A review of medicines for lowering blood pressure
A REVIEW OF MEDICINES FOR LOWERING BLOOD PRESSURE

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Vice Association Chairperson David Magnusson

General information on therapeutic groups:
ATC-codes: C02, C03, C07, C08 and C09
Why is the LFN conducting a review?

On adopting new reimbursement rules in October of 2002, it was not practically possible to review all medicines according to the new rules. Therefore, the LFN is now conducting a review of approximately 2,000 medicines to see if they should continue to be given reimbursement status in the future. Each of the medicines will be tried according to the new rules and will either retain or lose reimbursement status.

More health per tax crown
The purpose of the new reimbursement rules is to allow the Swedish population to extract as much health value as possible for every tax crown allocated to medicines. We eliminate those medicines that do not show sufficient effectiveness in relation to what they cost. However, this does not mean that we aim only to have inexpensive medicines in the medical reimbursement system. If a medicine has positive effects on a person’s health and quality of life, and on a socio-economic level as a whole, then it may also be worth paying for.

Three principles for making decisions
In reimbursement decisions for a medicine, we shall, among other things, evaluate whether or not it is cost-effective. This means that we weigh the effectiveness of the medicine against its cost. We also incorporate other principles into our evaluation: the needs and solidarity principle, which means that those who have the greatest medical needs shall receive more of our healthcare resources than other patient groups; and the human value principle, which means that we must respect the equal value of all individuals.

49 groups to be reviewed
In this review we are testing medicines in one therapeutic area after another. The review encompasses a total of 49 groups of medicines and the order in which they are tested is determined by how large the sales figures were for each respective group in 2003. The medicines that sold the most will be reviewed first.

Extensive research and groundwork
Before any decision is made, we perform a comprehensive investigation and analysis of data on medical effect and cost-effectiveness which we request from pharmaceutical companies in regard to their medicines. We also review the scientific, medical, and health economic literature available for the group
of medicines to be reviewed. In addition, we sometimes need to construct our own health economic models. We publish each completed review in a final report. The report documents the existing body of scientific knowledge for the group in question. Where possible, the agency also reports on an evaluation of each medicine’s cost-effectiveness. We also prepare a synopsis of the report to be printed separately.

**Assessment by independent external experts**
The assembled knowledge in regard to medical effect and health economic documentation which we present in the final report has been assessed by independent external medical experts. The report has also been circulated for comments to the SBU (The Swedish Council on Technology Assessment in Health Care), Medical Products Agency and the National Board of Health and Welfare. The companies and patient organisation groups concerned, as well as the county councils’ pharmaceutical reimbursement group, have also had the opportunity to give input.
A review of medicines for lowering blood pressure

The LFN (Läkemedelsförmånsnämnden) has concluded a review of medicines used to treat hypertension. In total the review covered approximately fifty pharmaceutical substances and a large range of products (original brands, generics and parallel imports) already part of the pharmaceutical reimbursement scheme.

This review is part of our ongoing evaluation of the entire list of medicines approved for pharmaceutical reimbursement. In it we establish whether a drug already reimbursed, should also be reimbursed in the future. Each medicine is evaluated and will either retain or lose its reimbursement status. The purpose of the exercise is to extract as much health as possible for every tax crown expended on medicines. This is the fourth therapeutic group to be presented. In earlier reviews we have treated the results from medicines against migraine, stomach acid and asthma, chronic obstructive pulmonary disease (COPD) and coughing.

Six groups of hypertension drugs
The treatment of hypertension today consists of medicines which affect the body in many different ways. The same medicine is used to treat a number of different diseases such as hypertension, heart failure, arrhythmia and the prevention of migraine. A number of medicines are also available as a fixed combination substance. The medicines used to treat hypertension are often divided into groups. These are:

- anti-hypertensive substances
- diuretics
- betablocking medicines
- calcium channel blockers
- ACE inhibitor (angiotensin converting enzyme)
- ARB (angiotensin-receptor-blockers)

Many companies decreased their price in order to retain reimbursement
One finding from our review is that prices vary greatly for many medicines used for treating hypertension despite having a similar effect. Many companies have chosen to decrease their prices in connection with our review in order to retain reimbursement status. These price decreases represent a savings of approximately 115 million Skr per year.
Three active substances lose reimbursement

In total approximately 46 pharmaceutical substances retain reimbursement. For 23 of these substances the reimbursement granted is restricted. In total society is estimated to save approximately 30 million Skr per year for the three medicines which will no longer be part of the reimbursement scheme. The choice to restrict reimbursement for a number of products depends on one of two things: either there are cheaper alternatives within the system or there are patient groups with special needs who cannot use the cheaper alternatives. Our estimates show that there is a further 250 million Skr which can be released into the system if givers of healthcare follow our restrictions for angiotensin-receptor-blockers (ARB).

**General and restricted reimbursement**

There are two types of reimbursement within the pharmaceutical reimbursement scheme:

- General reimbursement means that a medicine receives reimbursement for the whole of its approved area of use.

- Limited reimbursement means that a medicine is reimbursed only for a specific area of use or a specified patient group.

It is important that the county councils develop a support mechanism for prescribers to make it easier for doctors to follow restrictions so that decisions coming from the LFN are able to contribute to a cost-effective use of medicines.

**Total potential savings of almost 400 million Skr**

This review represents a total potential savings of 400 million Skr. The decisions come into force on the 1st of September 2008 regardless of whether they have been appealed or not. It is only if a court repeals a decision that the medicine in question has the possibility to reenter the benefits system. A list of the decisions which have been appealed will be available on our website at www.lfn.se.
Medicines and substances for treating high blood pressure which either lose reimbursement or receive restricted reimbursement from the 1st of September 2008

Table 1: Three medicines lose reimbursement completely.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Therapeutic group</th>
<th>Original product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lerkanidipine</td>
<td>Calcium channel blocker</td>
<td>Zanidip</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>ACE inhibitor</td>
<td>Inhibace, Inhibace Comp</td>
</tr>
<tr>
<td>Trandolapril and verapamil</td>
<td>ACE inhibitor, combination</td>
<td>Tarka</td>
</tr>
</tbody>
</table>

Table 2: Medicines which have lost their reimbursement and where another product containing the active substance will be available within the benefits system.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Therapeutic group</th>
<th>Original product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isradipine*</td>
<td>Calcium channel blocker</td>
<td>Lomir</td>
</tr>
<tr>
<td>Nifedipine, long-acting*</td>
<td>Calcium channel blocker</td>
<td>Adalat Oros</td>
</tr>
<tr>
<td>Kinapril**</td>
<td>ACE inhibitor</td>
<td>Accupro, Accupro Comp</td>
</tr>
</tbody>
</table>

* The substances will still be available in a reimbursed version, but on restriction (see Table 5).

** The substance will still be available on reimbursement, even though the original brand Accupro loses its reimbursement.

Table 3: All ARBs get limited reimbursement.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Therapeutic group</th>
<th>Original product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan*</td>
<td>ARB</td>
<td>Cozaar, Cozaar Comp, Cozaar Comp Forte</td>
</tr>
<tr>
<td>Eprosartan*</td>
<td>ARB</td>
<td>Teveten, Teveten Comp</td>
</tr>
<tr>
<td>Valsartan*</td>
<td>ARB</td>
<td>Diovan, Diovan Comp</td>
</tr>
<tr>
<td>Irbesartan*</td>
<td>ARB</td>
<td>Aprovel, CoAprovel</td>
</tr>
<tr>
<td>Kandesartan*</td>
<td>ARB</td>
<td>Atacand, Atacand Plus</td>
</tr>
<tr>
<td>Telmisartan*</td>
<td>ARB</td>
<td>Micardis, Micardis Plus</td>
</tr>
<tr>
<td>Valsartan and amlodipin</td>
<td>ARB combination</td>
<td>Exforge</td>
</tr>
</tbody>
</table>

Restriction: ARB is reimbursed only for patients who have tried but cannot use ACE inhibitors or as a complement to an ACE inhibitor.

* Also as fixed combinations containing hydrochlorothiazide.
Table 4 All beta blockers get limited reimbursement.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Therapeutic group</th>
<th>Original product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pindolol</td>
<td>Beta blockers</td>
<td>Viskén</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Beta blockers</td>
<td>Inderal, Inderal Retard</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Beta blockers</td>
<td>Seloken, Seloken Zoc</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Beta blockers</td>
<td>Tenormin</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Beta blockers</td>
<td>Emconcor</td>
</tr>
<tr>
<td>Karvedilol</td>
<td>Beta blockers</td>
<td>Kredex</td>
</tr>
</tbody>
</table>

Restriction: For newly commenced treatment of hypertension the above beta blockers are reimbursed only if patients have first tried other groups of medicines.

Labetalol         | Beta blockers     | Trandate                  |

Restriction: Labetalol is reimbursed only for treatment of hypertension during pregnancy.

Table 5: Four calcium channel blockers get limited reimbursement.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Therapeutic group</th>
<th>Original product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isradipine, long-acting</td>
<td>Calcium channel blocker</td>
<td>Lomir SRO</td>
</tr>
</tbody>
</table>

Restriction: Long-acting Isradipine (Lomir SRO) is reimbursed only for treatment of hypertension during pregnancy.

Nifedipine             | Calcium channel blocker      | Adalat                   |

Restriction: Short-acting Nifedipine (Adalat) is reimbursed only for treatment of hypertension during pregnancy and for the treatment of Morbus Raynaud.

Verapamil              | Calcium channel blocker      | Isoptin, Isoptin Retard  |

Diltiazem              | Calcium channel blocker      | Cardizem, Cardizem Retard, Coramil, Unotard |

Restriction: For treatment of hypertension, diltiazem and verapamil are reimbursed only if the patient cannot use vasodilating calcium channel blockers.

Table 6: One ACE inhibitor gets limited reimbursement.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Therapeutic group</th>
<th>Original product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosinopril</td>
<td>ACE inhibitor</td>
<td>Monopril</td>
</tr>
</tbody>
</table>

Restriction: Fosinopril is reimbursed only for patients with severe kidney function problems.

Table 7: One diuretic gets limited reimbursement.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Therapeutic group</th>
<th>Original product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torasemide</td>
<td>Diuretic</td>
<td>Torem</td>
</tr>
</tbody>
</table>

Restriction: Torasemide is reimbursed only for patients needing loop-diuretics but who cannot use furosemide.
Table 8: Three antihypertensive agents get limited reimbursement.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Therapeutic group</th>
<th>Original product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metyldopa</td>
<td>Antihypertensive agents</td>
<td>Aldomet</td>
</tr>
<tr>
<td><strong>Restriction:</strong> Methyldopa is reimbursed only for treatment of hypertension during pregnancy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxonidine</td>
<td>Antihypertensive agents</td>
<td>Physiotens</td>
</tr>
<tr>
<td>Doxazozin</td>
<td>Antihypertensive agents</td>
<td>Alfadil</td>
</tr>
<tr>
<td><strong>Restriction:</strong> For treatment of hypertension doxazosin and moxonidine are reimbursed only if the patient has first tried other groups of medicines.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These medicines turnover approximately 2 billion Skr
Sales of hypertension drugs within the benefits system reached 2.4 billion Skr in 2007 and are dominated by ARB drugs which stand for approximately 40 percent of sales value.

Socio-economic costs amount to some billions
Treatment of a particular disease does not only consist of costs for medicines. The disease can also cause other costs for society. Hypertension itself does not lead to high costs for society. However the diseases avoided by treating hypertension do lead to high costs. Examples of such diseases are stroke and heart failure which cost society a number of billions of Skr annually.

Principles for granting reimbursement
When judging if a medicine shall be included in the pharmaceutical benefits system we take the three principles detailed in the law on pharmaceutical benefits into account.

The three principles are:
- cost-effectiveness principle
- need and solidarity principle
- human value principle

We must evaluate if the use of a medicine is cost-effective, meaning that we weigh the utility of the medicine against the cost. We shall also observe the other two principles. The need and solidarity principle means that those in greatest medical need shall have more of healthcare resources than other patient groups. The human value principle means that the healthcare system shall have respect for the equal value of all people.

Similar effect – price comparisons sufficient
The health economic literature shows that the value of treating hypertension easily matches the cost of the treatment. However, we make decisions on in-
individual products. Therefore we are interested in how effective the medicines included in the review are when compared to each other.

The medical literature shows that effects and sideeffects are in the main similar for the different medicines when used in treating high blood pressure. Therefore comparing the cost of the pharmaceutical is enough to judge the cost-effectiveness for each medicine. The cost-effectiveness analysis in this review is as a result reduced to in many parts being a cost comparison.

**Important with a wide range of products**

There is a great need for a wide range of medicinal products which treat hypertension. One reason for this is that many patients need more than one medicine to treat their blood pressure. Often the same patient needs drugs from a number of different groups of medicines. At the level of the individual different patients can respond in different ways to treatment using the same medicine.

If we were to interpret the cost-effectiveness principle too narrowly then this would mean that we would only have one medicine left in many therapeutic groups. This would not however lead to a cost-effective use of the medicines. There is great value in having access to a number of different medicines in the same group. To a large extent this is why we let prices vary somewhat and have introduced a pricing corridor.

This means that we accept a higher price for a hypertension drug if the company marketing it can show that the medicine is a cost-effective alternative even at a higher price. A medicine which is considerably better than the others may be allowed a price which is over and above the pricing corridor.

**Reasoning behind decisions**

In the following sections we briefly account for the decisions where we have changed the reimbursement status of the medicine in question, in other words the medicine which has lost its reimbursement or received limited reimbursement. If you would like a more detailed picture of the other decisions then there is more information in the final report available on our website. There you can also read more on each individual decision.

Following all of the price decreases and with the price variance we allow using the pricing corridor most of the medicines retain their reimbursement. Only three active substances disappear completely from the benefits scheme while 23 of them get a limited reimbursement.
Of the 23 restrictions most of the medicines are in the groups of medicines known as ARB and beta blockers. All medicines within these two groups get limited reimbursement.

The three active substances which disappear from the scheme are a calcium channel blocker, an ACE inhibitor and a combination substance. There is also one original substance which disappears but there will be an alternative left within the system for this. This is for the ACE inhibitor Accupro which costs too much compared to the cheaper copies.

**Medicines leaving the benefits system**
In this section we briefly account for the reasons behind the decision to exclude the three active substances from the benefits system.

*Lercanidipine (Zanidip), cilazapril (Inhibace and Inhibace Comp) as well as trandolapril and verapamil (Tarka)*
Treatment using Lercanidipine, cilazapril and trandolapril and verapamil are not cost-effective compared to well-documented and cheaper medicines. The prices are too high in comparison to the alternatives.

The pharmaceutical companies Meda, Roche and Abbott Scandinavia have not submitted any documentation showing that their medicines have a better effect than other similar medicines and which supports the high price the companies want to charge.

**Medicines losing reimbursement but where the substance remains in the benefits system**
In this section we account for the reasons behind decisions for medicines losing their reimbursement but which in some form will remain in the benefits system.

*Isradipine (Lomir) and long-acting Nifedipine (Adalat Oros)*
The prices for Isradipine and long-acting Nifedipine are too high. A general treatment using these substances is therefore not cost-effective compared to well-documented and cheaper medicines. Lomir and Adalat Oros will therefore be excluded from the benefits system. However it is important to reimburse these active substances for a limited group of patients (see below).
**Kinapril (Accupro)**
The price for the original medicine Accupro is too high and treatment using this medicine is not cost-effective compared to better-documented and cheaper medicines. A generic form of kinapril at a lower price will be retained in the reimbursement system.

**Medicines attaining limited reimbursement**
In this section we account briefly for the medicines where we have chosen to limit reimbursement, either as a second line treatment or for patient groups with special needs.

**All ARB medicines get limited reimbursement**
All ARB medicines get limited reimbursement. ARB shall be reimbursed for patients who have tried but cannot use ACE inhibitors or as a complement to ACE inhibitors.

The prices for ARB medicines are too high for a general treatment using these substances to be considered cost-effective compared to well-documented and cheaper medicines. There are however smaller groups of patients where treatment with ARB medicines can be cost-effective compared to cheaper alternatives.

When treating patients with an uncomplicated form of hypertension calcium antagonists or a low dose of tiazide should be tried before treating the patient with ARB drugs.

**Limited reimbursement for all beta blockers**
All beta blockers will receive limited reimbursement on a group level. When commencing treatment for hypertension the medicines shall only be reimbursed for patients who have first tried other groups of medicines and not achieved their treatment objectives.

The SBU (Statens Beredning för Medicinsk Utvärdering) and Medical Products Agency (MPA) have concluded that beta blockers are not as good as the other large therapeutic groups for the treatment of high blood pressure. These conclusions are also supported in a number of newly published studies and meta-analyses.

Despite these findings beta blockers have a well-documented effect and an accepted place in therapy. For some patients who have tried some of the other therapeutic groups to lower blood pressure but not achieved the treatment objective, it may be both urgent and cost-effective to use beta blockers. Many
patients also use beta blockers to treat a number of other conditions. Beta blockers have demonstrated a good effect for treatment of conditions such as angina, heart failure and arrhythmia and will continue to be reimbursed for these conditions.

There is one exception to this where a beta blocker has its own restriction. This is for labetalol (Trandate) where we judge it to be important to reimburse the medicine for pregnant women. The MPA presents labetalol in its treatment recommendations ”Treatment of hypertension during pregnancy” from 1996 as an alternative for treatment of hypertension during pregnancy.

Four calcium channel blockers receive limited reimbursement
In total reimbursement will be restricted for four different active substances in this class. Long-acting Isradipine (Lomir SRO) will only be reimbursed for treatment of hypertension during pregnancy. Nifedipine (Adalat) will also be restricted but here the restricted use is for pregnant women and patients suffering from Morbus Raynauds disease.

In their treatment recommendations in ”Treatment of hypertension during pregnancy” from 1996 the MPA indicate Isradipine and Nifedipine as alternatives for treatment of hypertension in connection with pregnancy. Adalat is one of very few medicines approved for treatment under the indication Morbus Raynauds disease. This is an important condition to treat. The condition means the patient’s fingers and possibly toes turn blueish, lose feeling and can be damaged permanently.

General treatment using Isradipine and Nifedipine is however not cost-effective in comparison with well-documented and cheaper medicines as the prices for these substances are too high.

For treatment of hypertension verapamil (Isoptin and Isoptin Retard) and diltiazem (Cardizem, Cardizem Retard, Cardizem Unotard and Coramil) will only be reimbursed for patients who cannot use the calcium channel blockers amlodipine or felodipine. The prices for these medicines are too high and for that reason general treatment using these substances are not cost-effective in comparison with well-documented and cheaper medicines.

For treatment of angina the medicines shall continue to be reimbursed.

One diuretic gets limited reimbursement
Torsamide shall only be reimbursed for patients needing loop-diuretics but who cannot use furosemide. The price for torasemide cannot be supported
in view of the availability of cheaper diuretics and ACE inhibitors. General
treatment with this substance is not cost-effective in comparison with well-
documented and cheaper medicines.

It is however important to be able to offer loop diuretics as a treatment
alternative for some patients. In the cases where these patients cannot take
furosemide then torasemide is the only approved treatment alternative left.
Within this limited group it is reasonable for torasemide to receive continued
reimbursement.

**One ACE inhibitor gets limited reimbursement**
Monopril is only reimbursed for patients with seriously decreased kidney
function. The medicine is the only alternative for patients with decreased
kidney function if treatment is necessary using an ACE inhibitor. General
treatment using Monopril is however not cost-effective in comparison to
well-documented and cheaper medicines.

**Three antihypertensive agents get limited reimbursement**
Methyldopa (Aldomet), Moxonidine (Physiotens) and Doxazosin (Alfadil) all
get limited reimbursements. The medicines are not cost-effective compared
to other well-documented and cheaper blood pressure decreasing medicines.

Aldomet shall only be reimbursed for hypertension during pregnancy while
Physiotens and Alfadil, when they are used to lower blood pressure shall only
be reimbursed for patients who have first tried other groups of medicines but
not reached their treatment objectives.

In their treatment recommendations ”Treatment of hypertension during
pregnancy” from 1996 the MPA presents Methyldopa as a medicine without
any known deformity-inducing effects.

The medicine also adds a further effect mechanism for the treatment of
hypertension and is possible to combine with all of the five larger therapeutic
groups. This makes moxonidine a further possibility for combination treat-
ment.

The Medical Products Agency recommends the use of alpha blockers (doxa-
zosin) in its treatment recommendations from 2006 as an alternative com-
plementary therapy when the patient has tried the larger therapeutic groups.
There may therefore be some patients who need doxazosin as a treatment
option in complex cases.
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Procedure 2 – Work process and starting points for collating knowledge on health economics
1. Introduction

When Sweden implemented new rules for reimbursement the 1st of October 2002 it was not practically possible to immediately evaluate all of the medicines already reimbursed in accordance with the new rules.

The LFN is carrying out a review of approximately 2000 reimbursed medicines to ascertain if these should also in the future retain reimbursement. In the reviews we evaluate the medicines therapeutic area by therapeutic area. Medicines for lowering blood pressure are included in the group we are evaluating here.

In total the review covers 49 therapeutic groups and the order they are dealt with is decided based on how large the turnover was for each group in 2003. We treat the groups with the largest turnover first.

This final report is structured so that we first present various aspects of having high blood pressure. In chapter 2 we describe the condition and the follow on diseases for which people with hypertension run an increased risk. We also briefly describe some of the other diseases which can be treated using the medicines we discuss in this review.

In chapter 3 we go through the various medicines in the sub-groups. This division follows the international ATC code system.

In chapter 4 we describe the method we use to search for literature in the first phase of each review. In the chapter after that we detail the result of this search and the basis of fact we use later in the review.

In chapter 6 on health economics we write on the socio-economic costs which arise as a result of hypertension and how hypertension affects the quality of life of those afflicted with the condition.

In chapter 7 we begin by detailing the principles our decisions are based on and then continuing to describe our decisions. Chapter 8 comprises all of the decisions we have made based on our own initiative in this review and chapter 9 accounts for the price decreases we have made decisions on following applications from companies. Chapter 10 covers the reasons for our decisions.
2. The therapeutic group

- Estimates show that approximately 1.8 million Swedes suffer from hypertension and approximately 1.4 million need pharmaceutical treatment for their high blood pressure.
- There are a number of different groups of medicines which lower blood pressure and within each group there is a number of active substances.
- To achieve the treatment objectives a combination of two or more medicines is often needed.
- SCORE is an instrument for estimating the risk for cardiovascular disease and is based on observations for over 200,000 European patients.

2.1 A description of hypertension and its follow-on diseases
Approximately 1.8 million Swedes are estimated to suffer from hypertension and of these about 90 percent have mild to moderately raised blood pressure levels.[1] Roughly a third of the patients are 70 years or older meaning that every second person over the age of 65 has high blood pressure. Calculations show that approximately 1.4 million Swedes need pharmaceutical treatment for their high blood pressure.

All of the medicines the LFN has now gone through are used for treating hypertension but many of them are also used for treating other conditions, symptoms and diseases. The most common of these diseases is heart failure which afflicts two to three hundred thousand Swedes.

In this report we have mainly evaluated medicines in relation to their ability to cost-effectively treat high blood pressure. We have also overviewed the effect of the medicines in their treatment of heart failure.

We have not however examined the effect of the medicines in the treatment of the following diseases: angina, oedema, disturbances in the heart’s natural rhythm, peripheral cardiovascular diseases including Raynauds disease, prevention of migraine, kidney disease and some types of tremors. In some cases we comment on this further under each medicine in Chapter 3 and 10.

Hypertension
A condition which can become an illness
Hypertension is also called high blood pressure.[1] People with too high blood pressure have an increased risk of being afflicted by stroke (minor heart
attacks), myocardial infarction or heart failure. Coronary heart disease is the most common cause of death in Sweden. Hypertension can be serious if it is not controlled and treated, but often does not show any clear symptoms or warning signs. If a person has been afflicted by hypertension then the condition is often for the rest of that person’s life.

Two different types of pressure, systolic and diastolic
Blood pressure is the pressure which arises in the blood vessels when blood is pushed out by the heart to all of the organs and body parts. Blood is pumped out in the vessels at the rate of 60 to 70 heartbeats per minute when the body is at rest. Blood pressure is at its highest when the heart is contracting, and this is called systolic blood pressure. When the heart relaxes and rest between contractions blood pressure decreases to its lowest level, called diastolic blood pressure.

Blood pressure varies
Blood pressure is normally measured in millimetres of quicksilver, mm Hg, and is always indicated with two figures, for example 120/80. First we indicate the systolic pressure and then after the slash we indicate the diastolic pressure. How high the pressure is depends on how much blood is being pumped out, how strongly the heart contracts and the resistance in the smaller blood vessels out in the body. Blood pressure is not constant and varies over the day. It is higher when a person is physically active or upset and lower when a person relaxes and rests. Blood pressure is as a rule at its lowest during sleep in the latter part of the night.

What is too high when it comes to blood pressure?
Normal systolic blood pressure is around 110 - 130 mm Hg. A normal value for diastolic pressure is around 80 mm Hg. There is no well-defined border between normal blood pressure which can be said to be safe and one which is dangerous. Blood pressure over 140/90 mm Hg is characterised as high blood pressure. This does not mean that everyone with blood pressure over 140/90 needs pharmaceutical treatment.

Is it dangerous to have high blood pressure?
Hypertension makes it harder for the heart to pump and in the long-term makes the artery walls harder and less elastic. The risk in particular for stroke increases and also the risk of myocardial infarction, heart failure and worsened blood circulation in the legs. Lifestyle and age also affect blood pressure. For most people it is not possible to find one factor which has caused the high blood pressure. A number of factors can combine, such as inherited susceptibility, obesity, stress, eating habits and high alcohol consumption. In
our culture blood pressure, mainly the systolic kind, increases with age. This type of high blood pressure, which is the most common, is called primary or essential hypertension. Blood pressure can be lowered and sometimes kept under control by changes in lifestyle. Often pharmaceutical treatment is needed to reach the target blood pressure.

*Secondary hypertension*
For approximately 5% of people with hypertension the condition is due to a single, and sometimes treatable, factor. Then it is called secondary hypertension. Most common here is an underlying kidney disease. Other causes can be side-effects from medicines, such as oral contraceptives, complications when pregnant, or various hormone imbalance diseases. In these types of diseases too many hormones form and this increases the blood pressure. A narrowing of the main aorta, coarctatio, leads to elevated pressure only in the upper half of the body. This can be operated on, normally during childhood, and blood pressure afterwards is most often normal.

*A common condition*
Approximately every tenth citizen has hypertension which demands some form of treatment. If you only count the adult population then this number may be around every fifth person. A little more than half a million Swedes regularly take medicine for high blood pressure. Hypertension is therefore a common disease in our country. It is one of the absolutely most common reasons for regular visits to the doctor. For younger people and in middle age it is more common in men. For older people it is the other way around, hypertension is somewhat more common for women. Hypertension increases in industrial countries as a person’s age increases.

*When does hypertension become a disease?*
Moderately raised blood pressure is not classed as a disease. It is rather a condition which holds an increased risk for illnesses and early death. It is when the high blood pressure has begun to give a measurable effect on the heart, brain or kidneys that it should be classed as a disease. Untreated hypertension leads in the long run to damage to the body’s blood vessels in the form of arteriosclerosis and can then damage other organs. The risk for damage to the heart and in blood vessels increases the more risk factors a person displays. Examples of risk factors which the individual can influence are:

- smoking tobacco
- high cholesterol values
- controlling diabetes
• obesity
• wrong foods
• sedentary lifestyle
• high alcohol consumption

Three risk factors which cannot be influenced are
• age
• gender
• inherited susceptibility for coronary heart disease at an early age.

Arteriosclerosis in the brain leads to a narrowing of the small blood vessels inside. If a small blood clot then completely blocks the vessel this can lead to stroke which can affect speech or cause paralysis on one half of the body. Included in the term stroke is cerebral haemorrhage, which can cause similar symptoms to a clot but is a considerably less common complication. Hypertension can also contribute to myocardial infarction and heart failure. The blood vessels in the kidneys, eyes and legs can also be damaged by high blood pressure.

Symptoms
It may be possible to discern mild symptoms of high blood pressure such as a light headache and tiredness. Many people walk around with too high blood pressure and do not feel anything at all. The only way to know for sure if your blood pressure is elevated is to measure it. For really high blood pressure, malignant hypertoni, there may be clearer symptoms such as tiredness, nausea, severe headache and breathing difficulties. This is a life-threatening condition which is very unusual.

Systolic pressure most important
Systolic pressure is the best one at forecasting the risk of complications, at least if the patient is over 50 years old. One reason is that systolic pressure increases more with age and the less elastic the artery walls are. This reflects the degree of arteriosclerosis. Isolated systolic raised blood pressure means that the systolic pressure is higher than 140 while the lower one is normal, that is below 90. This is the most common form of hypertension for older people and should be treated in the same way when both types of pressure are raised.

Heart failure
For treatment of heart failure the same pharmaceutical groups as those used for high blood pressure are used to a large extent.
The pump is weakened
Heart failure is a condition meaning the heart cannot pump out enough blood into the body.[2] The condition often develops by degrees and can have existed for quite a while before any clear signs are noticed. Heart failure is also called heart compensation or heart insufficiency.

What happens when heart failure occurs?
When a person suffers from heart failure their heart cannot pump out enough blood into the body, meaning that the cells get too little sustenance and oxygen, resulting in the person becoming sick. Worsened blood flow can be because the heart cannot contract strongly enough or that the walls are too inflexible, meaning the heart has a difficult time filling up with enough blood in the relaxation phase. It could also be because the valves are not functioning properly, for instance they may not be opening enough or are not closing tightly enough to protect from backflow.

Common disease for older people
Approximately one out of a hundred people suffer from heart failure in their fifties, while every tenth person over the age of 70 is afflicted. Almost a third of all hospitalisations in regard to heart problems are made up of people with heart failure. Modern treatment using new medicines and other methods have been successful in increasing survival rates, increasing well-being and also decreasing the need for hospitalisations.

Hypertension and myocardial infarction common causes
The causes of heart failure are many and sometimes there is more than one reason. Heart failure can be due to:
• myocardial infarction
• high blood pressure
• cardiomyopathy, a disease which weakens the heart muscle
• valves or congenital heart disease
• rhythmic problems, too slow or too fast
• alcohol abuse
• follow-on from some other disease such as severe anaemia, lung disease, thyroid disorder, or diabetes
• diseases of the pericardium.

How dangerous is heart failure?
During later years medical knowledge on heart failure has increased and the treatment improved. This has decreased morbidity and improved quality of life for those affected. But heart failure is still one of the most difficult heart
illnesses, and survival depends on how serious the heart failure is. Approximately half of everyone with heart failure will die from the disease within five years of being diagnosed, but many can live considerably longer. This depends on age, how difficult the heart failure is and any other illnesses.

Gradually quality of life is affected
An older person with moderate heart failure and the right treatment can live roughly the same as a person of the same age without heart failure. When the disease gets worse the symptoms can get stronger and then it can be hard to even manage some moderate physical activity. Finally the worsened ability to pump blood affects the ability to carry out daily activities and the person becomes dependent on the help of others. The symptoms can also become worse if one is affected by other diseases which put the heart under strain such as the flu or lung infections.

Tiredness and breathing difficulties the most common symptoms
It is often difficult to know if you have heart failure as there are no symptoms which are unique, they can also appear for other illnesses. The symptoms can also have differing degrees of severity, from barely noticeable to very strong and can consist of:
- tiredness
- shortness of breath
- breathing difficulty and coughing at night
- need to urinate more often at night
- increased pulse
- sudden weight increase
- swollen ankles and legs

Angina
A number of the medicines we discuss in this review are also used for treating angina, angina pectoris.

The heart, like all muscles, needs oxygen in order to function.[3] This oxygen comes to the heart through blood vessels. If these blood vessels narrow then it is possible that not enough oxygen can be transported to the heart and then this can be affected by lack of oxygen and cramp, also known as angina.

Angina is often triggered by physical exercise and is expressed mainly as a pain in the breast. The risk of getting an angina attack can decrease if one stops smoking, exercises regularly and loses weight. Most common however is that treatment using medicines is also necessary.
If the symptoms cannot be decreased using two different medicines, or if the patient has a high risk of myocardial infarction, then often a surgical procedure is carried out on the blood vessels called revascularisation.

2.2 Treatment of high blood pressure

When treating hypertension the blood pressure level one is normally trying to reach with the treatment is around 140/90.\[1\] This is often called the "goal blood pressure". For older people especially it’s hard to decrease the systolic blood pressure. If a person has diabetes, kidney disease or a known cardiovascular disease then the pressure should be around 130/80 or lower. Older people have the best protective effect from the treatment.

For some patients treatment is without medicines

If one only has a slightly elevated blood pressure level then it is often enough to have a change in lifestyle. This may not affect the blood pressure a lot but it can decrease the other risk factors for cardiovascular disease. Blood pressure is affected by weight so many are helped by losing some weight. Regular exercise such as walking has also been shown to decrease blood pressure somewhat. Consuming too much alcohol is a common and often underestimated cause of high blood pressure. Drinking less leads most often to a clear decrease in blood pressure. Eating less salt is also normally part of the advice for fighting high blood pressure. Most people eat roughly double the amount of salt as the recommended doses.

Treatment using medicines for lowering blood pressure

The idea behind treatment of hypertension is not in the first instance to make one feel better, but to lower the risk of other diseases such as stroke and myocardial infarction in the long run.\[4\] The treatment only gives some protection. One can count on the treatment decreasing the risk of stroke by roughly a third and the risk of myocardial infarction by approximately a tenth. The protective effect for myocardial infarction is fairly small.

Limits for tablet-based treatment

There is no clear border where a person ought to take medicines against high blood pressure. For blood pressure of 180/110 or higher tablet treatment is however often recommended (for example, in the MPA treatment recommendation) even if other risk factors are not present. In the area straddling blood pressures of 140/90 and 160/100 the decision depends on other risk factors such as age, gender, diabetes, blood fats and smoking. So it is not only the measured blood pressure level which decides if tablet treatment is recommended. One should take the total risk for cardiovascular disease into
account. Once a person has started to medicate they have to continue for a long time, often the rest of their lives, and that is why an active dialogue with the doctor administering the treatment is important.

### 2.3 Risk valuation in practice – SCORE

The risk factors a person has for cardiovascular disease vary in both number and degree of severity. To be able to evaluate the overall risk for future heart disease the doctor treating the patient can use a number of aids (risk estimation instruments) such as the Framingham Risk Score, UKPDS Risk Engine and SCORE.

The MPA writes in its treatment recommendation – ”Prevention of atherosclerotic coronary heart disease” that these instruments may appear to be blunt but do anyway increase the certainty of evaluations if clinical experience is also used as an evaluation tool.[5]

The Framingham instrument is based on a 50-year long follow up of risk factors as well as cases of illness and death of the population of an American city, Framingham. The UKPDS Risk Engine contains details on patients with type 2 diabetes in Great Britain.

SCORE is an instrument designed by a group of researchers from the European Society of Cardiology.[6] They have based SCORE on a number of European populations from different countries which total over 200 000 people, of which almost 90 000 are women. Since 2004 there is a version specially tailored to Swedish conditions.

The Swedish SCORE diagram is available in its entirety in this report as a concrete example of what these estimation instruments can look like.

When you use SCORE you should be aware that the instrument has certain weaknesses. One of these is that the non-response rate in SCORE is larger and therefore the detail of the background data is worse than in the Framingham study. Another limitation is that the study does not give any answers regarding which treatment the patient is on during the follow up period. The results are in the first instance valid for patients between the ages of 40 and 65 years old. Blood sugar levels and diabetes disease are not either included as a variable in SCORE. A rough estimation indicates that concurrent diabetes means the numbers can be multiplied by two for men, and by four for women.[5]
A REVIEW OF MEDICINES FOR LOWERING BLOOD PRESSURE

Figure 1: The Swedish SCORE diagram; the greyscale indicates the entire risk from low risk (white) to high risk (black). Published with permission from the European Society of Cardiology.*

<table>
<thead>
<tr>
<th>Systolic blood pressure, mm Hg</th>
<th>Cholesterol, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>1</td>
</tr>
<tr>
<td>160</td>
<td>2</td>
</tr>
<tr>
<td>140</td>
<td>3</td>
</tr>
<tr>
<td>120</td>
<td>4</td>
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<tr>
<td>40</td>
<td>8</td>
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<tr>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

3. Medicines

- Sales of blood pressure lowering medicines amount to 2 billion Skr per year.
- Today most substances have lost their patent and the price for many medicines is between 50 öre and one Skr per day.
- ARB medicines are still under patent. Therefore they cost more than most of the other medicines and together stand for approx. 40 per cent of sales in Swedish crowns within this large therapeutic group.

3.1 Pharmaceutical treatment for high blood pressure

There are many different medicines which lower blood pressure.\textsuperscript{[7]} In order to achieve the desired decrease in blood pressure a combination of two or more medicines is often needed. It is better to have two different medicines at a low dose, than one at a high dose. This gives better effect and less side-effects.

The medicines only affect blood pressure as long as the patient takes them.\textsuperscript{[4]} This means that treatment is most often for life. There are however other factors that can lead to blood pressure varying over time, for instance blood vessels can renew after a longer period of time at a lower pressure and then flow resistance lessens. This means that in some cases the doctor can lessen medication somewhat after one or two years and even at times stop medication altogether. Blood pressure should always be checked regularly and the patient should be prepared to start treatment again.

In this report all medicines are listed in accordance with the international ATC code system. Based on the ATC codes for the medicines they are normally divided into groups. The five most common groups of blood pressure medicines are: diuretics (mainly the sub-group thiazides), beta blockers, calcium channel blockers, ACE inhibitors and ARBs.

A description of these five groups and one smaller one follows below. In the following lists all registered medicines and their corresponding ATC code is included. Some are not used at all for the treatment of hypertension and are therefore dealt with only very summarily.

C 02, Other Antihypertensive agents

The medicines in this group have very limited documentation in terms of proven protective effect on heart disease and stroke.\textsuperscript{[4]} In Sweden the medicines are used only in a limited fashion as blood pressure lowering medicines.
and are not suitable as a first line choice. Alpha blockers are also used for prostate conditions.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Substance name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyldopa</td>
<td>Aldomet</td>
</tr>
<tr>
<td>klonidine</td>
<td>Catapresan</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>Physiotens and generic</td>
</tr>
<tr>
<td>doxazosin</td>
<td>Alfadil and generic</td>
</tr>
<tr>
<td>hydralazine</td>
<td>Apresolin</td>
</tr>
<tr>
<td>bosentan</td>
<td>Tracleer</td>
</tr>
</tbody>
</table>

C 03, Diuretics
Thiazines induce salt and water, although weakly, and through this decrease the blood volume.[4] Resistance decreases also slightly in the small blood vessels and this decreases the pressure. Diuretics have been around for a long time, are well-proven and decrease the risk of stroke and myocardial infarction. They have furthermore shown they can decrease osteoporosis, which can be of benefit especially for women.[5] The reason for this is that calcium losses through urine decrease.

The light diuretic effect is often not felt after a period of a week.[4] Furosemide is an example of a type of more powerful diuretic. It also decreases blood pressure, especially for diabetes and kidney diseases where it can be difficult to lower the pressure otherwise. The preventive effects against myocardial infarction and stroke has however not been documented in randomised controlled studies.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Substance name</th>
</tr>
</thead>
<tbody>
<tr>
<td>bendrofluimethiazide</td>
<td>Salures</td>
</tr>
<tr>
<td>hydrochlorothiazide</td>
<td>Esidrex</td>
</tr>
<tr>
<td>Bendrofluimethiazide and potassium</td>
<td>Centyl-K mite</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Lasix, Lasix Retard and generic</td>
</tr>
<tr>
<td>bumetanide</td>
<td>Burinex</td>
</tr>
<tr>
<td>Torasemide</td>
<td>Torem and generic</td>
</tr>
<tr>
<td>spironolactone</td>
<td>Aldactone and generic</td>
</tr>
<tr>
<td>eplerenone</td>
<td>Inspra</td>
</tr>
<tr>
<td>amiloride</td>
<td>Only generic amiloride</td>
</tr>
<tr>
<td>Combinations of hydrochlorothiazide and potassium-saving substance</td>
<td>Moduretic and generic</td>
</tr>
</tbody>
</table>
C 07, Beta blockers
Beta blockers are medicines which decrease the beat of the heart and protect it from stress hormones and make the pulse slower.[4] They also counteract a blood pressure increasing substance, renin, which can be found in the body and is especially suitable if there is concurrent angina or earlier history of myocardial infarction.

They have proven and documented blood pressure lowering effect, although latest research indicates they have a somewhat worse protective effect than other blood pressure lowering medicines, especially older ones.[7, 8] Side-effects such as depression and tiredness were more common for older forms of beta blockers as they had an effect on more types of receptors.[4] They can be less suitable for those who have especially high demands when it comes to physical activity. The most common side-effect is cold hands and feet.

Beta blockers have undesired metabolic effects, especially in combination with diuretics, (mainly in regard to glucose metabolism) and increase the risk of relapse into type 2 diabetes.[5]

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Substance name</th>
</tr>
</thead>
<tbody>
<tr>
<td>pindolol</td>
<td>Viskén and generic</td>
</tr>
<tr>
<td>propranolol</td>
<td>Inderal, Inderal Retard and generic</td>
</tr>
<tr>
<td>metoprolol</td>
<td>Seloken, Seloken ZOC and generic</td>
</tr>
<tr>
<td>sotalol</td>
<td>Sotacor and generic</td>
</tr>
<tr>
<td>atenolol</td>
<td>Tenormin and generic</td>
</tr>
<tr>
<td>bisoprolol</td>
<td>Emconcor, Emconcor CHF and generic</td>
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<tr>
<td>esmolol</td>
<td>Brevibloc</td>
</tr>
<tr>
<td>labetalol</td>
<td>Trandate</td>
</tr>
<tr>
<td>karvedilol</td>
<td>Kredex and generic</td>
</tr>
</tbody>
</table>

C 08, Calcium channel blockers
Calcium channel blockers are medicines which expand small blood vessels and through this decrease blood pressure.[4] In large clinical studies they give as good an effect against coronary heart disease as thiazides and ACE inhibitors. The most common side-effects are swollen ankles, headaches and runny nose, all of which are due to the substance opening up the blood vessels.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Substance name</th>
</tr>
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<tbody>
<tr>
<td>Vasoselective</td>
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</tr>
<tr>
<td>amlodipine</td>
<td>Norvasc and generics</td>
</tr>
<tr>
<td>felodipine</td>
<td>Plendil and generics</td>
</tr>
</tbody>
</table>
A review of medicines for lowering blood pressure

<table>
<thead>
<tr>
<th>Isradipine</th>
<th>Lomir, Lomir SRO</th>
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</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>Adalat, Adalat Oros and generics</td>
</tr>
<tr>
<td>nimodipine</td>
<td>Nimotop</td>
</tr>
<tr>
<td>Lercanidipine</td>
<td>Zanidip</td>
</tr>
<tr>
<td>Cardioselective</td>
<td></td>
</tr>
<tr>
<td>verapamil</td>
<td>Isoptin, Isoptin Retard and generics</td>
</tr>
<tr>
<td>diltiazem</td>
<td>Cardizem, Cardizem retard, Unotard, Coramil</td>
</tr>
</tbody>
</table>

C 09 A and B, ACE inhibitors
The abbreviation ACE stands for angiotensin converting enzyme, that is to say the enzyme which converts angiotensin.[4] This therapeutic group has qualities which counteract the formation of a blood pressure increasing substance, angiotensin II, which the body forms itself. It also has a good effect against heart failure and is especially suitable if one suffers from heart failure or diabetes with kidney function problems. The most common side-effect is an irritating cough.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Substance name</th>
</tr>
</thead>
<tbody>
<tr>
<td>kaptopril</td>
<td>Capoten and generic</td>
</tr>
<tr>
<td>enalapril</td>
<td>Renitec and generic</td>
</tr>
<tr>
<td>lisinopril</td>
<td>Zestril and generic</td>
</tr>
<tr>
<td>ramipril</td>
<td>Triatec and generic</td>
</tr>
<tr>
<td>kinapril</td>
<td>Accupro and generic</td>
</tr>
<tr>
<td>cilazapril</td>
<td>Inhibace</td>
</tr>
<tr>
<td>fosinopril</td>
<td>Monopril and generic</td>
</tr>
<tr>
<td>Fixed combination with hydrochlorothiazide</td>
<td></td>
</tr>
<tr>
<td>enalapril and hydrochlorothiazide</td>
<td>Renitec Comp, Synerpril and generic</td>
</tr>
<tr>
<td>lisinopril and hydrochlorothiazide</td>
<td>Zestoretic and generic</td>
</tr>
<tr>
<td>ramipril and hydrochlorothiazide</td>
<td>Triatec Comp, Triatec Comp Mite and generic</td>
</tr>
<tr>
<td>kinapril and hydrochlorothiazide</td>
<td>Accupro Comp and generic</td>
</tr>
<tr>
<td>cilazapril and hydrochlorothiazide</td>
<td>Inhibace Comp</td>
</tr>
</tbody>
</table>

C 09 C and D, ARB
Angiotensin receptor blockers (ARB) are a group of medicines which block AT1 receptors.[3] It is these receptors which communicate the blood pressure raising effects of angiotensin II. The effect observed on treatment using ARB medicines is therefore similar to what is observed for an ACE inhibitor. ARB medicines are often used as an alternative to ACE inhibitors if side-effects are observed. This is because ARB medicines are considerably more expensive than most of the other medicines in this review.[9]
Other fixed combination substances
The most common type of combination medicine is a fixed combination where one of the two substances is hydrochlorothiazide, these are accounted for in each respective group above. This list only covers the fixed combination medicines which contain two active substances of which neither is hydrochlorothiazide.

### Fixed combination with hydrochlorothiazide

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Substance name</th>
</tr>
</thead>
<tbody>
<tr>
<td>losartan</td>
<td>Cozaar</td>
</tr>
<tr>
<td>eprosartan</td>
<td>Teveten</td>
</tr>
<tr>
<td>valsartan</td>
<td>Diovan</td>
</tr>
<tr>
<td>irbesartan</td>
<td>Aprovel</td>
</tr>
<tr>
<td>kandesartan</td>
<td>Atacand</td>
</tr>
<tr>
<td>telmisartan</td>
<td>Micardis</td>
</tr>
<tr>
<td>losartan and hydrochlorothiazide</td>
<td>Cozaar Comp, Cozaar Comp Forte</td>
</tr>
<tr>
<td>eprosartan and hydrochlorothiazide</td>
<td>Teveten Comp</td>
</tr>
<tr>
<td>valsartan and hydrochlorothiazide</td>
<td>Diovan Comp</td>
</tr>
<tr>
<td>irbesartan and hydrochlorothiazide</td>
<td>CoAprovel</td>
</tr>
<tr>
<td>kandesartan and hydrochlorothiazide</td>
<td>Atacand Plus</td>
</tr>
<tr>
<td>telmisartan and hydrochlorothiazide</td>
<td>Micardis Plus</td>
</tr>
</tbody>
</table>

3.2 Pharmaceutical treatment for heart failure
A number of the medicines which are used for treating heart failure will be covered in other reviews which the LFN is going to carry out.[10] These are for example digitalis and nitrates. Amongst the medicines we deal with in this review are diuretics, potassium-saving substances, beta blockers, ACE inhibitors and ARB medicines.

The standard treatment for heart failure with symptoms is ACE inhibitors in combination with beta blockers.[11] If the ACE inhibitor gives side-effects in the form of constant irritating cough then another medicine without this side-effect can be prescribed, namely ARBs. ARB or spironolactone are also recommended as a supplement to ACE inhibitors and beta blockers if the patient still has symptoms.
3.3 Pharmaceutical treatment for angina

A number of the medicines which are used for treating angina will be dealt with in other reviews which the LFN is going to carry out. These are for example acetylsalicylic acid, blood fat-reducing substances and nitrates. Amongst the medicines we go through in this review are beta blockers, calcium channel blockers and ACE inhibitors.

3.4 We pay a lot for treating high blood pressure

The market is big for blood pressure lowering medicines

Blood pressure lowering medicines are sold for around 2.4 billion Skr per year in Sweden and the number of defined daily doses (DDD) is almost a billion. How large a part of this is for the indication hypertension and how large a part is for other diseases, such as heart failure and angina is not known.

Within the pharmaceutical benefits system these medicines are almost exclusively prescribed as tablets or capsules. Some substances are also available in other dosage forms but we have chosen not to study these closer. (See also section 7.2.)

Pharmaceutical costs are only a small part of the cost for treatment. The cost for hypertension treatment shall be weighed against healthcare costs becoming considerably lower in the future if the number of strokes and myocardial infarctions can be decreased.

Today ARB stands for the greatest sales value, 920 million Skr per year (38 percent), followed by beta blockers and calcium antagonists. ACE inhibitors have the greatest share of sales counted in DDD, approximately circa 22 percent.

Generics are available today within all therapeutic groups in this review, except for ARBs. This means that prices for the medicines are relatively low and today hypertension can be treated with medicines from a number of groups for between 50 öre and one Skr a day. The exception to this is ARB which costs considerably more.

Sales for blood pressure lowering medicines have increased rapidly during the past years, the number of DDD has increased by 50 percent since the year 2000. The comparable increase in sales value is 11%. All therapeutic groups have increased their sales since the year 2000, excepting the group "other diuretics" whose sales are in principle unchanged. ARB stands for the greatest...
increase, four times more DDD were sold in 2007 compared to the year 2000.

The group “Antihypertensive agents” has increased in sales value since 2002. This depends almost exclusively on the introduction of Tracleer which is used to treat hypertension in the lungs (pulmonary hypertension).

**Figure 2**  
*Source: Apoteket AB*

**Figure 3**  
*Source: Apoteket AB*
Figure 4
Source: Apoteket AB

Sales, AUP

Anti-hypertensive substances
Thiazide diuretics
Other diuretics
Beta blockers
Calcium channel blockers
ACE inhibitors
ARBs

Figure 5
Source: Apoteket AB

Sales, DDD

Anti-hypertensive substances
Thiazide diuretics
Other diuretics
Beta blockers
Calcium channel blockers
ACE inhibitors
ARBs
4. Literature searches

- All work conducted on the LFN’s reviews shall be based on a scientific method and the agency has published guidelines detailing the course of action when we search for literature on both medical effect and cost-effectiveness.
- The LFN does not grade the evidence its conclusions are based on as this would demand that all conclusions be based on systematic reviews of the literature.
- The LFN employs a fact evaluation process which comprises a number of steps.

Work conducted on the LFN’s reviews of the medicines available and its evaluation of medical effect and health economic documentation revolves around three preconditions:

1. Work shall be based on a scientific method.
2. There is a limited time to hand for each review of each therapeutic group.
3. The LFN must take a stance regardless of the quality of the documentation and information to hand.

We have produced two documents describing how literature searches shall be done in connection with the review of the list of reimbursed medicines in Sweden. One of them is for medical literature and the other for material which is health economic in nature. Both of these have been detailed in earlier final reports from the LFN and they are included herein in Appendix 1.

4.1 Medical effect

In the procedure for conducting medical literature searches we write that: Knowledge overviews from the SBU are considered first and that the LFN does not carry out any further test of the results from the current systematic knowledge overviews.

In 2004 the SBU published a report entitled ”Moderately elevated blood pressure – a systematic literature overview (Moderately raised blood pressure – En systematisk litteraturöversikt)”. The report was most recently updated in April 2007.[7, 13]

The LFN has neither the ambition nor possibility to produce as comprehensive documentation of the same high quality as the SBU report.
We have instead concentrated our efforts on exploring how we can apply the conclusions of the SBU report to our own work.

The work done by the SBU has been structured in a different way to the LFN’s and therefore there are certain aspects which we must take account of in our evaluation.

- The SBU report is only applicable for some of the treatment areas touched on in this review.
- The systematic review the SBU has done has its starting point in pharmaceutical groups. It is not a systematic overview of the various blood pressure-lowering medications at the substance level (the total documentation comprises at least 140,000 published studies).

We believe in any case that the conclusions of the SBU provide the best possible support for Swedish government agency decisions in this area but in order to augment the picture given by the SBU report we have also included the following documentation when evaluating the medicines within this therapeutic area:

- The MPA treatment recommendation from 2006 – “Preventing arteriosclerotic heart disease (Förebyggande av aterosklerotisk hjärt-kärlsjukdom)”.[5]
- The review of literature carried out within the framework of the ”Health Technology Assessment NHS R&D HTA Programme” in the UK. The report is titled “Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.” Health Technology Assessment 2003, Vol 7: No 31. by Law, Wald, Morris.[14]
- Our own literature search on Hypertension and on heart failure as described in more detail below. This also conforms to the search procedure in Appendix 1.
- Other literature communicated personally by the LFN’s medical experts or found through non-systematic searches.
- Submitted data from the companies concerned.

Our own literature search
This literature search within the area of high blood pressure has been carried out by Apoteket AB at our request. The searches have been done on the following level:
1. Systematic overviews
2. Other overview articles, generally containing results from meta-analyses
3. Individual randomised clinical studies (RCT)

The searches were carried out in the Cochrane Library (for systematic overviews, other overview articles, individual randomised clinical studies (RCT)) and PubMed (for meta-analyses and RCT). The Cochrane Library consists of multiple databases. The most interesting ones for the searches have been:

1. The Cochrane Database of Systematic Reviews (CDSR)
The database containing systematic overviews carried out by various Cochrane centres.

2. The Database of Abstracts of Reviews of Effects (DARE)
The database containing both systematic overviews and other overview articles containing meta-analyses of good quality and carried out by individual research groups. DARE is produced by the English organisation CRD, Centre for Reviews and Dissemination, which is a sister organisation of the Swedish SBU and part of the international organisation INAHTA.

3. The Health Technology Assessment Database (HTA)
This database contains systematic overviews and reports produced by similar organisations to the SBU who are part of the international organisation INAHTA (The International Network of Agencies for Health Technology Assessment).

In section 5.5 we account for the results of our own search.

Value of evidence
In the cases where the LFN has gone through and indicates a value on the strength of the evidence in regard to the documentation for the medicine’s medical effect then this shall follow the valuation of evidence system utilised by the SBU.

We will however not grade our conclusions in this final report. Grading evidence demands a systematic literature review as the basis for conclusions made, as is the case with the SBU. In cases where we have based our decisions on a systematic review then it is the SBU report we are referring to and then the SBU’s valuation of evidence system.
The SBU states that a conclusion of "Grade of Evidence 1" indicates the support of at least two studies with a high evidence value in the collective scientific documentation and material.[7] If there are studies which contradict the conclusion then the grade of evidence can be lower. A conclusion with "Grade of Evidence 2" is supported by at least one study with high evidence value and two studies of medium evidence value in the collective scientific documentation and material. If there are studies which contradict the conclusion then the grade of evidence may however be lower.

4.2 Cost-effectiveness

Summaries of present knowledge within health economics are partly made on different grounds than those made on knowledge in regard to medical effect. This is mainly due to the results from a health economic perspective being strongly related to local conditions such as the patient population's makeup, price, clinical practice and other aspects.

We have carried out a review of the relevant literature to understand the cost-effectiveness of the various medicines which lower blood pressure. We have identified studies partly due to companies who market blood pressure lowering medicines in Sweden have compiled and referenced the literature in regard to cost-effectiveness of their substances, and partly through a systematic literature search carried out in PubMed and the Cochrane library. The results for the literature search are presented in section 6.2.

We have not actively tried to attain unpublished literature, but in some cases companies have sent these studies in and then we have included them. A procedural diagram of the order of work in literature review is presented in procedure 1, appendix 1.

When evaluating the relevance of the health economic analyses then the starting point is the guidelines for these analyses which we have published.

The most important factors which should be fulfilled are that the study is from a socio-economic perspective (in other words that all relevant costs and gains are included), that it is applicable to Swedish conditions and that the comparison is made to the most relevant treatment alternative. What is the most relevant alternative is dependent on the specific situation but in general it is the most cost-effective one.
4.3 **Quality of life**
We have also carried out a literature search to find material which casts light on patients with high blood pressure. Firstly searches were made for overview articles and then for general articles from the time of the last published overview article. For this type of search there is no predefined procedure. A description of the databases we searched in and the search terms we have used as well as a summary of the results is available in section 6.3.

4.4 **Company-reported data**
The LFN has requested all companies to send in documentation they find suitable for shedding light on the effect of their own medicines. In response the companies have submitted a large number of references. Only those references which we have been able to use as a basis for the review are referenced in this document.

4.5 **Evaluation of facts**
The external medical experts the LFN has utilised for the review have evaluated the summary of knowledge and the conclusions drawn in this report. In drafts of the final report we have consulted experts from the SBU, MPA and Board of Health and Welfare as well as the county councils’ pharmaceutical benefits group, our user council, companies concerned, disabled organisations and the pensioner organisations PRO and SPF. The Board of Health and Welfare has also given the opportunity to give feedback on our draft to the expert group working with the national guidelines for heart-related healthcare.

When we concluded our mapping phase (we divide each review into two phases, a mapping phase and a decision-making phase) and decided to continue with the review of substances which lower blood pressure, we informed the companies concerned on our preliminary findings and the documentation these findings were based on. We encouraged the companies in question to submit comments on the main references we had identified as well as any further documentation they wanted to submit.
5. Literature on the medical effect

- The LFN considers there to be good scientific evidence to say that the blood pressure lowering medicines in the groups tiazididiuretics, calcium channel blockers, ACE inhibitors and ARB medicines are equally good for treating uncomplicated hypertension for the average patient.
- The report from the SBU contains a very comprehensive basis of knowledge and was updated as recently as April 2007. The SBU report is therefore the most important source of information for the LFN decisions by far.
- The LFN concurs with the SBU conclusion that it is cost-effective to treat uncomplicated hypertension with one or more of the cheapest medicines which have an equal effect.
- It is more cost-effective to improve the treatment for people with a medium or high risk level than to treat many patients who have a low risk level.
- The MPA treatment recommendation which came out in 2006 also says that the different main groups of blood pressure lowering medicines are equal for general use but that ACE inhibitors and/or Thiazines or calcium channel blockers should be the first line treatment for uncomplicated high blood pressure.
- The LFN has carried out its own literature search in order to cover other important literature which lay outside the SBU report’s focus on mild to moderately elevated blood pressure. This search did not however lead to any other conclusions.

5.1 The SBU report “Moderately raised blood pressure”

The SBU report ”Moderately raised blood pressure” contains a very comprehensive basis of knowledge and the SBU published an update for the report in April 2007.[7, 13] For the LFN an up-to-date SBU report is not only the most accessible documentation but also the best possible documentation on which to base decisions and in this we have used the conclusions drawn from the updated SBU report.

For the area not covered by the SBU report we have used the documentation we judged to be the best available material and information for each decision.

We consider the SBU report to provide a solid foundation for saying that the blood pressure lowering medicines on average provide an equal treatment for uncomplicated high blood pressure.
Here we summarise the SBU’s conclusions. For the complete material we make reference to the SBU report.

- There is strong evidence to say that blood pressure lowering treatment decreases the risk of minor heart attacks, myocardial infarction and early death for men and women with high blood pressure.

- There is also strong evidence to say that the various groups of blood pressure lowering medicines normally used in Sweden (thiazidediuretics, beta blockers, calcium antagonists, ACE inhibitors and ARBs give a similar decrease in blood pressure (approx. 10/5 mm Hg) when the medicines are used separately.

- For individuals the effects derived from the various medicines can vary. Many patients may due to this need to change or add one or more medicines in order to lower their blood pressure sufficiently.

- The SBU writes there is strong evidence that the large therapeutic groups thiazidediuretics, calcium antagonists, ACE inhibitors, and ARBs have similar positive effects on the patients who have hypertension without any other illnesses (uncomplicated hypertension).

- It is also clear that the beta blockers are worse at preventing stroke and that this is probably because they are worse at decreasing blood pressure than the other medicines.

- There is data which indicates that treatment using blood pressure lowering medicines decreases the risk of myocardial infarction for those patients who have already had a stroke and it is proven that the risk of getting a new stroke decreases.

- At least half of all people with type 2 diabetes also have high blood pressure. There is strong evidence the effect on morbidity and mortality for coronary heart disease is larger if the patient who is being treated with blood pressure lowering medicines also has diabetes.

- Patients treated using ACE inhibitors and/or ARB (drugs which directly affect the renin–angiotensin–aldosterone system) develop type 2 diabetes to a lesser degree than patients treated using thiazides in combination with beta blockers or a calcium channel blocker.

- For patients with many risk factors for heart disease and concurrent diabetes type 2, an ACE inhibitor and ARB medicine can have a positive effect which is not connected to the blood pressure lowering effect of the drug.
• Blood pressure lowering treatment for an already bad kidney function makes it deteriorate more slowly. The long-term effect on kidney function is similar for the various therapeutic groups for those patients who have mild to moderate hypertension without any concurrent complicated kidney illness.

5.2 The MPA treatment recommendation

“Prevention of arteriosclerotic coronary heart disease”

The MPA published its treatment recommendation – “Prevention of arteriosclerotic coronary heart disease”[5], during 2006 and this is also excellent documentation and material for the LFN to base its decisions on despite it not being produced in accordance with the same process and thoroughness in regard to facts as the SBU report. In cases where the SBU report contains answers to the questions which the LFN must answer within the framework of our review, then the SBU report’s conclusions are of greater value to the LFN. The MPA has however another starting point in its work and this means that their treatment recommendations, as an example, take in more of comparisons between different pharmaceutical groups. In these cases the LFN derives great value from the work carried out by the MPA.

According to the MPA treatment recommendations ACE inhibitors and/or thiazines or calcium channel blockers should be the first line treatment for uncomplicated high blood pressure. For patients with a kidney illness due to diabetes or who run a large risk of developing diabetes the MPA recommends that ARB be used if the patient cannot take ACE inhibitors. Beta blockers are recommended as a supplement if these alternatives do not give enough effect or when the patient also has another concurrent illness.

Here is a summary of the MPA findings on treatment of high blood pressure. For the full material and documentation we refer to the treatment recommendations.

Treatment of high blood pressure

• The various therapeutic groups in general have mild side-effects and it has not been shown that treatment with the most common blood pressure lowering medicines has any negative effect on quality of life.
• It is often more effective to lower blood pressure by combining two or more medicines from different therapeutic groups at a low or moderate dose than giving individual medicines at a high dose.
• The choice of medicines should be tailored taking into account each individual patient’s risk profile and other illnesses.
• The choice of medicines is the same for women and men, considering side-effects.
• When treating hypertension one should in the first instance choose an ACE inhibitor and/or a thiazide diuretic at a low dose or a calcium antagonist. If the patient cannot take ACE inhibitors then one can use ARB medicines instead. Especially if the patient has concurrent diabetes and kidney disease.
• Beta blockers do have a place in treatment as part of combination treatment or in the concurrent occurrence of some other diseases such as arrhythmia or migraine.

5.3 MPA treatment recommendation
– “Diagnosis and treatment of chronic heart failure”

The MPA published a treatment recommendation in 2006 on heart failure treatment.[11]

Here is a summary of the MPA’s writings on treatment of heart failure. For the entire documentation and material we refer you to the treatment recommendation.

Pharmaceutical treatment
• Medicines in the groups aldosterone antagonists, beta blockers, ACE inhibitors and ARB medicines have been shown to decrease morbidity and increase the survival rate for patients who have problems with the functioning of the heart’s left ventricle in connection with heart contractions with or without heart failure.
• In the studies done no differences in treatment effects have been found between women and men.
• Treatment using these medicines are in general lifelong.
The medicines the MPA indicate as treatment alternatives are:

<table>
<thead>
<tr>
<th>Aldosterone antagonists</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>spironolactone</td>
<td></td>
</tr>
<tr>
<td>eplerenon</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Beta blockers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>metoprolol</td>
<td></td>
</tr>
<tr>
<td>bisoprolol</td>
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<tr>
<td>karvedilol</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ACE inhibitors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>kaptopril</td>
<td></td>
</tr>
<tr>
<td>enalapril</td>
<td></td>
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<tr>
<td>lisinopril</td>
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<tr>
<td>ramipril</td>
<td></td>
</tr>
<tr>
<td>trandolapril</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARBs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>valsartan</td>
<td></td>
</tr>
<tr>
<td>kandesartan</td>
<td></td>
</tr>
</tbody>
</table>

5.4 MPA treatment recommendation

- “Treatment of hypertension during pregnancy”

The MPA’s most recent treatment recommendation for treatment of hypertension in connection with pregnancy is from 1996.[15] Included in this are the products which may be used to lower blood pressure in connection with pregnancy. The list below contains the active substances covered by the decisions in this review.

<table>
<thead>
<tr>
<th>Generic name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyldopa</td>
<td></td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
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<tr>
<td>Furosemide</td>
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<tr>
<td>Torasemide</td>
<td></td>
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<tr>
<td>Metoprolol</td>
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<tr>
<td>Atenolol</td>
<td></td>
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<tr>
<td>Pindolol</td>
<td></td>
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<tr>
<td>Labetalol</td>
<td></td>
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<tr>
<td>Isradipine</td>
<td></td>
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<tr>
<td>Nifedipine</td>
<td></td>
</tr>
</tbody>
</table>
Information has been utilized here from the MPA’s treatment recommendation, Läkemedelsboken 2007/2008 and Läkemedel och fosterskador produced by Stockholm county council.[3, 16]

5.5 The National Board of Health and Welfare’s work on national guidelines for heart-related healthcare

The National Board of Health and Welfare has the task of producing national guidelines for good healthcare for patients with severe chronic diseases. Included in the guidelines are decision-making supports to aid prioritisation, based on the Parliament ruling on priorities in healthcare. The recommendations for priority treatment are ranked on a scale from 1 to 10 according to how urgent they are.

The guidelines also contain recommendations on methods which should not be used at all or as a matter of routine (”not-to-be-done”) and recommendations on methods where we are still lacking the evidence to motivate inclusion into routine healthcare (FoU).

The guidelines contain recommendations within the following areas[17]:

- Coronary heart disease (prevention, diagnosis and treatment of acute and stable coronary heart disease as well as postcare)
- Heart failure (diagnosis, treatment, postcare and palliative care)
- Arrhythmia (diagnosis and treatment)
- Heart problems and valvular heart disease (diagnosis and treatment)
- Congenital heart disease

The National Board of Health and Welfare has commented on the drafts of the LFN’s report. The LFN has in turn commented on the circulated version of The National Board of Health and Welfare’s guidelines.

Both government agencies have by and large drawn the same conclusions.

The National Board of Health and Welfare plans to publish the national guidelines for heart-related healthcare in February 2008.

5.6 Summary of our own searches for documentation of medical effect

The search the LFN has carried out in the medical literature has been apartly based on other premises than the SBU report. The LFN’s search is not limited to mild to moderate hypertension but aims to map the documented treatment effects from all blood pressure lowering medicines. The current ATC codes for the review are: C02, C03, C07, C08 and C09. The searches were limited to articles in English and Swedish.
When we say treatment effects we mean in the first instance clinically interesting variables (hard outcome variables such as death regardless of cause, and death due to coronary heart disease as well as larger events such as myocardial infarction and minor heart attacks). In the first instance we searched for clinical studies where said substance was the basic treatment in one of the arms of the study, and in the second instance where the substance had been one of a number of alternatives in the arms of the study. In cases like this it is often not possible to draw a conclusion on the effect of each individual substance as the data is almost always presented in aggregated form.

As we had no studies designed for the measure of effect myocardial infarction, stroke and death, the search has focused on studies (at least six months long) with intermediary measures of effect, such as enlarged heart muscle or egg-white in the urine.

It is extremely difficult to give a short and simultaneously fair summary of the results from the studies we have localised. The main conclusions from the results of the searches are by and large the same as those reached in the SBU report and in the MPA’s treatment recommendations.

The LFN has on multiple occasions given the companies concerned the opportunity to augment the investigative material compiled by the LFN with studies which they had knowledge of.
6. Health economics

- The utility value of treating high blood pressure compares well to the costs the treatment leads to.
- High blood pressure is a risk factor for severe diseases which cause high costs for society.
- For similar medicines a price comparison is enough to judge cost-effectiveness.

Effect equal – price comparisons enough
The health economic literature shows that the value of treating high blood pressure compares well to the costs the treatment leads to. The LFN however makes decisions based on the reimbursement of individual products. Due to this we are interested in how effective the medicines in the review are compared to each other.

The medical literature shows that effect and side-effects are equal for the various medicines when treating high blood pressure. Therefore it is sufficient to compare the cost of the medicines in order to evaluate cost-effectiveness. The cost-effectiveness analysis is by and large reduced in this review to a price comparison.

6.1 The diseases lead to large costs
High blood pressure itself does not lead any great costs or loss in quality of life. However, the conditions we are trying to avoid by treating high blood pressure are connected to very high costs for society. [7]

Stroke especially demands much resources from society. In the National Board of Health and Welfare's guidelines for stroke a Swedish costing study for the disease is presented. [18] The total extra costs for an individual afflicted by stroke for the first time is estimated at 648 000 Skr for men, and 630 000 Skr for women. The costs involved are mainly direct, approximately 80 percent. If we only count first strokes then the total direct costs in Sweden amounts to almost 10 billion Skr per year.

Stroke is judged to result in one million care days per year. Over and above this is a large drain on resources on the municipal level. In the national quality register "Riks-Stroke“ the total societal costs for stroke are estimated at 14 billion Skr per year.

Treatment costs for heart failure are also high. In Sweden approximately 200 000 individuals have been diagnosed as having heart failure. The annual direct health costs for heart failure in Sweden is estimated to be at least three billion Skr.[19]
Treating blood pressure using a medicine from one of the groups ACE inhibitors, calcium flow inhibitors or diuretics costs 200 Skr per year today. In most cases a combination of medicines is needed to reach the treatment objectives. There are a number of combination possibilities giving different effects and side-effects depending on for example other morbidity and medication. Which treatment is optimal for the patient must be decided in each individual case. The price of the medicine is then one factor to take into consideration.

6.2 Summary of our own searches for documentation on cost-effectiveness

Cost-effective to treat high blood pressure

The literature provides few answers to the questions which are relevant for us. The quality of many of the studies is low and it is hard to draw any conclusions which are applicable to Swedish conditions. Both medicine costs and healthcare cost are in a state of constant change. The prices of medicines against high blood pressure have changed greatly during the past years. This is mainly due to a number of patent expiries. Today we have generic competition within all medicine groups except for ARBs. This is a contributing factor in making it difficult to draw conclusions from studies based on an older pricing situation. The country which is examined also has a large influence. An analysis of treatment in a country where prices, income and the healthcare system differ greatly from Swedish conditions is of limited value.

More cost-effective to treat patients at high risk

The review of the literature does show however that it appears to be cost-effective to treat high blood pressure. It is more cost-effective to treat patients at high risk mainly for stroke and myocardial infarction than those at low risk. High blood pressure is just one of many risk factors for becoming ill and eventually dying from heart disease. The more risk factors an individual has the more cost-effective it is to treat blood pressure. It is most cost-effective to treat high blood pressure for people who already have known heart disease such as angina pectoris, or already had myocardial infarction or stroke, that is to say secondary prevention.

The SBU has modelled cost-effectiveness under Swedish conditions

One aspect modelled by the SBU was the cost-effectiveness of treating high blood pressure under Swedish conditions.[7] The model is built upon the assumption that the medicines have an equal effect. In the analysis a cost per quality of life adjusted year of life (QALY) is divided into the parameters of gender, initial systolic blood pressure, age, and other risk factors.
The other risk factors analysed are smoking and COPD.

It is more cost-effective to treat patients at high risk than those at low risk. Therefore it appears to be more cost-effective to treat men than women. Also it was more cost-effective to treat older patients, patients with higher initial blood pressure and patients with additional risk factors. The cost per QALY was estimated at 341 000 Skr at its highest. In many cases the treatment was a cost-saving.

When the model was published the generic prices for blood pressure lowering medicines were higher than today. The lowest prices were for beta blockers and diuretics, which were then first line treatment recommendations, and therefore also included in the model. The cost for treatment for 24 hours was assumed to be one Skr. If the effect was not sufficient the treatment was replaced by ACE inhibitors or calcium flow inhibitors, the cost for these was assumed to be five Skr per day. This gave a higher cost per QALY in all groups, at its highest the cost per gained QALY was 621 000 Skr.

In the SBU report the cost-effectiveness of treatment using multiple medicines was also analysed. It was assumed that medicines which cost two Skr per day were added to the first medicine. Treatment of older people was then cost-saving in general. In the younger age group the cost-effectiveness varied from cost-saving up to 405 000 Skr per QALY.

Today the prices have decreased considerably for many of the medicines used to treat high blood pressure and within most pharmaceutical groups there are substances available for approx. 50 öre per day, excluding ARB. The lower pharmaceutical prices mean of course that the treatment appears to be more cost-effective.

In the SBU model only the treatment of uncomplicated moderately raised blood pressure was analysed. Individuals at higher risk have however better medical use from the treatment and it is through this more cost-effective to treat these.

The SBU also writes that adequate treatment of all people suffering from hypertension would mean that more people than today would be treated, and that more medicines per person would be used, which would result in greater pharmaceutical costs than today.

**MPA conclusions**

The MPA also states in its treatment guidelines that it is cost-effective to treat high blood pressure and that the choice of medicine has great impact on
pharmaceutical costs and cost-effectiveness.[5] They refer to the SBU model and state that it is more cost-effective to treat people at high risk.

6.3 Summary of our own searches in documentation on quality of life

Quality of life and high blood pressure
A review of the literature shows that quality of life when suffering from hypertension is difficult to study. A number of different scales for estimating quality of life exist and this complicates comparisons.

The condition has little effect on quality of life
Patients who have high blood pressure seldom have symptoms of their disease and their ability to function is rarely decreased. High blood pressure therefore does not lead to any direct losses in quality of life. However, the long-term effects can have a large influence on a patient's health-related quality of life. Examples of these long-term effects include the diseases which high blood pressure can lead to such as stroke and myocardial infarction.

Pharmaceutical treatment gives small effect on quality of life
For pharmaceutical treatment of high blood pressure the direct effect on the health-related quality of life on a population level is very small. Some studies show that hypertension treatment gives positive effects on quality of life while others show negative effects. The results are seldom significant. Most patients who are treated with low to medium doses of medicines do not experience any serious problems due to side-effects. Serious side-effects from blood-pressure lowering treatment is rare. The different groups of medicines have a different mechanism and through this different types of side-effects. On a group level there is however no meaningful difference in the effect on quality of life between the groups of medicines.

Stroke leads to loss in quality of life
Stroke is the most common cause of a neurological disability for adults and the third most common cause of death after myocardial infarction and cancer in Sweden.

From the national stroke register it can be discerned that many stroke patients are completely or partly dependent on people close to them, and roughly a quarter of the patients experience speech difficulties after a stroke. This of course affects their quality of life negatively.[20] The SBU estimates quality of life values for stroke at 0.5 the first year after a stroke and 0.75 the subsequent years.
Myocardial infarction affects length of life
Myocardial infarction is the single most common cause of death for both men and women. But myocardial infarction also affects quality of life negatively, however not to the same extent as stroke. Quality of life is affected mainly in connection with the attack itself, but the symptoms fade with time. Already after six weeks many patients are free of symptoms and after one more year more patients have no symptoms. In the national quality register for coronary artery disease quality of life has been measured using EQ-5D. The average quality of life was 0.80 after six weeks and only marginally higher after one year, 0.81. Quality of life decreases most for patients in the younger age ranges. [21] In the SBU report quality of life is estimated to have decreased to 0.75 during the first year after the myocardial infarction and 0.95, in other words practically normal quality of life for the following year. [7]

Quality of life and heart failure
Heart failure is a common and serious condition. The degree of severity for heart failure varies, common symptoms are tiredness, shortness of breath and swollen legs. For light heart failure, the symptoms arise on light exercise, and for more severe heart failure the symptoms are present also when resting and affect the patient’s ability to carry out normal daily activities to the extent the patient becomes dependent on the help of others. Many patients also experience anxiety.

Within the framework of the national quality of life register the quality of life values have been estimated using EQ-5D. On average the patients estimated their quality of life to 0.6 one year after falling ill. How much quality of life is affected is however strongly affected by the degree of heart failure. Quality of life values vary between 0.5 and 0.75 dependent on how seriously ill the patients are.

Heart failure also means a greatly increased risk of early death. Only half of the patients are alive more than six years later. Despite treatment the disease continues and takes its toll in, amongst other things, repeated hospitalisations. [19]
FACTBOX

What is a cost-effective medicine
The use of a medicine is cost-effective if the cost is reasonable in comparison to the health benefits won by the medicines. The size of the bill for pharmaceuticals is therefore not a good measure of if we are using enough and the correct medicine. The crucial aspect is instead if the medicine is cost-effective, not just for healthcare, but for society as a whole. Finding out if a medicine is cost-effective gives us a foundation for prioritising and as a result use our resources optimally.

Utility weighed against the cost
What does it mean that the use of a medicine is cost-effective? It does not mean that all cheap medicines are cost-effective, and all expensive ones are not. When we calculate if a medicine is cost-effective we first put all of the costs together associated with using the medicine. This is mainly the price of the product. But also costs which arise when the patient has to visit a doctor to get the medicine, follow up treatment and any other healthcare resources needed, these side-effects of the medicine and so on. But we also calculate if the medicine involves savings in other parts of the healthcare system such as the patient not needing to visit the doctor as often, avoiding hospitalisation, operations and so on. This is however not enough to get a societal perspective. We also judge if a medicine means a patient can work and support herself rather than being sick-listed and perhaps going into early retirement. Here the benefits go to the private person, to production and to the State which avoids the costs for sick-listing and early retirement. If the patient is older then it may lead to that person managing better on their own without as much aid from the municipal elderly care services or from relatives. This is also a societal benefit added to the plus-side of a cost-effectiveness analysis. Then we weigh this total cost against the value generated by the medicine, mainly in the form of curing or alleviating a condition and a resultant increase in quality of life for the patient.

Does not need to lead to savings
Sometimes the good effects from a medicine are so large that they more balance off the costs. Then we say that the treatment is cost-saving. However we do not make such high demands to consider a medicine as cost-effective and that we therefore should reimburse the medicine. That people get well, avoid disabilities or having pain and can live a more normal life by taking a medicine has a value which society is willing to pay for.

Quality–adjusted year of life - QALY
When analysing a treatment’s cost-effectiveness the measure of effect gained “quality of life adjusted life years” (QALY) is often used. The principle behind QALY means that the time an individual is in a certain state of health is allocated a value (QALY-weighting) comparable to the health-related quality of life which is associated with the condition. Full health is given the value of 1 and death the value of 0. A quality-adjusted year of life is thereby defined as one year in full health. For various types of measuring methods the health-related quality of life an individual experiences is decided by different types of diseases. The QALY value (0 to 1) is a generic quality of life measure, the same scale can be used for all different types of conditions. This has advantages, for instance in prioritisation, when one treatment is to be compared with another treatment. A common and general instrument for measuring quality of life is EQ-5D. There are also a number of condition-specific quality of life measures. These are more sensitive to changes in the specific disease, but are difficult to utilise when comparing the disease and treatment with other options.
7. Principles for the LFN’s decisions

- The LFN shall base its decisions on balancing the cost-effectiveness of a medicine and patient needs.

- In the review of reimbursed medicines the LFN must make decisions regardless of the quality of the material and documentation.
- We base our decisions on the SBU’s systematic overview. Here the conclusion drawn was that four large pharmaceutical groups of blood pressure lowering medicines have an equal effect on preventing myocardial infarction, stroke and death.
- We have decided to accept the comparisons at a substance level using surrogate measures in this review.
- There are three important reasons the prices of medicines shall be allowed to vary even if they on average are equal. These reasons are 1) there is great value in having access to a number of medicines in the same group, 2) the differences in secondary qualities is large between the medicines and 3) we want to maintain price competition on the generics market.
- To regulate this price variation we have decided to utilise a pricing corridor.

7.1 General preconditions for the work of the LFN

When we decide if a medicine shall be part of the reimbursement scheme we must take into account the criteria indicated in the Law on pharmaceutical benefits. This means that we weigh the benefit of the medicine against the cost. We also consider that those in the greatest medical need shall have more healthcare resources than other patient groups, and we take the human value principle into account, meaning that healthcare shall respect the equal value of all people.[22]

7.2 Special conditions exist for the review of reimbursed medicines

As we previously mentioned work on the LFN’s review of reimbursed medicines has its starting point in three conditions:

1. Work shall be based on a scientific method.
2. There is a limited period of time available for the review of each therapeutic group.
3. The LFN must take a stance regardless of the quality of the documentation or material available.
When it comes to the method for literature searches then it is clear that it is mainly the first of these conditions which is of great importance for us. When it comes to the methods for making decisions then also the second and third point play a crucial role.

**Choosing measures of effect – many studied but few compared**

To know how effective medicines are you must first decide how the effect should be measured. For example we normally talk about hard data when we refer to studies which show that a group of patients treated with medicines A survive longer than the patients who have been treated with medicines B. Hard data can also be the number of patients who have had a myocardial infarction, number of cerebral haemorrhages, or similar.

In many clinical studies it is a difficult and tedious job to measure the results you really want to know something about. That is why one chooses to study something which is easier to measure, a surrogate measure of effect. The relationship between a surrogate measure and hard measures of effect can be strong or weak. An example of a surrogate measure of effect is blood pressure measured in millimetres of quicksilver (mm Hg). In general a decrease in blood pressure by a certain number of mm Hg using medicines results in a decreased risk for falling ill with coronary heart disease and the larger the decrease the larger the decrease in the risk.[7, 23]

When we carry out a review such as this one then decisions can be radically different depending on if we accept comparisons in blood pressure lowering effects (surrogate measures of effect) or if we demand data on myocardial infarction, stroke and death for comparison between different medicines. Consistently insisting that only hard data is sufficient would lead to just a few medicines retaining reimbursement for the therapeutic group for high blood pressure.

The best scenario would be to have access to all hard data for all meaningful use of all medicines. This is however only available for a small number of products and for a small share of the usage. In the other cases we must use the best available data. Furthermore, when other agencies across the world charged with approving medicines (MPA, EMEA, FDA) approve new medicines for the market then they also accept, in most cases, surrogate measures of effect as a basis for the approval.

In this review we utilise the SBU’s systematic overview, whose conclusion is that the five large pharmaceutical classes of blood pressure lowering substances have an equal effect on preventing myocardial infarction, stroke and death (with some restrictions for beta blockers).[7] Furthermore we have taken into
account the fact that some therapeutic groups have a specific effect on some conditions, such as heart failure and kidney disease. On top of this we have to evaluate the individual medicines in each group against each other. We have decided on a substance level to accept comparisons based on surrogate measures of effect in this review. As it is of interest that the patient lives longer and with a good quality of life than that she gets a lower blood pressure, the problem remains that it is not clear exactly what real patient utility one is paying for when calculations are based on surrogate measures of effect.

We are aware of this but believe that the consequences of without exception demanding hard data is worse than the risk of basing our decisions on the medicine’s ability to decrease blood pressure.

**Well-grounded decisions**

Discussions on evidence-based medicine (EBM) are held in many different fora currently. EBM is about using the best available evidence as a basis for decisions. The Board’s decisions mean that we weigh up and value the available information in the area.

We have decided to accept surrogate measures of effect as a basis for comparisons of effect in the review of medicines which lower blood pressure. In the section on choosing measures of effect we have described the positions we have taken which form a basis for this.

There may however be other situations where we will demand hard data. This depends on how well-established the relationship between hard data and surrogate measures of effect is in each individual case.

**Comparisons of effect**

We have come to the conclusion that many of the medicines used for lowering blood pressure are equal. We have not stated that different medicines or pharmaceutical groups are equal in all situations or that they will generate the same value for all patients. We can however not accept that the medicines differ too much in price when the beneficial effects are similar.

As we stated previously we believe the SBU report to be the best available documentation of knowledge for all of the areas which it concerns. Due to this we base our decisions on the conclusions drawn in the updated report published in April 2007.[7] In this report the SBU writes that there is strong evidence that the large pharmaceutical groups of thiazide diuretics, calcium antagonists, ACE inhibitors
and ARB have similar beneficial effects for patients who have high blood pressure without any other illnesses (uncomplicated hypertension). The SBU also says it has also found strong evidence that beta blockers are worse at preventing stroke and that this is probably because they decrease blood pressure slightly worse than the other medicines.

The SBU report only deals with treatment of mild to moderately elevated blood pressure. We must take the whole scope of use of the pharmaceutical groups into account. Because of this the MPA’s treatment recommendation ”Prevention of coronary arteriosclerotic disease” from 2006 is an important addition to this[5]. The SBU’s and MPA’s evaluations match up well. The MPA recommends that a patient in the first instance should get an ACE inhibitor and/or a thiazidediuretic at a low dose or a calcium antagonist for the pharmaceutical treatment of high blood pressure. The MPA also says that ARBs may be used if the patient cannot take ACE inhibitors and has diabetes which has led to kidney disease. They further say that beta blockers should still be used if the patient has concurrent arrhythmia or migraine.

Our review of the literature has not led us to draw any contradictory conclusions to this.

This review has not been restricted to mild to moderately elevated blood pressure. However in the main the SBU report has covered the studies we found in our own searches.

**Comparison of doses**

When we say that the treatment effects of the various medicines are similar then this is in situations where the patients have had an adequate dose. Due to this we have indicated a comparison dose for all medicines. Information on the comparison dose for the medicines concerned have been collected in the first instance from the literature review ”Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy” carried out within the framework for ”Health Technology Assessment NHS R&D HTA Programme” in Great Britain.[14]

In some cases the substance has not been included in this literature review and then we have collected data on comparable doses from *Läkemedelsboken. 2003/2004.[24]* In most cases these sources have contained information which matched up. Our medical experts in this review have also confirmed that the dose comparisons were reasonable.

We have informed all companies that we would compare the doses of the medicines using these references as a basis. Only a few companies had comments on this choice of reference doses.
We are only going through tablets and capsules
The few medicines prescribed within the benefits system in other dosage forms than tablets and capsules are generally prescribed for patients with a considerably greater need of care than uncomplicated high blood pressure. We believe that the need to have access to these alternatives, especially for patients who are difficult to treat, is large.

In general these medicines in these dosage forms are not made available on prescription. Therefore the dosage forms which are not tablets may remain in the reimbursement system without any further evaluation.

Some medicines get restricted reimbursement
Normally our decisions shall be on a product level and the medicine shall either be reimbursed completely or not at all. In special circumstances we do however have the possibility of making a decision to grant restricted reimbursement or reimbursement under certain conditions for some medicines. We aim restrictions at the healthcare system and the prescribers and conditions are set for the pharmaceutical companies.

In this review in our estimation general use of a number of medicines is not cost-effective in comparison with cheaper blood-pressure lowering medicines. There may however be smaller groups of patients where treatment using these medicines can be cost-effective, also when compared to cheaper alternatives.

For medicines which lower blood pressure we have therefore utilised the possibility of restricted reimbursement. The restrictions come in two types:

1. Restrictions meaning the patient must already have tried other treatment alternatives.
2. Restrictions for other, less delineated, patient groups with special needs.

The restrictions we have ruled on are listed in section 8.

The LFN allows a pricing corridor
Within a pharmaceutical group there are sometimes a number of medicines which exhibit a clinical effect which is equally good for the average patient. This is the case for a large number of medicines against high blood pressure. A too strict interpretation of the cost-effectiveness principle would mean that many medicines would lose their reimbursement status at their current prices. We do discern however reasons for prices to be permitted to vary and therefore this is reason enough to allow a pricing corridor.
One reason is that within many therapeutic areas there is a need for a range of products. People can respond differently to medicines, both in terms of effects and side-effects.

Another reason is that some medicines, which possess extremely similar qualities and completely equal treatment effects, have specific unique qualities which may be of value to a smaller group of patients. Such small differences are often difficult to measure and carry out a health economic analysis on. We can therefore not expect to receive such documentation. But by applying a pricing corridor we can allow room for and even encourage such small differences. The size of the pricing corridor reflects the value we place on the availability of a range of products within a certain area.

The pricing corridor is not an absolute price ceiling
This time we are using a pricing corridor. We do however accept higher prices for a blood pressure lowering medicine if the marketing company can show that the medicine constitutes a cost-effective alternative at its higher price. A medicine which is considerably better than the others may therefore be allowed to have a price which is over the pricing corridor.

The pricing corridor can vary from treatment area to treatment area
The need for a range of products varies considerably between the different therapeutic groups, this means that there is reason to allow the size of the pricing corridor to vary. It is however not possible to use any fixed formula or calculation method to decide how big the pricing corridor should be between the different groups. The size is decided based on an evaluation of these factors:

1) how much value is generated by there being more than one medicine available within the group in question
2) how important the differences are for the unique qualities the medicine possesses
3) how big a pricing corridor is needed in order to retain price competition within any substitutable groups within the framework for generic substitution

The LFN has previously presented the results from three reviews, medicines against migraine, stomach acid and the review of asthma, coughing and COPD.

In the review of medicines against diseases caused by stomach acid we also employed a pricing corridor.
The argument for a pricing corridor for medicines against high blood pressure
In this section we account for how we have used the criteria for a pricing corridor in the review of medicines which lower blood pressure, given that there is solid scientific evidence to say that a number of the blood pressure lowering medicines are on average equally good at treating uncomplicated high blood pressure.

1. How much value is generated by there being more than one medicine available within the group in question?
For the therapeutic area in question, medicines which lower blood pressure, we judge the need for a range of medicines to be great. This holds also true for other therapeutic areas. The reasoning behind this is that many patients need more than one medicine to control their blood pressure. Often the same patient needs to be treated with medicines from more than one of the pharmaceutical groups. At an individual level different patients respond differently to treatment with the same medicines. There is strong evidence for this in the SBU report.[7]

2. How important are the differences for the unique qualities the medicines possess?
In our estimation the differences from a secondary perspective between the blood-pressure decreasing medicines is big. The reason for this is that the medicines we are now reviewing are part of six pharmaceutical groups. Even if the conclusion is that the effect gained from most of these medicines is equal on a group level it is clear that they are different.

The medicines utilise different mechanisms for their effect, have very different approved indications, interact differently with other medicines and so on. We believe however that the differences between all substances within the groups are not that large. For example, the medicines in the groups ACE inhibitor and ARB can be considered as rather similar.[7, 25]

3. How big a pricing corridor is needed in order to retain price competition within any substitutable groups?
In our estimation at least two generics suppliers are needed in order to maintain healthy price competition within the generic substitution system. The reason for this is that we have been able to observe the absence of price competition within the generic substitution group if it is only the original brand producer and generics producer who supply the medicines. Neither does the presence of parallel imports generally result in any form of meaningful price competition.
For medicines which are substitutables we have been able to observe price competition if there are at least two generics on the market. For substances where the generic medicines are not substitutable for the original brand there may however be up to four or five generics suppliers who are on the market without price competition increasing much.
8. Decisions

The LFN has arrived at the following conclusions

• There is a need for having many different blood pressure lowering medicines within the pharmaceutical reimbursement system.

• At a reasonable cost it is important to be able to offer patients more than one treatment alternative within the five large therapeutic groups thiazidediuretics, beta blockers, calcium channel blockers, ACE-inhibitors and ARB.

• Today’s price differences between the various medicines are unacceptable within the reimbursement system. The price for treating a patient with the medicines during a 24-hour period using a standard dose varies from approx. 50 öre to almost 8 Skr.

• The criteria for a pricing corridor are fulfilled for medicines which lower blood pressure.

The LFN has decided to

• Set up a pricing corridor for medicines which lower blood pressure.

• This pricing corridor means that we accept prices up to 1.40 Skr per 24-hour period.

• Set up separate pricing corridors for beta blockers and ARB medicines, for these we accept prices up to 1.75 Skr and 5.97 Skr respectively per 24-hour period.

• Remove some medicines from the benefits system. This is for medicines where companies have not been able to demonstrate the utility value of the medicine in relation to the price and the price of the medicine has been higher than the highest pricing level in the pricing corridor.

• Limit reimbursement for a number of medicines which do not have a place in the pricing corridor but which have an important place in therapy for some patient groups with special needs or for patients who have already tried another treatment.

The LFN’s decisions have the following consequences

• Following the review approx. 20 active substances (unique treatment alternatives) may completely retain their reimbursement.

• 23 substances are reimbursed on restriction.

• Three substances have been judged to be so expensive in relation to their effect that they shall not be reimbursed at all.
• The LFN’s decisions in regard to removing some expensive medicines from the benefits system, restricting reimbursement for others and approving late price decreases means that we free up approx. 400 million Skr per year for other more urgent causes.
• Solely the restriction on ARB drugs can free approx 250 million Skr. 

Previously in this report we wrote that hypertension is a risk factor for diseases with a high degree of severity that cause great costs for society and that it appears to be cost-effective to treat high blood pressure. We have also stated that many of the medicines can be considered equal. Therefore a price comparison is enough in these cases to judge cost-effectiveness.

8.1 Decision in favour of a pricing corridor for medicines for lowering blood pressure

• The LFN has decided to utilise a pricing corridor for medicines for treating high blood pressure.
• The pricing corridor means that we allow prices up to 1.40 Skr per day.

In chapter 7 we described the three criteria we have for utilizing a pricing corridor. Therefore we have decided the pricing corridor shall be big enough to accommodate the possibility of more than one medicine remaining within all of the five larger therapeutic groups of thiazide diuretics, beta blockers, calcium channel blockers, ACE inhibitors and ARBs.

There are a number of reasons for having more than one medicine remaining in the benefits system for each group. The most important is that there is then a possibility of adapting treatment to individual needs and there is some kind of contingency plan if for example, a medicine were to be unexpectedly retracted from the market.

We have decided the pricing corridor shall have a floor price of 50 öre per day and that the corridor itself shall be 90 öre. Consequently the highest price per 24-hour period we accept for non-restricted medicines is 1.40 Skr at the strength we have indicated above as a reference dose.

A medicine may of course cost less than 50 öre per day but our comparisons are made from the floor price of 50 öre up. The reason for this is that an analysis of the market for blood pressure lowering medicines shows that there
are a number of active substances in different groups and over a long period of time where the treatment cost is close to 50 öre per day.

As the floor price is 50 öre we have concluded that a pricing corridor of 90 öre suits our criteria.

The same pricing corridor does not apply for beta blockers and ARB drugs. For these groups, which receive restricted reimbursement, the following applies:

- **beta blockers**: floor price of 50 öre and corridor of 1.25 Skr.
- **ARB**: floor price of 5.67 and corridor of 30 öre.

In accordance with our general guidelines we compare all prices at AUP levels (Apoteket’s sales price).[26]

**We allow a larger variation in price for beta blockers**
The highest price we accept per 24-hour period for beta blockers is 1.75 Skr at the strength we have indicated as a reference dose.

When the objective of the treatment is to lower blood pressure and to prevent the risk of future illnesses and death then beta blockers are less effective than other medicines.[7] The LFN has therefore decided that beta blockers shall be part of the reimbursement system but on a restricted basis.

Beta blockers are needed as a treatment alternative for other patients than those who only have hypertension and as a complement to other blood pressure lowering treatment.

Because all beta blockers are to be reimbursed with restrictions we have chosen another pricing corridor for them than other medicines. A number of the beta blockers are available as generics and have been available at low prices for a long time and there is therefore no reason for the LFN to have a different floor price for beta blockers than for other medicines. The floor price is also 50 öre per day for beta blockers.

The natural differences between beta blockers [27] and our wish to have at least two treatment alternatives available within the reimbursement system means that the pricing corridor may be larger for beta blockers than for the other groups. By setting the pricing corridor for beta blockers at 1.25 Skr per day we fulfil the criteria for a pricing corridor within this group.
We allow less variation in price for ARB drugs
The highest price per 24-hour period we allow for ARB drugs is 5.97 Skr at the strength we have indicated as reference dose.

ARB drugs do not have a proven effect which for general use explains their high price. The LFN has due to this decided to award ARB drugs restricted reimbursement.

As all ARB drugs are to be reimbursed on restriction we have set a separate pricing corridor for them than for other medicines. There is no ARB drugs available as a generic. We have therefore assumed that we will not be able to have at least two medicines from this group in the reimbursement system if we demand that the floor price also be 50 öre per day. The floor price for the pricing corridor for ARB has instead been set based on the cheapest price for an ARB drug during the spring of 2007. The floor price has therefore been set at 5.67 Skr per day.

In our estimation the differences in secondary qualities between the ARB drugs are small.[7] The pricing corridor for ARB drugs may because of this only be set at 30 öre per day. A pricing corridor of 30 öre is sufficient for us to gain access to more than one drug in the group.

8.2 Price-setting of doses and packages within the pricing corridor
The group of drugs which lower blood pressure is very large. There are almost 1 300 different products in the group if one considers substance, producer/importer, strength and package size. Many drugs in this review have been used for a long time and their prices are often legion with historical explanations. To be able to handle this great number of products the LFN has therefore decided the following for substitutable medicines affected by the decisions in the blood pressure review.

Tablets at a higher strength than the comparison dose the LFN has defined, may cost more than 1.40 Skr per tablet but the LFN does not allow a higher price per mg of active substance than the maximum per mg price for the reference dose.

Tablets at a lower strength may have the same price per tablet (AUP) despite there then being a higher price per mg of active substance. The LFN does not however allow tablets at the lower strength to have a higher per tablet price than the higher strength. We do, as an exception, allow this only if the price per tablet AUP in both cases is below 1.40 Skr.
The LFN’s price comparison is based on packages of 98 or 100 tablets. For tablets in smaller packages the LFN allows the price per tablet to be higher. However a smaller package shall not cost more than a larger package. Also here we make an exception if the price per tablet AUP in both cases falls under 1.40 Skr.

8.3 Decisions on individual medicines

In Table 1 below we show a summary of the board’s decisions. We account for the reasons and estimations behind the decision in chapter 10. For the medicines the LFN has excluded from the system, or where we have restricted reimbursement, there are specific explanatory decisions for each medicine.

The LFN’ decisions come into force immediately unless we indicate otherwise. This also applies for medicines which shall not continue to be part of the reimbursement system. Previously we have stated that decisions on the exclusion of a medicine from the pharmaceutical benefits system comes into force at the earliest three months after such a decision has been made public.

The medicines covered by this review are used by very large patient groups. As far as it is possible the LFN wants to give the country’s caregivers good possibilities of managing the patients who need a new prescription when a certain medicine has either lost its reimbursement or attained restricted reimbursement. In this review the LFN has therefore decided that all decisions will enter into force on the 1st of September 2008.

8.4 Decisions in regard to restrictions

- The LFN has decided to set restrictions for the reimbursement of some medicines.
- In total at least 250 million Skr can be freed for other more urgent purposes if these restrictions are followed out in the healthcare system.

The LFN has decided to set restrictions for the reimbursement of some medicines, see Table 2. It is important that the healthcare system adheres to the LFN’s reimbursement restrictions in order to ensure a cost-effective use of these medicines. In total 250 million Skr per year can be freed for other more urgent purposes if these restrictions are followed out in the healthcare system.

A number of the restrictions apply only for parts of the use of the medicine. For use in other indications the medicine is reimbursed. For example, the LFN’s decision that beta blockers be reimbursed for the indications angina,
heart failure, arrhythmia, prevention of migraine and more. It is only for the
treatment of hypertension that the restriction for beta blockers applies.

In the LFN’s estimation in this review the general use of a number of medici-
nes is not cost-effective in comparison with cheaper blood pressure lowering
medicines.

There may however be smaller groups of patients where treatment using the-
se medicines can be cost-effective, also in comparison with cheaper alternati-
ves. For medicines which lower blood pressure we have therefore utilised the
possibility for restricted reimbursement. There are two types of restrictions:

- Restrictions meaning the patient shall first have tried other treatment
  alternatives.
- Restrictions for smaller, well-defined patient groups with special
  needs.

An example of a smaller patient group with special needs is women who
are pregnant. The MPA recommends some medicines as possible treatment
alternatives for high blood pressure in connection with pregnancy. This is a
reason for the LFN to grant restricted reimbursement. At least one medicine
containing methyldopa, labetalol, isradipin or nifedipin will therefore be
awarded reimbursement but with the restriction: ”Only reimbursed for the
treatment of hypertension during pregnancy.” (see also section 5.4)
Table 1, Decisions in the review of medicines for lowering blood pressure.

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<th>Still in benefits system</th>
<th>Restricted reimbursement</th>
<th>Excluded from the system</th>
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<tr>
<td><strong>Combinations with Hydrochlorthiazide and potassium-saving agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beta blockers (C07)</strong></td>
<td></td>
<td></td>
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<tr>
<td>pindolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>propranolol</td>
<td></td>
<td></td>
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<tr>
<td>long-acting propranolol</td>
<td></td>
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<tr>
<td>metoprolol</td>
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<td></td>
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<tr>
<td>long-acting metoprolol</td>
<td></td>
<td></td>
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<tr>
<td>atenolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bisoprolol</td>
<td></td>
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<tr>
<td>labetalol</td>
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<td></td>
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<tr>
<td>karvedilol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Calcium channel blockers (C08)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mainly vasodilating</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td></td>
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<tr>
<td>Felodipine</td>
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<tr>
<td>isradipine</td>
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<td></td>
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<tr>
<td>long-acting isradipine</td>
<td></td>
<td></td>
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<tr>
<td>nifedipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>long-acting nifedipine</td>
<td></td>
<td></td>
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<tr>
<td>lerkanidipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac-selective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Still in benefits system</td>
<td>Restricted reimbursement</td>
<td>Excluded from the system</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>verapamil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diltiazem</td>
</tr>
<tr>
<td>ACE inhibitors (C09 A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kaptopril</td>
<td></td>
<td></td>
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<tr>
<td>enalapril</td>
<td></td>
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<tr>
<td>lisinopril</td>
<td></td>
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<tr>
<td>ramipril</td>
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<tr>
<td>kinapril</td>
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<tr>
<td></td>
<td></td>
<td>cilazapril</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fosinopril</td>
</tr>
<tr>
<td>ACE inhibitors and hydrochlorothiazide (C09 B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>enalapril and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lisinopril and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ramipril and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kinapril and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cilazapril and hydrochlorthiazide</td>
</tr>
<tr>
<td>ARBs (C09 C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eprosartan</td>
<td></td>
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<tr>
<td>Valsartan</td>
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<tr>
<td>Irbesartan</td>
<td></td>
<td></td>
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<tr>
<td>kandesartan</td>
<td></td>
<td></td>
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<tr>
<td>telmisartan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARBs and hydrochlorthiazide (C09 D)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>losartan and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eprosartan and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>valsartan and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>irbesartan and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kandesartan and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>telmisartan and hydrochlorthiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other combination products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metoprolol and felodipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>trandolapril and verapamil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>valsartan and amlodipine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In this Table we only show the different substances. That the substance is in one of the columns “still in system” or “restricted reimbursement” does not mean that the column heading covers all medicines containing this active substance. There are examples where we have excluded both individual original brand medicines and parallel-imports or generic medicines from the benefits system, but where the substance itself is still available in a reimbursed form.

**Table 2. Restrictions in the review of medicines for lowering blood pressure.**

<table>
<thead>
<tr>
<th>Restriction:</th>
<th>Medicine:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restrictions meaning that patient shall first have tried other treatment alternatives:</td>
<td></td>
</tr>
<tr>
<td>For hypertension the medicine is only reimbursed for patients who have first tried other pharmaceutical groups.</td>
<td>moxonidine (Physiotens) doxazosin (Alfadil)</td>
</tr>
<tr>
<td>When first being tried for treatment of hypertension the medicine is only reimbursed for patients who have first tried other pharmaceutical groups.</td>
<td>pindolol (Viskén) propranolol (Inderal, Inderal Retard) metoprolol (Seloken, Seloken ZOC) atenolol (Tenormin) bisoprolol (Emconcor) karvedilol (Kredex)</td>
</tr>
<tr>
<td>For hypertension the medicine is only reimbursed for patients who cannot use vasodilating calcium channel blockers.</td>
<td>verapamil (Isoptin, Isoptin Retard) diltiazem (Cardizem, Cardizem Retard, Cardizem Unotard, Cardiham)</td>
</tr>
<tr>
<td>Reimbursed only for patients who have tried but cannot use ACE inhibitors or as a complement to ACE inhibitors.</td>
<td>losartan (Cozaar, Cozaar Comp, Cozaar Comp Forte) eprosartan (Teveten, Teveten Comp) valsartan (Diovan, Diovan Comp) irbesartan (Aprovel, CoAprovel) kandesartan (Atacand, Atacand Plus) telmisartan (Micardis, Micardis Plus)</td>
</tr>
<tr>
<td>Reimbursement which is restricted to the treatment of patient groups with special needs:</td>
<td></td>
</tr>
<tr>
<td>Reimbursed only for patients who need loop-diuretics but cannot use furosemide.</td>
<td>torasemide (Torem)</td>
</tr>
<tr>
<td>Reimbursement only for the treatment of hypertension while pregnant.</td>
<td>methyldopa (Aldomet) labetalol (Trandate) isradipine (Lomir SRO)</td>
</tr>
<tr>
<td>Reimbursement only for treatment of hypertension while pregnant and for treatment of Morbus Raynaud.</td>
<td>nifedipine (Adalat)</td>
</tr>
<tr>
<td>Reimbursement only for patients with severely limited kidney function.</td>
<td>fosinopril (Monopril)</td>
</tr>
</tbody>
</table>
9. Many companies decreased their prices pending decisions

- During 2007 the companies have decreased their prices for a large number of blood pressure lowering medicines.
- Original brand companies have decreased the price for roughly 25 of their medicines.
- Total savings for these price decreases amount to 115 million Skr per year.
- The price decreases mean the LFN has been able to retain many medicines within the reimbursement system.
- From almost 50 blood pressure lowering pharmaceutical substances within the reimbursement system patients will continue to have access to all, barring three.

When the LFN analysed the medicines in this review it was clear that many medicines did not give value-for-money as the price of these medicines was too high. It was not reasonable for these medicines to then remain part of the reimbursement system considering the availability of equal alternatives at a lower cost. Many of the companies have therefore decreased the prices of their drugs in order to retain reimbursement.

This has occurred as we have had continuous contact with the companies concerned. The companies have been able to submit their own case and to comment on our conclusions. In the last step we sent out memos in regard to the pending decisions for the medicines we intended to change reimbursement status for. If the company wished then we offered an opportunity for a deliberation with the board. Many companies instead chose to decrease their prices.

In all of these cases the LFN has made it clear to the companies that we are prepared to listen to arguments in regard to the effect of the various medicines and for any smaller groups which might be eligible for restricted reimbursement. We have also stated that the cost-effectiveness of a medicine depends on the two components of effect and price.

The price decreases have been comprehensive during the entire review. One interesting observation is that almost 25 of the price decreases made have been for original brand drugs. Price decreases for original brands are otherwise very rare.
The price decreases the companies have made during 2007 result altogether in direct savings of 115 million Skr per year.

These price savings have meant the LFN can allow many of the medicines to remain within the benefits system. The patients through this will get access to the great majority of the blood pressure lowering medicines within the reimbursement system but at a considerably lower cost.
10. Reasons behind the LFN’s decisions

In this chapter the LFN accounts for the reasons behind the decisions listed in Table 1 in this report. We also account for the decisions on a more detailed level than the table permits.

Because prices differ we will in some cases make different decisions for medicines with the same active substance. It can then be the case that we exclude some individual original brand medicines, parallel imports or generic medicines from the benefits system but that the substance is still available in a reimbursed form.

In this report we have chosen to account for our decisions for all substances and to always indicate the original producer’s name. For substitutable medicines we do not however account for decisions in regard to all of the generic versions. As all parallel imports and parallel distributed medicines are substitutable for their direct import counterpart these product decisions are not either detailed here. Full information on reimbursement status and current prices for all medicines are available on our website www.lfn.se.

The comparison price indicated for substitutable medicines refers to the price of the cheapest available version of the medicine.

10.1 Antihypertensive agents (C02)

<table>
<thead>
<tr>
<th>Name of active substance</th>
<th>Pharmaceutical name</th>
<th>Sales 2007</th>
<th>Comparison dose</th>
<th>Comparison price</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydralazin</td>
<td>Apresolin</td>
<td>620 000 Skr</td>
<td>25 mg</td>
<td>0.92 Skr</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Aldomet</td>
<td>130 000 Skr</td>
<td>500 mg</td>
<td>2.12 Skr</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>Physiotens and generics</td>
<td>3.6 million Skr</td>
<td>0.2 mg</td>
<td>3.48 Skr</td>
</tr>
<tr>
<td>doxazosin</td>
<td>Alfadil</td>
<td>Alfadil 28 million Skr + generics 900 000 Skr</td>
<td>4 mg</td>
<td>4.60 Skr         (cheapest generic 1.40 Skr)</td>
</tr>
</tbody>
</table>

The SBU does not count this group as one of the five big ones and in comparison with the others this therapeutic group is less well-documented in regard to the ability to prevent coronary heart disease and death.
The medicines in this group are very different to each other and do not have the same documented effect as a number of other medicines. Due to this we cannot apply the reasoning behind a pricing corridor fully. In Swedish and international treatment recommendations there are however substances in this group which are included as recommended therapies when the patients have tried the large therapeutic groups. These recommendations mainly profile patients who need one of these medicines as a treatment option in a later stage of their blood pressure treatment.

It is furthermore of the greatest importance here to maintain a healthy price competition between the current substitutable groups.

Hydralazin (Apresolin) retains reimbursement
As Apresolin is a second line medicine which fills a medical need and is available at a low price the LFN has decided the product may remain within the benefits system.

This means that the LFN sees hydralazin as the most cost-effective medicine in the group. Hydralazin is an old active substance which lacks much of the documentation which modern blood pressure lowering medicines have.

The price per day for Apresolin is however low and already in the medicine’s text on indications it is stated that it is purely a second line medicine.[28] Apresolin’s indication text for hypertension says: ”Hypertension where treatment using beta blockers and diuretics has not given the required effect or is unsuitable.” The medicine fills a need for some individuals at a low price.

Antihypertensive agents which receive limited reimbursement
Methyldopa (Aldomet)
The LFN has decided that Aldomet shall continue to be reimbursed but with the following restriction:
Reimbursed only for treatment of hypertension during pregnancy.

In its treatment recommendation ”Treatment of hypertension during pregnancy” from 1996 the MPA writes about Methyldopa as a medicine without any known deformity-inducing effects.[5] The LFN therefore judges it to be important that Methyldopa receives continued reimbursement.

The medicine has only been approved for the indication high blood pressure. In Läkemedelsboken 2003/2004 the dose is indicated at 500 mg for Methyldopa.[24] The LFN has not been able to locate any other more reliable
A review of medicines for lowering blood pressure

information in regard to which dose is the most common and most relevant for comparisons with other types of blood pressure lowering therapies. The recommended dose according to the approved product summary is from 500 mg and up to 3 g per day. [29] Calculations based on the dose of 500 mg yield a per 24-hour cost of 2.12 Skr.

The price of Methyldopa is higher than 1.40 Skr per day which is the ceiling for the LFN’s pricing corridor. In our estimation then general usage of this substance is not cost-effective compared to well-documented and cheaper blood pressure lowering medicines.

The company, in its description of the product, has stated that Aldomet lacks documentation but is well-proven in clinical reality. They have not pointed out any patient group which could benefit from restricted reimbursement. They treat the product as a pure service product.

Sales of Methyldopa were only 130 000 Skr in 2007. There is no generic competition for these 20 to 140 year-round patients.

*Moxonidine (Physiotens)*
The LFN has decided to reimburse Moxonidine only under the following restriction:

**For hypertension the medicine is reimbursed only for patients who have first tried other pharmaceutical groups.**

The company owning the original brand Physiotens argue that the medicine should continue to be reimbursed. Their argument is that Moxonidine offers a further mechanism within the treatment area and can be combined with all of the five large therapeutic groups. Therefore Moxonidine offers a further combination possibility. [30, 31]

The LFN considers the company’s arguments to be well-supported and the price level for Moxonidine to be acceptable if the reimbursement for Moxonidine is restricted.

It has proved difficult to find any reliable information pertaining to which Moxonidine dose is the most relevant for comparisons with other blood pressure lowering therapies. A tablet of Moxonidine costs however from 3.48 Skr and the 24-hour cost is therefore somewhere between 3.48 Skr and approx. 10 Skr within the approved dosage interval. The company holding the original brand Physiotens has however referred to documentation making it reaso-
nable to assume that the average maintenance dose is somewhere between 0.2 and 0.3 mg per day.[32]

The price for Moxonidine is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. As a consequence we judge that general treatment with this substance is not cost-effective in comparison with well-documented and cheaper medicines.

For Moxonidine there is a generic but only from one producer and there is no meaningful price competition on the market.

*Doxazosin (Alfadil)*

The LFN has decided to reimburse doxazosin only on the following restriction:

**For hypertension the medicine is only reimbursed for patients who have first tried other pharmaceutical groups.**

The MPA recommends alpha blockers (doxazosin) in its treatment recommendation from 2006 as an alternative therapy when the patient has tried treatment using the large therapeutic groups.[5] There may therefore be certain patients who need doxazosin as a treatment option in complicated cases.

The LFN believes this is a sound reason for allowing doxazosin to continue to be reimbursed on a restricted basis.

To fulfil these needs doxazosin may, within its area of restricted use, cost up to 4.60 Skr per day. This is based on the number of available generics and the price of generic doxazosin the past year.

There are a number of doxazosin generics on the market but as the MPA has ruled that these shall not be substitutable for the original brand Alfadil there is no price competition on the market. Sales of doxazosin were approx. 29 million Skr in 2007 and the original brand Alfadil stood for all of 28 million Skr.

The price for Alfadil and most generics is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. As a consequence we judge that general treatment with this substance is not cost-effective in comparison with well-documented and cheaper medicines.

At the time of writing generic doxazosin is available at 1.40 Skr per day. There is however the possibility of this producer raising the price of its medicine
at any time. Furthermore, there is no documentation showing that doxazosin has an effect equal to the four large therapeutic groups. Therefore, not even at a price of 1.40 Skr per day should doxazosin be reimbursed without any restriction.

10.2 Diuretics (C03)

<table>
<thead>
<tr>
<th>Name of active substance</th>
<th>Pharmaceutical name</th>
<th>Sales 2007</th>
<th>Comparison dose</th>
<th>Comparison price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendroflumethiazide</td>
<td>Salures</td>
<td>61.5 million Skr</td>
<td>2.5 mg</td>
<td>1.12 Skr</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Esidrex</td>
<td>12 million Skr</td>
<td>25 mg</td>
<td>1.00 Skr</td>
</tr>
<tr>
<td>Bendroflumethiazide + potassium</td>
<td>Centyl-K mite</td>
<td>2.9 million Skr</td>
<td>1.25 mg</td>
<td>1.09 Skr</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Lasix and generics</td>
<td>40 million Skr</td>
<td>20 mg</td>
<td>0.51 Skr</td>
</tr>
<tr>
<td>Furosemide long-acting</td>
<td>Lasix Retard and generics</td>
<td>68 million Skr</td>
<td>30 mg</td>
<td>1.18 Skr</td>
</tr>
<tr>
<td>Spironolakton</td>
<td>Aldactone and generics</td>
<td>28.3 million Skr</td>
<td>50 mg</td>
<td>1.27 Skr</td>
</tr>
<tr>
<td>Amilorid</td>
<td>Amilorid Merck NM</td>
<td>4 million Skr</td>
<td>5 mg</td>
<td>0.77 Skr</td>
</tr>
<tr>
<td>Amilorid + hydrochlorothiazide</td>
<td>Moduretic, Moduretic Mite, and generics</td>
<td>28.6 million Skr</td>
<td>5 mg/50 mg</td>
<td>0.66 Skr</td>
</tr>
</tbody>
</table>

Limited reimbursement

<table>
<thead>
<tr>
<th>Name of active substance</th>
<th>Pharmaceutical name</th>
<th>Sales 2007</th>
<th>Comparison dose</th>
<th>Comparison price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torasemide</td>
<td>Torem and generics</td>
<td>4.2 million Skr</td>
<td>2.5 mg</td>
<td>2.35 Skr</td>
</tr>
</tbody>
</table>

The combination of good blood pressure lowering effects and prices which lie inside the pricing corridor mean the LFN has ruled that these medicines shall continue to be reimbursed.

This group is divided into sub-groups. For diuretics of the thiazide type there is documentation which shows that they decrease the risk of stroke and myocardial infarction. For the stronger type of diuretic, loop-diuretics, there are no such effects documented but when the kidney is not properly functioning these are needed in many cases in order to lower blood pressure sufficiently.

The SBU writes in its report: "Documentation is lacking for loop diuretics when it comes to the effect of protection from the complications of hypertension. These substances have a given place in any case for the treatment of some patients, especially those with worsened kidney function."[7]

Centyl K mite retains reimbursement

For Centyl K mite, containing bendroflumethiazide and potassium, the dose most often cited in the literature is 2.5 mg bendroflumethiazide. However the company has submitted a number of references, some of which are newly
published, showing that it is probable that the lower dose of 1.25 mg also results in the desired positive effects.[33, 34] The price for a lower dose lies within the LFN pricing corridor.

_Furosemide (Lasix) retains reimbursement_

Furosemide has a combination of a very low price, lower than our floor price for the pricing corridor, and a good effect for some patient groups with great medical need. This means that Furosemide retains reimbursement despite the lack of data on its ability to prevent myocardial infarction and minor heart attacks.

_Diuretics which receive restricted reimbursement_

_Torasemide (Torem) gets restricted reimbursement_

The LFN has decided to reimburse Torasemide only on the following restriction: **Reimbursed only for patients who need loop-diuretics but cannot use Furosemide.**

In the opinion of the LFN it is important for some patients to have access to loop-diuretics as a treatment alternative. In cases where these patients cannot take Furosemide there is only Torasemide which remains as an approved treatment alternative. Within this restricted group it is reasonable that Torasemide receives continued reimbursement.

Sales of Torem were just over 3 million Skr in 2005. There are generics available but price competition has not emerged properly on the market. Sales of generic Torasemide barely reach one million Skr per year. Use of the medicine can be expected to be considerably higher for treatment of oedema for heart failure patients than for treatment of high blood pressure.

Based on the approved dosage and the dose indicated for Torasemide in _Läkemedelsboken 2003/2004_ we believe that 2.5 mg is the dose of Torasemide which shall be included in the comparison.[24]

Using this dosage assumption the 24-hour cost for generic Torasemide is 2.35 Skr (AUP). For the original brand medicine Torem, only available as tablets of 5 and 10 mg the cost is 3.25 Skr for 5 mg. We believe the price for Torasemide is not reasonable in comparison with cheaper diuretics and ACE inhibitors. As a consequence we judge that general treatment with this substance is not cost-effective in comparison with well-documented and cheaper medicines.
The company marketing Torem has argued the medicine should be reim­bur­sed for patients who have tried but not tolerated treatment with Furosemide. [35-42]

**Spironolactone (Aldactone) retains reimbursement**

For patients suffering from hypertension, spironolactone is a second line medicine which fills a medical need and is available at a low price. The LFN has therefore decided to let the medicine remain in the reimbursement system.

This does not mean that the LFN considers spironolactone to be the most cost-effective of the medicines in the group. Spironolactone is an old active substance which lacks much of the documentation a modern blood pressure medicine has.

The price per day for Aldactone and generic spironolactone is however low and already in the indication text for the medicine it is presented as a purely second line medicine. Aldactone’s indication text says: "Ascites from liver cirrhosis. Other hepatic oedema, cardiac and renal oedema, where other oedema therapy is insufficient, especially when suspecting hyperaldosteronism. Hypertension where other therapy is insufficient or unsuitable. Primary aldosteronism where there are obstacles to carrying out an operation.”[43] The medicine therefore fulfils a need for some individuals.

**Amiloride retains reimbursement**

For patients suffering from hypertension amiloride is a supplementary medicine which fulfils a medical need and is available at a low price. The LFN has therefore decided to let the medicine remain in the reimbursement system.

This does not mean that the LFN considers amiloride to be the most cost-effective of the medicines in the group. Amiloride is an old active substance which lacks much of the documentation a modern blood pressure medicine has.

The price per day for Amilorid Merck NM is however low and already in the indication text for the medicine it is presented as purely a supplementary medicine for the treatment of high blood pressure.[44] Amilorid Merck NM has been approved for the indications: cardiac-related oedema, hypertension and cirrhosis of the liver with ascites. For hypertension the indication text says: "Hypertension: Amilorid Merck NM used as a complement to thiazides or other saluretic hypertension agents used to avoid loss of potassium in long-term treatment.” The medicine therefore fulfils a need for some individuals at a low price.
**10.3 Beta blockers (C07)**

<table>
<thead>
<tr>
<th>Name of active substance</th>
<th>Pharmaceutical name</th>
<th>Sales 2007</th>
<th>Comparison dose</th>
<th>Comparison price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited reimbursement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pindolol</td>
<td>Viskén and generics</td>
<td>3.4 million Skr</td>
<td>15 mg</td>
<td>1.67 Skr</td>
</tr>
<tr>
<td>propranolol</td>
<td>Inderal and generics</td>
<td>12.2 million Skr</td>
<td>160 mg</td>
<td>1.12 Skr</td>
</tr>
<tr>
<td>long-acting propranolol</td>
<td>Inderal Retard</td>
<td>12.4 million Skr</td>
<td>160 mg</td>
<td>1.75 Skr</td>
</tr>
<tr>
<td>metoprolol</td>
<td>Seloken</td>
<td>1.8 million Skr</td>
<td>2*50 mg</td>
<td>1.74 Skr</td>
</tr>
<tr>
<td>long-acting metoprolol</td>
<td>Seloken Zoc (and generics)</td>
<td>207.4 million Skr (+ 141 million Skr)</td>
<td>50 mg</td>
<td>1.73 Skr</td>
</tr>
<tr>
<td>long-acting metoprolol</td>
<td>Metoprolol GEA Retard</td>
<td>13.6 million Skr</td>
<td>50 mg</td>
<td>1.63 Skr</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Tenormin and generics</td>
<td>55.2 million Skr</td>
<td>50 mg</td>
<td>0.41 Skr</td>
</tr>
<tr>
<td>bisoprolol</td>
<td>Emconcor and generics</td>
<td>26.6 million Skr</td>
<td>10 mg</td>
<td>0.90 Skr</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Trandate</td>
<td>2.4 million Skr</td>
<td>400 mg</td>
<td>3.36 Skr</td>
</tr>
<tr>
<td>karvedilol</td>
<td>Kredex and generics</td>
<td>16 million Skr</td>
<td>25 mg</td>
<td>0.48 Skr</td>
</tr>
</tbody>
</table>

Beta blockers are less effective than the other medicines at lowering blood pressure and preventing the risk for future illnesses and death. There is a lot of support for this from the SBU and MPA.[5, 7] The LFN has therefore decided to only reimburse beta blockers on restriction.

We have said there is good support for this from both the SBU and the MPA. The MPA also underlines that beta blockers, especially in combination with diuretics, have undesirable metabolic effects which can lead to an increased risk of relapse into type 2 diabetes.

Despite this effect beta blockers have a well-documented effect and a given place in therapy. For some patients who have tried a number of other therapeutic groups to lower their blood pressure but not reached their treatment objectives in any other way, it can be both urgent and cost-effective to treat using beta blockers. Many patients also use beta blockers to treat a number of different conditions. Beta blockers have shown good effect for the treatment of for example angina, heart failure and arrhythmia.[45]

**All beta blockers receive restricted reimbursement**

The LFN has decided to have a general restriction for beta blockers:
Some of the beta blockers also have a clear niche use, such as treatment of hypertension during pregnancy. This type of niche use may also sometimes need to be reimbursed.

The reimbursement of beta blockers shall be restricted if one takes into account the conclusions drawn by the SBU and MPA and the recently published studies and meta-analyses which show that beta blockers cannot be said to be as good as the other large therapeutic groups in this review.[5, 7, 8]

For the treatment of uncomplicated hypertension these medicines shall therefore only be reimbursed for patients who have tried medicines from other pharmaceutical groups without having reached their treatment objectives. Most beta blockers should however remain reimbursed for treatment under other approved indications such as angina, arrhythmia, heart failure, following myocardial infarction and more.

**Beta blockers are considerably different to each other**

In the LFN’s estimation the differences in secondary qualities between beta blockers is large. An example of these differences is that there are beta blockers which are both selective and non-selective, being less or more soluble in fat, and being broken down or secreted in different ways. Furthermore, there is a third group which blocks both alpha and beta receptors.

The approved indications divide up beta blockers and they are used for treating different conditions. These conditions are of different character and vary in their degree of severity.

Some beta blockers are used for treating hypertension and concurrent angina. Others also have a role in the treatment of heart failure, preventive treatment of migraine or tremors.

**A separate pricing corridor for beta blockers**

The natural differences between beta blockers and the desire to have at least two available treatment alternatives within the benefits system means the pricing corridor may be larger for beta blockers than for the other groups.[27]

By setting the pricing corridor for beta blockers at 1.25 Skr per day we fulfil the criteria for this pricing corridor.

As beta blockers shall be reimbursed with restrictions it is not reasonable to have the same pricing corridor as for other medicines. The floor price is also 50 öre per day for beta blockers.
Long-acting metoprolol (Seloken ZOC)
Information in regard to doses for long-acting metoprolol is not expressly
detailed in the British HTA report the LFN uses as its main starting point for
the dose comparisons.[14] In Läkemedelsboken 2003/2004 it is stated howe­
erver that the relevant dose for long-acting metoprolol is 50 mg for treatment
of high blood pressure.[24]

Despite the medicines Seloken ZOC and Metoprolol Sandoz being substi­
tutable the more expensive original brand had sales of approx. 207.4 million
Skr in 2007. The substitutable and cheaper medicines showed sales of ap­
prox. 141 million during the same year.

Bisoprolol (Emconcor)
The original brand Emconcor has been registered under two different phar­
maceutical names. Only Emconcor is substitutable for generic bisoprolol.
Due to packages with a number of dosage steps Emconcor CHF is not sub­
stitutable. Emconcor CHF has roughly as large sales as the other medicines
with bisoprolol together.

Labetalol (Trandate)
We have decided that Trandate (labetalol) shall only be reimbursed under a
special restriction as its price lies outside the pricing corridor for beta block­
ers.
The LFN has decided to reimburse Trandate only under the following restric­
tion: Reimbursed only for the treatment of hypertension during pregnancy.

In its treatment recommendation ”Treatment of hypertension during preg­
nancy” from 1996 the MPA shows labetalol to be an alternative for treatment
of hypertension in connection with pregnancy.[15] The LFN considers it
therefore to be urgent that labetalol receive continued reimbursement.

Trandate is the only medicine available containing labetalol and in 2007
reached sales of almost 2.5 million Skr.

The cost for treatment is high and lies between 1.68 Skr and approx. 5 Skr
per day depending on dose. Usage is already today, according to information
supplied by the company, strictly restricted.

1The name of the drug has been changed but in the list of substitutable drugs which the MPA published
to come into force on 2007-12-19 the product is called Metoprolol Sandoz. It is substitutable for Seloken-
ZOC in the doses 25, 50, 100 and 200 mg.
**10.4 Calcium channel blockers (C08)**

<table>
<thead>
<tr>
<th>Name of active substance</th>
<th>Pharmaceutical name</th>
<th>Sales 2007</th>
<th>Comparison dose</th>
<th>Comparison price</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Still in benefits system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amlodipine</td>
<td>Norvasc and generics</td>
<td>70 million Skr</td>
<td>5 mg</td>
<td>0.54 Skr</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Plendil and generics</td>
<td>129 million Skr</td>
<td>5 mg</td>
<td>0.73 Skr</td>
</tr>
<tr>
<td><strong>Restricted reimbursement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>long-acting Isradipine</td>
<td>Lomir SRO</td>
<td>12.3 million Skr</td>
<td>2.5 mg</td>
<td>3.68 Skr</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Adalat and generics</td>
<td>6.6 million Skr</td>
<td>2*20 mg</td>
<td>3.32 Skr</td>
</tr>
<tr>
<td>verapamil</td>
<td>Isoptin + generika</td>
<td>4.3 million Skr</td>
<td>3*80 mg</td>
<td>2.49 Skr</td>
</tr>
<tr>
<td>long-acting verapamil</td>
<td>Isoptin Retard</td>
<td>13 million Skr</td>
<td>2*120 mg</td>
<td>3.66 Skr</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Cardizem</td>
<td>2.4 million Skr</td>
<td>3*60 mg</td>
<td>5.34 Skr</td>
</tr>
<tr>
<td>long-acting diltiazem</td>
<td>Cardizem Retard</td>
<td>29.2 million Skr</td>
<td>2*90 mg</td>
<td>5.28 Skr</td>
</tr>
<tr>
<td>long-acting diltiazem</td>
<td>Cardizem Unotard</td>
<td>5.1 million Skr</td>
<td>240 mg</td>
<td>5.30 Skr</td>
</tr>
<tr>
<td>long-acting diltiazem</td>
<td>Coramil</td>
<td>700 000 kr</td>
<td>200 mg</td>
<td>4.81 Skr</td>
</tr>
<tr>
<td><strong>Excluded from the benefits system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isradipine</td>
<td>Lomir</td>
<td>781 000 kr</td>
<td>2*2,5 mg</td>
<td>5.18 Skr</td>
</tr>
<tr>
<td>long-acting Nifedipine</td>
<td>Adalat Oros</td>
<td></td>
<td>20 mg</td>
<td>3.95 Skr</td>
</tr>
<tr>
<td>Lerkanidipine</td>
<td>Zanidip</td>
<td></td>
<td>10 mg</td>
<td>3.91 Skr</td>
</tr>
</tbody>
</table>

Calcium channel blockers are also used for a number of different indications. They can be divided up into two groups, one mainly affecting the walls of blood vessels called vasodilating, and one which also affects the heart, the cardiac-selectives.

For those patients suffering from hypertension (hypertoni) the LFN cannot find any evidence that the more expensive non-vasodilating calcium channel blockers (verapamil and diltiazem) have any extra advantage over competing medicines. The LFN has not found general use of these more expensive calcium channel blockers to be more cost-effective than cheaper blood pressure lowering medicines.

There may however be smaller patient groups where treatment using for example cardiac-selective calcium channel blockers could be cost-effective in comparison with cheaper alternatives. There is a lack of register data which can give reliable information on the reasons for prescriptions but other indications probably account for a considerably smaller part of the use of cardiac-selective calcium channel blockers. The LFN has therefore decided to only grant reimbursement for these medicines with special restrictions and conditions.
Calcium channel blockers which receive restricted reimbursement

*Long-acting Isradipine (Lomir SRO)*

The LFN has decided to reimburse Lomir SRO only under the following restriction:

**Reimbursed only for the treatment of hypertension during pregnancy.**

In its treatment recommendation “Treatment of hypertension during pregnancy” from 1996 the MPA indicated isradipine as an alternative for treatment av hypertension in connection with pregnancy.[15] The LFN judges it therefore to be urgent that a medicine containing Isradipine gets continued reimbursement. The forms available today are Lomir and Lomir SRO and of these Lomir SRO has the lower price today.

The price for long-acting Isradipine is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. As a consequence we judge that general treatment with this substance is not cost-effective in comparison with well-documented and cheaper medicines.

The company is not making any argument for the product to retain reimbursement for general use. They have however suggested the product be reimbursed for the following groups:

- older patients, over 70 years old

As support for their arguments the company points to data from the STOP 2 study which showed that felodipine and isradipine have a positive treatment effect for older patients (over 70 years old).[46] In this study however both medicines are used without any indication as to which patient got which medicine. It is not proven which of the medicines stands for the positive effect on the elderly. It has not been shown that isradipine adds anything extra of value compared to felodipine. Due to its higher price Isradipine cannot be considered cost-effective.

*Nifedipine (Adalat)*

The LFN has decided to only reimburse Adalat under the following restriction:

**Reimbursed only for treatment of hypertension during pregnancy and for treating Morbus Raynaud.**

In its treatment recommendation “Treatment of hypertension during pregnancy” from 1996 the MPA stated Nifedipine was an alternative for treatment of hypertension in connection with pregnancy.[15] In the LFN’s estimation then it is urgent that some medicine containing Nifedipine gets
continued reimbursement. The forms available today are Adalat and Adalat Oros, of these Adalat has the lower price today.

The price for nifedipine is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. In our estimation therefore general treatment with this substance is not cost-effective in comparison to well-documented and cheaper medicines.

The company argues the product should be allowed retain reimbursement. They have suggested it should be reimbursed for:

- patients with Morbus Raynaud disease

The LFN accepts the company’s argumentation and Adalat is one of the very few medicines, and the only one in this review, which is approved for the indication Morbus Raynaud.

*Verapamil (Isoptin and Isoptin Retard) and diltiazem (Cardizem, Cardizem Retard, Cardizem Unotard and Coramil)*

The LFN has decided to reimburse the medicines Isoptin and Isoptin Retard, Cardizem, Cardizem Retard, Cardizem Unotard and Coramil under the following restriction:

**For hypertension the medicines are only reimbursed for patients who cannot use vasodilating calcium channel blockers.**

The price for all of these is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. In our estimation therefore general treatment with this substance is not cost-effective in comparison to well-documented and cheaper medicines.

The medicines are used both for treating hypertension and angina. The distribution between these areas of use is not known.

For verapamil the indication text says: "Verapamil shall be used when treatment using diuretics and/or beta receptor blockers has not given the desired effect or is unsuitable."[47]

The companies marketing these medicines argue the products should continue to be reimbursed and then for the following groups:

- patients in need of a calcium channel blocker and who have tried a vasodilating variant but reacted to the side-effects from this.
- Patients in need of lowering their pulse and who have a contraindication for beta blockers, eg due to COPD.
The LFN judges that this restriction makes it possible to treat patients within both of these groups. The restriction also means that patients suffering from angina can get these medicines within the benefits system.

**Calcium channel blockers the LFN is excluding from the system**

*Isradipine (Lomir)*

The LFN values the utility in treatment using short-acting Isradipine (Lomir) in the same way as we value the utility for the long-acting version (Lomir SRO).

The company has submitted exactly the same argumentation for Lomir and Lomir SRO. The LFN cannot accept this argument as a reason for the reimbursement of the medicines. The LFN does judge a need however for some medicine containing Isradipine to retain reimbursement for the group pregnant women. The forms available today are Lomir and Lomir SRO and of these Lomir SRO has the lower price tag today.

**The LFN has therefore decided that Lomir shall be excluded from the benefits system.**

*Long-acting Nifedipine (Adalat Oros)*

The price for long-acting nifedipine is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. As a consequence we judge that general treatment with this substance is not cost-effective in comparison with well-documented and cheaper medicines.

The company argues the product should be allowed retain reimbursement. They have suggested it should be reimbursed for:

- Patients with hypertension and concurrent stable angina where treatment using a calcium antagonist is especially suitable.
- Patients with hypertension. Here one wants to give a calcium antagonist at a low dose.

To support their arguments the company claims that only Adalat Oros has a documented effect on morbidity for patients with both hypertension and angina. The LFN cannot accept this argument as a reason for the reimbursement of the medicine. Adalat Oros is not the only calcium antagonist which has a documented effect on morbidity for stable angina (angina pectoris).

The LFN has instructed the company to give evidence for their arguments.
using studies. They have not however submitted any documentation showing that low dose treatment using only Adalat Oros is an urgent alternative. Neither has the LFN found any such documentation via other sources.

**The LFN has therefore decided that Adalat Oros shall no longer be part of the benefits system.**

*Lerkanidipine (Zanidip)*
The price for lerkanidipine is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. As a consequence we judge that general treatment with this substance is not cost-effective in comparison with well-documented and cheaper medicines.

The company is not arguing the product should be allowed retain reimbursement for general use. They have suggested it should be reimbursed for these groups:

- Patients who get ankle oedema from felodipine and amlodipine
- Women, older and obese patients
- Patients with hypertension and diabetes type 2
- Patients with high blood pressure, diabetes type 2 and egg white in their urine.

To support their arguments the company claims that only Zanidip belongs to the third generation of calcium channel blockers, that it has a different mechanism to medicines previously approved in the group and that it has considerably milder side-effects than competing medicines.

The company backs up its argument for continued reimbursement for Zanidip (lerkanidipine) mainly through claiming the medicine has a better side-effects profile than other calcium antagonists, mainly when it comes to the prevalence of oedema of the legs. This would then mean that patients who cannot take the other calcium antagonists can here find a possibility for treatment with a subsequent decreased risk for cardiovascular disease.

The documentation which the company refers to in regard to side-effects of oedema of the legs in clinical studies comprises four references.[50-53] Two of these are different publications of the same study.[51, 52] In this three different calcium antagonists are compared. The blood pressure lowering effect was the same for the doses used. Lerkanidipine gave oedema of the legs for approx. 8% of the patients, which was a lower frequency than for the patients who got amlodipine. The frequency of oedema of the legs was lowest for the third calcium antagonist (lacidipine, not approved in Sweden).
In a third reference it was found that leg volume increases considerably more using amlodipine than with lerkanidipine[53], the fourth study referred to was a completely open study of little value evidence-wise[50].

The documentation sent in by the company in regard to side-effects from oedema comprises therefore only two relevant studies. In both cases the only comparison which is interesting is for Swedish conditions for amlodipine. The documentation is sparse on this.

In this review a large number of blood pressure lowering medicines will remain in the benefits system and the LFN does not consider it proven that Zanidip is cost-effective in this comparison. The company has only shown the medicine possibly has less side-effects in the form of leg oedema than amlodipine. A patient who cannot use amlodipine has access to over twenty other cheap and effective medicines to lower their blood pressure, of which felodipine is one of them.

The LFN has therefore decided that Zanidip shall be excluded from the benefits system.

### 10.5 ACE inhibitor (C09 A and B)

<table>
<thead>
<tr>
<th>Name of active substance</th>
<th>Pharmaceutical name</th>
<th>Sales 2007</th>
<th>Comparison dose</th>
<th>Comparison price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remains in system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic kaptopril</td>
<td>Three different generics</td>
<td>5.6 million Skr</td>
<td>2*25 mg</td>
<td>1.38 Skr</td>
</tr>
<tr>
<td>enalapril (and hydroclor-thiazide)</td>
<td>Renitec and generics (Renitec Comp/Synepril)</td>
<td>89 million Skr (26.2 million Skr)</td>
<td>10 mg</td>
<td>0.57 Skr</td>
</tr>
<tr>
<td>lisinopril (and hydroclor-thiazide)</td>
<td>Zestril and generics (Zestoretic)</td>
<td>12 million Skr (2.5 million Skr)</td>
<td>10 mg</td>
<td>0.54 Skr</td>
</tr>
<tr>
<td>ramipril (and hydroclor-thiazide)</td>
<td>Triatec and generics (Triatec Comp)</td>
<td>53 million Skr (7.2 million Skr)</td>
<td>2.5 mg</td>
<td>0.55 Skr</td>
</tr>
<tr>
<td>generic kinapril (and hydro-chlorothiazide)</td>
<td>Quinapril Alternova (Quinapril/Hydrochlorothiazid Alternova)</td>
<td>95 000 kr (440 000 kr)</td>
<td>20 mg</td>
<td>1.37 Skr</td>
</tr>
<tr>
<td>Restricted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fosinopril</td>
<td>Monopril and generics</td>
<td>1.3 million Skr</td>
<td>20 mg</td>
<td>4.20 Skr</td>
</tr>
<tr>
<td>Excluded from reimbursement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaptopril</td>
<td>Capoten</td>
<td>864 000 kr</td>
<td>2*25 mg</td>
<td>2.74 Skr</td>
</tr>
<tr>
<td>kinapril (and hydroclor-thiazide)</td>
<td>Accupro (Accupro Comp)</td>
<td>2.2 million Skr (3.3 million Skr)</td>
<td>20 mg</td>
<td>5.57 Skr</td>
</tr>
<tr>
<td>cilazapril (and hydroclor-thiazide)</td>
<td>Inhibace (Inhibace Comp)</td>
<td>7.2 million Skr (7.6 million Skr)</td>
<td>2.5 mg</td>
<td>3.55 Skr</td>
</tr>
</tbody>
</table>
There are a number of different ACE inhibitor medicines, for some of these the patent has expired and for others it is still valid. Price competition for most of the medicines which have lost their patents has been comprehensive. The price differences are large within this therapeutic group due to this and there are a number of products falling outside the proposed pricing corridor.

For those patients suffering from hypertension or heart failure the LFN cannot find any evidence that the more expensive ACE inhibitors add any marginal benefit in comparison to the cheaper competing medicines. The LFN has not found that general use of these more expensive ACE inhibitors is cost-effective in comparison with cheaper blood pressure lowering medicines.

In one case there is a smaller group of patients where treatment with one of these more expensive ACE inhibitors fosinopril (Monopril) could be cost-effective, also in comparison to cheaper alternatives. This applies for the treatment of patients with severely decreased kidney function. These medicines should therefore continue to be included in the benefits system but then restricted to patients with severely decreased kidney function.

Fixed combinations of ACE inhibitors and hydrochlorothiazide
There are many combination medicines on the market containing an ACE inhibitor and hydrochlorothiazide. The cost for hydrochlorothiazide is approx 1 Skr (AUP) per tablet to purchase a package of 100 tablets. The LFN therefore allows combination medicines containing an ACE inhibitor and hydrochlorothiazide to cost 1 Skr more than the highest price accepted for an ACE inhibitor by itself.

ACE inhibitors receiving restricted reimbursement
Fosinopril (Monopril)
The LFN has decided to reimburse fosinopril (Monopril) under the following restriction:
Reimbursed only for patients with severely decreased kidney function.

For Monopril the marketing company has proven that for patients with severely decreased kidney function Monopril can sometimes be the only possible alternative if one wants to treat using an ACE inhibitor.[54-60]

The LFN judges it important to allow fosinopril continued reimbursement as it is used for treatment of hypertension for patients with severely decreased kidney function.

The price for fosinopril is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. As a consequence we judge that general treatment with
this substance is not cost-effective in comparison with well-documented and cheaper medicines.

**ACE inhibitors which the LFN is excluding from the benefits system**  
*Original brand drug Capoten loses reimbursement but generic kaptopril remains in the system*

The price for the original brand drug Capoten is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. As a consequence we judge that general treatment with this substance is not cost-effective in comparison with well-documented and cheaper medicines.

A number of generic forms of kaptopril however are priced low and we will due to this allow them to continue in the reimbursement system.

The company marketing the original brand drug Capoten has not submitted any documentation to support the medicine retaining its reimbursement. They have only pointed out that the indications for Capoten differ from the indication for enalapril. There are however other ACE inhibitors which have these other indications and which are available at a low price. Therefore the LFN does not believe the high price for Capoten is motivated.

As a result the LFN has decided that Capoten shall be excluded from the reimbursement system.

*Original brand drug Accupro loses its reimbursement but generic kinapril remains in the system*

The price for the original brand drug Accupro is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. As a consequence we judge that general treatment with this substance is not cost-effective in comparison with well-documented and cheaper medicines.

A generic form of kinapril does however have a low price and will remain within the benefits system.

In its reply to the LFN the company has claimed that kinapril and other ACE inhibitors are cost-effective and also well-studied medicines. They say it could be expensive to change treatment for those who already today get Accupro and the change could cause problems for both patients and society. The company has not indicated any patient groups for which it thinks the medicine could be cost-effective.

The company has a reference showing that only a small number of patients
get side-effects in the form of coughing when treated with kinapril.[61]

Besides this there is no reason why the medicine shall continue to be reim-
bursed as the cost is more than five crowns higher than a number of other
close competitors. The LFN does not believe the reasons outlined above war-
rant the high price for Accupro.

The combination medicine Accupro Comp costs more than the leeway
allowed in the pricing corridor plus 1 Skr in addition for hydrochlorthiazide.

The LFN has therefore decided that neither Acupro nor Accupro Comp shall
continue to be reimbursed.

Cilazapril (Inhibace)
The price for Inhibace is higher than 1.40 Skr per day, the ceiling in the LFN
pricing corridor. As a consequence we judge that general treatment with this
substance is not cost-effective in comparison with well-documented and
cheaper medicines.

The company has not submitted any documentation to support the medicine
retaining its reimbursement. The LFN can therefore not find any reason for
the high price of Inhibace.

The combination medicine Inhibace Comp costs more than the leeway al-
lowed in the pricing corridor plus 1 Skr in addition for hydrochlorthiazide.

The LFN has therefore decided that neither Inhibace nor Inhibace Comp
shall continue to be reimbursed.

10.6 ARBs (C09 C and D)

<table>
<thead>
<tr>
<th>Name of active substance</th>
<th>Pharmaceutical name</th>
<th>Sales 2007</th>
<th>Comparison dose</th>
<th>Comparison price</th>
</tr>
</thead>
<tbody>
<tr>
<td>losartan (and hydrochlortiazide)</td>
<td>Cozaar (Cozaar. Comp, Cozaar Comp Forte)</td>
<td>210 million Skr (147 million Skr)</td>
<td>50 mg</td>
<td>5.97 Skr</td>
</tr>
<tr>
<td>eprosartan (and hydrochlortiazide)</td>
<td>Teveten (Teveten Comp)</td>
<td>3.9 million Skr (2.1 million Skr)</td>
<td>600 mg</td>
<td>5.75 Skr</td>
</tr>
<tr>
<td>valsartan (and hydrochlortiazide)</td>
<td>Diovan (Diovan. Comp)</td>
<td>55 million Skr (53 million Skr)</td>
<td>80 mg</td>
<td>5.97 Skr</td>
</tr>
<tr>
<td>irbesartan (and hydrochlortiazide)</td>
<td>Aprovel (CoAprovel)</td>
<td>64 million Skr (37 million Skr)</td>
<td>150 mg</td>
<td>5.94 Skr</td>
</tr>
<tr>
<td>kandesartan (and hydrochlortiazide)</td>
<td>Atacand (Atacand Plus)</td>
<td>242 million Skr (81.2 million Skr)</td>
<td>8 mg</td>
<td>5.94 Skr</td>
</tr>
<tr>
<td>Telmisartan (and hydrochlortiazide)</td>
<td>Micardis (Micardis.Plus)</td>
<td>10.5 million Skr (4.7 million Skr)</td>
<td>40 mg</td>
<td>5.67 Skr</td>
</tr>
</tbody>
</table>
The price for ARB medicines is higher than 1.40 Skr per day, the ceiling in the LFN pricing corridor. In our estimation therefore general treatment with this substance is not cost-effective in comparison to well-documented and cheaper medicines. There are however smaller groups of patients where treatment with ARB medicines can be cost-effective, also in comparison with cheaper alternatives.

The LFN does not consider there to be support for a clinically relevant difference between the various ARB drugs, when using comparable doses.[7]

All of the companies have argued strongly for their products. All use the arguments and studies which speak to their advantage. The direct comparison studies which the companies have sent in themselves to the LFN form a matrix where it is in principle impossible to draw any clear conclusion. There are many comparisons which have been done but most have been on very limited and carefully chosen patient groups. The results therefore do not tell us very much about how the medicines work in clinical reality. Most companies have been able to show that their own medicines are better than the competing medicines for a certain select patient group.[62-84]

A separate pricing corridor for ARB medicines
Because all ARB medicines are to be reimbursed on restriction we can have a separate pricing corridor for them. No ARB medicine is available as a generic.

We have therefore assumed that we are not going to be able to have at least two medicines from this group remain in the benefits system, if we demand that the floor price for these shall also be 50 öre per day. So the floor price for the pricing corridor for ARBs has instead been set based on the cheapest ARB medicine during the spring of 2007. The floor price has been set at 5.67 Skr per day.

We judge the differences in secondary qualities between the ARB medicines to be small.[7] The pricing corridor for ARB medicines may therefore only span 30 öre per day.

All ARB medicines receive restricted reimbursement
The LFN has decided to utilise a restriction when ARB medicines are reimbursed. 
Reimbursed only for patients who have tried but cannot use ACE inhibitors or as a supplement to ACE inhibitors.
For treatment of patients with uncomplicated forms of hypertension, before treating with ARB medicines the treatment should consist of calcium antagonists or low dose thiazide for cost reasons.
The MPA also provides evidence to support this in their treatment recommendations by writing: "When treating hypertension in the first instance an ACE inhibitor should be chosen and/or a thiazide diuretic at a low dose or a calcium antagonist. If the patient cannot take ACE inhibitors then ARBs can be used instead for concurrent nefropatia."

**Fixed combinations of ARBs and hydrochlorothiazide**

All ARB medicines are available as combination substances with hydrochlorothiazide. The LFN has decided that these combination substances shall be restricted in the same way as the individual ARB medicines. As the cost for hydrochlorothiazide is approx. 1 Skr (AUP) per tablet when purchasing a package containing 100 tablets of Esidrex, the LFN is allowing combination medicines of ARB and hydrochlorothiazide to cost 1 Skr more than the highest price accepted for the ARB medicine by itself.

### 10.7 Other fixed combination medicines

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Pharmaceutical name</th>
<th>Sales 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>metoprolol and felodipine</td>
<td>Logimax</td>
<td>30 million Skr</td>
</tr>
<tr>
<td>trandolapril and verapamil</td>
<td>Tarka</td>
<td>1.3 million Skr</td>
</tr>
<tr>
<td>valsartan and amlodipine</td>
<td>Exforge</td>
<td>800 000 Skr</td>
</tr>
</tbody>
</table>

The most common type of combination medicine is fixed combinations where one of the two substances is hydrochlorothiazide. These are accounted for under each individual group above. This list only deals with the fixed combination medicines containing two active substances where neither of them is hydrochlorothiazide.

**Felodipine and metoprolol (Logimax, Logimax Forte)**

Logimax contains the substances metoprolol and felodipine. At normal strength the doses are 5 and 50 mg respectively and the stronger tablet contains the doses 10 and 100 mg. The price for Logimax is currently 3.15 Skr per day, that is to say the same as the maximum price for felodipine and metoprolol each, respectively 1.40 Skr and 1.75 Skr per day.

The LFN has decided on a restriction for Logimax and Logimax Forte: **For newly commenced treatment of hypertension the medicine is reimbursed only for patients who have first tried other pharmaceutical groups.**

**Trandolapril and verapamil (Tarka)**

Tarka had sales of 1.3 million Skr in 2007. The price for Tarka is 6.20 Skr per day. The price for Tarka is higher than 2.80 Skr per day, the ceiling in the LFN pricing corridor as Tarka contains two active substances. In our judge-
ment therefore general treatment using these medicines is not cost-effective compared to well-documented and cheaper medicines.

The company has not submitted any documentation to support the medicine retaining its reimbursement status. Therefore, we cannot find any reason for the high price of Tarka.

The LFN has as a result decided to exclude Tarka from the benefits system.

**Valsartan and amlodipine (Exforge)**
Exforge contains the substances valsartan and amlodipine. At normal strength the doses are 80 and 5 mg respectively with the stronger tablet containing the doses 160 and 10 mg. The price for Exforge is not higher today than the maximum price for valsartan and amlodipine on their own, that is 5.97 Skr and 1.40 Skr per day respectively. The price for Exforge is 7.01 Skr per day.

The LFN has decided for a restriction for Exforge:
Reimbursed only for patients who have tried but cannot use ACE inhibitors or as a supplement to ACE inhibitors.

### 10.8 Comments on medicines not included in this review
There are a number of medicines which according to the ATC code system belong to the group of medicines used for treatment of hypertension but which clearly have another use. For various reasons we have chosen not to delve into these medicines in this review. In this section we account for these medicines and the reasons for this.

**Bumetanid (Burinex)**
Burinex has not been approved for the indication hypertension but only for treatment of oedema in connection with other diseases.[90] Taking into account the indication there is reason to believe the medicine is mainly used for severe conditions and that its use is limited. Therefore there is no need to make a deeper analysis of this medicine.

Burinex had sales of 1.5 million Skr in 2007.

**Bisoprolol (Emconcor CHF)**
Emconcor CHF has also been approved for the indication heart failure. [86] The medicine, which contains bisoprolol, has no unique pharmacological properties but is packaged uniquely with multiple dosage steps. Other medicines containing bisoprolol shall not be used (that is they have counter
indications) for the treatment of heart failure. Emconcor CHF shall therefore only be used to treat heart failure and not for the treatment of high blood pressure. Also, bisoprolol is one of the three recommended beta blockers in the MPA treatment recommendation for the treatment of heart failure. Due to this there is no reason to investigate further for this medicine.

Emconcor CHF had sales of 28 million Skr in 2007.

**Nimodipine (Nimotop)**
Nimotop (nimodipine) has only been approved for the indication "Prophylaxis and treatment of ischaemic symptoms due to vasospasm following a subarachnoid haemorrhage." [91] This indication is not part of this review. The medicine is intended for treatment of a severe condition and has also a limited use. Due to this there is no reason to investigate further for this medicine either.

Nimotop had sales of 180 000 Skr in 2007.

**Eplerenon (Inspra)**
Inspra is a newly registered medicine which has a similar effect as spironolactone. [85] Eplerenon has shown positive effects for heart failure following myocardial infarction. The LFN stated in its decision that Inspra could be considered cost-effective if it is used for the approved indication area as a second line treatment for heart failure after myocardial infarction. Inspra shall therefore not be used for the treatment of high blood pressure. As a result there is no reason to take a new stance in regard to reimbursement of Inspra in this review.

Inspra had sales of 8 million Skr in 2007.

**Bosentan (Tracleer)**
Tracleer (bosentan) has only been approved for treatment for the indication pulmonary arterial hypertension (PAH). [87] This therapeutic group is not part of this review.

Tracleer showed sales of 51 million Skr in 2007.

**Sotalol (Sotacor)**
Sotalol is available as a generic. The original brand drug is Sotacor. Sotalol is only approved for indications for arrhythmia. [88] The medicine will be part
of the review of medicines used for arrhythmia and angina and more.

Sotacor and generics had sales of 18.5 million Skr in 2007.

_**Esmolol (Brevibloc)**_
Also Brevibloc (esmolol) has only been approved for arrhythmia indications. [89] The medicine will be part of the review of medicines used for arrhythmia and angina and more.

Brevibloc showed no sales within the benefits system in 2007.
11. References

22. Lag (2002:160) om läkemedelsförmåner m.m.
34. Rasmussen, S., N. Borrild, and J. Vang Andersen, Efficacy and safety of 24 weeks of therapy with bendroflumethiazide 1.25 mg/day or 2.5 mg/day and potassium chloride compared with enalapril 10 mg/day and amlodipine 5 mg/day in patients with mild to moderate


Appendix 1 – The search procedure the LFN uses for literature search

Procedure 1 – Work process and starting points for collating knowledge on medical effect

1. Identify current systematic knowledge overviews
   a. General starting points for systematic knowledge overviews:
      i. Knowledge overviews from all organisations part of INAHTA (International Network of Agencies for Health Technology Assessment) are examined
      ii. Knowledge overviews from the SBU examined first
      iii. The LFN makes no further test of the results from the existing systematic knowledge overviews
   b. Search for knowledge overviews made in PubMed, Cochrane and INAHTA databases.
   c. Augmenting the systematic knowledge overviews
      i. If the overview is more than 2 years old it is added to through own searches
      ii. Searches in PubMed and Cochrane, or a relevant choice of search words used in the systematic overview
      iii. Studies with evidence grade of 2 or more are added to the original systematic knowledge overview.

2. Identification and gathering of relevant meta-analyses – Meta-analyses used where a systematic overview is lacking and in cases where the systematic overview exists but does not cover all of the treatment area relevant for the LFN’s work. Meta-analyses are also used if existing systematic reviews do not go into individual substances.
   a. Search for meta-analyses in PubMed, Cochrane and INAHTA databases
   b. Meta-analyses graded for evidence (in accordance with model from SBU report)

3. Gather relevant, published documentation from the MPA and National Board of Health and Welfare
   a. Eg product monographies, therapy recommendations, background material for workshops and national guidelines.

4. Gather company-reported effects
   a. Review of all abstracts and generally related whole articles
   b. If a systematic overview and meta-analyses are lacking then the company-reported effects are evidence graded (according to SBU template)
5. In most cases, and always if a systematic overview is missing, a non-systematic review of the literature is carried out. These non-systematic searches are mainly aimed at finding individual studies containing documentation on specific substances. These studies can be direct comparisons (head to head) or placebo-controlled.

   a. Work process for literature reviews
      i. Identify relevant search terms (medicines, illness)
      ii. Identify relevant time horizon (depends on age of medicine and so on)
      iii. Search in PubMed and Cochrane
      iv. Sift out clearly irrelevant references
         • No study on medical effect
         • Wrong illness
      v. Read abstracts (possibly entire articles) – sort data some more
      vi. Read what remains - compile
      vii. Grade for evidence

Procedure 2 - Work process and starting points for collating knowledge on health economics

1) Review of literature
   a) Work process for review of literature
      i) Identify relevant search terms (medicines, illnesses, economic terms)
      ii) Identify relevant time horizon (depends on medicine’s age and so on)
      iii) Search in PubMed and Cochrane
      iv) Add references sent in by companies

2) Sift out clearly irrelevant references
   a) No economic evaluation
   b) Wrong illness
3) Read abstracts (possibly entire articles) – sort data more
4) Read what remains - compile
5) Judge the quality and relevance for Swedish conditions
   a) Based on the LFN’s guidelines
This report accounts for the LFN’s review of medicines used to lower blood pressure. In 2007 they represented sales of 2.4 billion Skr. They constitute one of the larger therapeutic groups. The LFN’s review is aimed at deciding which medicines should continue to be reimbursed. The objective is to extract as much health as possible for every tax crown which goes to reimbursement of medicines.

The LFN states it is important to treat high blood pressure to avoid conditions such as stroke and heart attacks and that it also appears to be cost-effective to do so. Many medicines used for treating hypertension are equal when it comes to medical effect and side-effects but prices vary greatly.

This review has resulted in some medicines losing their reimbursement status as they are too expensive compared to similar alternatives. Some further medicines have received restricted reimbursement. Some of the expensive medicines shall not be used as a first line treatment, only when they are really needed.

If the decisions the LFN has made are put into action then 400 million Skr will be freed up each year.