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Report

Sector inquiry

TNF-alfa inhibitors

Competition before and after entry of biosimilars

Markten goed laten werken voor mensen en bedrijven

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Sector inquiry TNF-alfa inhibitors

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Management summary

ACM Sector Inquiry on competition with TNF-alfa inhibitors

In 2018-2019 the ACM took the initiative to examine the competition of TNF-alfa inhibitors in a sector study. TNF-alfa inhibitors are biological drugs that are mainly used for rheumatism patients, but also for psoriasis and Crohn's disease, for example. They constitute the category of medicines with the greatest budget impact in the Netherlands in recent years. In 2016, TNF-alfa inhibitors represented a total turnover of € 517 million and are used by 50,000 patients a year in the Netherlands. The costs per patient per year in the study period amount to approximately € 11,000.

At present, a total of five active substances are involved and some 13 drugs based on them, including the biosimilars (generic biological medicines), are now in use. Between 2015 and 2018, the patent on the active ingredient for three TNF alpha inhibitors expired, allowing biosimilars to enter the market. There are usually still secondary patents, for example on the excipients.

Despite the number of active ingredients and the introduction of biosimilars, the list prices of TNF-alfa inhibitors remained at a relatively high level for a long time, while the uptake of biosimilars remained low compared to, for example, biosimilars of oncological medicines. This prompted the ACM to investigate the effect of competition in the drug group TNF-alfa inhibitors before and after the expiry of patents on the active substances. The ACM distinguishes two forms of competition in this respect:

I. Competition between different active ingredients
II. Competition within active substances through biosimilars

Competition within the active ingredient is only possible after the expiry of the patent on the active ingredient. Competition between different active ingredients is possible both before and after the expiry of patents.

Through its sector research, the ACM wants to contribute to a well-functioning market in TNF-alfa inhibitors for people and companies. In addition, the sector research offers general lessons with regard to the market dynamics of biological medicines that fall under the hospital budget. In this report, the ACM presents its observations from the sector inquiry without a competition-law qualification, with regard to the market definition to be applied, dominant positions or abuse. This does not preclude the ACM from using the data from the sector inquiry in concrete cases as input for a legal assessment.

Main conclusions of the sector inquiry

1. *In the period before the expiry of the patents, price competition between different active ingredients was limited*

The ACM observes that the net purchase prices paid by hospitals for TNF-alfa inhibitors hardly fluctuated prior to the expiry of the patents on the active ingredient and that these net purchase prices were on average marginally below the pharmacy purchase price. An important part of the explanation for this limited price competition is the medical practice that existing patients are not transferred to another active ingredient without medical considerations. In view of the often chronic use of TNF-alfa inhibitors, this practice severely limits the scope for competition.

2. *Competition from biosimilars results in substantially lower net purchase prices of TNF-alfa inhibitors.*

After the expiry of the patent on the active ingredient of three originators and the market introduction of biosimilars, discounts for hospitals amount to more than 70% of the list prices of the medicines with the same active ingredient. However, the speed and extent of the price reductions vary from one TNF-alfa inhibitors to another. For the first TNF-alfa inhibitors to be patented in 2015 (infliximab), the price decrease was initially gradual and eventually amounted to 60%. The price of the most recently patented product (adalimumab) fell even more sharply shortly after the introduction of the biosimilar.

The gradually increasing price competition can also be explained by the fact that the prescribing specialists and their scientific associations were initially reluctant to switch existing patients from an originator to a biosimilar of the same active ingredient. Under the influence of medical studies, among other things, there is now a consensus that existing patients can also be switched responsibly.

3. The market share of biosimilars lags behind with subcutaneous administration.

Despite the price pressure exerted by biosimilars, the market share of biosimilars is lagging behind in some cases. In two of the three TNF-alfa inhibitors for which biosimilars are available on the market, the originator has managed to remain by far the largest supplier for the time being. There are several possible explanations for the limited entry of biosimilars.

First of all, switching patients to another drug involves a costly effort for the hospital. This is particularly true for drugs that are administered by the patient himself using a lancing pen (subcutaneously). Patients have to be informed and get used to another lancing pen. Hospitals therefore do not achieve a complete changeover of 100% with these drugs. Per hospital, a rest population of about 5-20% of the patients usually lags behind the originator. Moreover, the switching costs offer the originator a structural advantage: with the same net prices between originator and biosimilar but with extra costs for switching, the hospital will continue to opt for the originator.

Another possible explanation for the limited entry of biosimilars is the conditional discounts applied by originators. Such a discount system encourages the hospital to continue to use the originator for a large proportion of patients. If a hospital does want to switch to a biosimilar, it will pay a much higher price for the group of patients who are unwilling or unable to switch.

This is because the discount on the list price when switching is no longer valid in its entirety and the original drug for the rest of the population is still needed. This can also make the switch to a biosimilar financially unattractive for the hospital, even though the biosimilar manufacturer offers a lower net purchase price than the originator.

What can hospitals do?

Purchasing hospitals play a crucial role in creating a level playing field in the markets for biological medicines, whether or not through a purchasing cooperation agreement. During the study, the ACM identified several good practices that deserve to be followed up. These good practices are:

I. **Equal Opportunity Procurement**: Creating a tender process with fair opportunities for all suppliers. This in any case includes a clear tender process with clear rules that are also enforced.
II. **A well-designed preference policy** to take advantage of the scope for competition when prescribing to new patients in the event of medical equivalence of different active ingredients. A large majority of hospitals are already working on this to a greater or lesser extent.

What can health insurers do?

The contracts between health insurer and hospital are crucial for the financial incentives that hospitals experience in their purchasing policy. The ACM notes that health insurers have different views about their role, particularly with regard to contributing to competition in the market between originators and biosimilars.

The ACM also sees that taking an active role by health insurers can contribute to a healthy market structure with long-term competition from biosimilars. A number of health insurers, for example, offer higher reimbursements for biosimilars in specific cases than for originators. Health insurers can further fulfil this guiding role by:

I. **Compensation, at least temporarily, for the originator's *first-mover advantage*.** This may take the form of a (temporary) higher fee for the biosimilar, for example. In this way, hospitals can reduce the extra costs associated with a switch - which may include having to pay the list price for the residual population - financing.

II.**Further improve incentives for efficient procurement and use of medicines.** The ACM sees that health insurers are actively considering the incentives that come from their fees for effective purchasing. The ACM encourages health insurers to continue to do so. Forms of shared savings between health insurers and hospitals can make a positive contribution to appropriate use and the elimination of margin differences, which encourage hospitals to prescribe more expensive drugs with higher margins.

What can the government do?

Originators may threaten that if a hospital switches to another drug, the list price will have to be paid for the rest of the population. The greater the difference between the actual net purchase price (the average price per daily dose for a particular drug that the hospital charges on the basis of the actual volume purchased) on the one hand and the pharmacists' purchase price (AIP price) on the other hand, the greater the degree of the threat. The AIP price is capped by the Medicines Pricing Act (WGP)-max price, which in turn is based on reference prices from a number of neighboring countries.[1]

A large difference between the WGP-max price and the net purchase price (such as 50% or more) gives the originator the concrete opportunity to use this price difference as a lever vis-à-vis the hospitals.

The ACM therefore recommends that the Ministry of Health, Welfare and Sport adjust its price regulation on this point in order to reduce the threat of high prices for the rest of the population - and thus the risk of exclusion of biosimilars.

What will the ACM do now?

The findings of this sector study have prompted the ACM itself to make an active contribution to creating a more level playing field between originator and biosimilar medicines. The ACM will pay particular attention to those situations in which the originator has a strong competitive advantage over the biosimilars. Switch costs, the existence of a rest population and the related preference of hospitals to stay with the originator at comparable prices play an important role in this.

In particular, the ACM considers that the practice of offering conditional discounts by originators to hospitals may under certain circumstances be restrictive of competition. Where practices with a potential exclusionary effect are identified, the ACM examines these signals and takes enforcement measures where appropriate.

[1] Without a contract with the pharmaceutical manufacturer, the hospital in principle pays the pharmacists' purchase price (AIP), also known as the list price. The list price charged by the manufacturer is limited by the WGP-max price (Maximum Price of Medicines Act). This WGP-max price is established on the basis of list prices in a number of surrounding countries.

The research
The ACM started this sector inquiry in the summer of 2018. The research focused on the drug group TNF-alfa inhibitors. This includes five active ingredients. In addition, the study also paid attention to other biological medicines that may be substitutes for TNF-alfa inhibitors for rheumatoid arthritis patients, such as IL (interleukin) inhibitors, B&T cell inhibitors and JAK inhibitors. The investigation focused on the Dutch market.

First of all, approximately 30 Dutch hospitals (and the purchasing groups to which they may have belonged) were questioned in writing, among other things about net prices paid per drug between 2012 and 2018, contract conditions, sales per drug, and the purchasing process. This data request was limited to the three most important TNF-alfa inhibitors (infliximab, etanercept and adalimumab) and one interleukin inhibitor (rituximab).

After the data request, oral interviews were conducted with six hospitals. Five health insurers were interviewed by telephone or in person. The insurers' reimbursement prices were partly requested from them and partly taken from Vektis data. The pharmaceutical companies of both originator and biosimilar TNF-alfa inhibitors were questioned in writing.

In the course of the study, interviews were also held with various stakeholders, including patient associations, sector organisations of hospitals, hospital pharmacists and the industry, NZa and the Ministry of Health, Welfare and Sport.

Accountability for data use
In chapter 3 the ACM presents the charts of the editions to the different TNF-alfa inhibitors. These are based on the net purchase prices of all hospitals surveyed. That is to say: these charts are ultimately based on the total expenditure of a hospital per drug divided by the number of daily doses of that drug that are provided in the hospital in question, and this per year. So also the volumes are included. Subsequently, the relevant data were further aggregated by always taking the net purchase prices of all hospitals that take the drug as an average. The exact discounts per hospital and per drug are therefore not visible, but the trends are.

Because the underlying data may be confidential in nature, the ACM has carried out the above operations, as a result of which the data concerned can no longer be traced. As a consequence, the publication of the graphs does not unduly favour or disadvantage market participants. Moreover, in this case the ACM has a major interest in publication. The graphs provide the reader of the report with a better understanding of the interaction between market participants, market trends and past entry, including the apparent effects on price and market share. This is important in order to be able to present the results of the sector inquiry effectively and transparently**.**

1. Introduction

1.1 Purpose and Background

In June 2018 the ACM announced a sector inquiry into the market for TNF-alfa inhibitors, a type of drug used to treat rheumatism and a number of other common auto autoimmune diseases. TNF-alfa inhibitors are expensive medicines that are used chronically by large numbers of patients. In the Netherlands, expenditure per patient amounts to approximately € 11,000 per year.[2] With about 50 thousand patients, the total expenditure on TNF-alfa inhibitors in 2016 amounted to almost € 550 million.

At the start of the investigation, the ACM had no concrete indications of possible violations of competition law with regard to TNF-alfa inhibitors. However, there were general indications that the market in this sector did not function optimally. Two observations in particular gave rise to a further mapping of this market:

- Although there are various alternatives for patients, the prices at which these drugs are put on the Dutch market (the list prices) remain relatively high.
- Where patents on drugs have expired, entrants have not in all cases gained a firm foothold.

The aim of the study is to map out whether and how the competition with regard to TNF-alfa inhibitors works, where any obstacles lie and how these can be solved. By answering these questions, the ACM wants to give the impetus to an improvement of the competition in the field of TNF-alfa inhibitors and of the market structure.

This is important because the budget impact - the share of this drug group in the total expenditure on drugs - is large. The removal of barriers to competition in these market(s) will potentially lead to major savings for the health care sector if this ultimately leads to price reductions. In addition, the lessons learned from this research are relevant to competition in extramural biological medicines in general.

1.2 Research questions and reading guide

In the sector inquiry, the ACM asked itself the following questions:

- What room is there, on the basis of medical interchangeability, for competition with regard to TNF-alfa inhibitors?
  a) between the various active ingredients; and
  b) between originators and biosimilars of the same active substance.
  This question will be discussed in Chapter 2.
- Is there actual (effective) competition and what impact does this have on the development of the prices of these medicines? This is the subject of chapter 3.
- How can any difference between the (theoretical) scope for competition and actual competition be explained? What is the role of the various actors within the system: manufacturers (originators and producers of biosimilars), hospitals, specialists, health insurers and the government? This is the subject of chapter 4.

Finally, in Section 5, the ACM examines how competition can be strengthened between different market players, the role of regulation in this respect and how the ACM itself can contribute to more effective competition.

[2] Figures for 2016, Source: NZa 2019: Monitor of medicines in specialist medical care, p. 15.

1.3 Delimitation of the investigation

The drug group TNF-alfa inihibitors is central to this research. There are currently five different active substances in the group of TNF-alfa inhibitors: adalimumab, etanercept, infliximab, golimumab and certolizumab pegol. The sector research focuses on the first three products. These represent the largest turnover. The patents on all three of these active ingredients expired between 2015 and 2018. They have different forms of administration, especially lancing pens (subcutaneous administration) or infusions (intravenous administration).

Table 1.1 TNF-alfa inhibitors

Active ingredient	Originator - manufacturer (brandname)	Administration	Trade license in The Netherlands	1st biosimilar On market	Number of biosimilars in 2018	AIP-price** 2018 / patient/ year
Infliximab*	MSD (Remicade)	Intravenous	1999	2015	4	€ 8.245
Etanercept*	Pfizer (Enbrel)	Subcutaneous	2001	2016	1	€907
Adalimumab*	Adalimumab (Humira)	Subcutaneous	2003	2018	4	€ 13.231
Certoluzimab Pegol	UCB (Cimzia)	Subcutaneous	2009	N/A	N/A	€ 12.071
Golimumab	Janssen (Simponi)	Subcutaneous	2009	N/A	N/A	€ 12.700

* For these drugs, the ACM has done data analysis in this study.
** This is the AIP price of the originator per patient per year. The price is rounded off to the nearest euro. The amount in the table is a calculation based on the AIP price for a certain dosage.

In addition to the five TNF-alfa inhibitors, the ACM has also looked at possible therapeutic alternatives with a different mechanism of action. These are other biological drugs such as B&T cell inhibitors and IL inhibitors, and other synthetic drugs such as JAK inhibitors. A number of these drugs can also be used for the indications for which TNF-alfa inhibitors are used. The table below shows that there are currently a total of seven drugs with a different mechanism of action than TNF-alfa inhibitors that can be used for rheumatoid arthritis. There are a total of eight of these drugs for which at least one indication overlaps with an indication for which TNF-alfa inhibitors have been registered.

In addition to qualitative research, the ACM has also applied data analysis to four drugs within the group of TNF-alfa inhibitors and the therapeutic alternatives. This concerns the three largest TNF-alfa inhibitors infliximab, etanercept and adalimumab, and the B-cell inhibitor rituximab. In terms of turnover, rituximab is the largest drug in the group with a different mechanism of action, and the only drug in this group that is off-patent.

Table 1.2 Potential therapeutic alternatives for TNF-alfa inhibitors

Mechanism of Action	Amount of originators	Administration	Amount with registration for RA	At least 1 overlapping indication with TNT-alfa inhibitors	Amount with biosimilars on the market
B&T-Cell inhibitors	3	Infusion	2	2	2 for drug rituximab
Interleukin-inhibitor	5	Subcutaneous	2	4	0
JAK-inhibitors	2	Oral	2	2	0[3]
Total	**10**		**7**	**8**	**2 for rituximab**

The research focuses on the Dutch market. Given the particularities of the national funding system, it is likely that the Netherlands is a separate geographic market. Although manufacturers of the medicines in question are based outside of the Netherlands and operate worldwide, they negotiate for the Dutch market with specific teams per hospital or group of hospitals.

In this report, the ACM presents its observations from the sector inquiry without attaching any competitive qualification to them, for example in regards to the market definition to be applied, dominant positions or abuses of dominant positions.[4]

1.4 Supply, reimbursement and price regulation of intramural medicines

TNF-alfa inhibitors and the possible therapeutic alternatives referred to above are intramural medicines or medicines in specialist medical care.[5] In other words, the prescription of these medicines and their financing are provided by the hospital. The pharmaceutical manufacturer supplies the drug to the hospital - whether or not through the intervention of a wholesaler or licensee. Hospital prescribers prescribe the medicines to the patient. Administration can take place both inside and outside the hospital. This depends on whether the drug is administered by infusion or by means of a lancing pen.

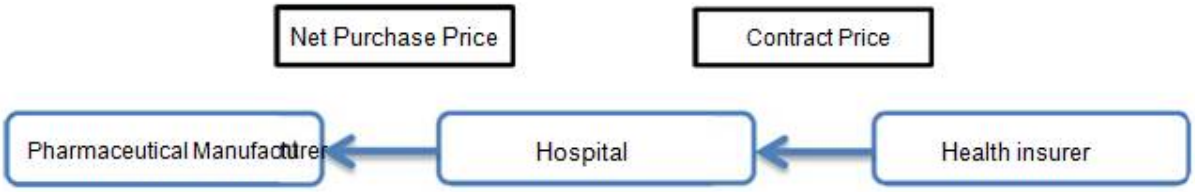
Figure 1.1 Physical delivery of intermural medicines

Hospital purchase price and maximum price

In the relationship between the hospital and the manufacturer, the net purchase price (NIP) is ultimately the most important factor. This is the actual transaction price that is established after negotiations or through a tender and that includes, for example, discounts based on realised volumes. If there is no contract between the hospital and the manufacturer, the manufacturer's list price, also known as the pharmacy purchase price (AIP), applies. The AIP is limited by the maximum price that the manufacturer may charge on the basis of the Medicines Pricing Act (WGP-max). The WGP-max is based on a basket of reference prices in four other European countries.[6]

[3] Since JAK inhibitors are not biological medicines, biosimilars are by definition not involved. However, there are no other generic versions of these relatively new drugs either.
[4] This does not preclude the ACM from using the data from the sector inquiry in concrete cases where such legal qualifications are made.
[5] This has been the case since 2012. In that year, the TNF-alfa inhibitors were transferred from extramural to intramural.
[6] The reference countries in the examined period were Belgium, Germany, France and the United Kingdom. Germany will soon be replaced by Norway.

Figure 1.2 Remuneration intramural medicines



Contract price from the health care insurer to the hospital

For the hospital, in addition to the net purchase price (NIP) that it pays to the manufacturer on the expenditure side, the reimbursement that the hospital receives from the health insurer on the income side is also important. The reimbursement for the purchase of medicines that are reimbursed individually is part of the contract negotiation between the health care insurer and the hospital, and is limited by the so-called NZa-max rate per resource.[7] This NZa-max rate is based on the manufacturer's list price referred to above (but including VAT) and is therefore in turn limited by the WGP-max rate. This limit works as follows: if the WGP-max increases over time as the prices in the reference countries rise, the NZa-max does not increase. However, the NZa-max can decrease.

Summary of prices

Table 1.3 summarizes the above mentioned prices. The actual prices paid are the net purchase price (from hospital to manufacturer) and the reimbursement price (from healthcare insurer to hospital). The list price used by the manufacturer is the pharmacist's purchase price (AIP). This price is determined unilaterally by the manufacturer. Hospitals pay this list price if they do not have a contract or if they have not stipulated discounts in the contract. This list price is legally limited by the WGP-max price. The remuneration price is limited by the NZa-max price.

Table 1.3 Prices intramural medicines

Payment Stream	Transaction Price	List Price	Legal limit
A. Hospital > Manufacturer	1.Net Purchase Price (NIP)	2. Pharmacist purchase price (AIP) or List price	3. WGP-max
B. Health insurer > hospital	4. Remuneration price	N/A	5. NZa-max

1.5 Biological medicinal products

TNF-alfa inhibitors and their therapeutic alternatives are biological drugs.[8] Biological drugs are made on the basis of living organisms and have a much larger and more complex molecular structure than synthetic drugs. Other important characteristics of biological drugs are:

- Complex and long production process - the average production time of the drugs in this study is over 6 months.
- Limited shelf life - depending on the specific drug, drugs treated in this sector inquiry have a shelf life of between 2 and 5 years.
- Administration - These drugs are usually administered via an infusion (intravenous) or subcutaneous (self-administration with a lancing pen). Each subcutaneous branded drug has its own lancing pen.

These characteristics of biological medicines have implications for the operation of competition. For example, compared to synthetic drug manufacturers, biological drug manufacturers have higher production costs and a higher risk of stockpiling.

[7] Hospitals may charge health insurers for TNF-alfa inhibitors and many other expensive medicines separately from the rates for treatment: these are the so-called add-on medicines. All medicines relevant to this research fall under the so-called expensive medicines. These are medicines that on average cost more than € 1,000 per patient per year. Medicines that do not fall under this category are fully reimbursed via the DBCs.
[8] JAK-inhibitors are an exception to this.

1.6 Biosimilars

After the expiry of the relevant patents, generic versions of the medicinal product may be placed on the market. In the case of biological medicinal products, these generic versions are called biosimilars. A biosimilar is largely the same as the biological medicine with a patent on the active ingredient (also referred to as the reference product), but not exactly the same. This also applies to the various production rounds - batches - of the original biological medicines. A common definition of a biosimilar is: a medicine without clinically significant differences with the reference product.[9]

[9] See for example Zelenetz (2016), Biosimilars in Oncology in Oncology & Hematology Review, 2016;12(1):22–8.

2. Medical interchangeability

Different medicines can only exert competitive pressure on each other if they are medically interchangeable. This section first discusses the interchangeability of different active ingredients, whereby the ACM distinguishes between interchangeability within the category of TNF-alfa inhibitors, and interchangeability between TNF-alfa inhibitors and biological medicines with a different mechanism of action. The interchangeability of different TNF-alfa inhibitors with the same active ingredient (originators and biosimilars) will then be discussed. Medical interchangeability does not mean that these drugs actually compete with each other: the extent to which competitive pressure from the various drugs translates into price pressure is the subject of chapter 3.

2.1 Medical interchangeability between different active substances

The extent to which different medicines are considered medically interchangeable is not fixed, but is determined in a field of power dynamics between a government that determines for which indications drugs are registered, medical-scientific associations and other bodies that make recommendations with regard to the interchangeability of medicines, hospitals and purchasing groups that develop policy on the basis of their own studies and literature studies and the preferences of individual prescribers and patients. Below, the ACM discusses the frameworks laid down at these various levels, and the conditions within which hospitals have room to determine their preference for a medicine on the basis of efficiency:

1. Registration: several drugs have been registered for the indication.
2. Medically substantive recommendation: the patient is a 'new patient'.
3. Medically substantive consideration by the hospital or the purchasing group: the hospital considers the resources to be equivalent.
4. Medically substantive consideration by the prescriber and the patient: they have no preference for a particular form of administration.

Requirement 1 Several drugs have been registered for the indication.

Two different active ingredients are rarely registered for exactly the same conditions. Within the gene therapy group TNF-alfa inhibitors, etanercept and adalimumab are the two active substances with the greatest overlap. Both for rheumatological conditions and dermatological conditions, these two products have similar registrations. However, Adalimumab is also registered for indications related to Gastro-intestinal and Liver Diseases (hereinafter: MDL) and ophthalmology. For these indications there is no overlap between adalimumab and etanercept. In the case of MDL, there is a large overlap between adalimumab and infliximab.

In this sector study, the ACM looked at 15 indications for which a TNF-alfa inhibitor can be used. All five TNF-alfa inhibitors are registered for the indications rheumatoid arthritis and psoriatic arthritis. For these indications, the doctor therefore has a choice of several registered medicines for a new patient. However, there are also 6 indications for which this choice does not exist because there is only one TNF-alfa inhibitor with a registration for this indication. An example of this is eye disease uveitis, for which only adalimumab can be used. Adalimumab is the only registered TNF-alfa inhibitor for a total of 3 indications, infliximab for 2 and etanercept for 1. In addition, there are 2 other indications for which there is only a choice of 2 TNF-alfa inhibitors. Furthermore, for use with specific target groups within a specific medical indication, such as children and pregnant women, often only one drug is registered.
The overlap between the indications of TNF-alfa inhibitor and other active substances with a different mechanism of action is much smaller. Of the 15 indications for which TNF-alfa inhibitors have been registered, B&T cell inhibitors, IL inhibitors and JAK inhibitors are only potential alternatives to the (albeit relatively large) indications of rheumatoid arthritis and psoriatic arthritis. Based on the indication registrations, there are 11 potential alternatives for rheumatoid arthritis and for psoriatic arthritis 8.

Requirement 2 New patient

The guidelines of the medical specialists who use TNF-alfa inhibitors state that patients who use a certain active ingredient cannot be put on another product without medical reason. All hospitals surveyed in the context of this sector inquiry confirm that they are also acting in accordance with this guideline. Medical reasons for transferring a patient are (i) limited effectiveness or (ii) relevant side effects. This means, therefore, that in practice hospitals only have the choice between different active ingredients at the time that a patient is new, when a patient has not yet been prescribed a TNF-alfa inhibitor.

The broad consensus on the practice of not transferring existing patients to other active substances limits the potential interchangeability of the various substances to new patients in particular. It is important to note that patients who use TNF-alfa inhibitors are, in general, chronic patients. Based on Vektis declaration data, the ACM concludes that approximately 80% of the patients who used infliximab, etanercept or adalimumab in a year used the same drug in the previous year. For this group of patients, the hospital does not have the room to make a choice based on efficacy.

Requirement 3 The hospital considers the resources to be equivalent.

Hospitals have their own medical policy in which they determine which medicines can be used for which indications. On the basis of their own additional literature review, for example, one hospital may come to the conclusion that drugs are medically equivalent while another hospital may find a particular drug inferior for a particular disorder. Guidelines from the professional group - for example from the Dutch Society for Rheumatology (NVR) and European League Against Rheumatism (EULAR)[10] - play a role in this. However, these guidelines are not decisive, if only because, for example, these guidelines are amended only once every ten years. In the meantime, new drugs are coming onto the market and the insights into, for example, the side-effects of specific drugs are getting better and better.

The NVR guideline from 2009[11] states that TNF-alfa inhibitor must first be used and that B&T cell inhibitors must only be used if the TNF-alfa inhibitor does not work sufficiently. The EULAR guideline from 2016 sets the various mechanisms of action (including the JAK inhibitors) at the same level. The hospitals with which the ACM spoke indicated that drugs with a different mechanism of action are generally only used if a TNF-alfa inhibitor is insufficiently effective. A number of hospitals indicated that experiences with the TNF-alfa inhibitors were an important factor in this respect. According to these hospitals, more is known about these drugs, including their side effects. According to these hospitals, this is an important consideration when using the newer TNF-alfa inhibitor (certolizumab pegol and golimumab) and drugs with a different mechanism of action only at a later stage.

Requirement 4 Prescriber and Patient have no preference for a particular form of administration.

Hospitals indicate that patients and prescribers often prefer subcutaneous administration to intravenous administration. This is why, for example, infliximab (which only has an intravenous administration) is hardly prescribed for new rheumatoid arthritis patients. (With the exception of patients who are unable to prick themselves or who have poor compliance, where an intravenous administration is recommended). The form of administration may also be a factor that may contribute to the use of JAK inhibitors, especially for rheumatoid arthritis and psoriasis. This is because JAK inhibitors are administered as tablets (i.e. via the mouth).

10 Smolen et al. (2017), EULAR Recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update.
11 NVR (2009), Diagnostics and treatment of rheumatoid arthritis, Van Zuiden Communications BV.

Room for choices based on efficacy

Looking at the first condition - the indications for which the drugs are registered - the impression is created that rheumatoid arthritis and psoriasis leave a lot of room for choice on the basis of their efficacy. However, the broad medical consensus on the practice of not transferring existing patients to another active substance strongly limits this scope. The extent to which hospitals use the remaining space to substitute drugs on the basis of efficacy considerations depends on the extent to which hospital pharmacists, professional groups and individual prescribers are in agreement about this interchangeability. In the summer of 2018, the ACM asked the hospitals about their current preferences for three important indications for which a TNF-alfa inhibitor could be used. In addition to rheumatoid arthritis and psoriasis, the ACM also asked about the preferred drugs for Crohn's disease. It is striking that for all three indications it applies that two active substances together form more than 90% of the indicated preservatives. It can be seen that for rheumatoid arthritis and arthritis, psoriatic drugs adalimumab and etanercept are the preferred drugs. For both indications, adalimumab and etanercept are preferred drugs approximately as often. For Crohn's disease, the preferred drugs are adalimumab and infliximab, with hospitals using infliximab as a preferred drug approximately twice as often as adalimumab.

Table 2.1 Preferred medicines per indication

Indications	Preferred medicines (with split)
Rheumatoid arthritis (rheumatology)	adalimumab and etanercept (50-50)
Arthritis psoriatic (dermatology)	adalimumab and etanercept (50-50)
Crohn Disease (MDL)	adalimumab and infliximab (35-65)

* This table lists (only) the two preferred medicines per indication, which together account for more than 90% of the preferred means.

The table above shows, on the one hand, that there is room for hospitals to make choices on the basis of efficacy, but, on the other hand, that in order to be able to make use of this room, collaboration between different departments is required - such as between rheumatology and MDL, and/or dermatology. After all, a hospital can shift more volume if the same or complementary choices are made for the various indications (such as adalimumab as a preferred drug for the three indications mentioned above or the combination of etanercept and infliximab as preferred drugs).

2.2 Medical interchangeability within an active substance

For both new and existing patients

Hospitals can use biosimilars for both new and existing patients. Where an existing patient is not put on another active substance without medical reason, a switch to a biosimilar without medical reason is possible. That is why hospitals have considerably more room to shift volume when biosimilars are available on the market. Until about 2015, the various professions were still reluctant to prescribe biosimilars for patients who already use an originator. This reluctance can be seen, for example, in the guideline for the Dutch Society for Rheumatology from 2014. In this guideline, switching existing patients to a biosimilar was still equated with a switch to another active ingredient.[12] The guideline therefore said not to switch existing patients. However, the guideline did state that new patients can be put on a biosimilar without any problem.

Much has now changed in the way rheumatologists - and other professions too - look at this. Discussions with hospitals have shown that the reluctance of a few years ago of doctors and pharmacists to prescribe biosimilars is largely over. This is confirmed in the ACM study by the reactions of both biosimilar manufacturers and hospitals. Both national experiences (e.g. the switch to infliximab and etanercept) and international experiences - including the authoritative Norwegian

[12] NVR (2014), Directive on the effective use of biologicals in rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis. 2014 update Dutch Society for Rheumatology.

Norswitch study from 2016[13] - have contributed to this. This shift can also be seen, for example, in the NVZA (Dutch Association of Hospital Pharmacists) Toolbox Biosimilars from 2017. The starting point is that switching is in principle possible and the NVZA mentions specific factors for not switching to a biosimilar.[14]

A number of hospitals indicate that some patients are still reluctant. Biosimilar producers also see restraint on the part of patients as a barrier, particularly in the case of subcutaneous drugs. Switching to a biosimilar means that the patient also has to use a different lancing pen, and patients may experience this as a barrier. At the same time, hospitals have the experience that with good guidance most patients make the transition without problems. "Reuma Nederland"(Rheumatism the Netherlands) indicates that communication and counselling are crucial. This interest group for rheumatoid arthritis patients is of the opinion that there should always be opportunities for patients not to make the switch. For some patients the transition would be too burdensome.

For all indications

Biosimilars are often registered for the same indications as the originators. This is due to the so-called extrapolation principle. If a biosimilar manufacturer demonstrates that a drug for one indication has no relevant clinical differences with the originator, the European Medicines Agency (EMA) assumes that this applies to all indications.

Conclusion

In view of the above, the medical interchangeability of originator and biosimilar is no longer in question.

[13] Jørgensen et al. (2017), Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial, Lancet; 389: 2304- 2316
[14] A practical guide for the successful implementation of biosimilars in specialist medical care.

3. The competitive pressure on TNT-alfa inhibitors

In the previous chapter, the ACM discussed substitutability on the basis of registrations, guidelines, its own policy and the preferences of hospitals and prescribers. In order to determine to what extent there is or has been competitive pressure between drugs for rheumatoid arthritis - both before and after patent expiry - the ACM investigated the net purchase prices paid by the hospitals and the volumes that are purchased. To this end, the ACM has collected from 30 hospitals (consisting of the 20 hospitals with the highest turnover for TNF-alfa inhibitors and 10 random other hospitals) the net purchase prices of the three largest TNF-alfa inhibitors in turnover (infliximab, etanercept and adalimumab) and the turnover-largest alternative with a different mode of action (the b-cell inhibitor rituximab). In addition, the ACM requested information from them about, among other things, the preferential policy and the policy with respect to biosimilars.

This chapter describes the results of this question. First of all, this shows that the prices at which most hospitals purchased TNF-alfa inhibitors in the period prior to the expiry of the patents on the original products were barely below the list prices. Secondly, after the expiry of these patents, the price of the active ingredient in question fell sharply. Particularly in the case of infusion agents (infliximab and rituximab), biosimilars are gaining a lot of market share in the sale of the active ingredient in question.

In etanercept and adalimumab - subcutaenously administered drugs - the market share of the biosimilars is lagging behind, although prices are falling sharply. The lagging market shares of biosimilars are due not only to the discounts offered by the originators for these products, but also to the fact that hospitals are unable to transfer some of the patients to a biosimilar. By doing so, they keep a rest population on the originator. Switching to a biosimilar costs a hospital more time and money with subcutaneous drugs. This gives originators of subcutaneous drugs a greater advantage over biosimilars.

The net purchase prices are reported per defined daily dose (DDD) in this chapter. This is a measure by which the costs of medicines with different active ingredients can be compared on the basis of costs per day.

3.1 List prices

The ACM investigation clearly shows that manufacturers do not compete on list prices. This is most evident in the list prices of biosimilar producers which in some cases are even higher than the list price of the originator before the entry of biosimilars. Manufacturers compete by giving a discount on the list price to the hospital, but not by lowering the list price itself.

Manufacturers have a number of strong incentives to keep the list price as high as possible, even when there are competitive means on the market:

- First, manufacturers can gain bargaining power vis-à-vis hospitals by offering discounts against the list price. Such discounts may be subject to conditions. A higher list price also allows a manufacturer to use individual discounts to discriminate between different customers and/or to make discounts conditional on the hospital's purchases (volumes).
- Secondly, the widespread use of reference prices - such as the WGP-max price - in different EU countries and even outside the EU provides an incentive to keep list prices high. A reduction in the list price in the Netherlands has the effect of lowering the prices in the other countries.

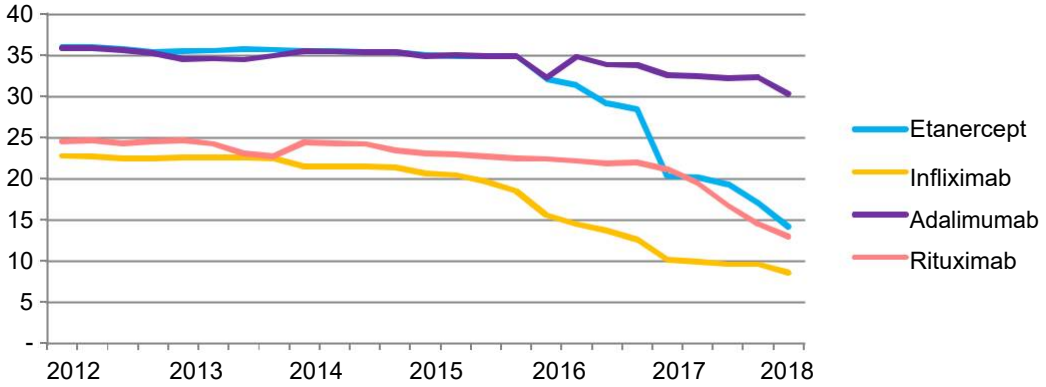
Even if high list prices are not charged as such, they can have a negative impact on competition and price levels in the sector. The ACM discusses this in more detail in chapter 4.

3.2 Competition between active substances

In the previous chapter it was described that the scope for competition between different active ingredients is limited by various factors, including the medical practice that existing patients are in principle not switched from one active ingredient to another. The ACM's study shows that hospitals have had limited success in using the remaining space to negotiate discounts. The figure below shows that the net purchase prices hardly changed until the entry of biosimilars. Moreover, these net purchase prices are very close to the list prices (not shown in the figure below). The price decreases only start when biosimilars are introduced on the market in 2015. This initially takes place at infliximab (2015).

Figure 3.1 Net purchase price / active substance

(Price in Euro/DDD)



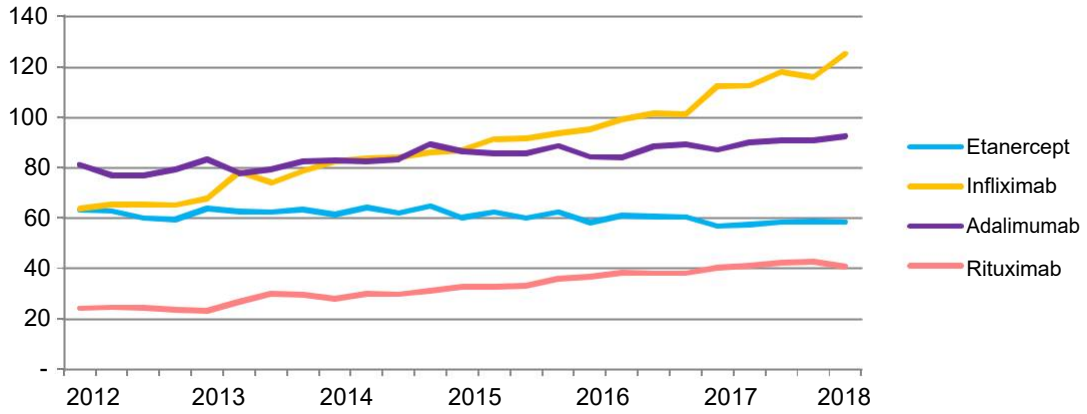
ACM analysis based on data requests at 30 Dutch hospitals. DDD stands for defined daily dose. This is a standardized measure with which costs per patient per day can be compared between different medicines.

It would appear that the various products that came onto the market during the same period also came onto the market at roughly the same price. Figure 3.1 shows that the net purchase prices of adalimumab and etanercept on the one hand and of rituximab and infliximab on the other hand are close to each other until the entry of biosimilars. The newer generation of products - etanercept and adalimumab - is more than 40% more expensive than infliximab and rituximab (see also table 1.1 in chapter 1). Etanercept and adalimumab were introduced 2 and 4 years respectively after infliximab).

After an active ingredient has gone off-patent, the prices of other active ingredients that have not yet gone off-patent also fall. The latter decrease to a much lesser extent than the prices of the active ingredient that has gone off-patent. This movement can be seen, for example, at the moment when etanercept is patent pending. Benepali, the biosimilar for etanercept, is used in Dutch hospitals from the second quarter of 2016. Until the first quarter of 2018, the price of etanercerpts decrease on average by 60%. During the same period, adalimumab - which is not yet off-patent - is already available for use in the Netherlands 10% to 15% cheaper. With the lower price of the originator product Humira, AbbVie anticipates in its pricing possibly already the accession of biosimilars for its active ingredient (adalimumab) in 2019. There are indeed a few hospitals that keep Humira as a preferred drug after 2016 and are able to negotiate some discounts with it. From 2016, more hospitals opt for new patients etanercept (lower price due to biosimilar competition) as their preferred drug.

The volumes of the various active ingredients appear to be developing independently of the net purchase price of the various active ingredients. It is precisely during the period in which, as a result of biosimilar entry, a large price difference arises between etanercept and adalimumab, for example, that the more expensive adalimumab is sold more often. Chapter 4 discusses possible explanations for this development. The figure below shows the development of the volumes of a fictitious hospital on the basis of the average volume developments at the 30 hospitals that supplied data on this subject to the ACM.

Figure 3.2 Development of number of patients per active substance in a fictitious hospital (Number of patients)



ACM analysis based on data requests at 30 Dutch hospitals.

The ACM did not request any data about the TNF-alfa inhibitors golimumab and certoluzimab. These products have been on the Dutch market since 2009. Both the turnover share and the patient share of these two drugs together (as a share of all 5 TNF-alfa inhibitors) were well below 10% in 2015 and 2016.

3.3 Biosimilar competition

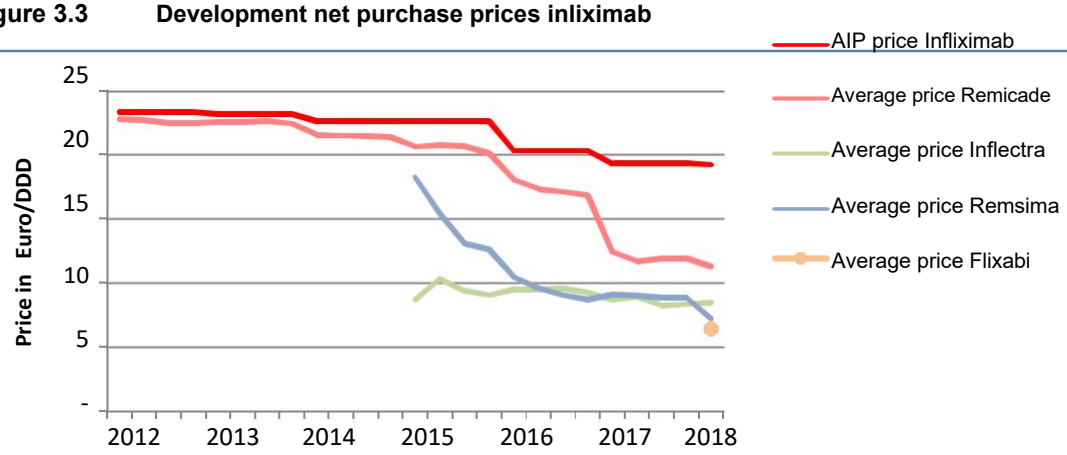
The developments with regard to biosimilar competition for the active substances for which biosimilars have come on the market are discussed below in chronological order.[15]

Infliximab

The active ingredient infliximab (originator remicade) is the first TNF-alfa inhibitor for which biosimilars have been introduced on the market. This happened in the first half of 2015. The figure below shows how the net purchase prices of infliximab developed. The AIP price is the same for all infliximab variants.

[15] The ACM has requested data up to and including the first quarter of 2018. The active ingredient adalimumab was not off-patent at that time.

Figure 3.3 Development net purchase prices inliximab



ACM analysis based on data requests at 30 Dutch hospitals.

The first biosimilar on the market is Inflectra by Pfizer. (This manufacturer is also the originator of the other active ingredient etanercept.) Inflectra entered the market in 2015 with a discount of about 60% compared to the list price of infliximab. The second biosimilar, Remsima (by manufacturer Mundipharma), initially gave a smaller discount, but the discount percentages have been close to each other since 2016. Flixabi (manufacturer Biogen) was launched in early 2018 with an even lower price (-70% compared to the price of Remicade in the first quarter of 2012). The price of Remicade is also falling in the meantime, but much later than the biosimilars. In the first quarter of 2018, Remicade's price is still more than 30% higher than that of the most expensive biosimilar for infliximab.

As can be seen in the figure below, Remicade loses a considerable part of the market due to the arrival of biosimilars. Both Remsima (Mundipharma) and Inflectra (Pfizer) have a higher market share than Remicade (MSD) in the first quarter of 2018.

Figure 3.4 Development of market shares of the active ingredient infliximab

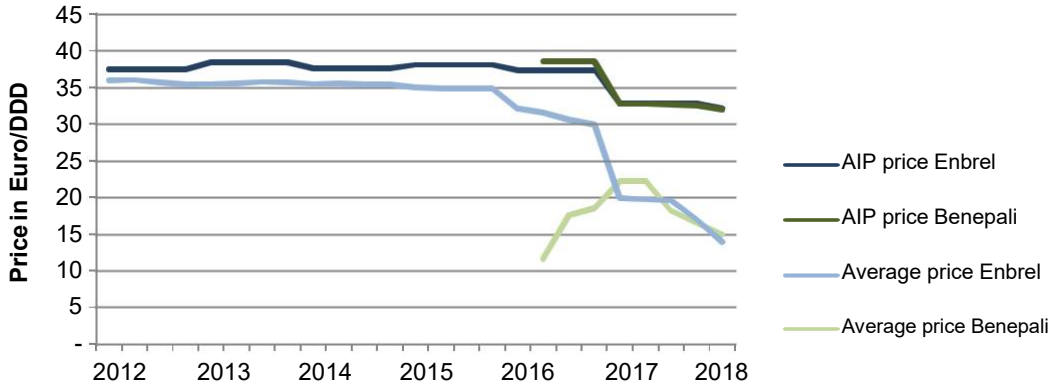
ACM analysis based on data requests at 30 Dutch hospitals

All hospitals surveyed by the ACM take a biosimilar for infliximab. More than half of these hospitals have fully switched to a biosimilar. These hospitals have been able to put all patients on the biosimilar over an average period of 6 months. There is therefore no residual population for these hospitals. Hospitals indicate that switching patients is relatively easy with this drug because it is an infusion that the hospital prepares itself. However, a number of hospitals indicated that they had monitored patients additionally for this drug during the switch, because for many hospitals it was the first switch to a biosimilar.

Etanercept

The second active substance for which at least one biosimilar has been placed on the market is etanercept. Pfizer - the manufacturer of the originator Enbrel - gave hospitals a limited discount when biosimilar Benepali (Biogen) was launched on the market in 2016. The discount on Benepali is initially almost 70% compared to the price of Enbrel. From 2017 onwards, the prices of Enbrel and Benepali will be closer to each other. The price of Enbrel fell sharply in the 3rd quarter of 2016, while the price of Benepali went up and fell again in 2017. Compared to Remicade at infliximab, Enbrel reacts more quickly to the lower price of the biosimilar. In addition to Biogen, Sandoz has now also registered a biosimilar with Erelzi on the Dutch market. So far, however, Erelzi has been able to gain limited market share.

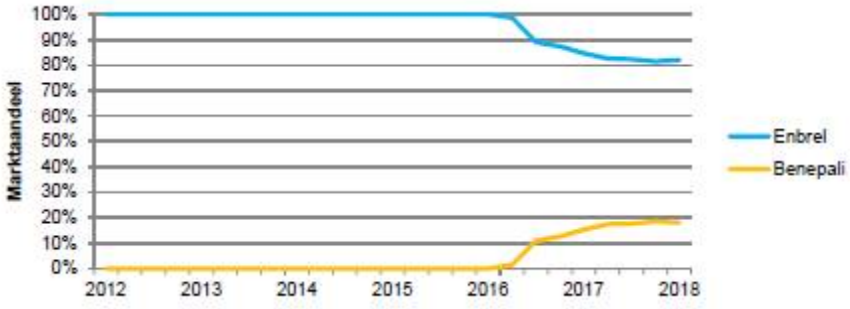
Figure 3.5 Development net purchase price etanercept



ACM analysis based on data requests at 30 Dutch hospitals

The average price of etanercept has fallen by almost 60% due to the arrival of biosimilars on the market. However, the average price per patient is still twice as high as the average price of infliximab. The price reductions achieved so far have only been combined to a limited extent with market share gains by the biosimilars. As can be seen below, Enbrel has managed to maintain a market share of over 80%.

Figure 3.6 Development market shares of the active substance etanercept



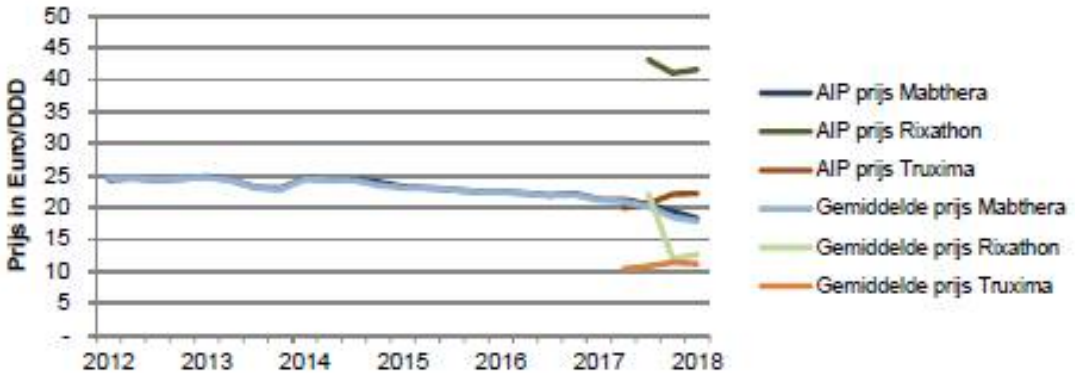
ACM analysis based on data requests at 30 Dutch hospitals

Eight of the hospitals surveyed by the ACM made the switch from Enbrel to the biosimilar Benepali. They have all transferred at least 50% of the patients to Benepali. Six hospitals have a transfer rate of 80%, of which one hospital has even transferred more than 90% of its patients from Enbrel to Benepali. There are also two hospitals that have transferred about 5% of their patients to Benepali. It seems that these hospitals only put new patients on the biosimilar. At the switch, all hospitals had to deal with a rest population of patients who could not be transferred to the biosimilar. Hospitals indicate that an important factor here is that patients administer their own etanercept with a lancing pen. Although most patients with the right support can make this switch, there is a small group of patients who cannot and/or do not want to go along with it.

Rituximab

Rituximab is the third of the products we investigated for which biosimilars have come on the market. Although the active ingredient has been off-patent in the European Union since February 2013, the biosimilars will not be on the market until 2017. The biosimilar manufacturers indicate that they could not enter the market earlier due to secondary patents. The Figure below shows that hospitals receive hardly any discount on Mabthera (from manufacturer Roche) when biosimilars enter the market. The biosimilar Truxima (by manufacturer Munipharma) will be launched on the market in 2017 with a discount of more than 50% compared to Mabthera's list price. Rixathon (from Sandoz) will follow later in 2017 with a price that will soon fall to Truxima's price level. Hereby, the biosimilars will gain a significant market share.

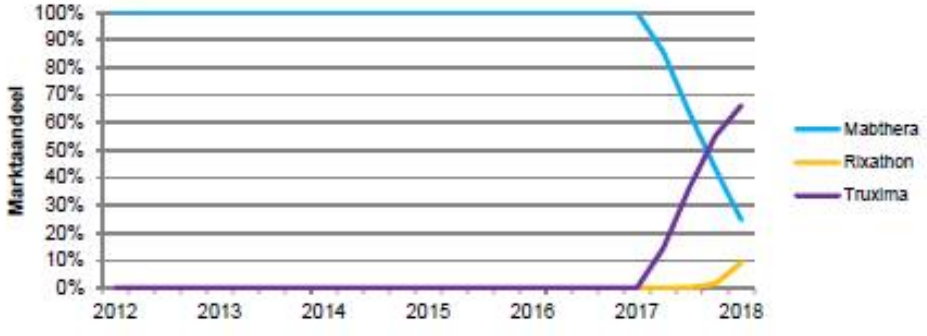
Figure 3.7 Development net purchase price rituximab



ACM analysis based on data requests at 30 Dutch hospitals.

The chart below shows that Truxima has conquered 70% of the market in a short period of time. Mabthera's market share fell to 25% in the first quarter of 2018. The market share of the biosimilar Rixathon is still limited at the beginning of 2018. The high list price of Rixathon (Sandoz) is striking in the graph above. The vast majority of hospitals that use a biosimilar switch 100% of their patients to the biosimilar in a short period of time. As with infliximab, the fast and often complete switch can be explained by the method of administration (infusion). Nevertheless, some hospitals have switched less than 50% of their patients to the biosimilar.

Figure 3.8 Development market share of the active substance rituximab

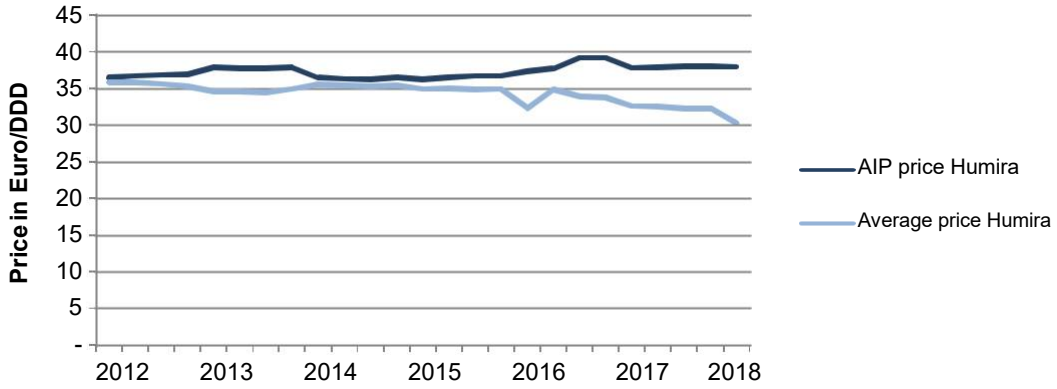


ACM analysis based on data requests at 30 Dutch hospitals

Adalimumab

Adalimumab went off-patent in November 2018. As the data we collect runs up to the first quarter of 2018, the effect of this is not visible in Figure 3.9. However, it can be seen that AbbVie gave an average discount of 5 to 10% as from 2015.

Figure 3.9 Development net purchase price adalimumab



ACM analysis based on data requests at 30 Dutch hospitals

Four biosimilar producers have registered for the Dutch market. These are Sandoz, Amgen, Mylan and Biogen. Three biosimilar producers have managed to gain market share for the year 2019. It is estimated that this is about 20% of the market for the three in total. The ACM has not collected any data within the sector research on the price reductions of the buyer since Humira's patent was granted. Hospitals interviewed in the context of the sector inquiry have indicated that the net purchase prices of adalimumab have fallen sharply compared to the list price. This is in line with discount percentages mentioned in public reporting.

Conclusions biosimilar competition

Research by the ACM shows that the entry of biosimilars into the market leads to sharp price decreases for all active ingredients (up to discounts of more than 70%). With the infliximab and rituximab infusions it is visible that several biosimilar manufacturers are entering the Dutch market. The combined market share of the biosimilar producers already exceeds 70% for these products at the beginning of 2018. With subcutaneous products, the picture looks different. In the case of etanercept, there is currently one biosimilar manufacturer that has a market share of around 20%. The market share of the second biosimilar is probably below 5%. When adalimumab went off-patent, four products attempted to enter the Dutch market, of which three actually entered, and prices fell considerably. Various market parties surveyed in the context of the sector inquiry have indicated that the form of administration (infusion or subcutaneous) and the number of competitors entering the market, among other things, helped determine how quickly and by how much prices fell.

4. Statements of market outcomes

This chapter addresses the explanations the ACM has identified for the market outcomes discussed in the previous section: the limited price competition between different active substances; the strong price decreases of TNF-alfa inhibitors due to biosimilar competition; and the relatively limited increase in market share of biosimilars that are administered subcutaneously. This chapter looks at this in turn: (i) hospital cooperation between prescriber and pharmacist; (ii) characteristics of therapeutic competition between different active ingredients, (iii) characteristics of biosimilar competition; and (iv) behaviour of purchasers and suppliers.

4.1 Cooperation within the hospital

The study shows that cooperation between the hospital pharmacist and the prescribers for hospitals is a necessary condition for effective purchasing. In this way, the cooperation is also an important building block for exploiting the scope for competition between active ingredients and for biosimilar competition. After all, a hospital only has negotiating power if it is able to purchase more or less of a medicine on the basis of offers from drug manufacturers. It is crucial for this bargaining power that the purchasing pharmacist and the prescribers are on the same wavelength with regard to medical policy. All the hospitals surveyed in this sector study indicate that they now have a working group on expensive medicines, which includes both hospital pharmacists and prescribers, and in which the hospital's preference policy is developed on the basis of both medical and efficacy considerations. Nevertheless, the ACM sees differences between hospitals: some hospitals are more inclined than others to focus on the actual prescribing behaviour of specialists. For many hospitals, this intensive collaboration is a relatively new development. These hospitals state that the purchasing of medicines has become more professional in the general sense in recent years. They cited the increasing focus by the health insurance company on the costs of medicines as a reason for their organisation. This recent increase in professionalism and the rather lower importance of costs was indicated by a number of hospitals as an explanation for the fact that in the past medical interchangeability has only led to limited price pressure. They also mention some examples of medicines where the hospital is now able to negotiate discounts on the basis of competition between active ingredients.

4.2 Characteristics of therapeutic competition

Therapeutic competition is competition between different active ingredients. It is difficult for this competition to get off the ground. The most relevant factors with regard to the nature of therapeutic competition and the limited level of competition in this area are set out below.

Chronic patients

Before entry by biosimilars took place and opportunities for switching within the same active substance arose, it appears that, despite the theoretical scope for competition, hospitals had only been able to negotiate discounts to a very limited extent. The rather limited price pressure caused by therapeutic competition - despite medical interchangeability - can largely be explained by the long-term use of these products. Without a medical reason, a patient is not prescribed a medicine with another active ingredient. This means that for the majority of patients it is already certain which medicine they will receive. In the case of TNF-alfa inhibitors, approximately 80% of the patients already used the same medicine in the previous year. The remaining 20% consists mainly of patients who are using a TNF-alfa inhibitor for the first time…

Effect of past prescribing patterns

Because of the often chronic use of TNF-alfa inhibitors, the prescription patterns from the past are an important factor for the current use of the drugs. A number of hospitals, for example, indicate that they currently use etanercept as a preferred drug, but still use a relatively large amount of adalimumab because this drug was often prescribed in the past. According to one health insurer, the use of etanercept and adalimumab is also relatively widespread in the Netherlands because in the past these drugs could also be prescribed extramurally.

Price pressure older and newer active substances

Once a medicine is used by a large number of patients, the price pressure of a new active ingredient on that medicine will be limited because the share of new patients is limited, so that purchasers can only make a different choice for a part of the patients. This works in favour of older medicines. For newer medicines, the share of existing patients is smaller than the share of new patients, which makes it easier for purchasers to exchange these medicines for alternatives. This may explain the fact that in the more recent TNF-alfa inhibitors certoluzimab and golimumab (which the ACM has not investigated in detail), both the volumes and the turnover lag significantly behind compared to the other TNF-alfa inhibitors.

Deviate from preferred medicines

Hospitals generally have different criteria for a preferred policy for a particular drug. It is important that rheumatologists and other specialists generally want to have all resources at their disposal. After all, for specific patients, the choice of a drug other than the preferred drug may be desirable. Deviation criteria mentioned by hospitals in this context are (i) specific indications, (ii) co-morbidity, and (iii) specific groups such as pregnant women or women who wish to have children. In addition, it is always possible that a drug does not work properly for a specific patient. In these cases, too, the rheumatologist wants to have as many different options as possible in order to switch to another drug. A hospital therefore does not have the freedom not to purchase one or more active ingredients at all: this is a restriction to organise very fierce competition for the market.

Effect of the going off-patent of other active substances

Accession of biosimilars not only leads to competition between manufacturers of the same active substance, but also changes the dynamics of competition between active substances. The ACM sees this, for example, in the entry of biosimilars for Enbrel (etanercept). In response to the fall in the price of etanercept, several hospitals have opted for this product as a preferred product to adalimumab. However, at that time, a few hospitals chose adalimumab as their preferred drug. With this strategy, the hospital in question was able both to obtain a higher discount on adalimumab and to benefit from the generally lower net purchase prices for etanercept.

Incentive from contract agreements with health insurer

An important component in the competition between medicines is the financial incentive for the hospital that follows from the contracts with the health insurance company. TNF-alfa inhibitors are expensive medicines and are reimbursed separately by the insurer as an add-on.[16] Health insurers reimburse the medicines on the basis of reference prices. With this, the health insurer puts a certain amount of pressure on the hospital to purchase more cheaply without taking away the entire advantage of cheaper purchasing from the hospital. Health insurers indicate that they want to use the reference price on the one hand to approach the net purchasing price and on the other hand to grant the hospital part of the purchasing advantage in order to maintain incentives for efficient purchasing by the hospital.

Margins and reference prices

The ACM observes that there are large differences in the margins between the price reimbursed by the health care insurer and the net purchasing price of various medicines paid by the hospital. In this case, the hospital may have the incentive to convert a lot of volume. Improving the information position of health insurers can help to remove unwanted incentives.

In addition, the ACM sees that the individual health insurers determine reference prices in various ways. These differences have an effect on the differences in margins between medicines and therefore on the financial incentives experienced by hospitals.

- Some health insurers determine the reference prices for each active ingredient. The disadvantage of this is that it does not provide healthcare providers with a strong incentive to opt for a cost-effective active ingredient: the incentive may even be to purchase a more expensive drug if the hospital can achieve a higher margin on this.[17]

- Other health insurers indicate that they determine the reference price per cluster of medicines. In such clusters, for example, the TNF-alfa inhibitors are combined with a number of therapeutic alternatives. Such reimbursement rates give hospitals the incentive to choose the most cost-effective drug within the cluster.

Some health insurers mention practical objections to this second method: there should then actually be a price per indication. This means that a lot of prices have to be determined with increasing complexity.

Subsequent calculation vs. ceiling agreements

Health insurers indicate that more and more agreements with hospitals are made on the basis of subsequent calculation. This means that there is no longer a volume limit on the reimbursement of these medicines. Between 2017 and 2019, all health insurers will see a strong increase in such agreements. Health insurers have indicated that this trend carries the risk that appropriate use and dose optimisation will not be sufficiently stimulated. At the same time, such agreements give the health insurance company the opportunity to focus more closely on the purchasing agent of the medicines. This is because health insurers generally attach conditions to the use of subsequent calculation agreements - such as the provision of price information and the distribution of purchase discounts according to the shared savings principle.

4.3 Characteristics of biosimilar competition

Biosimilar competition is competition between different (original and generic) variants of the same active ingredient. This can only start after the patent on the active ingredient has expired, but in principle there are fewer barriers afterwards.

[16] The reimbursement of the medicine is then not part of the DBC.
[17] Bigger difference between net purchase price and the reimbursement price.

Complexity biological medicine

The number of pharmaceutical companies that can make a biosimilar is considerably smaller than the number of pharmaceutical manufacturers that can make a generic product. The former is much more difficult from a technical point of view and the registration requirements are also higher for generic variants of biological medicines. This largely explains why there are few biosimilar manufacturers, and some of them are originators themselves.[18] One aspect is that a biosimilar can never be an exact copy of the originator because it concerns living organisms. A biosimilar manufacturer must therefore carry out its own equivalence studies and safety studies. This means that registering a biosimilar costs considerably more time and money than registering a generic chemical drug.[19]

Secondary patents

In addition, when the patent on the active ingredient expires, the original product can still be patented. For example there can still be a patent on the additives, on the production process or on the form of administration. In practice, therefore, biosimilar manufacturers often produce on the basis of a licence from the originator. The licence fees in question are in addition to the other costs that the relevant biosimilar manufacturer has to bear. Therefore, as a result of the above factors, the investment required to bring a biosimilar to the market is significantly higher than for a regular generic product. This further limits the scope for price reductions in relation to the originator.

Larger part patients contestable

In contrast to switching to another active substance, existing patients can also be transferred to a biosimilar. All hospitals now indicate that both new and existing patients can be transferred to a biosimilar. Discussions with hospitals have shown that the reluctance of doctors and pharmacists to prescribe biosimilars, as was the case a few years ago, is largely over. Both scientific studies - including the Norswitch study[20] from 2017 - and the hospitals' own experiences have contributed to this. The contestability of most (new and existing) patients means that prices generally fall considerably when biosimilars enter the market.

Switching costs give originators an advantage over biosimilars

Switching patients to biosimilars does involve costs for the hospital. The switching hospital will temporarily have to invest in instructing the patients concerned. In addition, the required administrative procedures can be considerable. A number of hospitals indicate that the biosimilars should therefore be at least a certain percentage - for example 5% - cheaper than the originator to make up for the switch costs. This gives the originator manufacturers an advantage. This advantage is reinforced by the fact that hospitals indicate that it is not possible to explain to patients that they will be put on a different drug if this can only be done for relatively limited cost savings. According to hospitals, patients are sensitive to the possibility of achieving considerable savings, even though they do not feel the costs directly.

[18] In the literature, the following entry barriers are mentioned for biosimilar monoclonal antibodies such as TNF-alfa inhibitors: production, regulation, intellectual property rights, lack of incentives, limited substitutability and lack of capacity of the entrant. See Moorkens et al. 'Overcoming barriers to the market access of biosimilars in the European Union: the case of monoclonal antibodies', Frontiers in pharmacology, 8 June 2017 | https://doi.org/10.3389/fphar.2017.00314.. See also Blackstone and Joseph, 'The economics of biosimilars', American Health & Drug Benefits 2013, 469-478; Shepherd, 'Biologic drugs, biosimilars and barriers to entry', Health Matrix Cleveland 2015;, doi: 10.2139/ssrn.2403068.

[19] However, it is sufficient to carry out these studies only for one indication. If equivalence is demonstrated for one indication, equivalence for other indications is assumed.

[20] See in particular the Nor-switch study into the application of the biosimilar of a TNF-alfa inhibitor in Norway: Jørgensen e.a., 'Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial', The Lancet. 10 June 2017, https://doi.org/10.1016/S0140-6736(17)30068-5.

Rest population

Although the majority of patients can be transferred to a biosimilar, this does not apply to all patients. Hospitals take into account the fact that they cannot transfer 5% to 20% of the patients (the rest population) to a biosimilar in the case of the injectable adalimumab and etanercept drugs. A few hospitals indicate that they may still be below 5% if the hospital makes every effort to do so. Hospitals generally indicate that the preparation and supervision of patients is crucial for acceptance. They also indicate that patients' acceptance of a switch to a biosimilar is easier with drugs that are administered by infusion in the hospital. The experience of the patient is affected less with the new infusion than with another medicine. This is also clearly reflected in the size of the rest populations of the drugs investigated in this study. As discussed below, the size of the (expected) rest population is crucial for the economic conditions under which people switch to a biosimilar. There is a risk that this rest population will then have to pay a higher price for the old drug than before, which may cancel out the advantage of a lower purchase price on the biosimilar for the other patients.

4.4 The effect of the practices on market outcomes

Both the behaviour of the originators to maintain their lead and the way in which the hospitals organise their tenders determine the effectiveness of the competition in the markets for TNF-alfa inhibitors. In addition, the conditions in the contracts between pharmaceutical companies and hospitals, and (indirectly) the research funding of hospitals, are relevant.

Reaction of the originator to possible entry biosimilars

Apart from any strategic behaviour in the markets concerned, both switch costs and the existence of a rest population contribute to the advantage that an originator, as the original supplier of the hospital, has over a biosimilar. Originators use this lead to consolidate their market position.

The market share retained by the originator after entry appears to be largely determined by the way in which the originator anticipates or reacts to the entry of biosimilars, in particular the extent to which the originator rapidly decreases prices by offering discounts to maintain market share. It is noteworthy that for the originator Remicade and Mabthera, prices did not fall until the market share of these originator products had already fallen sharply. The price of Enbrel, on the other hand, went down quickly after the entry of the biosimilars, as a result of which Pfizer was able to maintain a large market share. The sharp drop in Humira's prices also makes it more likely that Humira will maintain a high market share.

Conditional discounts and lowest-price guarantees

The ACM notes that several pharmaceutical manufacturers make use of conditional discount structures for rheumatic medicines. Such discounts may, for example, depend on:

- A minimum purchase volume
- A minimum percentage of the volume purchased from the manufacturer
- Ranking in the hospital's preference policy
- Duration of the contract

For the four originators investigated in this study, a conditional discount was included in 20 to 50% of the contracts concluded at the beginning of 2018.

The discount structures are mainly used by manufacturers of originator medicines when biosimilar producers join. Such discount structures may put competitors at a disadvantage. This effect is more pronounced the larger the group of patients who cannot be converted to a biosimilar. This residual population will continue to use the originator drug. With the two infusion drugs, the ACM sees that there is little or no rest population. There is a rest population for the etenercept and adalimumab injection drugs. For this rest population, the originator can calculate the (much higher) list price. The greater the difference between the list price and the net purchase price, the greater the benefit that follows for the originator.

Tenders by hospitals

The way in which purchasing hospitals organise their tenders can further strengthen the originator's lead. As a result, in the long term the supply may be reduced by the withdrawal of biosimilars from the market, which in turn reduces the choice available to hospitals.

The risks of intransparent procedures

The questionnaire among biosimilar manufacturers shows that several suppliers do not consider the tenders and choices made by the hospitals/purchasing groups to be transparent. In some cases, the biosimilar manufacturers explicitly state that they did not have a fair chance in the tenders. They also point out that this has consequences for several years, since the hospitals usually conclude contracts for several years.

After-bidding by originators

The ACM received various signals that sometimes there are selective or non-selective follow-up bids (extra bidding rounds that were often not known in advance), either on the initiative or request of the originator who was in danger of falling out of the boat and wanted to make a lower bid, or on the initiative of the purchasing hospital that had a strong preference for the originator. This may be financially advantageous for the hospital or purchasing group in the short term, but is undesirable in the long term. First of all, it removes the incentives to make a competitive offer in the first place. Secondly, it reduces the incentives and opportunities for biosimilar producers to make bids in the future if the originator can wait for his bid and then surpass it without having to make a sharp bid right from the start. This applies both to the specific active ingredient and, more generally, to competition in post-patent biological medicines. However, the ACM has also seen that there are hospitals/purchasing groups that have not responded to (a request for) such after bids from the originator.

Research financing

Hospitals receive research funding from several manufacturers of the medicines included in this study, for example to assess the effects of the use of these medicines at an earlier stage of the condition. However, financing research that is legitimate and valuable in itself can also be seen as an important form of indirect influence on doctors' prescribing behaviour. A number of hospitals indicate that research funding from pharmaceutical manufacturers (often in the past) has sometimes stood in the way of effective procurement.

These hospitals claim that they no longer experience this problem by introducing effective incentives within the hospital as well - for example, by means of shared savings from which prescribers can pay for their own research. In some cases, the research in question is also financed directly by the hospital itself. In addition, a number of hospitals indicate that the prescribers themselves are now avoiding contact with pharmaceutical manufacturers on ethical grounds.

5. Strengthening competition

The ACM concludes that competition between active substances has been limited for TNF-alfa inhibitors in the period up to and including 2015. During that period, there was also less preference among hospitals on the basis of efficiency considerations. More recently, the number of hospitals that have adopted such a preference policy has increased. The extent to which this actually leads to a stronger negotiating position - and hence lower prices - will have to be determined in the course of time. Competition after the expiry of patents has led to considerably lower prices for three TNF-alfa inhibitors and also for the examined B cell inhibitor. An important difference is that, except for medical reasons, in principle no patients are transferred from one active ingredient to another, while there is room between different variants of the same active ingredient to transfer patients to another product without medical reasons. Nevertheless, relatively few hospitals have actually switched to Subcutaneous administered biosimilars, while they do benefit from the price reductions that have been introduced as a result of the introduction of biosimilars. The ACM sees the limited effective entry of biosimilars as a risk to the market structure and the competitive process in the longer term if biosimilars are discontinued or no longer developed as a result.

The ACM sees a role for all parties in the market, including itself as a market regulator, in strengthening the competition between biologic intramural medicines. In addition, innovations in the regulatory framework can also contribute to this. Below, the ACM discusses successively I. the role of the purchasing market parties (hospitals and health insurers) II. the regulatory framework and III. the role of the ACM.

5.1 Hospitals

Purchasing hospitals play a crucial role in creating a more level playing field in the markets for biological medicines, whether or not through a purchasing cooperation agreement. During the study, the ACM identified several good practices that contribute to this and deserve to be followed up. These good practices are:

I. **Procurement on the basis of equal opportunities**: Creating a tender process with fair opportunities for all providers. In any case, this is part of the process:

   a. A clear tender process with clear rules

   b. The credible enforcement of and compliance with these rules

   c. Competitors should not be aware of each other's bids.

   d. The originator and biosimilar manufacturers make an offer for the same period, which means that the originator cannot apply retroactive rebates to medicines already supplied.

II. **Conducted preferential policy**: The preference policy is used to take advantage of the scope for competition in the event of medical equivalence between different active ingredients. A large majority of hospitals are already working on this to a greater or lesser extent.

III. **Consideration of longer-term effects:** Further development of preferential policies in hospitals with a view to long-term effects is a positive development. Hospitals sometimes consciously choose a biosimilar on other grounds than the most financially advantageous offer in the short term. In addition, during the study, a hospital purchasing group indicated, for example, that they would like to include in the contracts that discounts would continue to apply to existing patients, even if the hospital were to switch to a different preferred drug.

The ACM encourages the use of such principles in order to strengthen effective competition between and within active substances.

5.2 Health insurers

The contracts between health insurer and hospital are crucial for the financial incentives that hospitals experience in their purchasing policy. The ACM notes that health insurers have different views about their role, particularly with regard to contributing to competition in the market between originators and biosimilars. For example, a number of health insurers make a distinction between the reimbursement of biosimilars and originators in specific cases. Other health insurers have so far failed to see a role for themselves in this.

The ACM sees that an active role of health insurers contributes to a healthy market structure with long-term competition from biosimilars. Health insurers can fulfil this role by:

Compensation, at least temporarily, for the originator's *first mover advantage*. This may take the form of a (temporary) higher remuneration for the biosimilar. Hospitals can, for example, finance the extra costs associated with a switch - which may include having to pay the list price for the rest of the population. The ACM expects this to have a positive effect on the market structure and competition in the longer term. In order to be able to influence the results of the tender, it is also important that the health insurance company unambiguously commits to such a policy before the decision on the tenders is taken.

Further improve incentives for efficient procurement and use of medicines
The ACM sees that health insurers are actively considering the incentives that come from their fees for effective purchasing. It encourages health insurers to continue to do so. The margins between the various active ingredients can vary greatly, and it is noteworthy that in the products reviewed by the ACM in this sector study, there appears to be a financial incentive for hospitals to use the more expensive product in particular. In addition, the ACM observes that the financial incentives for appropriate use (partly based on dose optimization) of medicines are limited. The increase in volumes seems to confirm this picture. Contracts under which hospitals are allowed to retain part of their savings through appropriate use of medicines in order to use them for research (*shared savings*) may provide positive incentives.

5.3 Regulatory framework

Originators may threaten that if a hospital switches to another drug, the list price (AIP-price) will have to be paid for the rest of the population. This is potentially a strong power tool that allows originators to exclude competitors with conditional discounts. This possibility is stronger the greater the difference between the actual net buyer on the one hand and the AIP price on the other hand. The AIP price is capped by the WGP max price, which in turn is based on reference prices from some neighboring countries.

Until now, the underlying assumption has been that buying hospitals are able to negotiate a lower price after entry of biosimilars and that further price regulation is not necessary for this. However, a large difference between the WGP max price and the net purchasing price (such as 50% or more) gives the originator the concrete opportunity to use this price difference as a lever vis-à-vis the hospitals.

The ACM therefore recommends VWS to adjust the price regulation in this respect by reducing the threat of high prices for the residual population - and thus the risk of exclusion of biosimilars. This would be possible by aligning the WGP max price more closely with the negotiated prices by basing the WGP max price per product on the average net purchasing price. Adjusting the WGP max price can only be done by means of a change in the law.

5.4 Supervision ACM

The findings of this sector study have prompted the ACM itself to contribute to the creation of a more level playing field between originator and biosimilar medicines. The ACM will pay particular attention to those situations in which the originator has a strong competitive advantage over the biosimilars. Switch costs, the existence of a residual population and the related preference of hospitals to stay with the originator at comparable prices play an important role in this.

In particular, the ACM considers that the practice of offering conditional discounts by originators to hospitals may under certain circumstances be restrictive of competition. Where practices with a potential exclusionary effect are identified, the ACM examines these signals and enforces them where appropriate.

In addition, as part of the evaluation of its 'Guidelines for the joint procurement of medicines for specialist medical care,[21] the ACM is currently reviewing possible obstacles for hospitals and health insurance companies to join procurement and thereby increase their bargaining power. On the basis of the findings, the ACM will examine whether adjustments to the Guide can further contribute to a good balance between the purchasing power of health insurers and hospitals and the supply of originator and biosimilar medicines, and thus to effective market forces.

5.5 In conclusion

The ACM carried out a sector study into the drug group TNF-alfa inhibitors because it concerns a group with a high turnover, high numbers of patients and persistently high prices, while there are relatively many therapeutic alternatives available. By mapping the functioning of the market in this sector, the ACM also wanted to learn lessons for comparable markets of pharmaceutical products.

The ACM notes that there is no single comprehensive solution to strengthen the functioning of these markets. Effective market forces and competition based on a healthier market structure must be achieved in the interplay between hospitals, health insurers and regulation. By disseminating the best practices of hospitals and health insurance companies; and by creating a more effective market environment. regulatory framework contributing to reducing the gap between manufacturers' list prices and net purchase prices. The ACM will itself contribute to effective market functioning by examining and enforcing signs of anti-competitive behaviour, such as conditional rebates. The ACM expressly invites purchasers and other parties in the market to share these signals.

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[21] https://www.acm.nl/sites/default/files/old_publication/publicaties/15959_leidraad-gezamenlijke-inkoop-geneesmiddelen- voor-medisch-specialistische-zorg-2016-06-22.pdf.