound overview of the world of biosimilars need to read through a variety of scientific literature. When searching "pubmed" there are nearly 900 articles, which can be detected with the key words "biosimilar" and "review".

Sometimes it is even not clear, what a biosimilar is or what not.[2] On the other hand, approval of biosimilars in countries such as for example India or China might not have been authorized following a strict regulatory process required for approval by European Medicines Agency (EMA) and Food and Drug Administration (FDA).

This leaves room for terms such as non-original biologics, non-biosimilar biologics, or similar biologics. Such drugs are not only developed and launched in India and China but also in several other countries and regions (Asia, South and Middle America & Africa).

Because the biosimilar story is very complex, scientific reviews often not concentrate on biosimilars itself, but rather on certain (side)-aspects, such as clinical indications, manufacturing, purification, analytical comparability, or special regulatory aspects.

Several groups of originator molecules and their respective biosimilars have the same target and thus accordingly the respective clinical indications are addressed in review articles. The most prominent examples are biosimilars indicated for inflammatory diseases such as rheumatology[3], Crohn's disease[4], inflammatory bowel disease[5], or psoriasis[6]: infliximab, etanercept,

 

adalimumab and rituximab. These biomolecules are all tumor necrosis factor (TNF)-α inhibitors.

In oncology indications, biosimilars of granulocyte colony-stimulating factor and epoetin have already been available for almost a decade[7], and biosimilars of monoclonal antibodies such as trastuzumab are more recent developments.[8, 9]

Furthermore, several biosimilars are already approved for dermatological indications.[10]

## 3. Regulatory Aspects

The "International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use" issues regularly guidelines detailing specifications of biopharmaceuticals as well as comparability of structure profiles during process scale-up and changes in manufacturing process.

According to EMA, a biosimilar is a copy version of an already approved biopharmaceutical drug with (very) similar biologic activity, physicochemical characteristics, efficacy, and safety. Further guidance can be found in several EMA publications.[11, 12, 13] To ensure similar efficacy and safety, comparability should be analyzed at quality, preclinical and clinical level.[14]

The FDA similarly recommends a stepwise approach for demonstrating biosimilarity between a proposed biosimilar product and a biological originator (innovator) product.[15, 16] Further regulatory requirements for biosimilars in various countries across the world were reviewed by Chugh et al.[17]

Accumulated experience with biosimilars continues to reshape regulatory requirements, generally leading to a reduced burden of clinical trials.[18] Biosimilars do not need to undergo the same intense clinical trials as their originators for their approval, however, they must not show clinically relevant differences to the originator drug and must have equivalent safety and efficacy parameters. Subsequently, regulatory requirements for market approval are very detailed and demand a variety of analytical methods and tools for characterization and comparison. Regulatory aspects are, for example, reviewed by Kabir et al.[19] Of note, European Public Assessment Reports (EPARs) of biosimilars approved in the EU via the centralized procedure are also a very helpful source of information.[18] In the US, FDA established several centers such as the Oncology Center of Excellence (OCE). These centers are responsible for approval of products within their field and subsequently regulatory assessments documents can be found within the respective sub home pages.[20] Guidelines from the FDA were also reviewed for example from the view of gastroenterologists.[21]

Because nonclinical animal studies are considered also as an integral part of biosimilar development, animal studies conducted for EMA and FDA submission were also reviewed in detail.[22]

## 4. Assessing Analytical Similarity of Biosimilars

The similarity of a biosimilar to its originator has to be assessed with a large number of analytical methods.[23] Biosimilar assessment should include a detailed analytical comparison of the structural and functional properties of the proposed biosimilar and reference product.[24] Designing a state-of-the-art analytical similarity study, which meets current regulatory requirements in the US and EU requires a thorough methodical approach. If the proposed biosimilar product and the reference product are shown to be highly similar with respect to the analytical and pharmacokinetics parameters, they should

 

probably also be similar with respect to the efficacy parameters.[25]

Statistical approaches may be combined with the analytical methods, which assess critical quality attributes to distinguish clinically meaningful differences of biosimilars to originator products.[26]

For some biosimilars on the market or close to, the analytical testing required for these products is published in scientific literature, either by groups or companies involved in the development or by independent research groups. Examples are:

- Infliximab: Pfizer[27], Samsung Bioepis[28], Celltrion[29, 30], and research groups[31]
- Rituximab: Shanghai Henlius Biotech,[32] and Aryogen and research groups[33]
- Bevacizumab: Amgen[34]
- G-CSF: Accord Healthcare, Intas,[35] and Eurofarma[36]
- peg-G-CSF: Intas,[37] Apotex[38]
- Tocilizumab: Hisun Pharmaceuticals[39]
- Trastuzumab: Probiomed,[40] and Celltrion[41]

Note: Adalimumab will be discussed separately.

## 5. Glycosylation of Biosimilars

Glycosylation profiles of biosimilars are getting a key critical quality attribute for their development.[42, 43] Glycosylation can not only affect the structure of proteins, but also their biological activity, serum half-life, pharmacokinetics, pharmacodynamics, and immunogenicity.[44, 45] Accordingly, ICH issued guidelines detailing specifications of biopharmaceuticals as well as comparability of such structure profiles during process scale-up and changes in manufacturing process.[46, 47]

As a summary, glycosylation should be controlled and monitored throughout the development and production processes of therapeutic proteins. In addition to "classical" high pressure liquid chromatography and mass spectroscopy methods, an upcoming technology for the analysis of glycosylation pattern are lectin microarrays.[48] Several microarray platforms were developed for different applications.[49]

A comprehensive study around the utility of lectin arrays for the assessment of therapeutic glycoproteins was conducted by a research group within the FDA.[50] Using a commercially available lectin chip containing 45 lectins, the binding patterns of a broad variety of therapeutic proteins, including monoclonal antibodies were assessed. Lectins show a high affinity to protein-glyco-structures, therefore binding signals were generally consistent with the previously known glycan patterns for the respective glycoproteins.

## 6. Market

Market aspects were addressed in a few review articles. Though in 2010 US Congress created an abbreviated application pathway for biosimilars, only 25 biosimilars were approved under this pathway, of which still not all are available for treatment of patients. Issues for limited biosimilar market entry and uptake were analyzed by Sarpatwari et al.,[51] and recommendations for reform were given. Potential future savings in the US including experience from the first marketed biosimilars were discussed by Mulcahy et al.[52] It was estimated that biosimilars will reduce direct spending on biologic drugs by 54 billion USD from 2017 to 2026 (about 3% of total estimated biologic spending) with a range of 24 to 150 billion USD.

An example for price reductions are Neulasta® biosimilars. Coherus's Udenyca® and Mylan's Fulphila® launched at 33% discounts to Neulasta's® wholesale acquisition cost. Sandoz's FDA approval of Ziextenzo resulted into a slightly deeper discount of 37%.

 

In US and Europe, the cost-saving potential of biosimilar medicines are not yet fully exhausted by health care providers, which still approach biosimilar medicines with caution. Reasons are limited biosimilar knowledge, low prescribing comfort, and safety and efficacy concerns.[53] In an overview of biosimilar policies in 10 European pharmaceutical markets (Belgium, France, Germany, Greece, Hungary, Italy, Poland, Spain, Sweden, and the UK) important heterogeneity in policies on biosimilars was observed between (and even within) the selected countries (demand-side policies, pharmaceutical prescription budgets or quotas and monitoring of prescriptions, potential financial incentives or penalties), which may partly explain variations in biosimilar uptake.[54] These data were analyzed two years previously, and in the meantime prescriptions of biosimilars clearly advanced.

In Asia, where the high cost of biologics remains still unaffordable for most patients the development of biosimilars plays a more important role than in developed countries and hundreds of biopharmaceutical companies have already established their manufacturing facilities.[55]

## 7. The Biosimilars

This chapter summarizes general information about biosimilar products, MoA, clinical indication(s), and patent and market situation for the respective biomolecules.

The most comprehensive biosimilars and biogenerics pipeline resource (http://www.biosimilarspipeline.com/) included as of September 2019 about 1,050 biosimilars, and more than 560 biobetters as well (a biobetter refers to a recombinant protein drug that is improved over the originator and is also called second line product).

In general, biologics with blockbuster status and sales of more than 1 billion USD per year are targeted as biosimilars rather than biologics with smaller annual sales. Currently there are about two dozen of blockbuster originator biomolecules for which biosimilars are marketed, in clinical or at least near to clinical development.

The different types of biosimilars, which are currently marketed or in development, can be grouped into antibodies, fusion proteins, smaller proteins (hormones / peptides), and small biomolecules.

Because detailed information for all biosimilars would exceed the scope of this review article, only a part of the marketed biosimilars are presented here. Adalimumab as the best-seller product is discussed with more detailed aspects, such as with a competitive field and the detailed analytical portfolio required for regulatory comparison of identity and release testing.

### 7.1. Adalimumab

#### 7.1.1. Molecule

Adalimumab (Humira®) is a human monoclonal IgG1 / kappa antibody. Humira® was the third TNF-α inhibitor on the market, but the first fully human antibody directed towards this target. Adalimumab consists of a tetramer of two heavy and two light chains with one N-glycosylation site per heavy chain.

#### 7.1.2. Mode of Action

TNF is a cytokine produced primarily by activated macrophages and T-cells. It normally binds to TNF-α receptors (TNFRs), leading to the inflammatory response of autoimmune diseases (Figure 1). By binding to TNF, adalimumab is reducing the inflammatory response triggered via TNFR signaling pathways.[56]

 

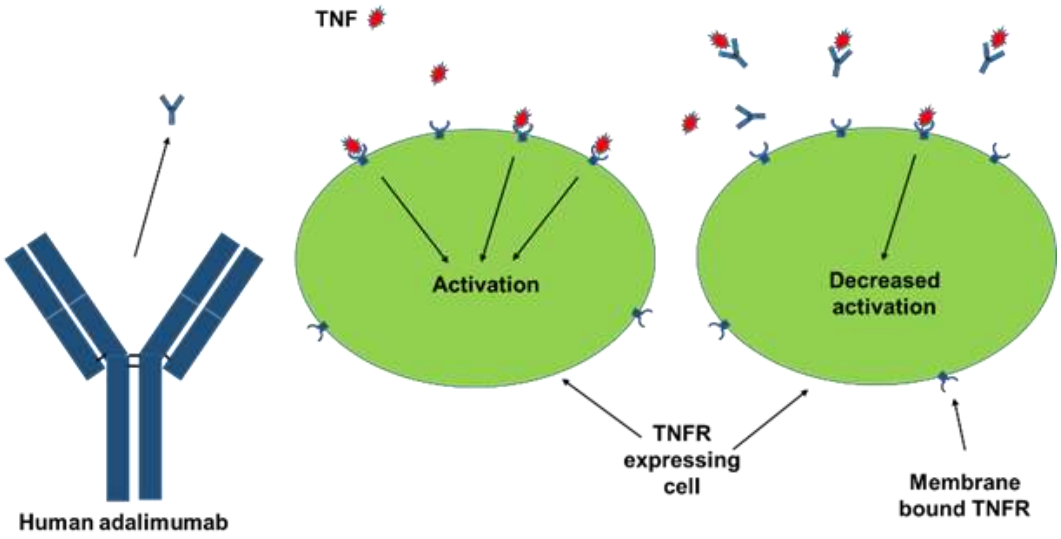


Figure 1: Schematic view for MoA of adalimumab

### 7.1.3. Indication

Adalimumab is indicated for treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, moderate to severe chronic psoriasis, moderate to severe hidradenitis suppurativa, and juvenile idiopathic arthritis.

To date, several adalimumab biosimilars have entered the EU market. Thus, some clinical data are already available on adalimumab biosimilars.[57]

### 7.1.4. Patent Situation

The initial patents of the Humira® product owned by AbbVie expired in 2016 in US and in EU in 2018. In the last years, AbbVie has secured more than 100 (US) patents covering Humira® formulations, manufacturing techniques and methods to treat multiple diseases. These additional patents will expire between 2022 and 2034 and AbbVie pursued litigation to keep biosimilars off the US market until 2023. To break AbbVie's monopoly, companies had to engage in time-intensive, expensive patent litigation. To avoid this, in 2019, eight companies have settled with AbbVie (Table 1). The deals reached in US give AbbVie still about three years of exclusivity on the market. As a result, AbVie continues to make considerable profit while additionally will participate through licenses on the sales of competitors starting in 2023. However, in Europe it is looking different, here competition to Humira® started in October 2018.

 

Table 1: Adalimumab license deals in the US

| **Company** | **Biosimilar / approval** | **License entry date** |
|---|---|---|
| Amgen | Amjevita® / Sep 2016 | Jan 2023 |
| Boehringer Ingelheim | Cyltezo® / Aug 2017 | Jul 2023 |
| Sandoz (Novartis) | Hyrimoz® / Oct 2018 | Sep 2023 |
| Samsung Bioepis / Biogen | Hadlima® / Aug 2019 | Jun 2023 |
| | **Stage** | |
| Mylan | Phase III | Jul 2023 |
| Fresenius Kabi | Early clinical stage | Sep 2023 |
| Momenta | Phase III, on hold | Nov 2023 |
| Pfizer | Abrilada™ / Nov 2019 | Nov 2023 |
| Coherus | Phase III finalized | Dec 2023 |

### 7.1.5. Market

In 2018, AbbVie's Humira® generated 17.2 billion € in sales, which was top selling globally. Some biosimilars were already approved by EMA and also by US-FDA, but launch is on hold in the US due to patent litigation. Furthermore, many other biosimilars are still in development (see competitive field). In contrast to the US, biosimilars are already marketed in Europe and the year 2019 already show the effect for Humira® sales. It can be expected that biosimilars may take halve of the Humira® market in Europe within a year.

Surprisingly there are several additional commercially successful anti-TNF-α molecules as well (sales 2018):

- Enbrel® (etanercept, a fusion protein): 4.45 billion € (Amgen) and 461 million € (Pfizer)
- Simponi® (golimumab): 1.83 billion € (Janssen / Centocor); 785 million € (Merck & Co)
- Remicade® (infliximab): 4.68 billion € (J&J, about 2/3 of the market)

### 7.1.6. Competitive Field

It exceeds the scope of the present article to present competitive fields for all biosimilars, however, one example is shown for adalimumab as of September 2019 (Table 2). As can be observed in this table, the market is already crowded with approved biosimilars, and some more products can be expected to be launched during the next years as well.

 

Table 2: Competitive field for adalimumab

| **Company, Country** | **Product Name** | **Stage of Development** |
|---|---|---|
| AbbVie, USA | Humira® | **Originator**; marketed worldwide |
| Alvotech, Switzerland / Iceland | AVT02 | Phase III |
| Amgen, USA | Amjevita™<br>Amgevita™<br>Solymbic® | Approved by FDA in September 2016<br>Marketed in EU |
| Baxalta / Shire, USA;<br>Momenta, USA | BAX923 / M923 | Phase III with positive results;<br>collaboration terminated by Shire |
| Biocad, Russia | BCD-057 | Phase III finalized |
| BIOCND, South Korea | BCD 100 | Phase I |
| Bio Thera Solutions, China | Qletli<br>(BAT1406) | Approved in China in December 2019 |
| Boehringer Ingelheim, Germany | Cyltezo® | Approved by FDA in August 2017 and by EMA in September 2017; not marketed in EU |
| Celltrion, South Korea | CT-P17 | Phase III |
| CinnaGen, Iran | CinnoRA® | Marketed in Iran |
| Coherus Biosciences, USA | CHS-1420 | Phase III with positive results |
| Dong-A ST, South Korea | DMB-3113 | Phase I in Japan |
| Fresenius Kabi, Germany<br>(formerly Merck, Germany) | Idacio®, Kromeya®<br>(MSB11022) | Marketed in EU; marketed by Mylan (NL/UK) |
| Fujifilm / Kyowa Hakko Kirin Biologics, Japan | FKB327<br>Hulio® | Approved by EMA in July 2017; will be marketed by Mylan / Biocon |
| Hetero, India | Mabura | Marketed in India |
| Hisun Pharma, China | Zrc-3197 | Submitted for approval in China in September 2018 |
| Innovent Biologics, China | IBI-303 | Phase III worldwide, submitted for approval in China in November 2018 |
| LG Life Sciences, South Korea;<br>Mochida Pharmaceutical, Japan | LBAL | Phase III; marketing planned in South Korea and Japan |
| Momenta, USA | M923 | Phase III; development stopped |
| Oncobiologics / Viropro, USA | ONS-3010 | Phase III |
| Pfizer, USA | Abrilada™<br>(PF-06410293) | Approved by FDA in November 2019 |
| Prestige Biopharma, Singapore | PRP1502 | Phase I |
| Samsung Bioepis, South Korea;<br>Biogen, USA | Imraldi®<br>Hadlima® | Marketed in EU; Approved by FDA in August 2019<br>Approved in South Korea in September 2017 |
| Sandoz, Switzerland | Halimatoz® Hefiya®<br>Hyrimoz™ | Approved by EMA in June 2018 and in October 2018 by FDA |
| Shanghai Henlius Biotech (Fosun), China | HLX03 | Phase III in China |
| Shanghai Junshi Biosciences, China | UBP1211 | Submitted for approval in China in November 2019 |
| Torrent Pharmaceuticals, India | Adfrar™ | Marketed in India |
| Zydus Cadila, India | Exemptia™ | Marketed in India |

 

### 7.1.7. Assessment of Analytical Similarity

As many biosimilars of adalimumab are already on the market or are close to, the analytical testing of this antibody is well documented. Liu et al., and Sivendran et al. published their efforts in scientific journals for Amgen [58,59], Lee et al. for Samsung Bioepis,[60] Magnenat for Merck,[61] and Bandyopadhyay for Cadila.[62] Of course, all these tests have to be discussed with regulatory authorities. The outcome can be viewed on the respective home pages of the US-FDA and EMA. A typical outcome of the required analytical portfolio of release tests, which was required by US-FDA for the Amgen product is presented in summary in Table 3.

Table 3: Release testing for adalimumab as requested by US-FDA

| Intention | Test type | Comment |
|---|---|---|
| **Primary structure** | Amino acid analysis | Extinction coefficient, UV and cation exchange |
| | Amino acid sequence | Peptide mapping (HPLC -MS/MS) |
| | Deamidation | Peptide mapping (HPLC -MS/MS) |
| | Oxydation | Peptide mapping (HPLC-MS/MS) |
| | N-terminal variants | Peptide mapping (HPLC-MS/MS) |
| | C-terminal variants | Peptide mapping (HPLC-MS/MS) |
| | Molecular weight / intact mass | Intact and reduced de-glycosylated mass by RP-HPLC and MS (Heavy and light chain) |
| | Protein content | Protein concentration (UV280) |
| **Higher order structure** | Infrared spectroscopy | Fourier transform infrared spectroscopy (FTIR) |
| | Thermodynamic stability | Differential scanning calorimetry (DSC) |
| | Circular dichroism (CD) | Near-UV CD (tertiary structure) |
| | Disulfide bond / linkage | Peptide mapping (HPLC-MS/MS) |
| **Glycosylation / carbohydrate structure** | N-linked glycan (site) | 2-AB labelling and HILIC-HPLC |
| | Glycosylation profile | 2-AB labelling and HILIC-HPLC |
| **Purity / impurity (size related)** | Aggregate/monomer | Size exclusion chromatography (SEC)-HPLC with light scattering detection |
| | Aggregate/monomer | Analytical ultracentrifugation (AUC) |
| | Electrophoretic mobility / purity | Non-reduced / reduced CE-SDS |
| | Sub-visible particles | Submicron particles by dynamic light scattering (DLS)<br>Subvisible particles by micro flow imaging and light obscuration |
| | Host cell protein (HCP) | HCP-ELISA<br>RP-2D-LC with MS<br>2D-DIGE (Gel electrophoresis) |
| | Residual DNA | Residual DNA |
| ***In-vitro* activities** | Binding | TNFα binding affinity (ELISA) |
| | Binding | Inhibition of sTNFα-induced chemokines in |

 

| Intention | Test type | Comment |
|---|---|---|
| | | blood |
| | Binding to transmembrane TNFα | MT-3 cell based binding affinity |
| | Apoptosis | U-937 cell based assay |
| | Neutralization of bioactivity | Inhibition of sTNFα - induced cell death in L929 cells |
| | Reverse signaling / apoptosis | Induction of apoptosis by reverse signaling |
| | Reverse signaling | Inhibition of sTNFα-induced IL-8 in HUVEC cells (specificity against LTα) |
| | Macrophage induction | Induction of regulatory macrophages |
| | Proliferation inhibition | Inhibition of T-cell proliferation |
| | Effector function | CDC, CHO M7 cell based |
| | Effector function | C1q binding affinity (ELISA) |
| | Effector function ADCC | ADCC using CHO M7 as target and NK as effectors |
| **Binding to Fc receptors** | FcRn | FcRn binding affinity, 293T-7A1 cell based |
| | FcγRIIIa V type | FcγRIIIa V type binding affinity (Alpha LISA) |
| | FcγRIIIa F type | FcγRIIIa F type binding affinity (Alpha LISA) |
| | FcγRIIa | FcγRIIa binding affinity (Alpha LISA) |
| | FcγRI | FcγRIa binding affinity (Alpha LISA) |
| **Charge variants** | Isoelectric focusing (IEF) | Capillary IEF |
| | Cation exchange (CEX) | CEX-HPLC |
| **Excipients / general properties** | General property | pH |
| | General property | Osmolality |
| | General property | Deliverable volume |
| | General property | Appearance / color / clarity |
| | Excipient | Polysorbate 80 |

### 7.2. Bevacizumab

#### 7.2.1. Molecule

Bevacizumab (Avastin®) is a typical humanized monoclonal IgG1/kappa antibody comprised of a tetramer of two heavy and two light chains with one N-glycosylation site per heavy chain.

#### 7.2.2. Mode of Action

Bevacizumab inhibits angiogenesis (formation of new blood vessels) by blocking the interaction of vascular endothelial growth factor A (VEGF-A) with its receptors, VEGF receptor-1 or VEGF receptor-2 (Figure 2). Bevacizumab can therefore also slow the growth of new blood vessels in tumors.[63]

 

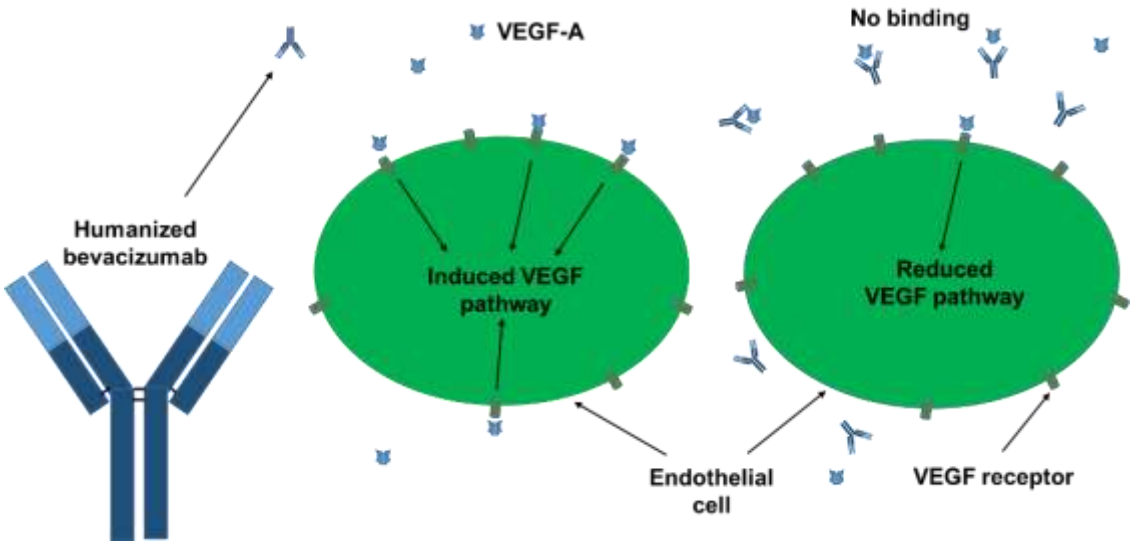


Figure 2: Schematic view for MoA of bevacizumab

#### 7.2.3. Indication

Bevacizumab is indicated for various cancers including metastatic colorectal cancer, non-squamous non-small cell lung cancer, metastatic renal cell carcinoma, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

#### 7.2.4. Patent Situation

Bevacizumab patents expired in US in 2019 and expire in EU in 2022. Roche as owner of the originator will defend the date in Europe and all biosimilar developments in late stage will have to wait for market entry until expiration of the originator patents.

#### 7.2.5. Market and Competitive Field

The originator product, Roche's Avastin® was approved by FDA in 2004 and by EMA in 2005. Avastin® had sales of 6.17 billion € in 2018 making it a popular target for biosimilar developers, from which the Amgen product is already approved. In developing countries non-originator biologicals are marketed as well.

### 7.3. Denosumab

#### 7.3.1. Molecule

Denosumab (Prolia®, Xgeva®) is a fully human IgG2 monoclonal antibody and has a molecular weight of 147 kDa. It consists of two heavy and two light chains. Each light chain shows 215 and each heavy chain 448 amino acids with four intramolecular disulfide bridges.

#### 7.3.2. Mode of Action

Bone remodeling is driven most notably by osteoblasts secreting new bone and osteoclasts breaking down bone structures. Pre-osteoclasts express on their surface the receptor activator of nuclear factor-kappa B (RANK), a member of the tumor necrosis factor receptor (TNFR) superfamily.[64] RANK is activated by RANKL (RANK-Ligand), which exists as cell surface molecule on osteoblasts. Activation of RANK by RANKL promotes the maturation of pre-osteoclasts into osteoclasts. Denosumab inhibits maturation of osteoclasts by binding to and inhibiting RANKL similar to the natural function of the endogenous RANKL inhibitor osteoprotegerin (Figure 3). This MoA thus counters the progression of osteoporosis.

 

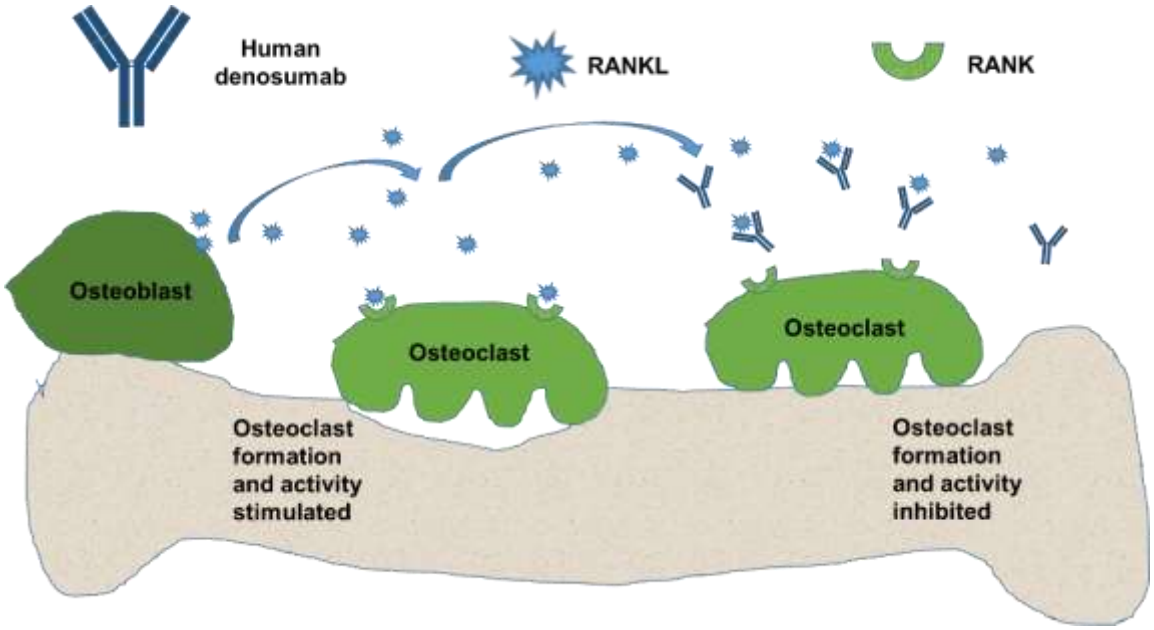


Figure 3: Schematic view for MoA of denusomab

#### 7.3.3. Indication

Denosumab is indicated for the treatment of patients with osteoporosis at high risk for fracture (Prolia®), giant cell tumor of bone, hypercalcemia in malignancy and for the prevention of skeletal-related events in patients with bone metastases from solid tumors.[65]

#### 7.3.4. Patent Situation

Expiry dates of basic Prolia® patents related to the antibody and treatment of patients range from 2017 to 2023 in US and from 2017 to 2021 in EU.

#### 7.3.5. Market and Competitive Field

Denosumab was first approved as Prolia® by EMA in 2010, and then as Xgeva® and Prolia® by FDA in 2010 (as the first RANKL inhibitor). It was developed and marketed by Amgen. In 2018, Amgen´s sales were 2.03 billion € (Prolia®) and 1.57 billion € (Xgeva®).

### 7.4. Infliximab

#### 7.4.1. Molecule

Infliximab (Remicade®) is a chimeric (mouse / human) monoclonal IgG1 / kappa antibody. Like etanercept and adalimumab, infliximab is also a TNF-α blocker. It is composed of human constant and murine variable regions with a molecular weight of approximately 144 kDa. 25% of the polypeptide chain are murine derived (binding epitope for TNF), 75% are human (IgG fragment).

#### 7.4.2. Mode of Action

TNF is a cytokine produced primarily by activated macrophages and T-cells. It normally binds to TNFRs, leading to an inflammatory response of autoimmune diseases. By binding to TNF, infliximab is reducing this inflammatory response triggered via TNFR signaling pathways (Figure 4).[66, 56]

 

#### 7.4.3. Indication

Remicade® is indicated for treatment of Crohn's disease, psoriatic arthritis, ulcerative colitis, psoriasis, ankylosing spondylitis, and rheumatoid arthritis,[67] in most of the cases applied together with methotrexate (clinical design).

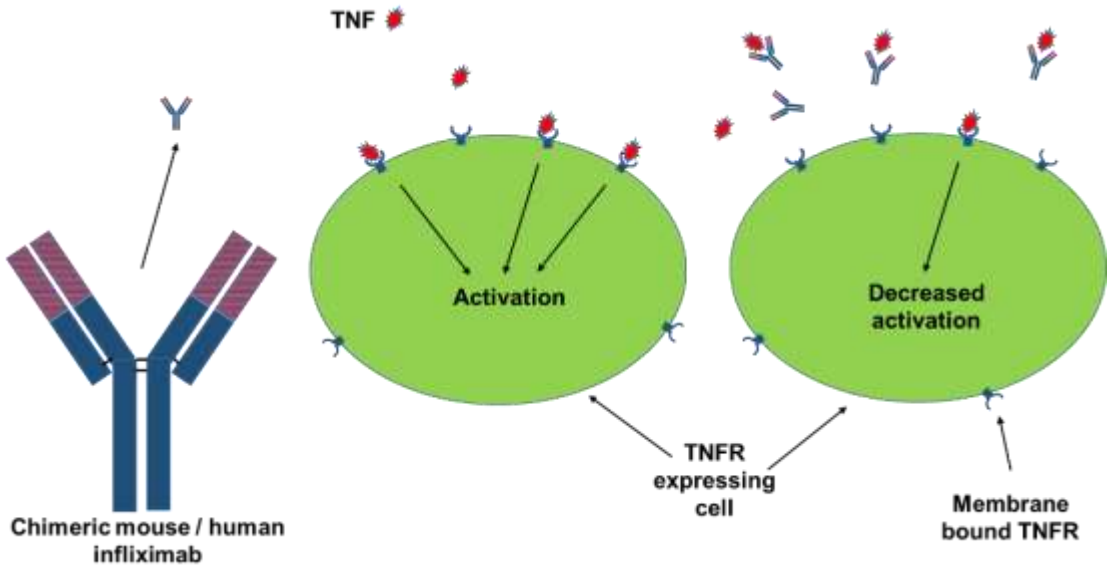


Figure 4: Schematic view for MoA of infliximab

#### 7.4.4. Patent Situation

The main patent of Remicade® expired in 2015 (EU) and in US in 2018. J&J (Janssen), the owner of the originator molecule is trying to delay the market entry of biosimilars with additional patents, however, is struggling to defend their validity at court.

#### 7.4.5. Market and Competitive Field

J&J sells Remicade® in US, Mitsubishi Tanabe in Japan and parts of Asia, Xian Janssen in China, and MSD in Europe and in ROW. Total worldwide sales of J&J in 2018 were 4.68 billion €. About 2/3 of the market was owned by J&J, but biosimilars are already on the market, i.e. Flixabi®, Inflectra®, Renflexis™, Remsima®.

### 7.5. Nivolumab

#### 7.5.1. Molecule

Nivolumab, (Opdivo®), is a fully human monoclonal IgG4 antibody. It has a molecular weight of 143.6 kDa and is targeted to the cellular programmed cell death protein-1 (PD-1).

#### 7.5.2. Mode of Action

Programmed cell death ligand 1 or ligand 2 (PD-L1 or PD-L2) is upregulated on 40-50% of melanomas and has limited expression otherwise. Both ligands bind to PD-1, a protein on the surface of activated T-cells. If PD-L1 binds to PD-1, a T-cell becomes inactive and inhibited from attacking a tumor. The inhibitory effect results from promotion of apoptosis in antigen specific T-cells while simultaneously blocking

 

apoptosis in suppressor T-cells. Nivolumab binds to PD-1, thus blocks PD-L1 or PD-L2 from binding to PD-1, and T-cells can again attack tumor cells, (Figure 5).[68]

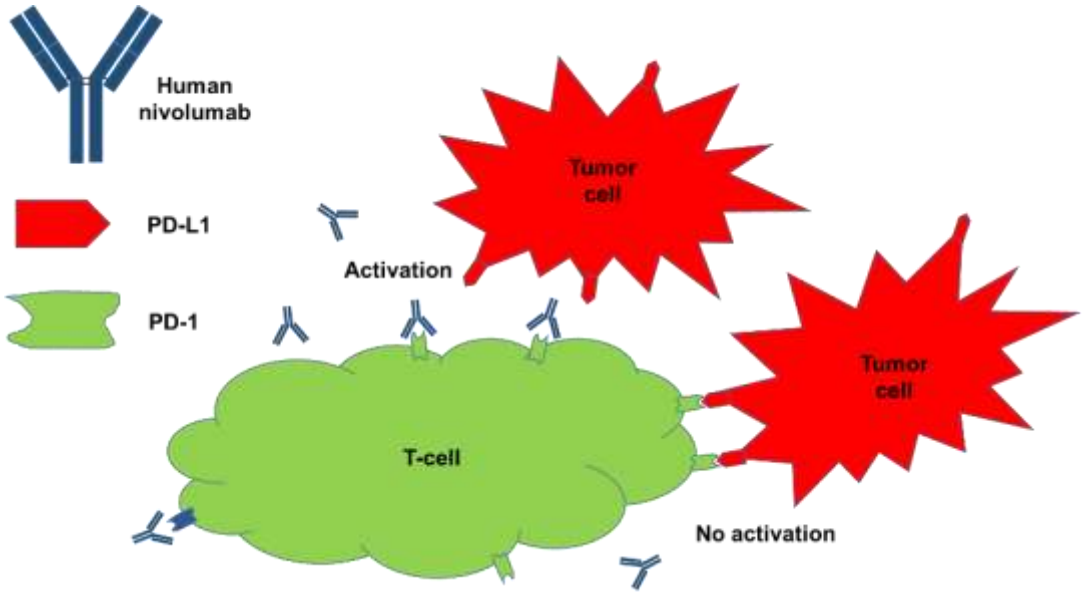


Figure 5: Schematic view for MoA of nivolumab

#### 7.5.3. Indication

Opdivo® is indicated, among other cancer types, as a first or second line treatment for inoperable or metastatic melanoma. This includes advanced non-small cell lung cancer,[69] metastatic melanoma, advanced renal cell carcinoma, squamous cell carcinoma of the head and neck.

#### 7.5.4. Patent Situation

Owner of the originator product Opdivo®, Bristol-Myers Squibb (BMS) and collaborator Ono Pharmaceuticals filed several patent families around this drug, with expiration dates of up to 2027 in US and 2026 in EU. This includes patents directed to the inhibition to PD-1. BMS is filing lawsuits against competitors marketing antibodies with this target (e.g. Merck US).

#### 7.5.5. Market and Competitive Field

Opdivo® was approved as first PD-1 immune checkpoint inhibitor in the world for its first indication by FDA in 2014 and in EU in 2015. In 2018, BMS had sales for Opdivo® of 5.92 billion €, up from 4.17 billion € in 2017 (3.18 billion € in 2016).

### 7.6. Rituximab

#### 7.6.1. Molecule

Rituximab (Rituxan®, MabThera®) is a chimeric IgG1/kappa monoclonal antibody targeting CD20, which is primarily detected on the surface of B-cells.

#### 7.6.2. Mode of Action

Rituximab binds to amino acids 170-173 and 182-185 on CD20 protein. CD20 is widely expressed on B-cells, from early pre-B-cells to later in differentiation, but it is absent on terminally differentiated plasma cells. CD20 may play a role in $Ca^{2+}$ influx across plasma membranes, maintaining intracellular $Ca^{2+}$ concentration and activation of B-cells. Rituximab destroys both normal and

 

malignant B-cells that have CD20 on their surfaces, and is therefore used to treat diseases, which are characterized by having too many overactive or dysfunctional B-cells (Figure 6).[70]

#### 7.6.3. Indication

Rituxan® is applied for treatment of many lymphomas and leukemia's, transplant rejection and some autoimmune disorders.[71] Rituximab is also used off-label to treat difficult cases of multiple sclerosis, systemic lupus erythematosus and autoimmune anemias.

#### 7.6.4. Patent Situation

Rituxan® patents expired in 2013 in EU and in 2016 in US. Several biosimilars are already marketed.

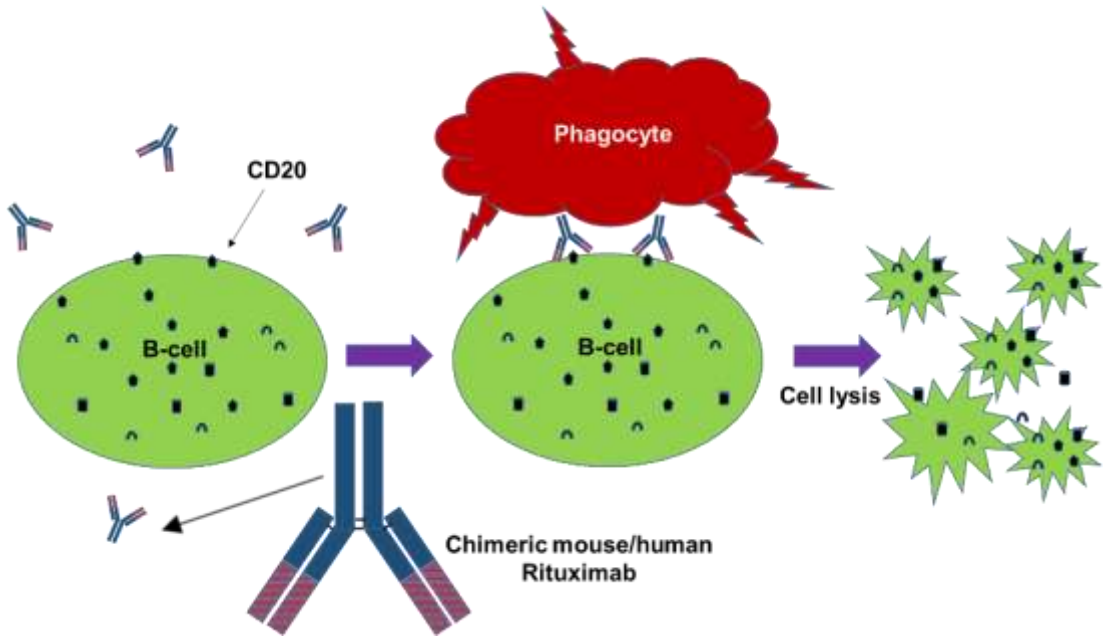


Figure 6: Schematic view for MoA of rituximab

#### 7.6.5. Market and Competitive Field

Roche's Rituxan®, the originator product, was approved by FDA in November 1997 and MabThera® by EMA in June 1998. Rituxan® had sales of 6.07 billion € in 2018. In respect of the blockbuster sales, many companies are developing or marketing biosimilars of this drug, e.g. Celltrion, Hospira, Amgen, Pfizer, Sandoz. Rixathon® and Truxima® are already approved.

### 7.7. Trastuzumab

#### 7.7.1. Molecule

Trastuzumab (Herceptin®) is a humanized monoclonal IgG1 antibody comprised of a tetramer of two heavy and two light chains with one N-glycosylation site per heavy chain.

#### 7.7.2. Mode of Action

The HER2 pathway promotes cell growth and cell division via HER2 receptor. When HER2 is over-induced and dimerized, cell growth accelerates, which can lead to tumor formation.[72] Trastuzumab binds to domain IV of the extracellular segment of HER2 receptor preventing it from dimerization and activation of its signaling pathways (Figure 7).

 

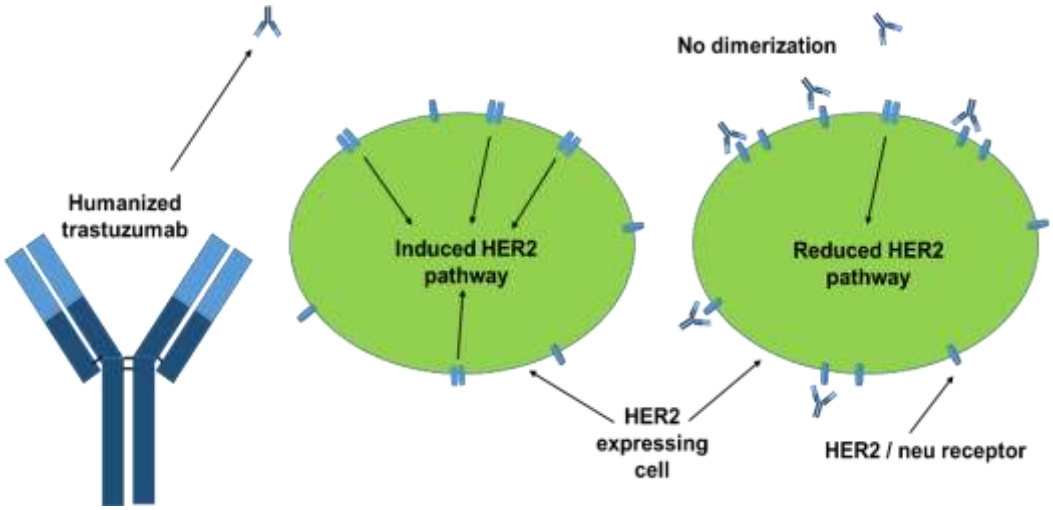


Figure 7: Schematic view for MoA of trastuzumab

#### 7.7.3. Indication

Herceptin® is indicated for the treatment of HER2-positive metastatic breast cancer patients.[73] It is also approved for adjuvant treatment of HER2 over-expressing breast cancer and metastatic gastric cancer.

#### 7.7.4. Patent Situation

Primary patents for Herceptin® expired in 2014 in EU and in US in 2019. Further patents related to dosage and composition of the drug are under litigation and already invalidated in some countries.

#### 7.7.5. Market and Competitive Field

Roche's Herceptin®, the originator product, was approved by FDA in 1998 and by EMA in 2000. Herceptin® had worldwide sales of 6.28 billion € in 2018. Several biosimilars are approved or submitted for approval at FDA and EMA.

### 7.8. Ustekinumab

#### 7.8.1. Molecule

Ustekinumab (Stelara®) is an IgG1 kappa fully human monoclonal antibody with a molecular weight of 149 kDa containing a single N-linked glycosylation site at the Asp 299 amino acid residue of each heavy chain.

#### 7.8.2. Mode of Action

Ustekinumab blocks interleukin IL-12 and IL-23, which activate T helper cells ($T_h$ cells).[74] Specifically, it is targeting the p40 shared subunit of IL-12 and IL-23, which subsequently cannot bind to their distinct receptors (Figure 8). $T_h$ cells play an important role in the immune system, particularly in the adaptive immune system. Dependent on their $T_h$ cell subtype they release a specific pattern of cytokines.

 

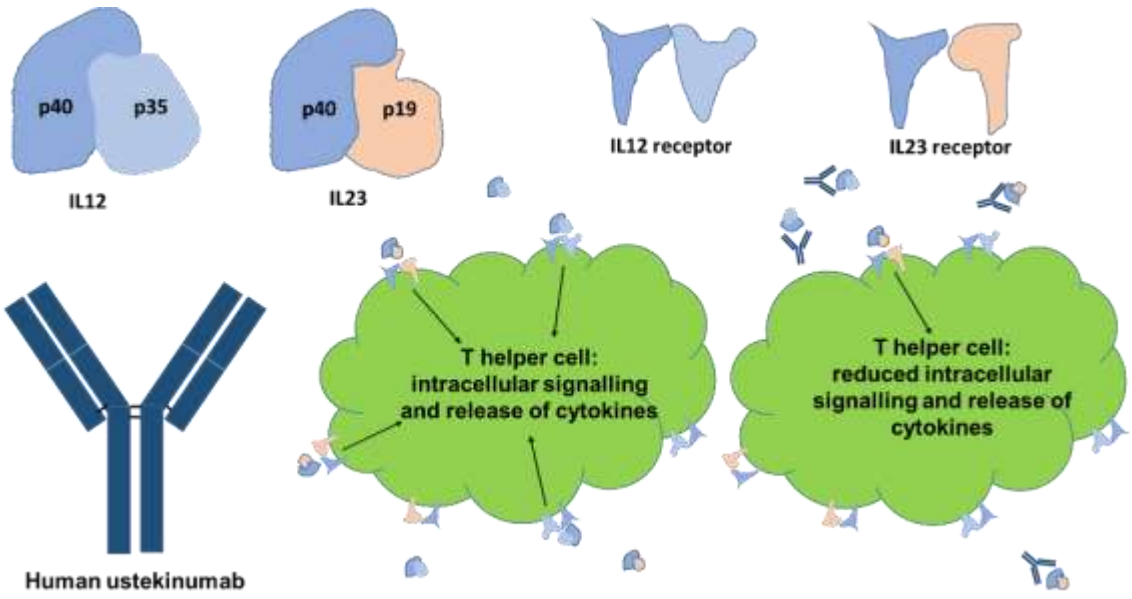


Figure 8: Schematic view for MoA of ustekinumab

#### 7.8.3. Indication

Stelara® is indicated for treating patients with moderate to severe plaque psoriasis and also to treat active psoriatic arthritis alone or with methotrexate.[75] In 2016, it was also approved to treat Crohn's disease.

#### 7.8.4. Patent Situation

The patent protection for Stelara® will be until the end of 2023 in US and mid 2024 in EU. Because in 2014 AbbVie has lost a patent dispute in which it tried to show that Janssen's Stelara® infringed on two patents targeted to IL-12-targeting antibodies, which are owned by AbbVie, the patents seem to be safe.

#### 7.8.5. Market and Competitive Field

The originator product Stelara® of J&J (Jannsen) and Centecor has been first approved in Europe in 2008 and in US in 2009. In 2018, Stelara® had sales of 4.53 billion € making it an attractive target for biosimilars. However, large companies such as Novartis, Ely Lilly, and Boehringer Ingelheim (in collaboration with AbbVie) are marketing or developing own originator antibodies targeting other interleukins but aiming at the same indications as ustekinumab.

### 7.9. Abatacept

#### 7.9.1. Molecule

Abatacept (Orencia®) is a fusion protein composed of the Fc region of the immunoglobulin IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The molecular weight of abatacept is about 92 kDa.

#### 7.9.2. Mode of Action

To activate a T-cell and subsequently produce an immune response, an antigen-presenting cell must show two signals to the T-cell. One of those signals is the major histocompatibility complex (MHC), combined with the T-cell receptor (TCR), and the other signal is the CD80 / CD86 molecule. Abatacept binds to CD80 / CD86 and prevents the second signal. Without the

 

second signal, the T-cell cannot be activated (Figure 9). Abatacept is thus down-regulating the activation of T-cells by binding to CD80 / CD86 ligand proteins and modifies inflammation and immune activity, which causes major symptoms of rheumatoid arthritis.[76]

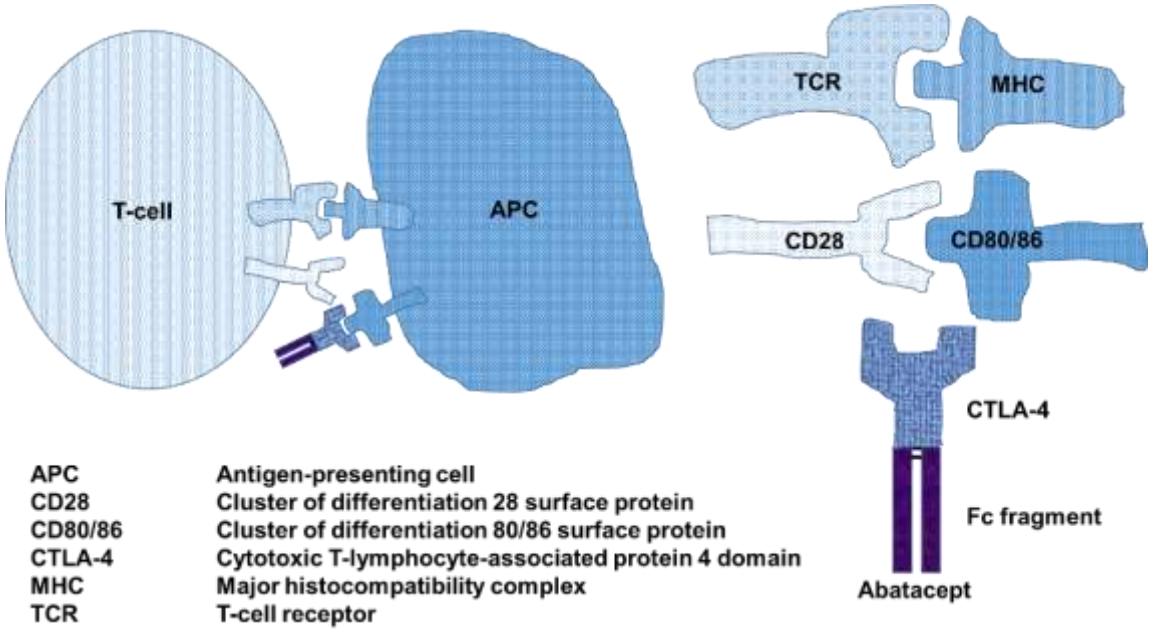


Figure 9: Schematic view for MoA of abatacept

#### 7.9.3. Indication

Orencia® is indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis.[77] It is also indicated for juvenile idiopathic arthritis and adult psoriatic arthritis.

#### 7.9.4. Patent Situation

Patents on Orencia® expired in US in October 2019 and in Europe in December 2017. When challenged by Momenta, the validity of a formulation patent for Orencia® was upheld in 2016.

#### 7.9.5. Market and Competitive Field

The originator product, Bristol-Myers Squibb's Orencia®, was approved by FDA in 2005 and by EMA 2007. In 2018, Orencia® had sales of 2.71 billion €. Potential biosimilar products are at a very early stage.

### 7.10. Aflibercept

#### 7.10.1. Molecule

Aflibercept (Eylea®, Zaltrap®) is a recombinant fusion protein consisting of VEGF- binding portion from the extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of a human IgG1 immunoglobulin. Together with glycosylation of the Fc-part, its molecular weight is 115 kDa.

#### 7.10.2. Mode of Action

Like ranibizumab, aflibercept is an inhibitor of VEGF. It binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF-110. The binding of aflibercept to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of

 

endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation (Figure 10).[78]

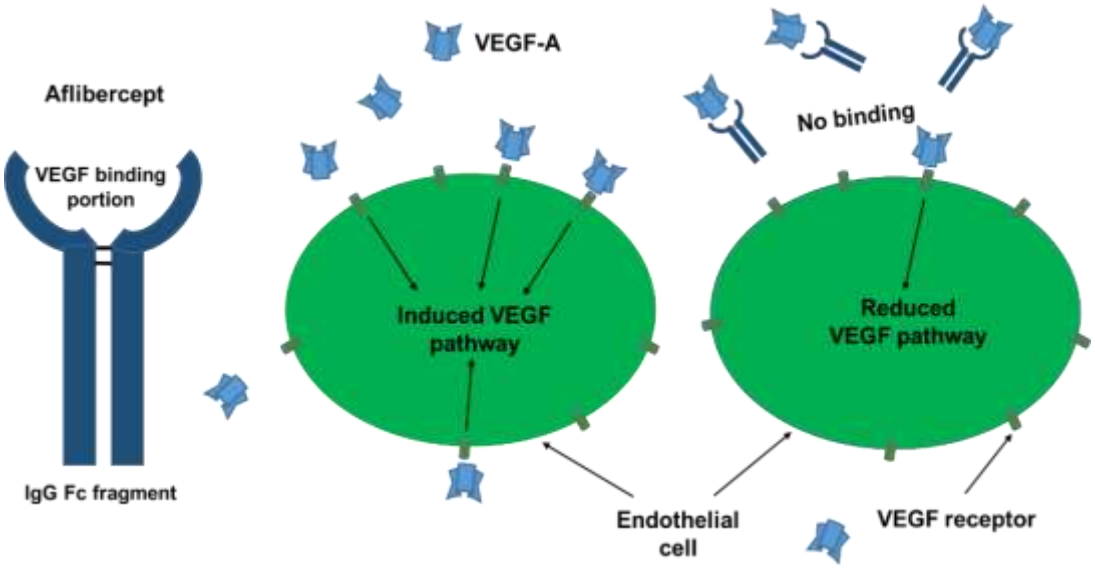


Figure 10: Schematic view for MoA of aflibercept

#### 7.10.3. Indication

Eylea® (aflibercept) is indicated for the treatment of neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion, diabetic macular edema, and diabetic retinopathy.[78] Zaltrap® (ziv-aflibercept) is indicated in combination with 5-fluorouracil, leucovorin, irinotecan (cytostatic medication) for metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing therapy.

#### 7.10.4. Patent Situation

A basic US patent for aflibercept will expire in 2020 (with extension to 2023), European patents will expire in 2021. Other patents in combination with their extensions may be valid until 2027 and it remains to be seen whether these patents can prevent the market entry of biosimilars.

#### 7.10.5. Market and Competitive Field

The originator product from Regeneron was co-developed with Bayer and approved by FDA (2011), and EMA (2012) for the treatment of eye diseases under the trade name Eylea®. The second originator was co-developed with Sanofi and approved by FDA (2012), and EMA (2013) for the treatment of cancer under the trade name Zaltrap®. In 2018, global net sales alone of Eylea® from Regeneron were 5.99 billion €.

### 7.11. Etanercept

#### 7.11.1. Molecule

Etanercept (Enbrel®) is a dimeric human receptor fusion protein consisting of the extracellular ligand-binding domain of human 75 kDa (p75) TNFR linked to the Fc-part of human IgG1. The Fc-part of etanercept contains CH2 domain, CH3 domain and the hinge region. The molecular weight is approximately 150 kDa.

#### 7.11.2. Mode of Action

TNF is a cytokine primarily produced by activated macrophages and T cells. One of the naturally occurring receptors is a 75 kDa

 

(p75) TNFR. Monomers of the extracellular portion of TNFR are physiologically cleaved from cell surface (soluble TNFR, sTNFR) and bind with high affinity to circulating TNF-α. As such, they act as competitive inhibitors to TNF-α preventing it from binding to cell-bound TNFRs. Thus, the fusion protein etanercept competitively inhibits binding of TNF-α to TNFRs, rendering TNF-α biologically inactive (Figure 11).[56] Etanercept also modulates indirectly different biological functions such as expression of adhesion molecule E-selectin, production of IL-6 and matrix metalloproteinase 3 (MMP-3), as well as IL-1.

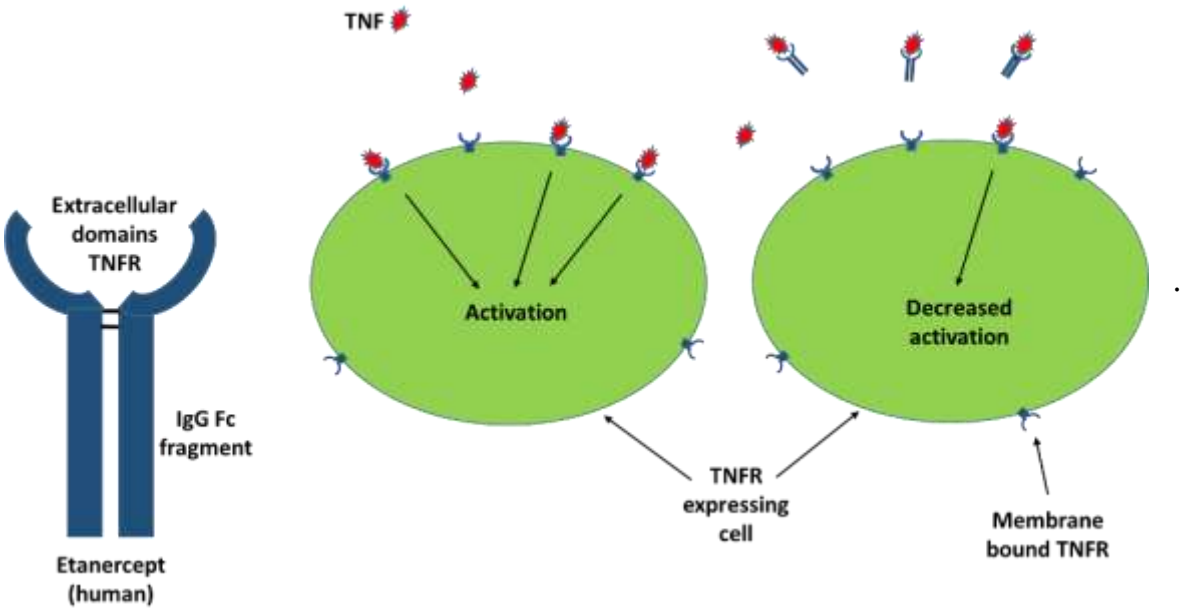


Figure 11: Schematic view for MoA of etanercept

### 7.11.3. Indication

Etanercept is applied for treatment of rheumatoid arthritis, poly-articular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis.[79]

### 7.11.4. Patent Situation

Enbrel® patents expired in 2012 in US and in 2015 in Europe. However, Amgen, the owner of originator Enbrel® fights to hold off biosimilars from the market until 2029 with new preparation patents.

### 7.11.5. Market and Competitive Field

Amgen's Enbrel® (co-marketed by Pfizer) has received its first approval by FDA in 1998 and by EMA in 2000. In 2018, Enbrel® had sales of 4.45 billion € (Amgen) and 461 million € (Pfizer). In respect of these blockbuster sales many companies are developing or marketing biosimilars of the drug, e.g. Sandoz and Merck. Benepali® is already approved by EMA and Erelzi™ by EMA and FDA.

 

### 7.12. Darbepoetin alfa

#### 7.12.1. Molecule

Darbepoetin alfa (Aranesp®) contains in comparison to natural erythropoietin five amino acid changes (at N30, T32, V87, N88, T90) resulting into creation of two new sites for N-linked carbohydrate addition. It has a three-fold longer serum half-life compared to epoetin alpha and epoetin beta. It is a 165-amino acid protein with a molecular weight of 37 kDa.

#### 7.12.2. Mode of Action

Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.[80] Erythropoietin interacts with progenitor stem cells to increase red cell production. Binding of erythropoietin to the erythropoietin receptor leads to receptor dimerization, which facilitates activation of janus kinase - signal transducers and activators of transcription (JAK-STAT) signaling pathways within cellular cytosol. Activated STAT proteins are translocated to the nucleus where they function as transcription factors, which regulate the activation of specific genes involved in cell division or differentiation process (Figure 12).

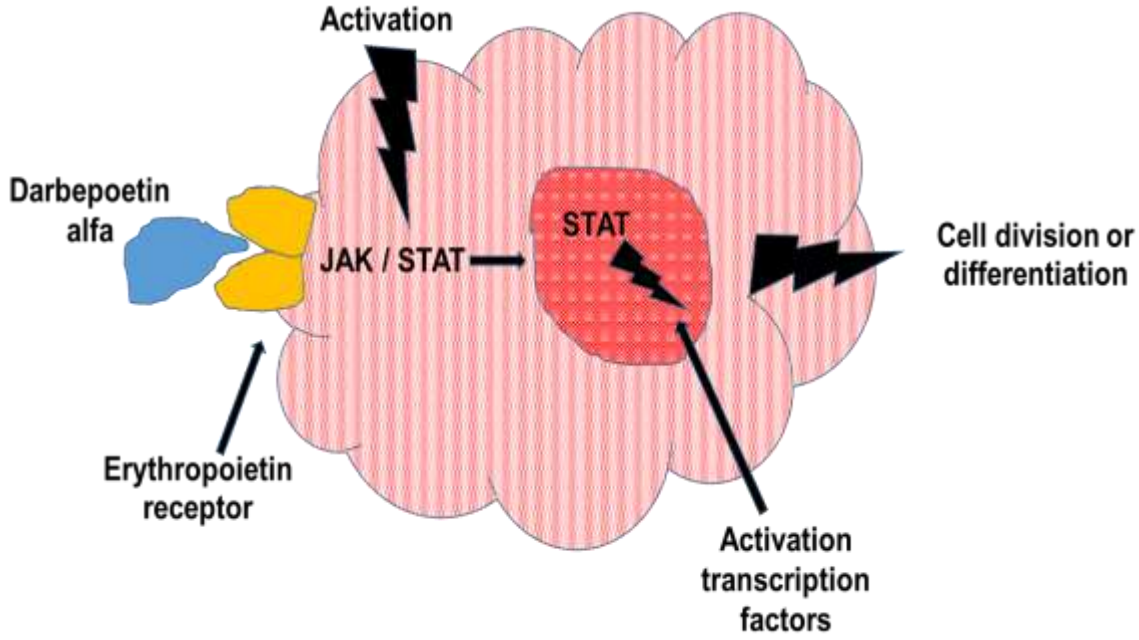


Figure 12: Schematic view for MoA of darbepoetin alfa

#### 7.12.3. Indication

Aranesp® is indicated for the treatment of anemia due to chronic kidney disease, including patients on dialysis and patients not on dialysis.[81] Aranesp® is also indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelo-suppressive chemotherapy.

#### 7.12.4. Patent Situation

Patents on Aranesp® will expire in US in May 2024 and already expired in Europe in July 2016.

 

#### 7.12.5. Market and Competitive Field

The originator product, Amgen's Aranesp®, was approved by FDA and EMA in 2001. Amgen co-developed the product with Kyowa Hakko Kirin (Japan), which sells the drug in Japan and other Asian countries as Nesp®. In 2018, Aranesp® had sales of 1.67 billion €. Until now, some biosimilars are marketed in Japan and in India.

### 7.13. Insulin

#### 7.13.1. Molecule

Animal sourced insulins are now rarely available in developed countries and even use of recombinant human insulin is declining in different markets whereas insulin analogues are dominating the market since years. Basal insulins are long acting, bolus insulins are fast acting.

#### 7.13.2. Mode of Action

The various insulin analogues (Table 4) have each different amino acid modifications resulting into different MoAs as presented in the table below.[82]

Table 4 Insulin analogues

| Insulin analogue | Modification | Molecular weight | MoA |
|---|---|---|---|
| Insulin lispro | Proline B28 replaced by lysine and lysine B29 replaced by proline | 58.1 kDa | Fast acting, blocking of multimers |
| Insulin aspart | Proline B28 replaced with aspartic acid | 58.3 kDa | Fast acting, blocking of multimers |
| Insulin glulisine | Asparagine B3 replaced by lysine and lysine B29 replaced by glutamic acid | 58.2 kDa | Fast acting, blocking of multimers |
| Insulin glargine | Asparagine N21 replaced by glycine and two arginines added to carboxy terminus of B chain | 60.6 kDa | Long acting, initial precipitation and delayed absorption |
| Insulin detemir | A special fatty acid - myristic acid bound to lysine B29 | 59.1 kDa | Long acting, affinity for albumin |
| Insulin degludec | Threonine B30 deleted, at lysine B29 conjugated to hexadecanedioic acid via gamma-L-glutamyl spacer | 61.0 kDa | Ultra-long acting, formation of multi-hexamers in subcutaneous tissues |

#### 7.13.3. Indication

Insulin is indicated to treat high blood glucose including diabetes mellitus type 1 and 2, gestational diabetes, and complications of diabetes such as diabetic ketoacidosis and hyperosmolar hyperglycemic states. Insulin is also used with glucose to treat high blood potassium levels. Depending on the disease type and stage, different insulin analogues or mixtures thereof are prescribed.

#### 7.13.4. Patent Situation

Patent protection of recombinant human insulin has expired for more than 15 years

 

and also patents for many analogues have been expired so far, e.g. for Lantus® and Humalog®.

#### 7.13.5. Market and Competitive Field

The originator product of insulin lispro, Eli Lilly's Humalog® was approved in 1996 by FDA and EMA as the first insulin analogue. In 2018, global sales of Humalog® were 2.63 billion €. This was topped by Sanofi-Aventis's Lantus® (insulin glargine), which had a turnover of 3.57 billion €.

### 7.14. Interferon-β1a

#### 7.14.1. Molecule

Interferon-β1a (IFN-β1a, Avonex®) is a cytokine in the interferon family. It is a 166 amino acid glycoprotein with a single N-linked carbohydrate chain on Asn-80 residue. The molecular weight is 20 kDa. Commercial IFN-β1a preparations show core-fucosylated glyco-forms differing in sialylation and glycol-antennary degree.

#### 7.14.2. Mode of Action

IFNs comprise a family of secreted α-helical cytokines induced in response to extracellular biomolecules through stimulation of toll-like receptors. IFN-β1a is acting on a variety of processes and molecules within the immune system. For example, it balances the expression of anti-inflammatory and pro-inflammatory cytokines. Other activities of IFN-β1a include inhibition of T-cell activation (Figure 13). The beneficial effect on multiple sclerosis results from a variety of immunomodulatory and anti-proliferative actions.[83] In the central nervous system, IFN-β1a balances expression of pro- and anti-inflammatory agents, reduces number of inflammatory cells which cross the blood brain barrier, and increases production of nerve growth factor thus improving neuronal survival.

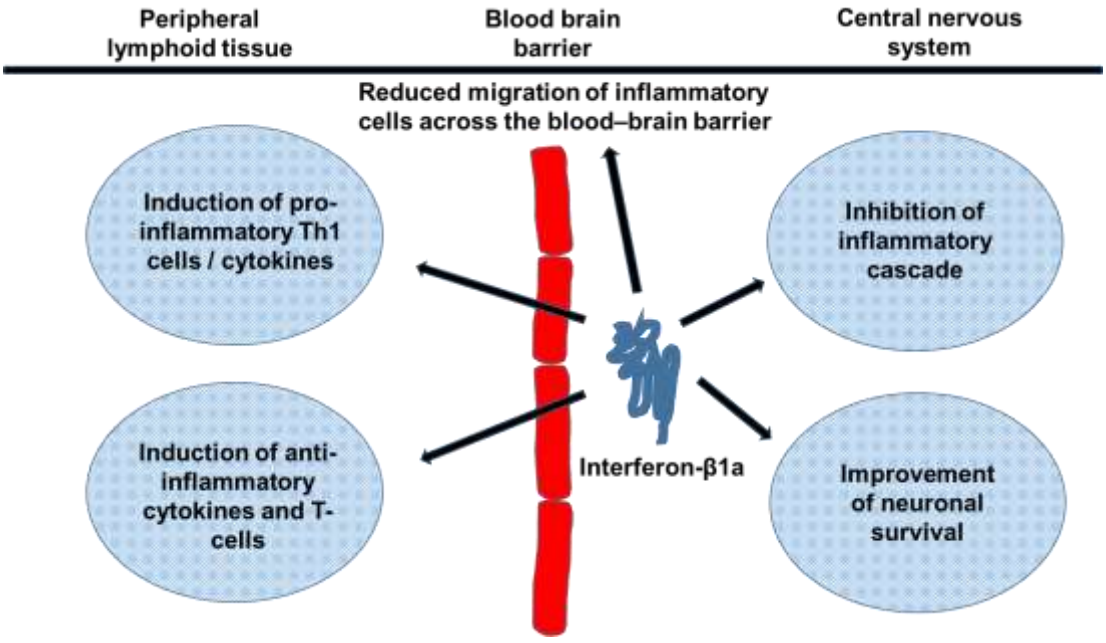


Figure 13: Schematic view for MoA of Interferon-β1a

 

#### 7.14.3. Indication

Avonex® is indicated for treatment of relapsing forms of multiple sclerosis to slow accumulation of physical disability and to decrease frequency of clinical exacerbations in patients with first clinical episode and magnetic resonance imaging consistent with multiple sclerosis.[83]

#### 7.14.4. Patent Situation

True composition of matter patents expired for Avonex® in 2013. These patents were regarded to have limited utility to keep competitors off the market. Whether other patents for the drug's use in treating diseases, valid until September 2026, may block potential competitors remains to be observed.

#### 7.14.5. Market and Competitive Field

Avonex®, developed by Biogen, was approved in US in 1996, and in Europe in 1997. It is the leading multiple sclerosis therapy in the US, with around 40% of the market in US and 30% in Europe. The competitor Rebif® from Merck (co-marketed by Pfizer in US) was approved in Europe in 1998 and in US in 2002.

In 2018, sales for Avonex® were 1.68 billion € and for Rebif® 1.4 billion €. Different biosimilars were already developed in emerging markets.

### 7.15. pegG-CSF

#### 7.15.1. Molecule

Pegfilgrastim (pegylated granulocyte colony stimulating factor, pegG-CSF, Neulasta®) is a variant of G-CSF coupled to a polyethylene glycol (PEG) moiety at the N-terminus of human G-CSF. This pegylated form has a longer half-life, thus reducing the necessity of daily injections (half-life extended from 3.5 h to 15 - 80 h). A G-CSF molecule consists of 175 amino acid residues (18.8 kDa) and is manufactured in E. coli. PEG tailing adds 20 kDa to the molecular weight of G-CSF.

#### 7.15.2. Mode of Action

Pegfilgrastim binds to the G-CSF receptor, stimulates the proliferation of progenitor cells and their maturation into neutrophils.[84] Pegfilgrastim also stimulates the release of neutrophils from bone marrow and increases their phagocytic activity. Pegfilgrastim treatment can thus be applied to fight against infection in patients undergoing chemotherapy (Figure 14).

 

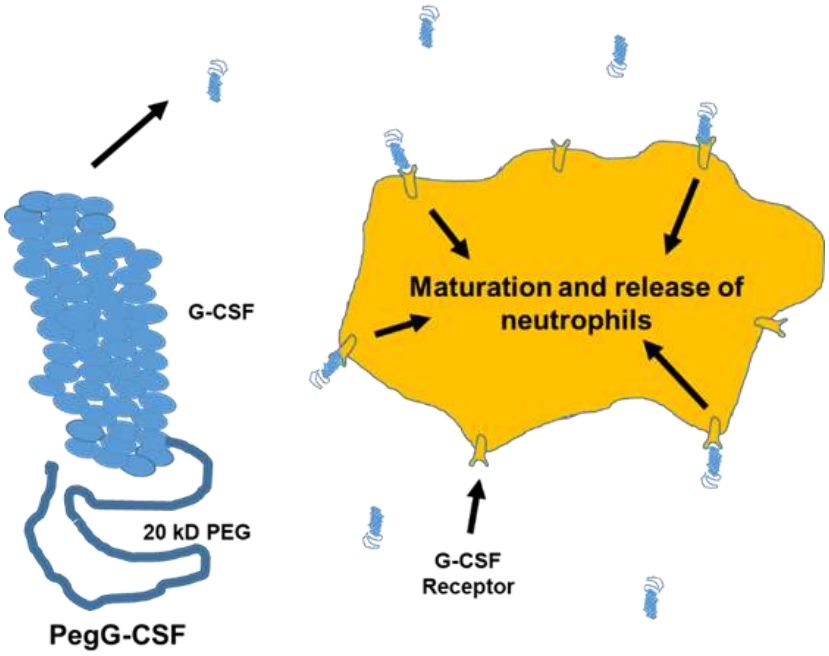


Figure 14: Schematic view for MoA of pegfilgrastim

### 7.15.3. Indication

Indications for pegfilgrastim are to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelo-suppressive anticancer drugs associated with clinically significant incidence of febrile neutropenia, and to increase survival in patients acutely exposed to myelo-suppressive doses of radiation.[85]

### 7.15.4. Patent Situation

The patents on Neulasta® expired in US in October 2015 and in Europe in August 2017. In December 2014, Apobiologix already submitted its biosimilar Lapelga® to FDA for approval and triggered a patent infringement litigation from Amgen, however, in September 2016 won the lawsuit.

### 7.15.5. Market and Competitive Field

The originator product, Amgen's Neulasta®, was a co-development with Kyowa Hakko Kirin and was approved by FDA in January 2002 and by EMA in March 2002. In 2018, Neulasta® had worldwide sales of 3.37 billion €. Previously, Roche possessed marketing rights for the product. A biobetter variant is marketed by Teva (Israel) and a variety of biosimilar candidates are already in development or already approved.

## 7.16. Parathyroid hormone (PTH)

### 7.16.1. Molecule

Parathyroid hormone (PTH, Natpara®, Preos™, Preotact®) is a polypeptide containing 84 amino acids (9.4 kDa). Only the 34 N-terminal amino acids are required for the bioactive conformation and biologic activity. Teriparatide (Forteo®, Forsteo®), a PTH analogue, consisting of these 34 amino acids has the same efficacy as PTH.

### 7.16.2. Mode of Action

PTH secreted by chief cells of the parathyroid glands is the primary regulator of calcium and phosphate metabolism in bone and kidney. It is acting upon the PTH-1 receptor in bone and kidney, and the PTH-2 receptor in the central nervous system,

 

pancreas, testis, and placenta. PTH mainly increases serum calcium levels. Thus, chronically elevated PTH will deplete bone stores (Figure 15). However, intermittent use activates osteoblasts more than osteoclasts, which leads to an overall increase in bone formation and increased bone mineral density.[86]

### 7.16.3. Indication

Teriparatide is indicated for treatment of osteoporosis in postmenopausal women and men at high risk for fracture and for glucocorticoid-induced osteoporosis in men and postmenopausal women. PTH is indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.[86]

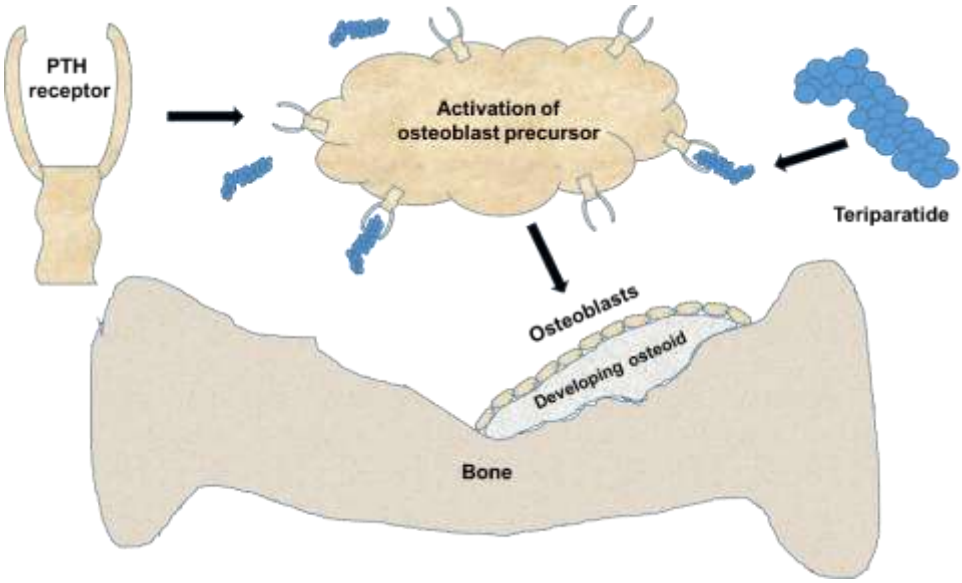


Figure 15: Schematic view for MoA of teriparatide

### 7.16.4. Patent Situation

The patents of Forteo® expired in US and Europe in August 2019. Ely Lilly accused Teva on infringing patents for preparing the market entry of its teriparatide biosimilar, which will be applied with a pen injector.

### 7.16.5. Market and Competitive Field

Full length PTH is marketed by Shire as Natpara®. The originator product of teriparatide, Eli Lilly's Forteo®, was approved by FDA in 2002 and EMA in 2003. In 2018, Forteo® had worldwide sales of 1.38 billion € and Natpara® of 202 million €. In contrast to PTH, biosimilars of teriparatide are already marketed, approved for market or in development.

## 8. Biosimilars on the Market

Despite regulatory hurdles resulting into a considerable financial investment to develop a biosimilar product for market release, there are now nevertheless for nearly every originator biomolecule having commercial success an increasing number of biosimilars approved or in development. The milestone for each biosimilar developing company (more than 1,000 entities world-wide) is the due date for expiration of the major patent (families) from the originator drug (including claims related to the sequence of

 

the gene or protein). Furthermore, in-use, formulation or clinical development patents may also delay marketing of biosimilars.

As of due date September 2019, the following biosimilars were approved on the US market (Table 5) and on the EU market (Table 6).

Table 5: Biosimilars approved in US

| **Product name** | **Manufacturer** |
|---|---|
| **Adalimumab** | |
| Amjevita® | Amgen |
| Cyltezo® | Boehringer Ingelheim |
| Hadlima® | Samsung Bioepis, Biogen |
| Hyrimoz® | Sandoz |
| **Bevacizumab** | |
| Mvasi® | Amgen, Allergan |
| Zirabev® | Pfizer |
| **Epoetin alfa** | |
| Retacrit® | Pfizer, Hospira |
| **Etanercept** | |
| Erelzi® | Sandoz |
| Eticovo®j | Samsung Bioepis, Merck |
| **Filgrastim** | |
| Nivestym® | Pfizer |
| Zarxio® | Sandoz |
| **Infliximab** | |
| Inflectra® | Pfizer, Hospira |
| Ixifi® | Pfizer |
| Renflexis® | Samsung Bioepis |
| Avsola™ | Amgen |
| **Insulin** | |
| Admelog® | Sanofi |
| Basaglar® | Eli Lilly, Boehringer Ingelheim |
| **Pegfilgrastim** | |
| Fulphila® | Biocon, Mylan |
| Udenyca® | Coherus |
| **Rituximab** | |
| Truxima® | Celltrion |
| Ruxiene® | Pfizer |

 

| **Product name** | **Manufacturer** |
|---|---|
| **Trastuzumab** | |
| Ogivri® | Biocon, Mylan |
| Ontruzant® | Samsung Bioepis |
| Herzuma® | Celltrion |
| Trazimera® | Pfizer |
| Kanjinti® | Amgen |

Table 6: Biosimilars approved in EU

| **Product name** | **Manufacturer** |
|---|---|
| **Adalimumab** | |
| Amgevita® | Amgen |
| Solymbic® | |
| Cyltezo® | Boehringer Ingelheim<br>Not marketed |
| Imraldi® | Samsung Bioepis |
| Halimatoz®/Hefya®/Hyrimoz | Sandoz |
| Hulio® | Mylan |
| Idacio®/Kromeya® | Fresenius |
| **Bevacizumab** | |
| Mvasi® | Amgen |
| Zirabev® | Pfizer |
| **Enoxaparin sodium** | |
| Inhixa® | Techdow Europe |
| Thorinane® | Pharmathen |
| **Product name** | **Manufacturer** |
| **Epoetin** | |
| Abseamed® | Medice Arzneimittel Pütter |
| Epoetin alfa Hexal® | Hexal |
| Binocrit® | Sandoz |
| Retacrit® | Hospira |
| Silapo® | Stada Arzneimittel |
| **Etanercept** | |
| Benepali® | Samsung Bioepis |
| Erelzi® | Sandoz |

 

| **Product name** | **Manufacturer** |
|---|---|
| **Filgrastim** | |
| Accofil® | Accord Healthcare |
| Biograstim® | CT Arzneimittel |
| Filgrastim Hexal® | Hexal |
| Filgrastim Ratiopharm® | Ratiopharm |
| Ratiograstim® | |
| Grastofil® | Apotex |
| Nivestim® | Hospira/Pfizer |
| Tevagrastim® | Teva |
| Zarzio® | Sandoz |
| **Follitropin alfa** | |
| Bemfola® | Finox Biotech |
| Ovaleap® | Teva |
| **Infliximab** | |
| Flixabi® | Samsung Bioepis |
| Inflectra® | Hospira |
| Remsima® | Celltrion |
| Zessly® | Sandoz |
| **Insulin** | |
| Abasaglar® | Eli Lilly, Boehringer Ingelheim |
| Insulin lispro® | Sanofi |
| Lusduna® | MSD |
| Semglee® | Mylan |
| **Pegfilgrastim** | |
| Pelgraz® | Accord (Intas) |
| Udenyca® | Coherus |
| Fulphila® | Biocon / Mylan |
| Pelmeg® | Cinfa / Mundipharma |
| Ziextenzo® | Sandoz |
| Grasustek™ | Juta Pharma |

 

| Product name | Manufacturer |
|---|---|
| **Rituximab** | |
| Blitzima® | Celltrion |
| Ritemvia® | |
| Rituzena® | |
| Truxima® | |
| Rixathon® | Sandoz |
| Riximyo® | |
| **Somatropin** | |
| Omnitrope® | Sandoz |
| **Teriparatide** | |
| Movymia® | Stada Arzneimittel |
| Terrosa® | Gedeon Richter |
| **Trastuzumab** | |
| Herzuma® | Celltrion |
| Ontruzant® | Samsung Bioepis |
| Kanjinti® | Amgen |
| Trazimera® | Pfizer |
| Ogivri® | Mylan |

## 9. Biosimilar Markets Worldwide

In addition to Australia, Canada, US, Europe, Japan, New Zealand, and South Korea, there is also a market in a few developing countries. Biosimilars developed and approved in countries such as China and India might not have been authorized following the strict regulatory process required for approval in the EU and US. EMA and FDA requirements demand a rigorous comparability assessment with the reference product. The companies, which have developed similar biologics primary for their home markets also try to sell their products in other not strictly regulated countries as well. An overview of selected companies working on local markets in developing countries is presented in Table 7.

 

Table 7: Selected companies working on local markets

| |
|---|
| **Argentina**<br>Biosidus, Gema / Amega Biotech, Laboratorio Elea |
| **Brazil**<br>Bionovis, Cristalia, Eurofarma Laboratórios |
| **China**<br>Alphamab, Bio-Thera, Generon Corporation, Geneluk, Gene Science, Genova, Jiangsu T-mab BioPharma, Luye Pharma Group, MabTech, Qilu Pharmaceutical, Shanghai Celgen Bio-Pharmaceutical, Shanghai CP Guojian Pharmaceutical, Shanghai Henlius Biotech, Shanghai Zhangjiang Biotechnology, Sunshine Guojian Pharmaceutical, Suzhou Genemen Biotech, Tianjin SinoBiotech, Zhongkai |
| **Egypt**<br>MinaPharm |
| **India**<br>Aurobindo, Biocon, Zydus Cadila, Cipla, Claris Life Sciences, Dr. Reddys, Emcure, Glenmark Pharmaceuticals, Hetero, Intas, Lupin, Torrent Pharmaceuticals, Ranbaxy Laboratories, Reliance Life Sciences, USV, Zenotech Laboratories |
| **Iran**<br>Aryogen, CinnaGen, Pooyesh Darou Biopharmaceutical |
| **Mexico**<br>Probiomed |
| **Russia**<br>Biocad, IVFarma |
| **Thailand**<br>Siam Bioscience |
| **Vietnam**<br>Nanogen Biopharmaceutical |

Not unexpectedly, most of these biosimilar developing companies are located in China, India and Latin America – countries, which have huge populations, sustainable markets and a high medical need. From all these countries, companies in India seem to be the most advanced. Some of the biosimilar products from India already got approvals in EU or US:

- Filgrastim: Accord Healthcare (Intas, India)
- Pegfilgrastim: Biocon, India; (with Mylan, US)
- Trastuzumab: Biocon, India (with Mylan, US)
- Pegfilgrastim: USV (India)

Even in developing countries, the market for certain biosimilars seems to be overcrowded. For example, in India, there are (at least) eight local companies with biosimilars for filgrastim on the local market.

 

For the blockbuster antibody rituximab, worldwide almost 50 companies are developing this drug in parallel. This huge run to the market will show how originator companies and, if applicable, governmental price finding institutions will react to this. In Northern European countries higher market penetration and individual changes (switches, interchangeability) with little governmental regulation was already observed.

## 10. Further Potential Targets for Development of Biosimilars

There are other groups of biomolecules, for which biosimilars are in development, but only to a small extent. One of these group are enzymes used for the treatment of rare diseases such as lysosomal storage disorders (Enzyme Replacement Therapy, ERT). Because these diseases are very rare with only hundreds to thousands of persons affected worldwide the market it very small and thus not very attractive for biosimilar developers.

One example is agalsidase alfa and agalsidase beta for the treatment of Fabry disease.[87] Fabry disease is an X-linked lysosomal storage disease. It is caused by deficiency of the enzyme α-galactosidase A (α-Gal A) leading to excessive deposition of neutral glycosphingolipids in cells. In November 2018, JCR Pharmaceuticals has launched its biosimilar agalsidase beta in Japan. JCR developed the drug in partnership with Amicus Therapeutics and GlaxoSmithKline. Currently there are no plans for marketing in EU and US. Similarly, Fabagal® is available from Isu Abxis, South Korea.

ERT is also the first-line treatment for Gaucher disease (GD). Cerezyme® (imiglucerase) was approved by the FDA in 1994. Patents have expired allowing the development of non-originator biological products, however, the three currently available enzymes are distinct molecules and were registered as new products, not biosimilars (Revel-Vilk 2018).[88]

In Mexico, the imiglucerase Asbroder® (in other countries trade name Abcertin®[89]) has been approved for the treatment of GD. In Russia, Glurazyme® from Generium is available on the market.

Another group of biomolecules as a potential target for the development of biosimilars can be found in the sector of blood molecules or coagulation factors, especially in hemophilia. Currently, there are no biosimilar medicines licensed for the treatment of hemophilia. The reasons for the lack of biosimilar developments in this case are different to lysosomal storage disorders. For factor VII and IX concentrates, there are already many different products on the market or in the pipeline. Next-generation products and biobetters will replace the current factor concentrates rather than biosimilar products.[90] They receive approvals rather based on trials and (bio) analytical studies comparing them with a prior established reference product.

On the other hand, in developing countries most often plasma derived products are used for treatments. Only a few local companies develop similar biologics for their own markets and export to other developing countries. Recombinant factor VIIa (rFVIIa) is one example for this scenario. The most commonly used rFVIIa is eptacog alfa (trade name NovoSeven®, NovoNordisk), and for this originator a biosimilar is marketed in Iran by AryoSeven.[91]

## 11. Conclusion

In general, the biosimilar market is steadily expanding and for some originator molecules such as adalimumab the market is already very competitive and complex. Other markets will be soon very crowded as well.

 

In US and Europe, the cost-saving potential of biosimilar medicines are not yet fully exhausted by health care providers and the next few years will be very exciting in respect of how the market sales of originator products will be erased by biosimilars. It is not yet clear how many companies can have finally commercial success within crowded competitive fields of certain originator products such as adalimumab. Patent litigation is in some cases a possibility to defend the market of the originator. To reduce costs in developing countries, own biosimilars are already manufactured and marketed for example in Asia and South and Middle America. In these regions, more products will be seen on the market in the next few years. We are now entering into the period of biosimilar development, in which the first patents of blockbusters have been already expired and others will follow in the next few years. In Europe, regulatory agencies have 14 years of experience with biosimilars and their advice is in many cases valuable for other markets as well. Nobody can predict what exactly will happen in the different market regions, but this decade will give us at least a lot of answers and maybe lead to new directions in the development of biosimilars.

 

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