



THE DENTAL AND
PHARMACEUTICAL BENEFITS AGENCY

The development of pharmaceutical expenditure in Sweden

– Managed Entry Agreements is an increasingly important tool for cost control as well as for early and equal access

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Summary

Managed Entry Agreements between pharmaceutical companies and county councils dampen the cost increase and provide better conditions for early and equal access. The pharmaceutical industry is expected to refund nearly one billion SEK to the county councils in 2017, an increase from SEK 720 million in 2016.

A report on the developments of the pharmaceutical expenditure in Sweden, by the Swedish Dental and Pharmaceutical Benefits Agency (TLV)¹, notes that Managed Entry Agreements (MEA) provide the opportunity to cope with uncertainties when bringing new innovative and effective pharmaceuticals to patients faster and more equally. They also make considerable resources available for other urgent healthcare needs.

There are major challenges in the pharmaceutical field both in Sweden and internationally. The trend is for new pharmaceuticals to be introduced at an earlier stage, which means that the uncertainties surrounding these pharmaceuticals are often high. In the coming years, it is likely that the factors that increase the cost of pharmaceuticals will be stronger than the cost-cutting effects. However, MEAs will become an increasingly important tool to dampen cost increases, together with generic competition and measures in the form of reassessments and price reductions for products that are older than fifteen years.

Facts about Managed Entry Agreements in Sweden

Since 2014, Swedish county councils and pharmaceutical companies have agreed, via Managed Entry Agreements, that companies shall refund a certain amount of the pharmaceutical costs to the county councils for certain products. TLV coordinates this process in the context of three-party deliberations and continuously monitors the outcome of the agreements.

The county councils and the pharmaceutical companies have currently twenty-two (22) ongoing MEAs to ensure cost-effectiveness for out-patient pharmaceuticals in the benefits scheme. Total expenditure for products with MEAs amount to some SEK 4 billion before refund, approximately 15 per cent of the benefits scheme, and estimated savings are approximately 25 per cent.

The therapeutic fields with the most agreements are hepatitis C, cancer and subcutaneous TNF inhibitors. It is also these fields where expenditure and treatment costs is highest, and where several companies compete.

In the agreement between the Swedish government and the Swedish Association of Local Authorities and Regions (SKL) on government grant for the pharmaceutical

¹ TLV (2017a) Uppföljning av läkemedelskostnader, June 2017, in part complemented with analyses from TLV (2017b) Prognos för besparing från sidoöverenskommelser helåret 2017, June 2017.

benefits, the government and SKL share the refunds that the MEAs generate. In 2017, 70 percent of the refund goes to county councils and 30 percent to the government, which means SEK 658 million and SEK 282 million respectively. In 2018, their respective share will be 60/40.

1 Introduction

The Dental and Pharmaceutical Benefits Agency, hereafter TLV, has a mandate to monitor and analyse the developments in the pharmaceutical, pharmacy and dental care markets in Sweden. One of TLV's aim is to develop the value-based pricing in order to ensure that pharmaceuticals are cost effective throughout their entire lifecycle.

TLV's mandate include monitoring and analysing the developments of both pharmaceutical cost and expenditure on a continuous basis. This includes monitoring the agreement between the government and the pharmaceutical industry association and report the savings generated by the agency's efforts to develop pricing². Sections of the latest analysis of the development of pharmaceutical expenditure report (June 2017) are summarized in this translated report.

TLV's mandate further include to continuously monitor and report savings generated by Managed Entry Agreements (MEA) entered into by pharmaceutical companies and the county councils as a part of the processing for certain pharmaceuticals in the benefits scheme. Sections of the latest analysis of the forecast of savings from managed entry agreements for 2017³, from June 2017, are also included in this report.

The purpose of this condensed report is to further the understanding on the developments of pharmaceutical expenditure and the role of MEAs in Sweden.

1.1 Outline

Section 2 describes the current MEAs followed by a section on the driving forces behind cost development, factors that affect expenditure; product mix, volumes and prices.

The role of MEAs is described in section 4. In section 5 follows regional developments for selected pharmaceuticals. Specifics regarding the agreement between the government and the pharmaceutical industry association in described in appendix 1. Savings in the benefits scheme due to the 15-year rule and TLVs reassessments is described in appendix 2, followed by appendix 3, where TLVs reassessments, carried out during 2017-2017, are listed.

² TLV (2017a) Uppföljning av läkemedelskostnader juni 2017

https://www.tlv.se/Upload/Ovrigt/Uppfoljning_lakemedelskostnader_170615.pdf

³ TLV (2017b) Prognos för besparing från sidoöverenskommelser helåret 2017, Prognos 1, juni 2017

https://www.tlv.se/Upload/Ovrigt/Prognos2017%20overenskommelser_20170701.pdf

2 Current Managed Entry Agreements

This chapter presents a list of current MEAs and the overall refunds paid by companies to county councils in 2015 and 2016. Also, the full-year forecast for 2017 is presented based on available data.

2.1 Current agreements

Until June 30, 2017, there were 18 pharmaceutical products covered by MEAs. In addition to these, three MEAs between county councils and companies regarding a number of hepatitis C pharmaceuticals have expired. Pharmaceuticals with MEAs account for just under 15 percent of the total cost of pharmaceuticals included in the benefits system (total cost was approximately SEK 28 billion in 2016).

Table 1. Pharmaceuticals for which county councils and companies have or have had a Managed Entry Agreement, as well as total sales (before refunds) within the benefits scheme, for a period of 12 months up to and including April 2017 in SEK millions.

Field	Pharmaceutical	Time from inclusion in the benefits scheme	Managed Entry Agreement from	Managed Entry Agreement up to and including	Sales in SEK thousands for 12 months up to and including April 2017
Hepatitis C	Sovaldi*	Oct-14	Jul-15	Dec-17	287 234
	Viekirax/Exviera*	Feb-15	Apr-15	Dec-17	52 933
	Eplusa	Sep-16	Jan-17	Dec-17	196 692
	Zepatier	Sep-16	Jan-17	Dec-17	81 232
	Daklinza**	Dec-14	Dec-14	Dec-16	150 030
	Harvoni**	Feb-15	Feb-15	Dec-16	413 341
	Olysio**	Oct-14	Nov-14	Jun-15	6 845
Cardiac failure	Entresto	Apr-16	Apr-16	Dec-18	7 199
Cancer	Xtandi*	Jul-15	Jul-15	May-19	336 644
	Zytiga*	Jun-15	Jun-15	May-19	84 139
	Zykadia	Dec-15	Dec-15	Jun-17	11 896
	Revlimid	Mar-08	Mar-17	Feb-19	297 930
	Mekinist	Jun-16	Jul-16	Jun-18	33 832
TNF	Enbrel*	Jun-02	Apr-16	Sep-17	562 349
	Benepali*	Mar-16	Apr-16	Sep-17	280 908
	Cimzia	Mar-10	Oct-16	Sep-17	121 741
	Humira	Mar-03	Oct-16	Sep-17	1 119 169

PCSK9-inhibitors	Repatha	Jun-16	Jul-16	Dec-17	5 656
	Praluent	Feb-17	Feb-17	Dec-17	308
Others	Raxone	Oct-16	Nov-16	Apr-18	5 924

Note: Sales for hepatitis C include both within and outside the benefits scheme.

** The product has had more than one agreement.*

*** The agreement for the product has expired.*

Source: TLV, E-Health Authority.

Within the framework of these MEAs, risk sharing is managed regarding uncertainties related to use and effect in clinical routine practice. Risk sharing helps to ensure cost-effective use despite the uncertainties that exist (usually in the cancer area, for example). Risk sharing can also mitigate the risks of high budget impact and thereby displacement effects. An example of this is the cost for hepatitis C treatment, which would be extensive if list prices were charged the county councils, without any volume-dependent refunds. This was especially the case when these pharmaceuticals were newly introduced. The MEAs also create competition between older biological substances whose patents have expired and where equivalent biosimilars have been introduced on the market (TNF inhibitors). TNF inhibitor price dynamics are achieved via MEAs and the control of volumes in the county councils instead of via the 'product-of-the-month' system, that is in effect for off-patent synthetic substances.

In several cases, combinations of these elements can be found in different agreements. The way in which risk sharing is designed depends on the uncertainties and the current market situation.

2.2 Outcome 2015 – 2016

The extent of the MEAs has increased over time. The first within the hepatitis C field came into place at the end of 2014, but it was only during 2015 that significant refunds were generated. At that time, the sum the refunding companies paid back to the county council amounted to almost SEK 260 million. During 2016, the county councils' refund increased to SEK 720 million. In 2016, several new agreements were concluded, including TNF inhibitors in the autumn.

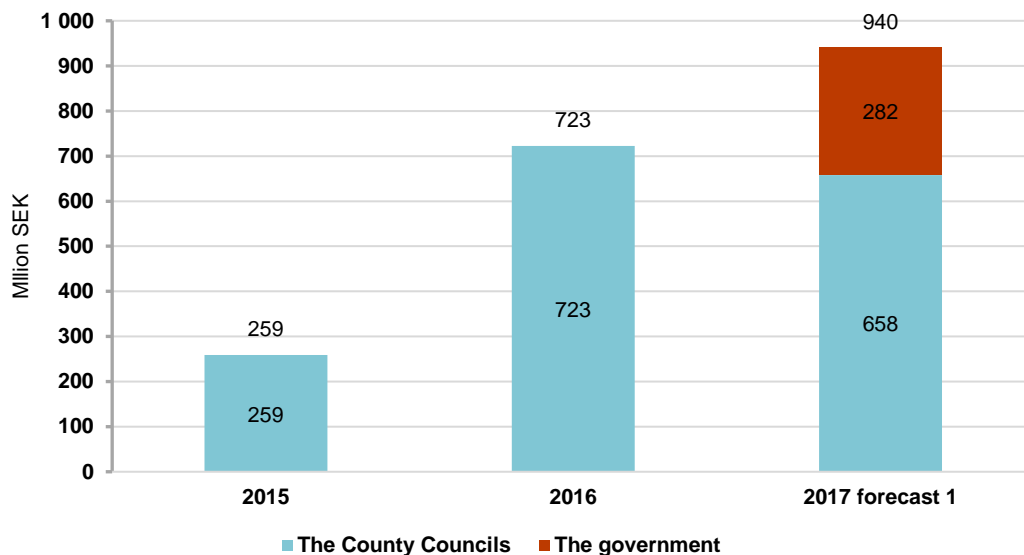
2.3 Forecast for 2017

Refunds are expected to increase further in 2017, partly because some agreements only gained partial effect in 2016. However, several factors affect the outcome. Outcome is due in part to the volume trend and to the pharmaceutical used when several options are available and where the level of refund varies. In the event that the list price for a product is lowered during the agreement period, it will result, according to the standardised agreements, in that the level of the refund is reduced accordingly. Should the list price be lowered to the level stipulated in the agreement, the refund will be eliminated altogether. Refunds can thus decrease without increasing the actual costs to society. The termination, or addition of new MEAs, will also affect the level of refunds.

Based on available data, refunds are forecasted to reach approximately SEK 940 million in 2017. One uncertain factor refers to the development of hepatitis C, which to date has largely driven the increase in refund level. Expenditure for hepatitis C pharmaceuticals have decreased by more than 35 percent in the first four months of 2017 compared with the same period in 2016. This decrease is due to several factors. Fewer new patients have been treatment initiated during the beginning of 2017, as compared to 2016.

In addition, new treatment options available and used during the beginning of 2017 are cheaper compared to 2016. The list prices for some hepatitis C pharmaceuticals have been lowered in 2017 (Viekirax, Exviera and Zepatier). Lower refunds due to lower list prices do not in themselves affect the costs to society, but the price development does affect the outcome of the total refunds.

Figure 1. Outcome of the Managed Entry Agreements 2015 - 2016 and forecast 1, June 2017.



Note: The outcome of refunds in 2014 amounted to a just a few million SEK and is therefore not included in the chart.

Source: TLV analysis

Given the agreement between the government and SKL, the government would thus receive SEK 282 million and the county councils SEK 658 million of the total forecasted refunds of SEK 940 million in 2017.

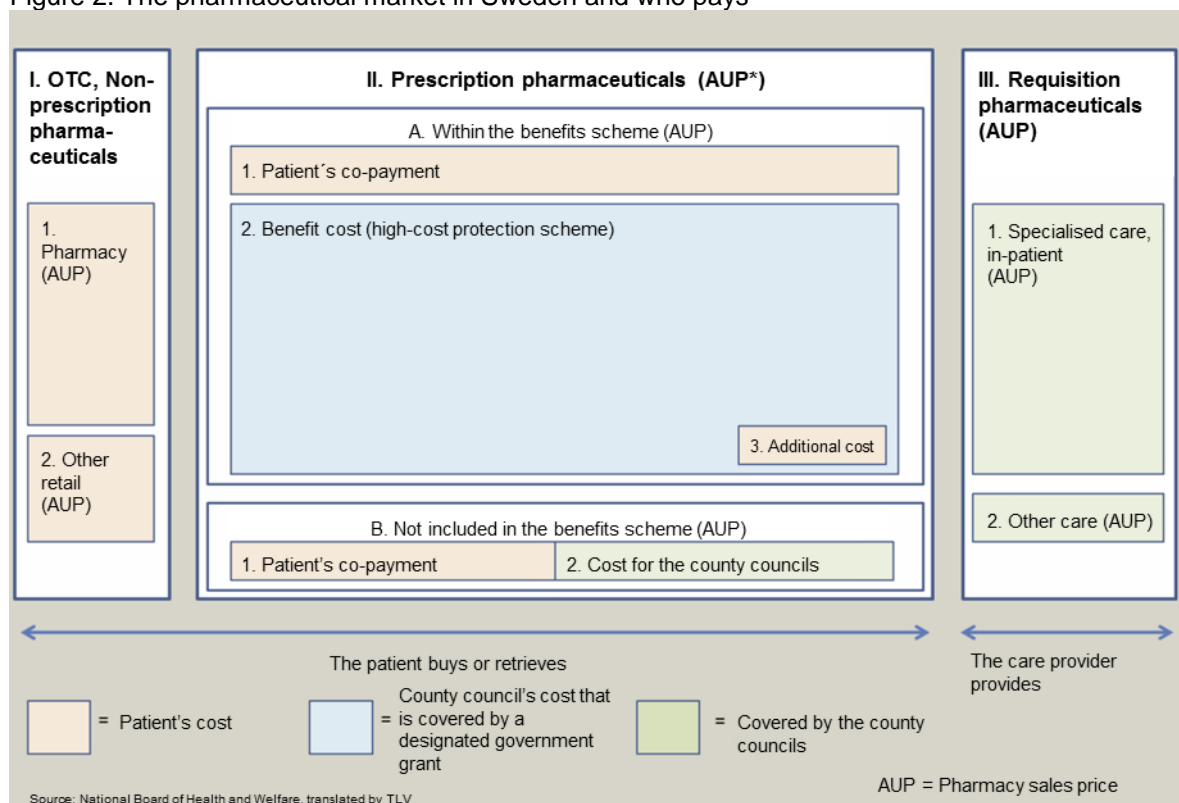
3 Driving forces behind cost development

In order to put TLV's work in perspective, the following sections show an analysis of those factors that have influenced cost developments most since 2009. All effects that affect pharmaceutical expenditure are reported, including those other than TLV's reassessment work and the so called 15-year rule (see appendices).

3.1 Segments and payers of pharmaceuticals

The figure below shows the various sales channels for pharmaceuticals in Sweden as well as who pays for them.

Figure 2. The pharmaceutical market in Sweden and who pays



Note: For a more detailed description, see to National Board of Health and Welfare's report 'Pharmaceutical sales in Sweden', April 2015.

The focus of the expenditure analysis is the total cost of out-patient prescription pharmaceuticals where the public sector has the responsibility for costs. This includes the costs for prescription pharmaceuticals in the benefits scheme (II.A in the figure above) as well as certain pharmaceuticals not included in the benefits scheme (II.B). The highest expenditure in the II B group are pharmaceuticals prescribed according to the Swedish Communicable Diseases Act, mainly for the

treatment of HIV and hepatitis. The full cost for those medicines are covered by the government, and there is no co-payment for the patient.

The prerequisites for analyses of the costs of prescription pharmaceuticals in the benefits scheme are good in Sweden. There is a good infrastructure of data via pharmacies and the E-Health Authority. This data is also well structured and available from the E-Health Authority. Data for prescription pharmaceuticals not prescribed in the benefits scheme are also available from the E-Health Authority, but it is not possible to distinguish which part of the cost of these pharmaceuticals is borne by the patient and which part by the county council (II.B). Since the cost of pharmaceuticals prescribed without benefits and financed by county councils is high and growing, this needs to be incorporated into the analysis.

3.2 Factors that affect expenditure

The total expenditure development can be divided into different components, each of which affects the change over time. The development is affected by changes in:

- volume,
- price or
- product mix

The volume component refers to the expenditure change that is explained by changes in volumes of existing products. Volume change is calculated per product (*i*) as the difference between the current month's volume (q_{it}) to the current month's price (p_{it}) compared with the same month's volume for the previous year (q_{it-12}) to the current month's price.

$$\text{volume change}_{it} = (q_{it} - q_{it-12}) * p_{it}$$

The expenditure change due to a price change is defined as the cost of the product a year ago ($p_{it-12}q_{it-12}$) compared to the cost for the current month for the same volume ($p_{it}q_{it-12}$). If the price has increased, the cost of the current month will be higher and if the price has decreased, the cost will be lower.

$$\text{price change}_{it} = (p_{it} - p_{it-12}) * q_{it-12}$$

The product mix component is affected by the addition of new products and the loss of other products. A product is defined as new during the twelve first months of the benefits. Product mix change is calculated residually, i.e. as the change in expenditure that is not explained by either volume or price changes.

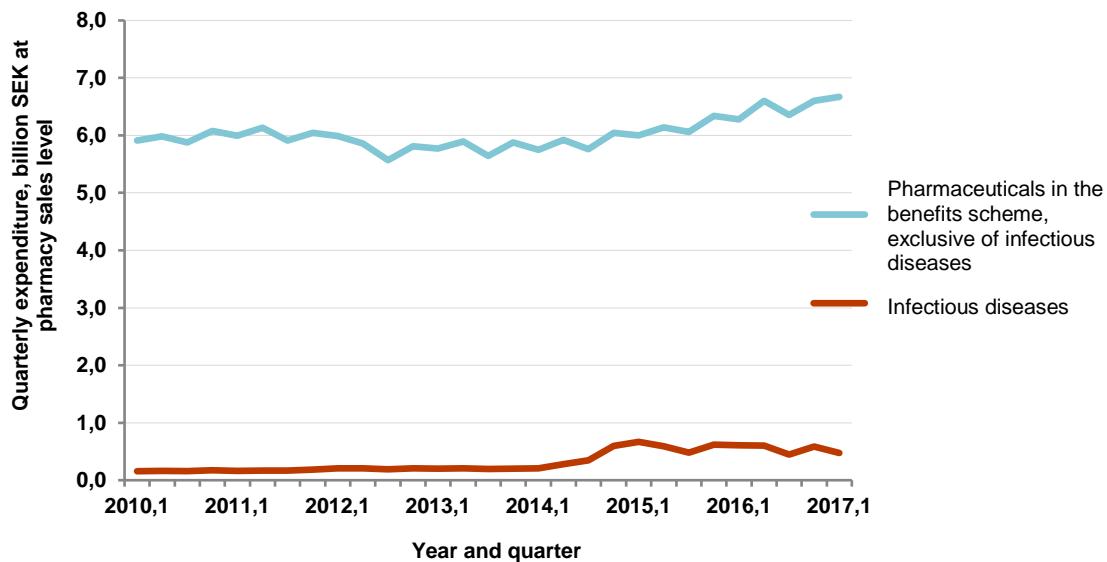
$$\begin{aligned} \text{product mix change}_{it} \\ = p_{it}q_{it} - p_{it-12}q_{it-12} - (q_{it} - q_{it-12}) * p_{it} - (p_{it} - p_{it-12}) * q_{it-12} \end{aligned}$$

A product is defined as a certain substance, form of preparation and strength⁴ based on the Swedish Medical Product Agency's classification of substitutability. Products not included in a substitution group are classified according to NPLid⁵. Parallel imported products are bundled with the original product. This classification means that different packaging sizes are combined and prices are calculated as cost per dose. The calculation is per month and product, but can also be aggregated to show the change for a group of pharmaceuticals (therapeutic area) and or over a longer duration.

3.2.1 Total cost development

Expenditure changes are reported on a quarterly basis to minimise variations in volume effect due to the different number of days in the measurement periods, while still allowing new trends to be observed relatively quickly. Figure 3 shows quarterly expenditure from Q1 2009 to Q1 2017. The total cost of pharmaceuticals in the benefits scheme, exclusive of infectious disease control (ATC J05A), was until 2012 about SEK 6 billion per quarter, or approximately SEK 24 billion per year. During 2012 and 2013, cost levels decreased due to large patent expires. From the end of 2014, costs have increased and during 2016, the total cost of this area was SEK 25.8 billion.

Figure 3. Total cost of pharmaceuticals in the benefits scheme exclusive of infectious disease control (ATC J05A), as well as pharmaceuticals for infectious disease control costs, SEK billion, quarterly 2009 Q1 - 2017 Q1



Source: E-health authority and TLV analysis

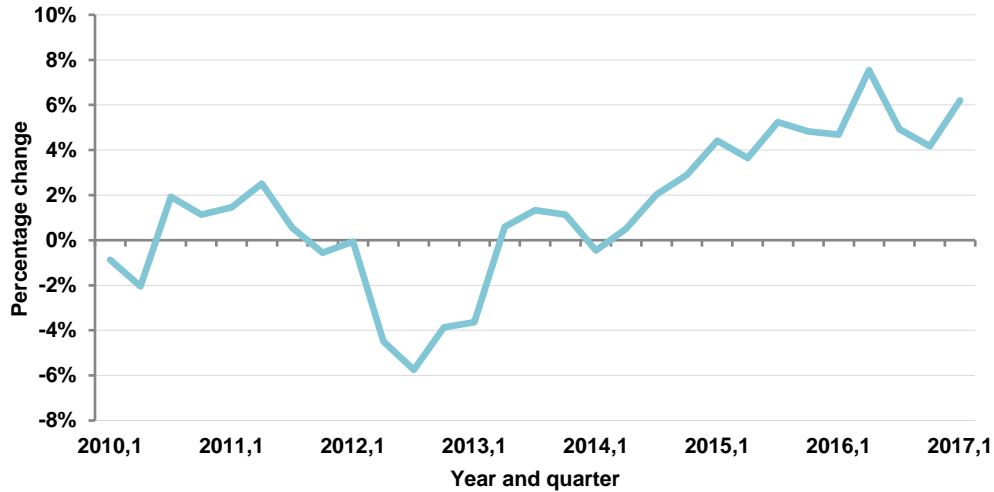
From year-end 2014, the cost of pharmaceuticals covered by the Swedish Communicable Diseases Act has increased. This is largely due to the introduction of new hepatitis C pharmaceuticals. In 2016, the cost of pharmaceuticals for infectious diseases amounted to SEK 2.2 billion. In total, costs were SEK 28 billion for the two areas combined in 2016.

⁴ For the substance adalimumab, two different forms of preparation have been grouped together

⁵ Unique identifier of pharmaceutical product according to the National Product Register for Pharmaceuticals

In percentage terms, the annual increase of expenditure for pharmaceuticals in the benefits scheme, excluding infectious diseases, has on average been five percent since 2015. During the first quarter of 2017, expenditure increased by six per cent.

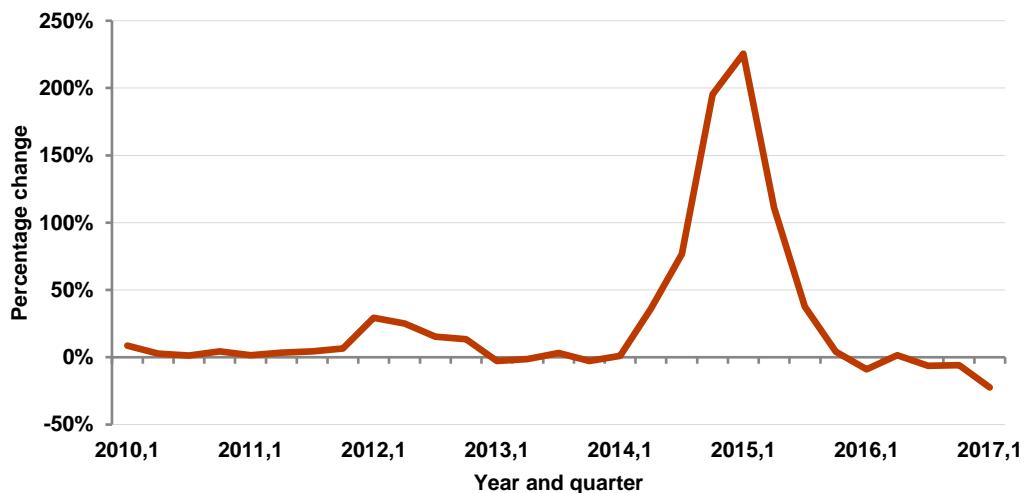
Figure 4. Cost change of pharmaceuticals in the benefits scheme exclusive of infectious disease control (ATC J05A) compared with the same period of the previous year, SEK billion, quarterly 2009 Q1 - 2017 Q1



Source: E-health authority and TLV analysis

For pharmaceuticals prescribed under the Swedish Communicable Diseases Act, the development of expenditure in percentage terms was high at the end of 2014 and the beginning of 2015 as a result of new hepatitis C pharmaceuticals. For the first quarter of 2017, costs fell by about 20 percent. This is partly due to fewer patients being treated and partly due to falling prices.

Figure 5. Cost change for infectious disease control pharmaceuticals (ATC J05A) compared with the same period of the previous year, SEK billion, quarterly 2009 Q1 - 2017 Q1



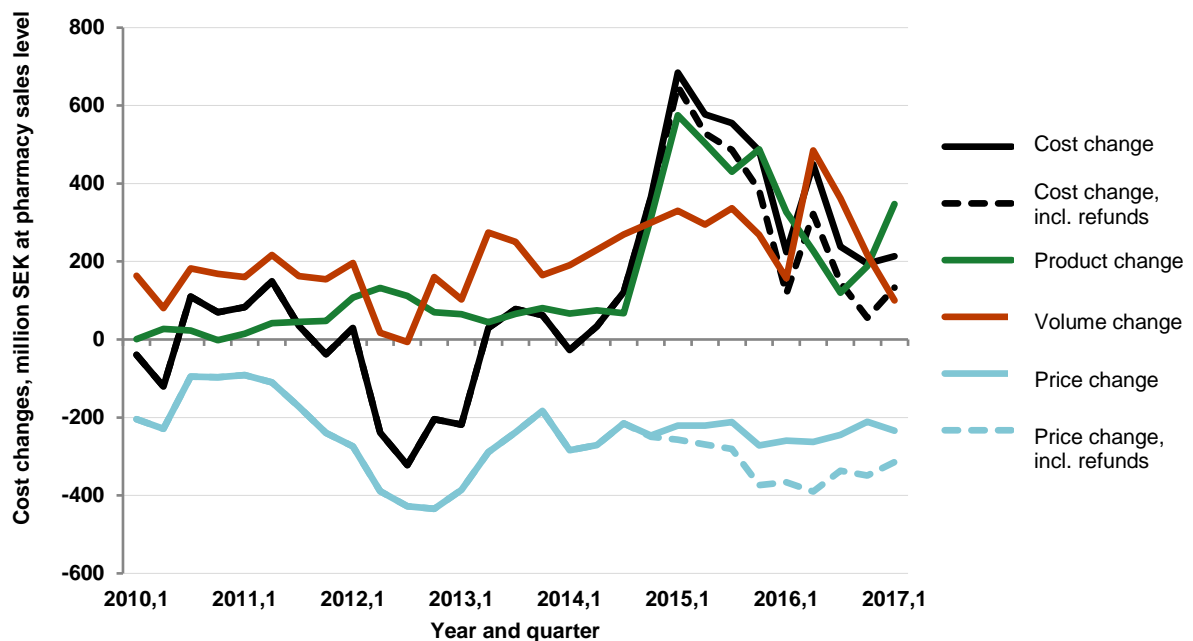
Source: E-health authority and TLV analysis

If expenditure change is analysed in accordance with the method described in appendix 2, it is clear that it is primarily product mix changes and price changes that have had a significant impact (Figure 6). During 2012 and 2013, price changes on existing products meant that the cost to society was SEK 2.7 billion lower than the year before for the same volume. This is mainly because major patents expired for older medicines. After 2013, the effect of price changes has been less, but on average, the cost to society has been SEK 240 million lower per quarter during this period due to reduced prices for existing pharmaceuticals.

After 2014, the effect of product mix changes has meant that total pharmaceutical expenditure has increased sharply. During 2015, costs increased by approximately SEK 2 billion due to the use of new pharmaceuticals. It is primarily the introduction of new hepatitis C pharmaceuticals that has driven this increase. During the first quarter of 2017, the expenditure change due to new products has increased again. This is due to the fact that a new group of hepatitis C pharmaceuticals has been approved for inclusion in the benefits scheme.

The volume change, which describes the change in costs due to changes in the use of existing products, has on average contributed to an increase in pharmaceutical expenditure of approximately SEK 200 million per quarter. During 2015 and especially 2016, the volume change has been slightly higher than the average. This is mainly due to increased use of NOAK preparations (new oral anti-coagulants), cancer pharmaceuticals and TNF inhibitors.

Figure 6. Cost changes for pharmaceuticals in the benefits system compared with the same period in the previous year, broken down into different components, SEK million, per quarter 2010 Q. 1 - 2017 Q 1.



Source: E-health authority and TLV analysis

From 2015 and onwards, repayments from MEAs (refunds) have had a dampening effect on expenditure changes. Repayment means that the county council receives retroactively a portion of the cost that they have incurred for a product. This therefore affects the price paid.

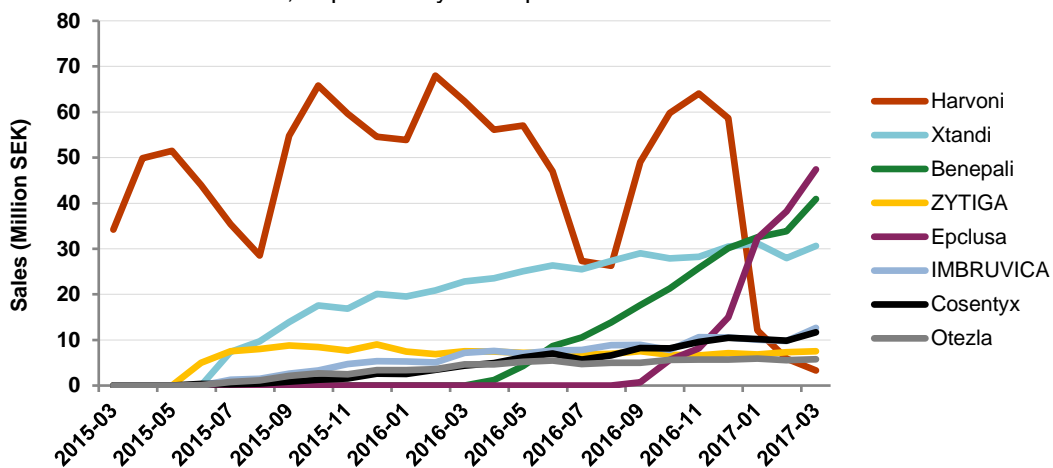
The major cost changes from 2015 onwards are analysed in more detail in the following sections. The focus is on events during the period April 2016 through March 2017.

3.2.2 Cost changes due to new pharmaceuticals after 2015

Of the pharmaceuticals that entered the pharmaceuticals benefits scheme after January 2015 (Figure 7), several of them have taken volumes from existing products and thus did not exert any great impact on overall cost changes. Examples of such products are Harvoni and Epclusa, which are new hepatitis C pharmaceuticals, and Benepali, which is a biosimilar to Enbrel. These products have, in fact, led to a cost reduction as they are cheaper than the products they replaced.

Other pharmaceuticals are products that do not directly replace an existing product. Xtandi and Zytiga are new pharmaceuticals for prostate cancer and IMBRUVICA is a pharmaceutical for blood cancer. Cosentyx and Otezla are two IL-inhibitors that are used primarily for various types of psoriasis.

Figure 7. Costs for best-selling pharmaceuticals approved after 2014, SEK million, per month 2015-01 - 2017-03, at pharmacy sales price level.



Note: For the pharmaceuticals in the figure above, there were in as of June 2017 MEAs in place between county councils and the respective companies for Xtandi, Benepali, ZYTIGA and Epclusa.

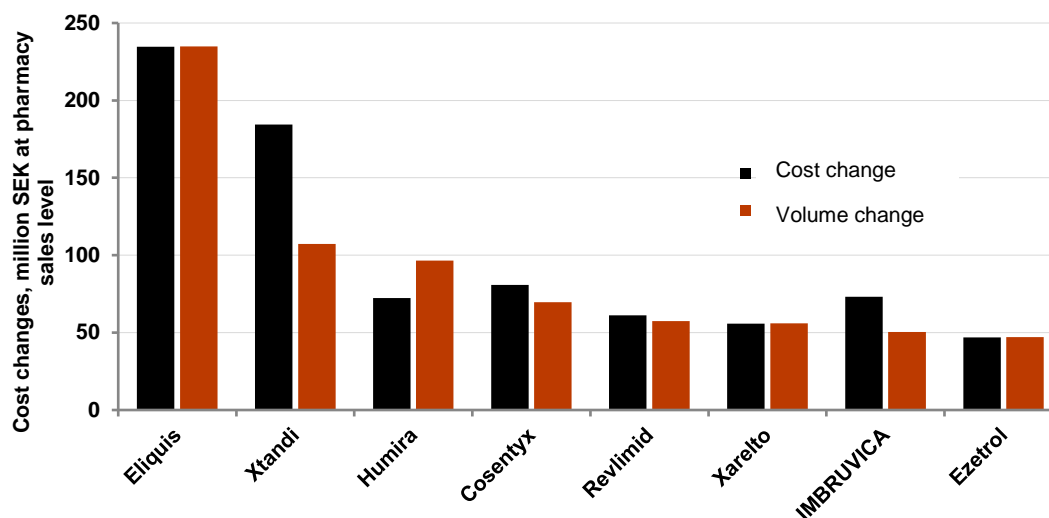
Source: E-health authority and TLV analysis

3.2.3 Cost changes due to increased volumes

During the period May 2015 to April 2016, costs due to increased volumes of existing products have increased by approximately SEK 1.2 billion. Figure 8 shows that the group of pharmaceuticals that has contributed most to this increase is NOAK preparations (Eliquis and Xarelto). These two together have increased costs

by around SEK 290 million during the period. The fact that cost change and volume change are not the same for several of the products is due to the fact that some products have been introduced during the period and are thus considered as product mix changes, e.g. Xtandi and IBRUVICA. Others have also had a lower price during the period, the clearest example of this being Humira.

Figure 8. Total cost change and cost change due to volume for pharmaceuticals with the highest volume changes, SEK million, moving annual total through March 2017



Note: Of the pharmaceuticals shown in Figure 8, there were in June 2017 MEA between county councils and the respective companies for Xtandi, Humira and Revlimid.
Source: E-health authority and TLV analysis

3.2.4 Cost changes due to changed prices

The table below shows the substances where the cost change as a result of price change has been the greatest. Price changes as a result of MEA refunds are excluded as they cannot be reported at substance level due to confidentiality. During the period April 2016 through March 2017, it was primarily substances in the product-of-the-month (PV) system⁶ where the cost changes as a result of reduced prices were the highest. For all substances with the greatest price change, the price has fallen due to competition in the product-of-the-month system. For the substances aripiprazole, duloxetine and quetiapine, competition emerged during 2015 and prices continued to fall in 2016.

The reason for the price reduction for the substance imatinib was that the patent for the original Glivec expired at the end of 2016 and competition emerged in December of the same year. The price change has taken place over four months with competition and it is therefore possible to expect further cost reductions in the future. Other substances have been in the product-of-the-month for a longer period. The reason why the cost change is not as great as the price change is that the lower

⁶ Products-of-the-month are the generic substitutable pharmaceuticals that have the lowest price and that the pharmacies must offer their customers when they replace pharmaceuticals. Every month, the product in each package size group with the lowest unit sales price, and that the pharmaceutical company has confirmed can be provided to the entire market with a sufficient durability for the entire pricing period price, becomes the product-of-the-month.

prices lead to increased volumes. However, the net effect in all cases is reduced costs.

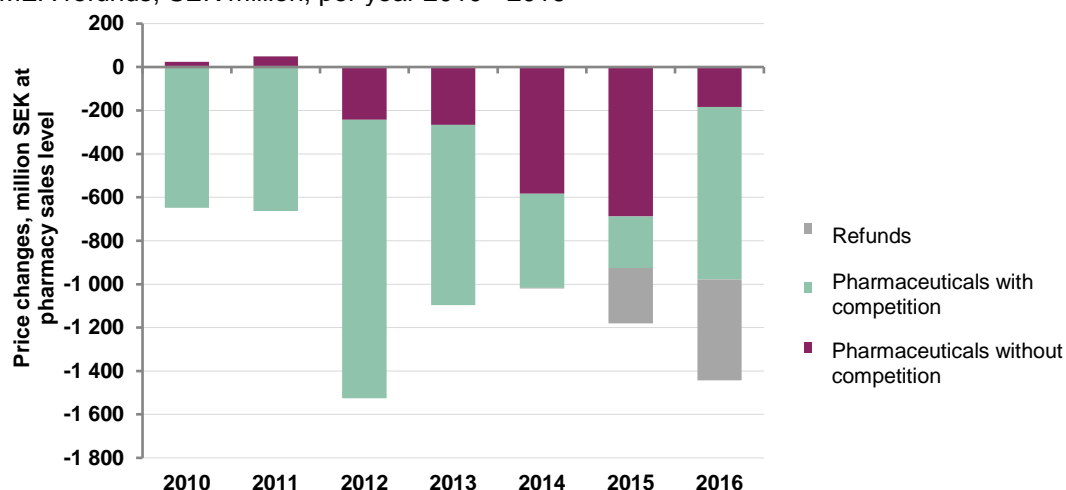
Table 2. Substances where the cost changes due to reduced prices have been greatest, excluding refunds, SEK million, moving annual total up to and including March 2017

Substance	Cost change	Price change
aripiprazol	-101	-114
duloxetine	-46	-49
quetiapin	-44	-46
imatinib	-31	-46
metoprolol	-32	-33
desogestrel	-43	-31
mometasonfuroat	-26	-28
esomeprazol	-15	-26

Source: E-health authority and TLV analysis

During 2014 and 2015, cost reductions due to price reductions for existing products have been greater for non-generic products not subject to substitution than for products subject to substitution. This is due in part to the fact that the effects of patent expiries on the product-of-the-month system have been relatively small in 2014. However, the main reason is that TLV has worked more actively to develop value-based pricing through reassessments and that the agreement between the government and the Pharmaceutical Industry Association (the so called 15-year rule) has led to lower prices for many older pharmaceuticals. In 2015, and above all in 2016, refunds due to MEAs represent a relatively large proportion of the total price change. 2016 was also a year of major savings within the product-of-the-month system due to, among other aspects, major patent expiries.

Figure 9. Price changes compared to the previous year broken down into pharmaceuticals with competition, product-of-the-month, (PV), and products without competition (non-PV) and MEA refunds, SEK million, per year 2010 - 2016



Note: Products-of-the-month are the generic substitutable pharmaceuticals that have the lowest price and that the pharmacies must offer their customers when they replace pharmaceuticals. Every month, the product in each package size group with the lowest unit sales price, and that the pharmaceutical company has confirmed can be provided to the entire market with a sufficient durability for the entire pricing period price, becomes the product-of-the-month.

Source: E-health authority and TLV analysis

4 The role of Managed Entry Agreements

The payer challenges in the pharmaceutical field are great in Sweden as well as globally, and the development in this sector is moving towards new pharmaceuticals with large potential effects being introduced at an increasingly earlier stage. To a large extent, this development is a consequence of the EMA's accelerated approval and regulatory framework for orphan pharmaceuticals. Early introduction gives patients the benefit of faster access to pharmaceuticals, at the same time as it implies the need to accept a higher level of uncertainty about how a pharmaceutical will be used, and not least about its effects in routine clinical practice.

According to QuintilesIMS⁷, the number of new innovative substances launched during 2007 to 2013 has been around 20-30 per year. From 2014 to 2021, it is estimated that approximately 40 to 45 new innovative substances will be introduced annually. This development will drive the cost of prescription pharmaceuticals in outpatient care as well as requisitions within inpatient care in the coming years. The National Board of Health and Welfare's forecast for the years 2017 to 2019 also shows increasing costs for pharmaceuticals in the coming years.⁸ It is not just new pharmaceuticals that drive cost increases, the use of existing pharmaceuticals is also increasing in several areas, e.g. NOAK (new oral anti-coagulants), prostate cancer and TNF inhibitors.

The increased uncertainties arising from early introduction need to be managed from the public perspective. Otherwise, costs in the pharmaceutical budget will increase without increasing the benefits, which risks jeopardizing cost-effectiveness in pharmaceutical use and, in the long run, affecting the possibilities of financing new pharmaceuticals.

Better follow-up in routine clinical practice can be one way to deal with the uncertainties that exist. By better utilizing existing data sources and, if necessary further developing these, actual benefits gained can be off set against the benefits found in studies and which are affected by various degrees of uncertainty. The methods used to transfer results from clinical trials to clinical routine use need to be developed and quality assured so that the outcome of the follow-up becomes a relevant base for making renewed decisions. The government has commissioned TLV to carry out two pilot studies aimed at developing methods for monitoring the therapeutic effect of pharmaceuticals in routine clinical practice and contributing to better assessing cost effectiveness over time. The assignment shall be reported by 31 December 2018 at the latest.

⁷ QuintilesIMS LifeCycle New Product Focus, QuintilesIMS Institute, Mar 2017

⁸ Pharmaceutical sales in Sweden, National Board of Health and Welfare, April 2017.

Three-party deliberations and MEAs are tools for dealing with the uncertainties that may arise when introducing new potentially innovative pharmaceuticals. When correctly formulated, refunds through such agreements can help to ensure cost-effectiveness over time despite the uncertainties that exist. However, their formulation is affected by the data available for follow-up. Lack of relevant, easily accessible and current data may mean that follow-up will not be possible. MEAs are based on the fact that relevant follow-up is possible in order for the identified risks to be managed.

When such follow-up is possible and relevant, three-party deliberations between county councils, pharmaceutical companies and TLV will enable early use of new innovative pharmaceuticals. This even applies when there is significant uncertainty about use, medical outcome and cost-effectiveness. It may also be possible to handle budget challenges if there is a risk that many patients may be candidates for treatment at a very high collective cost. In practical terms, it is usually simpler to initially share the risks and, if it turns out that they are not too great, to then reduce or eliminate risk sharing.

An additional challenge for funding systems is that several of the top-selling pharmaceuticals are effective but costly biologics. These pharmaceuticals are not substitutable in pharmacies in the same way as synthetic pharmaceuticals. Therefore, competition and price pressure do not automatically arise when patents expire and competition from biosimilars (copies of the biological medicine) arises. For this type of pharmaceutical, three-party deliberations and MEAs can be effective tools to help create better conditions for competition. In order for competition to take effect in this area, county councils need to coordinate (including within the framework of the NT-Council⁹ recommendations) and change their internal governance so that the company whose pharmaceuticals have the lowest cost also gets the largest volumes.

A consequence of coordinated MEAs between county councils is that they will have the same terms and conditions regarding price and costs of using the pharmaceuticals covered by the agreements (for other pharmaceuticals, updated nationwide list prices are available).

4.1 The government and county councils share the refunds

For the period 2017 – 2019, an agreement between the government and the Swedish Association of Local Authorities and Regions (SKL) governs the compensation to the county councils. For 2018 and 2019, the agreement is valid as a declaration of alignment. The county councils receive a specially-funded government grant for pharmaceutical benefits, etc. Several elements are included in this grant; partly the cost of medicines and merchandise in the benefits scheme, partly the cost of hepatitis C, and partly an item for other infectious disease pharmaceuticals plus

⁹ The NT (New Therapies) Council has a county council mandate to issue recommendations on approaches to new pharmaceutical therapies. It is appointed by county council health and welfare directors.

various transfers made from the benefits scheme to inpatient care or other procurements. The basis for the government grant is the National Board of Health and Welfare's annual forecast of pharmaceutical costs. It is the forecast from April 2017 that forms the basis for the government grant 2017.¹⁰

4.2 Government grant for the pharmaceutical benefits scheme, etc.

According to the National Board of Health and Welfare's forecast, benefit costs for pharmaceuticals and merchandise in the benefits scheme are calculated to amount to SEK 23,442 million in 2017, which corresponds to a cost increase of 6.2 percent compared with 2016.

The costs for new hepatitis C pharmaceuticals, calculated according to the National Board of and Welfare's forecast from April 2017, amount to SEK 1,225 million for 2017, which is a decrease of 15.0 percent compared with 2016. The compensation is 70 percent of the forecasted cost, which means that county councils receive SEK 858 million for hepatitis C in 2017.

Should the cost of benefits and or hepatitis C differ by more than 3 percent compared with the forecast, a 50 percent risk-sharing of the excess deviation will come into force. If costs increase by more than 3 percent over the forecast, the government will account for half of the excess cost. In the opposite case, the county council pays back 50 percent.

In addition to the cost of pharmaceutical benefits and hepatitis C, government contributions of SEK 1,620 million are also allocated to an 'other' category. This includes costs for certain other infectious disease pharmaceuticals and various transfers of medicines from the benefits scheme to inpatient care or merchandise that has been procured outside of the benefits scheme.

Table 3. Government grant for the pharmaceutical benefits scheme, etc. 2017, and risk sharing limits, SEK million.

	Government contributions 2017	Upper limit +3 percent	Lower limit -3 percent
Benefits scheme	23,442	24,145	22,739
Hepatitis C	858	884	832
Other	1,620		
Total	25,920		

Source: Agreement on the government's contribution to county councils for costs for pharmaceutical benefits, etc. for 2017, serial number S2017 / 02911 / FS.

4.2.1 Nationally-unified pricing system

The agreement also emphasises the importance of maintaining a national pricing scheme while the entire system is being evaluated by a government inquiry (SOU dir. 2016:95). In cases where individual county councils enter into their own

¹⁰ National Board of Health and Welfare, Pharmaceutical Sales in Sweden - Analysis and Forecast 2017 - 2019, April 2017

discount agreements regarding pharmaceuticals in the benefits scheme, the discount will be deducted from next year's government grant. The reason for this is to create incentives for county councils to unite via the national process within the framework of three-party deliberations where county councils, companies and TLV cooperate. The overall objective is to maintain equivalent conditions nationwide regarding pharmaceutical pricing. These reservations do not apply to inpatient pharmaceutical products, which are to be procured in the usual manner.

4.2.2 TLV responsible for forecasting refunds

During 2016, the county councils retained the full refund from the companies under the grant agreement between the government and SKL. In the 2017 agreement, the parties will share the refund.

According to a change in regulatory instructions (S2017 / 03604 / FS), TLV is given the task of forecasting the refund for the full year 2017 twice a year (June 30 and December 13). The December forecast will provide the basis for a preliminary settlement of the refund in connection with the payment of government grants to the county councils in February 2018 (relating to the costs in December 2017). A final reconciliation of the outcome of the 2017 refund will take place in March 2018. Any deviations between the forecast and final outcome will be adjusted at the latest in connection with the payment of government contributions in May.

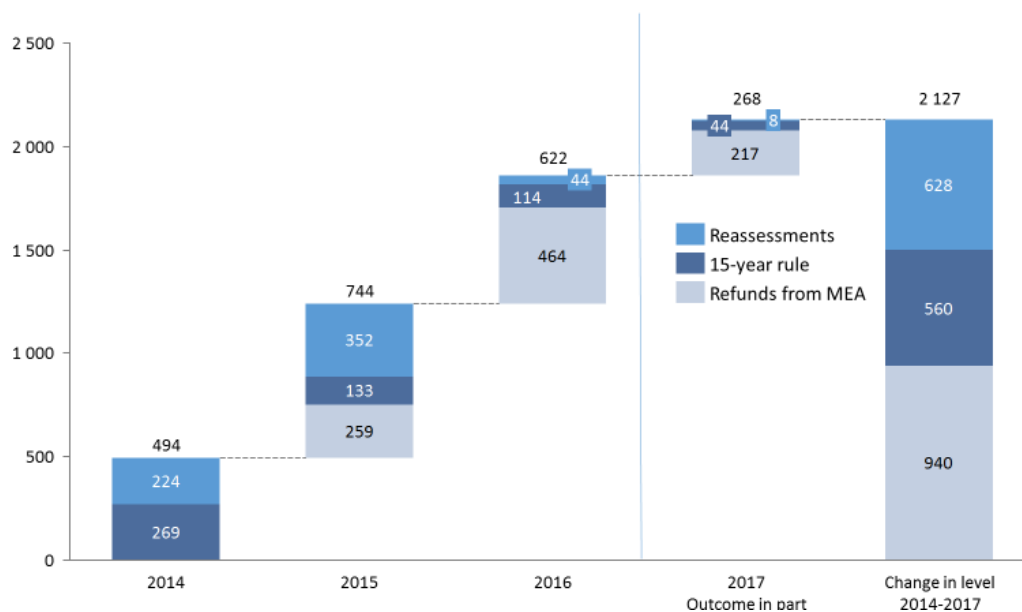
4.2.3 Focus for 2018 and 2019

The focus of the agreements for 2018 and 2019 is that the arrangements should be the same and that the starting point is the National Board of Health and Welfare's forecast. This forecast is due 30 October each year, which means that the grant for 2018 will be based on the forecast that the National Board of Health and Welfare submits on October 30, 2017. For the years 2018 and 2019, 60 percent of the refund due to the MEAs will accrue to the county councils and 40 percent to the government.

4.2.4 Incentives, governance and Managed Entry Agreements

Most indications suggest that cost-driving factors will be stronger than cost-dampening factors in the coming years. In order to manage forthcoming financing challenges, there is still a continuous need for interventions in the form of reassessments and the 15-year rule. In the future, however, MEAs may become an increasingly important instrument for contributing to the early, orderly and cost-effective introduction of new potentially innovative pharmaceuticals. MEAs also make it possible to free up resources by reducing costs in the biosimilars field, as well as in other areas where effective competition dynamics has not occurred. The goal is to achieve the best possible conditions for a reasonable cost scenario from a public perspective, but also for more effective pharmaceutical use. Since MEAs began to be used in a more structured manner in 2015, the amount of refunds has increased. In 2016, MEAs generated greater savings than the other interventions combined. The assessment is that this will also be the case in 2017 (see Figure 10).

Figure 10. Reassessments, the 15-year rule and refund changes per year plus total level changes from 2014 to 2017, million SEK*.



Note: * The refund during 2017 is based on TLV's forecast in June 2017. The 15-year rule is theoretically calculated and may be lower if generic competition arises first. Only the effects of adjudicated reassessments are reported.

However, refunds from MEAs should not be seen as a pure saving for the county councils. In order for MEAs to have their desired effect, underlying control of clinics, primary care centres and similar units may need to be adopted. The incentives for using pharmaceuticals can, for example, be influenced by how individual clinics can avail themselves to parts of the refund. This is especially evident in TNF inhibitors, where the biggest savings effect occurs if existing patients are switched to the most cost-effective alternative. Relevant management of pharmaceutical use in county councils is important in order to maintain the credibility of the contractual agreements in relation to the companies.

At the same time, the differences in the costs of pharmaceuticals according to their list prices are increasing compared with the costs that apply following the refunds from the MEAs. The funding for county councils' pharmaceutical costs is, however, based on costs at list price. There may, therefore, be grounds for the fact that the government, as a financier of the county councils' pharmaceutical costs, also receives a share of the reimbursements received by the councils from companies.

So far, county councils have had good incentives to conclude MEAs when the full refund has accrued to them. The new government grant agreement may affect the incentive for county councils to take part in contractual agreements. To what extent this construction of the division of reimbursement affects the occurrence of new MEAs, and or what kind of contractual agreements are entered into, should therefore be followed over time.

5 Regional developments for selected pharmaceuticals under MEAs

This section describes developments in certain areas with new pharmaceuticals where MEAs have been in place for at least one year and where a greater presence and use should be seen in all county councils. The focus is to describe the spread in use between county councils over time.

The areas described are hepatitis C, prostate cancer and cardiac failure. In hepatitis C and prostate cancer, pharmaceutical use was in place before the benefits scheme decision itself. Entresto, used for cardiac failure, has been covered by the benefits scheme and a MEA since April 2016.

5.1 Direct Acting Antiviral (DAA) drugs – Hepatitis C

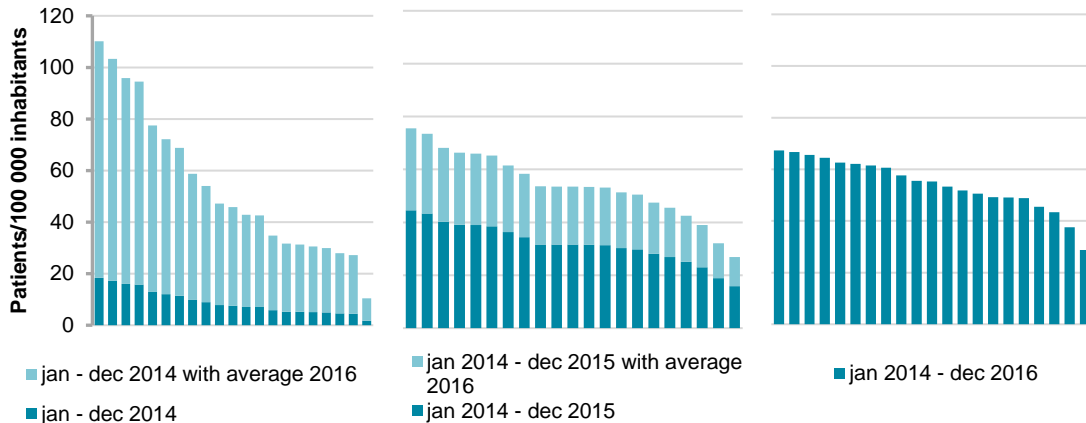
Hepatitis C has a somewhat special character insofar as there is a relatively large group of patients (a total of approximately 40,000-50,000 individuals) who carry the virus, and among these the most severely ill are prioritized for treatment. Initially, the benefits decision applied to only the most severely ill (patients with fibrosis grade 3 and 4), after which some less seriously ill patients (fibrosis grade 2) were also included. The least affected patients who rarely have any discomfort (fibrosis grade 0 and 1) have not been covered by the benefits decision. Treatment is short and consists of a cure of between two and six months. The new hepatitis C pharmaceuticals have been the subject of a jointly planned introduction in the county councils, which means a recommendation of the NT Council and a joint implementation and monitoring protocol. Between January 2014 and December 2016, approximately 5,600 patients were treated with new hepatitis C pharmaceuticals in Sweden.

The prevalence of hepatitis C differs between county councils and a variation in the number of patients treated can thus be expected. Because the exact occurrence is difficult to measure, it is risky to analyze in detail the differences between county councils. Different councils may have different strategies for contacting their patients, which may affect variety in use over time. Some may have had the opportunity to quickly identify the most severely ill patients and thus attained a high level of use early, which may then subside after the patients have finished their treatment. Other county councils may have gradually increased their treatment over time.

It is not easy to describe spread and change of the same in a satisfactory way. One way of illustrating differences in use is to look at the number of treated patients per 100,000 inhabitants. As usage has increased rapidly over time, it may be difficult to distinguish changes in spread from changes in level. A statistical measure of spread that adjusts for that the average changes over time, is the coefficient of variation.

The lower the coefficient of variation, the lower the spread. Measured as coefficient of variation, the differences in hepatitis C use decreased from 0.51 in December 2014 to 0.23 in December 2015. In December 2016, the difference had decreased further to 0.18. Differences have decreased over time while usage has increased.

Figure 11. Distribution of new hepatitis C patients accumulated over time based on the 2016 average. The number of patients per 100,000 inhabitants and county council has decreased over time while use has increased.



Note: Each bar represents a specific county council.
Source: National Board of Health and Welfare and Statistics Sweden.

Figure 11 shows the number of new patients being treated per 100,000 inhabitants and county council through 2014, 2015 and 2016. In 2014, the average county council treated nine patients per 100,000 inhabitants. By 2015, this number had risen to 32 patients per 100,000 inhabitants and by the end of 2016, approximately 54 patients per 100,000 inhabitants had been treated in the average county council.

In order to make the figures comparable regarding levels, the 2014 and 2015 rates have been adjusted to the average number of new patients through 2016. This adjustment is added to the actual numbers of new patients at the bottom of the figure for 2014 and 2015. The figure shows that the number of new patients has increased over time. It is also clear that the county councils that initially had the lowest levels of use have increased their use over time and gradually approached the levels of the other county councils.

The figure shows that the spread is high in 2014; several county councils have an adjusted use that is higher than the actual 2016 level and *vice versa*. This indicates a large spread. This spread gradually decreased during 2015 and 2016.

The treatment start of new patients that was high initially in some county councils may over time have decreased as relevant patient groups have undergone hepatitis C treatment. There are still differences between county councils, but even the incidence of the disease differs and, therefore, deeper analyses are needed to explain these differences more in more detail.

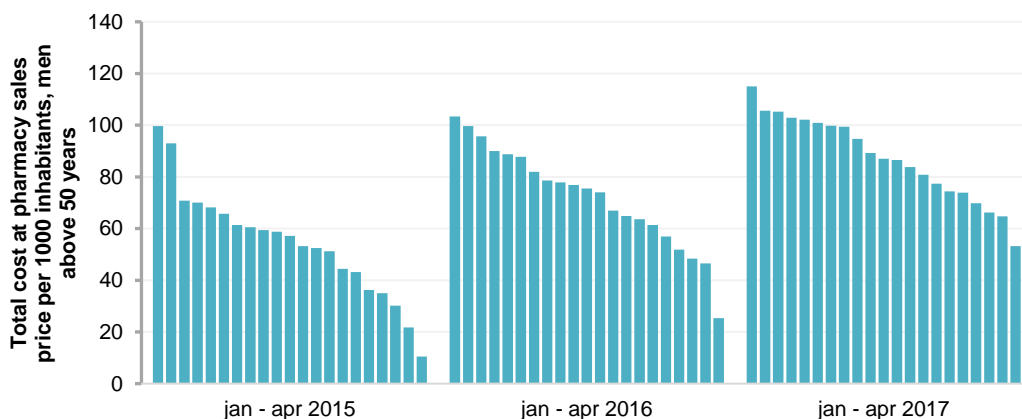
5.2 Prostate cancer – Xtandi and Zytiga

Xtandi and Zytiga are prostate cancer pharmaceuticals that received market approval in July 2013 and September 2011 respectively. They have been in the benefits scheme since July 2015 and June 2015 and it is also from these dates that MEAs have reduced the actual treatment costs. Prior to the positive subsidy decisions, both pharmaceuticals were primarily used in the hospital setting. Initially, the county councils had different forms of agreement or no agreement at all, but in the period prior to the benefit decision, all county councils had the same agreement. Following the benefit decisions and MEAs, all county councils have the same agreement governing the treatment costs of Xtandi and Zytiga.

One way to illustrate the differences over time is to look at total sales (AUP – pharmacy sales prices) per thousand inhabitants over 50 years. Sales are a relatively good measure of use because treatment lengths are similar between county councils and list prices have remained unchanged over time since the benefit decisions in June / July 2015. Age-standardizing the sales statistics for men takes into account the fact that usage may vary between county councils due to differences in gender and age structure.

Regarding prostate cancer, the incidence of new patients is characterised by a continuous influx over time. Therefore, the rate of use at an early stage should not affect the level of use later. In this way, prostate cancer differs from, for example, hepatitis C, where early-onset treatment by some county councils may be expected to lead to lower use at a later stage because the group of patients is limited and the treatment is curative. Given the character of new onset disease, the cost per 1000 men over 50 years in outpatient and inpatient care can be a comparable measure of the use of Xtandi and Zytiga. Figure 12 shows the cost before the grant decision during the first quarter 2015, after the benefits decision in the first quarter 2016, and during the first quarter 2017.

Figure 12. Total cost at pharmacy sales level (SEK) for Xtandi and Zytiga during the first quarters 2015, 2016 and 2017, per 1,000 inhabitants (men over 50 years) and county councils.

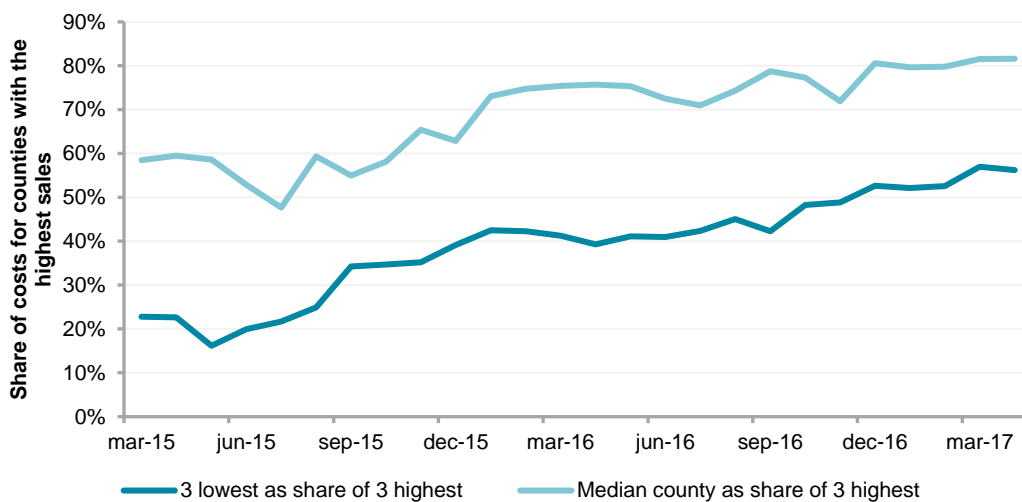


Note: * Benefit decisions and Managed Entry Agreements apply from June or July 2015 onwards
Source: E-Health Authority and Statistics Sweden

Use was relatively high in some county councils prior to the subsidy decisions, and differences between county councils were also relatively large. But already one year later, when the pharmaceuticals had been in the benefits scheme with MEA;s for about half a year, the use had become more even. Measured as coefficient of variation, the differences decreased from 0.38 in the first quarter 2015 to 0.26 in the first quarter 2016. During this period, several of the county councils approached their highest use, although some still relied on relatively low usage. In the first quarter 2017, the coefficient of variation was 0.18, which indicates that the use has become even more even between the county councils. There are more with a high level of use at the same time as those with the lowest use have approached the levels of other county councils. Differences in usage can still be found, but they seem to decrease over time.

Figure 13 shows another way of illustrating developments in the county councils that have had the lowest use in relation to those who have had the highest. The figure shows sales in the three lowest-use counties (moving three months total) along with the councils that have costs around the median as a proportion of sales in the three county councils with the highest usage.

Figure 13. Costs for Xtandi and Zytiga in the three county councils with lowest costs as well as the median cost councils as a proportion of those with the highest costs, moving 3 months, pharmacy sales price (SEK) per 1000 men over 50 years, outpatient and inpatient care.



Source: E-Health Authority and Statistics Sweden

During the period prior to the subsidy decisions, costs in the three county councils with the lowest use accounted for approximately 15-20 percent of the costs in the county councils with the highest use. After the benefits decisions had been taken and the MEAs begun to apply, the councils with the lowest costs have gradually increased their use compared with the highest use councils. A similar development applies to the councils with median cost levels.

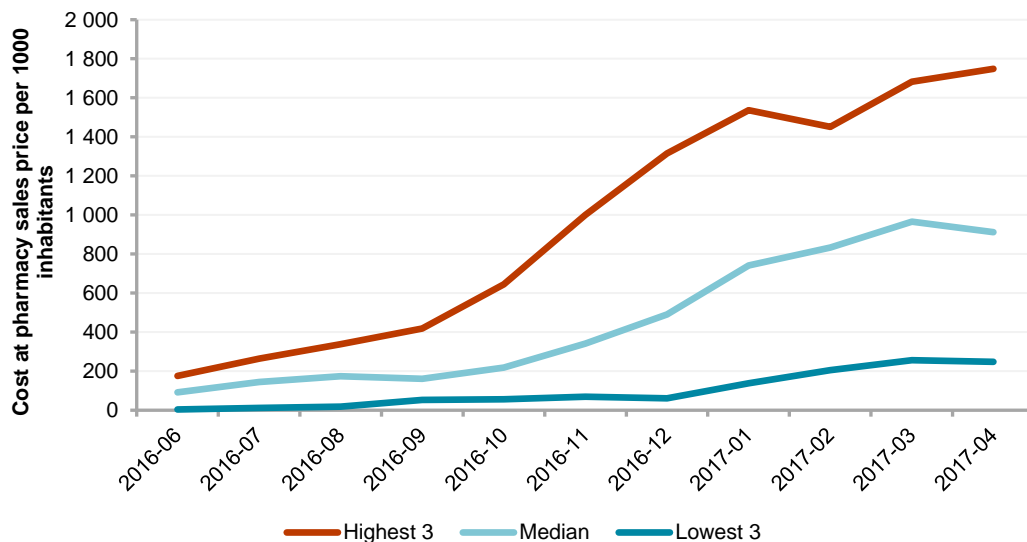
In this outline, it is not possible to determine the main reason for the more even use. The benefits scheme decision itself and the MEAs to ensure cost-effective use, together with the county councils' work with a jointly arranged implementation, are certainly strong contributing factors.

5.3 Cardiac failure – Entresto

Entresto is a new pharmaceutical product for the treatment of severe cardiac failure. Treatment is relatively costly compared to existing base treatments (ACE inhibitors / ARB). Although the pharmaceutical is considered effective in preventing cardiovascular death or hospitalization, there is still some uncertainty about its effect in routine clinical practice as well as how many patients are to be treated. Potentially, up to 80,000 patients may be eligible for treatment with Entresto given the approved indication. The benefits scheme decision is limited to adults with chronic symptomatic cardiac failure with reduced pump capacity. Entresto is covered by the county councils' jointly arranged implementation.

The focus of this description is to illustrate how differences in use between county councils have developed over time. It often takes a long time for a brand new pharmaceutical to achieve widespread use, and it was only in January 2017 that all county councils prescribed Entresto for outpatient care. Since Entresto has been in the benefits scheme for just more than one year, it is relevant to analyse development over three-month periods.

Figure 14. Total cost at pharmacy sales price (SEK) for Entresto in the three county councils with the lowest costs, those with costs around the median, and those with the highest costs in April 2017, per thousand inhabitants over 50 years, moving three months total.



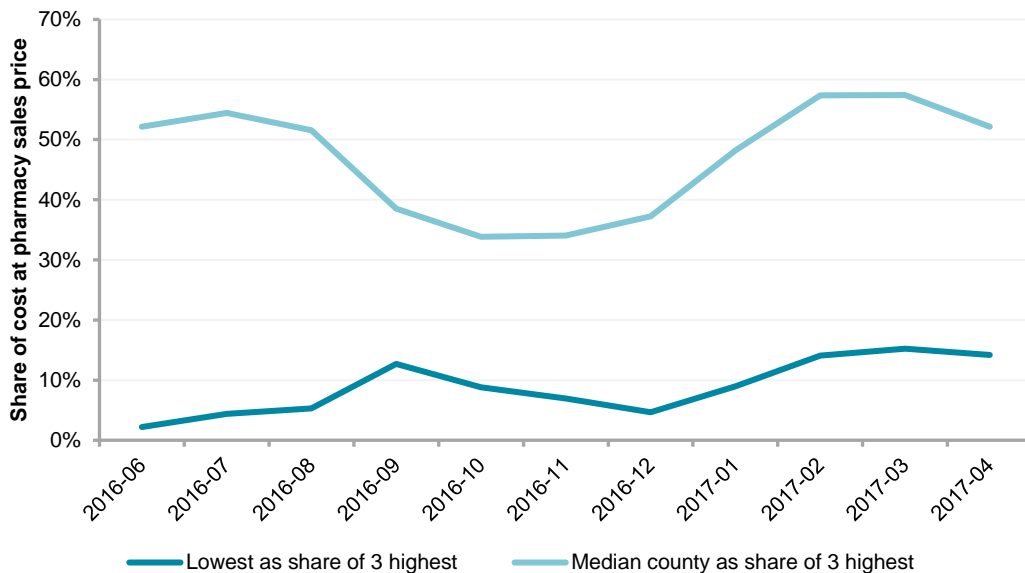
Source: E-Health Authority and Statistics Sweden

The figure shows sales per thousand inhabitants over 50 years in the three county councils with the lowest use in April 2017 (moving three months total) compared to the three county councils with the highest use and those with around median use during the same period. In the councils with the highest use, use increased already

in the fall of 2016. The median-use county councils began to increase their use somewhat later in winter 2016, while the lowest-use county councils increased their use early 2017. In recent months, the rate of increase has decreased for the three county councils with the lowest use as well as for the median-use councils. The increase for the county councils with the highest use declined slightly in early 2017, but has now continued to increase, albeit at a somewhat slower pace.

To illustrate this development more closely, Figure 15 estimates sales in the three county councils with the lowest sales and those around the median sales level as a proportion of the three highest-selling county councils.

Figure 15. The total cost at pharmacy sales level for Entresto for the three councils with the lowest sales and those around the median level as a proportion of the three councils with the highest sales, per 1000 inhabitants over 50 years, moving three months total



Source: E-Health Authority and Statistics Sweden

There is no indication that either group of county councils has yet begun to approach the group with the highest use. Sales in the median-use councils amount to approximately 50 percent of sales in the three councils with the highest sales, while the equivalent figure the lowest-use councils is around 10 percent. The relative increase that could be seen around the turn of the year 2016 / 2017 has declined in recent months.

It seems that the differences in the use of Entresto between county councils have not yet begun to decline. However, it is not possible to draw any further conclusions about this development in the shorter perspective. Nor is it known how developments would have appeared in the absence of MEAs and orderly implementation. Entresto can illustrate the challenges involved in managing the introduction of a pharmaceutical that is expected to have good effects but where the costs can be very high when there are potentially many patients that may be treated.

Differences in use may be due to several factors. They can illustrate that the county councils have different organizations and conditions for meeting patients in need of Entresto. According to the NT Council recommendation, for example, treatment of Entresto should be initiated at cardiac failure and base treatment should be optimized before implementation. The variation in the rate of implementation may be due to differences in how efficiently patients with adequate baseline treatment can be identified and for which there thus are reasons to consider supplementing with Entresto. There may also be a need to gather knowledge about whether the effects in routine clinical practice are as good as those according to clinical trials.

Sources

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Appendix 1: Agreement regarding savings

The so-called 15-year rule means that the prices of pharmaceuticals older than 15 years from the date of market approval are lowered by 7.5 percent. Since 1 November 2014, this pricing rule has been regulated by law and in TLV regulations (TLVFS 2014: 9). The first price reduction in January 2014, however, was voluntary and supported by an agreement between the Swedish government and the Pharmaceutical Industry Association (LIF).

The agreement (government decision 2013-09-12 Ref S2013 / 6192 / FS) on the 15-year rule applies to savings equivalent to SEK 800 million in levels of reduction between 2014 and 2017 calculated as AIP (pharmacy purchase price) based on prices in October 2012 and volumes for the full-year 2012. It is on these conditions that the agreement is evaluated. This saving does not have the same effect when calculated on current prices and volumes. The reasons for this are that use may have changed, which TLV's report to the Government in December 2014 pointed out, and that lower prices due generic competition have occurred since October 2012. When the effect on benefit scheme costs in the report's next section is calculated, the starting point is the factual savings given the actual prices and volumes that applied at the price reduction.

Table 4. Current situation and projection of savings according to the agreement between the government and LIF, SEK million AIP, comparison based on volume and price October 2012.

Status	Year	Saving (AIP)
Outcome	2014	400
Outcome	2015	121
Outcome	2016	130
Potential outcome *	2017	61
Calculated savings		712
Savings according to the agreement		800
Difference		-88

Note: * Known exception through May 2017 as well as potential price reductions in June and December 2017. AIP= pharmacy purchase price level.

Source: E-health authority and TLV analysis

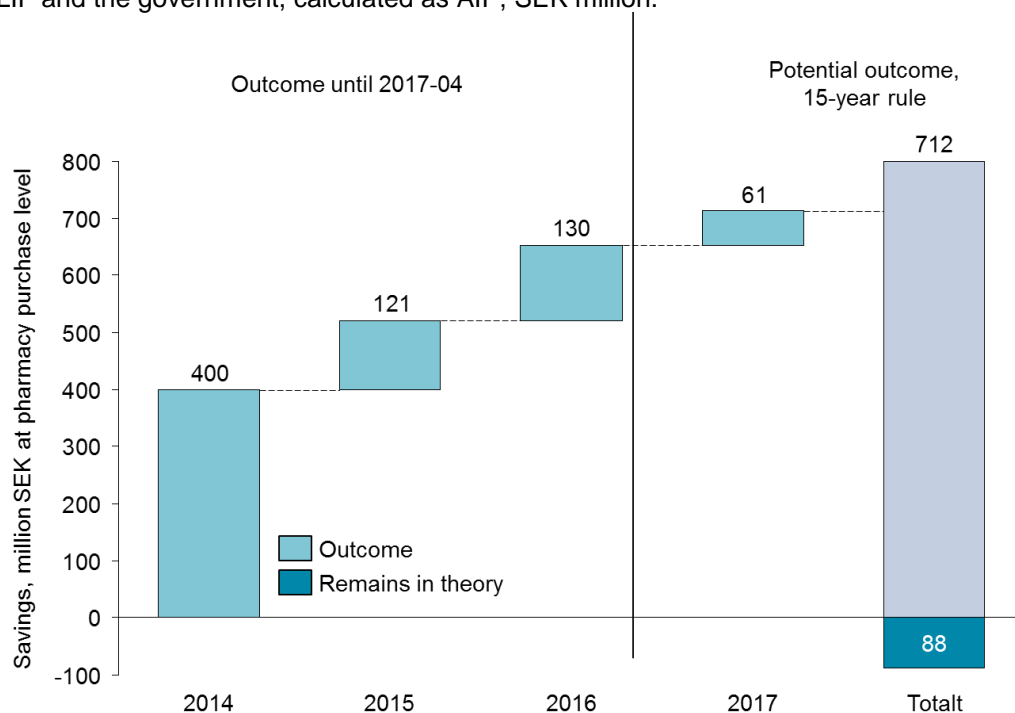
The outcome so far is within the framework of what TLV previously has reported to the government. TLV's impact assessment (dnr 2265/2014) on how the regulation of the 15-year rule should be formulated showed that the savings were estimated to be high in the first years (2014 and 2015) and lower in 2016 and 2017. The result of the impact assessment was that the savings were not estimated at SEK 800 million but rather at around SEK 700 million. The consequence of the analysis was that price reductions under the 15-year rule take place twice a year in June and

December. This speeds up savings and increases the savings effect slightly during the period covered by the agreement. In June 2017, the savings were estimated at SEK 712 million.

The savings regarding the AIP according to the 15-year rule are based on prices and volumes applicable in October 2012. All reductions in prices from October 2012 are included in the savings regardless of whether generic competition arose or whether the price was reduced in a reassessment. The only price reductions that are not included are those cases where the company is granted exemption from a price reduction of the product in question.

The preliminary outcome through to the end of 2017 is SEK 712 million based on known exceptions from potential price reductions in June and December 2017 (Figure 16).

Figure 16. Saving expectations 15-year rule 2014 – 2017 according to agreement between LIF and the government, calculated as AIP, SEK million.



Note: AIP = pharmacy purchase price level.
Source: E-health authority and TLV analysis

Experience shows that some products are granted exemption from price reductions. In accordance with TLV's regulations and general guidelines (TLVFS 2014: 9), TLV may rule on an exemption from a price reduction if the affected company can show that special reasons exist. For instance, the price of the product may have previously been reduced by 65 percent or more in connection with, for example, a reassessment. The price of the product after a price reduction may also be too low in relation to its sales volume, manufacturing and distribution costs.

The loss of savings due to the permanent exemptions granted by TLV to date amount to approximately SEK 11 million. In addition, pharmaceuticals worth a further SEK 4 million have been granted a fixed-term exemption. They are, however, included in Table 4 as potential savings in 2017. Based on the pharmaceuticals that are covered by the 15-year rule, savings of SEK 800 million are expected to be achieved around the year 2019.

Appendix 2: Savings due to the 15-year rule and TLV's reassessments

Saving expectations according to the budget proposal for 2014

According to the 2014 budget proposition, it is apparent that the government expected reduced benefit costs for the period 2014 to 2017 of SEK 1,175 million. This includes the actual effects of the 15-year rule as well as effects of TLV's reassessment work and of developing value-based pricing. Although these effects are separate posts in the budget proposition, they are largely linked.

Table 5. Savings in benefit costs in accordance with the budget proposal for 2014, SEK million.

Year	Reassessments	15-year rule	Total	Accumulated savings
2014	100	370	470	470
2015	200	70	270	740
2016	150	95	245	985
2017	100	90	190	1 175
Total	550	625	1 175	3 370

Source: Government, E-Health Authority and TLV Analysis

Of the savings of SEK 1,175 million up until 2017, benefit costs have been reduced by SEK 550 million through reassessments and SEK 625 million through the 15-year rule. Accumulated over the period 2014 to 2017, this means a total saving of approximately SEK 3.4 billion.

Method of calculation

The savings on benefit costs are calculated on the basis of the actual prices and volumes applicable during the period when the intervention came into force. Volumes are based on the previous 12-month period. The price effect of TLV's decisions can therefore be distinguished. The calculation thus differs from how the savings are calculated based on the AIP, which is based only on prices and volumes from October 2012. In cases where prices are reduced due to generic competition before the 15-year rule came into force, these pharmaceuticals are not counted as a saving on benefit costs according to the 15-year rule. In such cases, prices have already been lowered and do not affect benefit costs. In calculating the savings based on the AIP above, all price reductions are taken into account and compared with the October 2012 prices.

With the method developed by TLV, the savings effect is attributed to the first intervention that occurs, which is usually a reassessment. If the price has been lowered more than 7.5 per cent in a reassessment, the 15-year rule will not have a

savings effect. In the calculations, the savings need to be attributed to the correct intervention if they are to be broken down into reassessment and the 15-year rule. Some of the pharmaceuticals reassessed in 2014 would have been covered by the 15-year rule in December 2016 or 2017. This applies, for example, to Symbicort, whose price dropped significantly in December 2014 but which would have been reduced by 7.5 percent according to the 15-year rule in December 2015.

These effects are due to reassessments from 2014 and 2015, but in 2016 and 2017, portions of the savings were transferred from reassessments to the 15-year rule. The review of Enbrel in January 2016 also speeded up the savings due to the 15-year rule, which would otherwise come into force in June that year. Consequently, the effects of reassessments are reduced accordingly insofar as they would have been lowered according to the 15-year rule later on. In this report, the 15-year rule thus amounts to the savings that it would theoretically have given, even if a reassessment has lowered prices in advance.

The announced price cuts for June and December 2017 are included in the effect of the 15-year rule when taking into account the exceptions granted (known up to and including May 2017). The effects of the 15-year rule in June and December 2017 are theoretically calculated in the sense that all companies with products whose prices shall be reduced will also do so. Volume is based on moving 12 months total through April 2017. This means a certain overestimation of savings because additional exemptions are likely to be sought and granted. Historically, however, these exceptions have not been extensive in economic terms. In total, they amount to approximately SEK 8 million in permanent exemptions, and approximately SEK 3 million in fixed-term exemptions calculated as benefit cost savings.

Outcome of saving expectations on the benefits

The total savings of SEK 1,188 million calculated to 2017 thus in total exceed the estimated savings by some SEK 13 million (see Table 6).

Compared to the December 2016 follow-up report regarding analysis of the developments of pharmaceutical expenditure and savings, savings have decreased by just over SEK 10 million. This decrease is due to the fact that the planned price reduction according to the 15-year rule for the blood cancer pharmaceutical Glivec (substance imatinib) in December 2016 was not implemented before generic competition occurred.

The method used to calculate the effect of the 15-year rule excludes pharmaceuticals that were first included in the product-of-the-month system. This mainly affects the estimated outcome for 2017, where savings are now estimated to amount to SEK 52 million compared to SEK 62 million according to the previous calculation from autumn 2016. However, the savings on Glivec (imatinib) are significantly greater than the 7.5 percent in the product-of-the-month (see Table 2).

The effects of the 15-year rule have been described based on the pharmaceuticals that will potentially have lower prices in the future. Those already under the ceiling

for the 15-year rule are not included. Even pharmaceuticals whose prices have already been lowered by generic competition are excluded from the calculation. As stated above, the savings provided by the 15-year rule are ascribed to this intervention, even if the price has already been reduced due to a reassessment. Only reassessments where a decision has been made are covered by the calculation.

Table 6. Current situation and projection of savings on benefit costs 2014 - 2017, million SEK * (previous report in November 2016 in brackets)

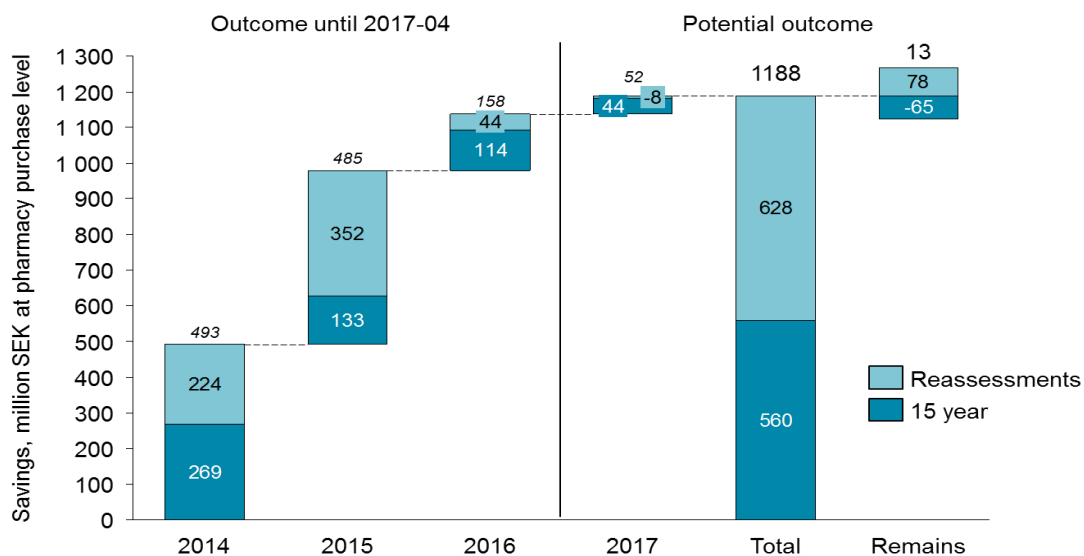
Status	Year	Reassessments	15-year rule	Total	Accumulated savings
Outcome	2014	224	269	494 (493)	494 (493)
Outcome	2015	352	133	485 (483)	979 (976)
Outcome	2016	44	114	158 (159)	1 136 (1135)
Partial outcome *	2017	8	44	52 (62)	1 188 (1197)
	Total	628	560	1 188 (1 197)	3 797 (3 802)

Note: * Outcome 2017 regarding known reassessments as well as preliminary outcome of the 15-year rule. The projection uses moving annual total through April 2017.
Source: E-health authority and TLV analysis

Total savings between 2014 and 2017 are estimated to amount to SEK 3.8 billion compared with expectation of approximately SEK 3.4 billion. The total savings thus exceed the expectation by SEK 400 million. It is the earlier accrued savings from the reassessments that have generated the increased overall savings.

The figure below shows the outcome broken down by reassessments and the 15-year rule.

Figure 17. Current situation and projection of savings, 2014 - 2017, broken down into reassessments and the 15-year rule (SEK million).



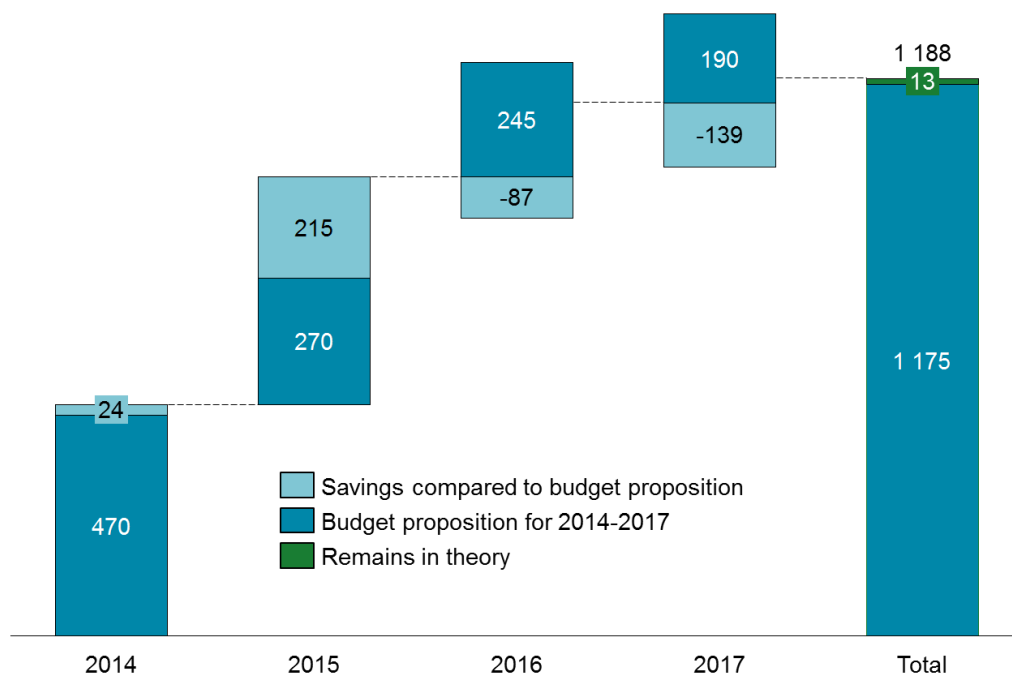
Source: E-health authority and TLV analysis
Note: 2017 outcome in part

By 2017, the effect of the reassessment of the blood cancer pharmaceutical Revlimid will be included. This reassessment led to a 5% price reduction for Revlimid, which came into force on April 1, 2017, and is expected to generate benefit cost savings of SEK 15 million on a full-year basis, or approximately SEK 10 million in 2017. In general, reassessments are expected to generate benefit cost savings of SEK 628 million, which is SEK 78 million more than the expected SEK 550 million. The extent of the savings resulting from reassessments was greater in the period 2014-2015 compared with the period 2016 to 2017. However, only reassessments for which a final decision has been made are included in this calculation for 2017.

As stated in the previous section, the 15-year rule has not generated as much savings as initially estimated. It is expected to give savings of approximately SEK 560 million, which is SEK 65 million less than the expectation of SEK 625 million.

Figure 18 illustrates savings compared to expectation and shows that the savings have been achieved earlier, especially in 2015.

Figure 18. Outcome of savings compared to expectations according to the budget proposition for 2014, 2014 - 2017, SEK million.



Source: E-health authority and TLV analysis
Note: 2017 outcome in part

In the section below, reassessments that have been carried out are reported individually with the date of price reduction as well as the savings for the benefits scheme and for the patient.

Method for savings calculation

To calculate the savings resulting from the measures taken until April 2016, the following analysis has been made.

The analysis is based on sales data for the period 2011-01-01 to 2015-08-01 (benefits, AUP, packaging, doses, ddd; prescribed with benefit). Sales data are linked to information on substitutability at the lowest level (substitution level-3). Substitution level-3 means substitutability at the level of substance, form of preparation and strength (based on a decision by the Medical Products Agency).

The analysis is made at the level of substitution level-3 and for each sales month, the AUP sales value is calculated per unit. Units are defined by DDD in cases where they are registered for the substitution group and by doses (tablets, liquid volumes, etc.) in cases where DDD is not registered. Since exchange groups can arise over time, the historical calculations may also change.

Changes in AUP per unit compared to the previous month are multiplied by sales volume (units) 12 months back in time (moving 12). An aggregate cost change for the exchange group (AUP moving 12) is then obtained for each individual month. Only positive savings effects have been included and for the 15-year rule, price changes over 8 percent have been excluded in order not to risk capturing price reductions due to generic competition. Change of benefit cost is based on multiplication of cost change AUP with benefit ratio (benefit / AUP) in the exchange group.

The interventions TLV implemented within the framework of the reassessments and the 15-year rule are linked to the individual months when the estimated cost changes are expected to occur following price change decisions. Cost changes four months ahead are summarized to obtain the full effect of the intervention.

For unrealised savings and expected savings, product-level savings are calculated by multiplying the difference between the current AUP price level and the price following the expected reduction with the sales volume during 2014 (number of packages). The benefit cost saving is the calculated savings multiplied by the benefit ratio (benefit / AUP) that the product had in 2014.

Appendix 3: TLV reassessments carried out in 2015, 2016 and 2017

Table 7. Reassessments carried out in 2015, 2016 and 2017

Substance	Date of price reduction	Saving* AUP (SEK million)	Saving* benefits scheme (SEK million)	Saving* for patients (SEK million)
formoterol	2015-04	2.0	1.5	0.5
flutikasonpropionat	2015-04	9.5	4.8	4.7
salmeterol	2015-04	2.9	2.2	0.7
budesonid	2015-04	52.9	28.4	24.5
salbutamol	2015-04	4.4	2.5	1.8
mometasonfuroat	2015-04	0.1	0.1	0.0
indakaterol	2015-05	1.1	0.9	0.2
adalimumab	2016-01	41.7	41.1	0.5
certolizumabpegol	2016-01	6.5	6.4	0.1
darifenacin	2016-01	1.0	0.8	0.2
etanercept	2016-01	20.1	19.8	0.3
golimumab	2016-02	19.9	19.6	0.3
tafluprost	2016-04	1.0	0.7	0.3
bimatoprost	2016-04	2.2	1.4	0.8
travoprost	2016-04	4.5	2.9	1.6
certolizumabpegol	2016-10	2.5	2.5	0.0
golimumab	2016-10	9.4	9.3	0.1
lenalidomid	2017-04	14.9	14.8	0.1

AUP= pharmacy sales price level.

Source: TLV