Universitat de Girona
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# STUDY OF THE EFFICIENCY IN THE PRESCRIPTION OF ANTIHYPERTENSIVE AGENTS BASED ON EFFICACY ACCORDING TO THE ATOM STUDY RESULTS

**FINAL DEGREE PROJECT**

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*To Clàudia…my best life partner.*

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## 1. ABBREVIATIONS

| | |
|---|---|
| **HT** | Hypertension |
| **BP** | Blood pressure |
| **SBP** | Systolic blood pressure |
| **DBP** | Diastolic blood pressure |
| **CV** | Cardiovascular |
| **OD** | Organ damage |
| **LDL** | Low-density lipoproteins |
| **HDL** | High-density lipoproteins |
| **GFR** | Glomerular filtration rate |
| **HbA1c** | Glycosylated haemoglobin |
| **ECG** | Electrocardiogram |
| **CVRF** | Cardiovascular risk factor |
| **RF** | Risk factor |
| **CKD** | Chronic kidney disease |
| **JNC-8** | Joint National Committee-8 |
| **ESH/ESC** | European Society of Hypertension/ European Society of Cardiology |
| **NICE** | National Institute for Health and Care Excellence |
| **HCTZ** | Hydrochlorothiazide |
| **DHP** | Dihydropyridine |
| **RAS** | Renin-angiotensin system |
| **ACE** | Angiotensin-converting enzyme |
| **AHT** | Arterial hypertension |
| **PAD** | Peripheral artery disease |
| **ABPM** | Ambulatory blood pressure monitoring |
| **HBPM** | Home blood pressure monitoring |
| **QALY's** | Quality adjusted life years |
| **ICER** | Incremental cost-effectiveness ratio |
| **BMI** | Body mass index |
| **MOOSE** | Meta-Analysis of Observational Studies in Epidemiology |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-Analysis |
| **mg** | milligrams |
| **mmHg** | millimetres of mercury |
| **$Kg/m^2$** | Kilograms/meters$^2$ |

## 2. ABSTRACT

**Background/Aim**

The hypertension is the persistent elevation of SBP ≥ 140 and/or DBP ≥ 90 mmHg. It is the most common condition seen in primary care, approximately 7% of the outpatient visits are due to hypertension. On average, a hypertensive patient would cost twice that of a normotensive individual, because hypertension is a risk factor for other diseases.

The aim of the study is to calculate the cost-effectiveness of the reduction and control of hypertension using antihypertensive active ingredients.

There are only few studies comparing the efficacy and/or effectiveness of the most commonly used antihypertensive drugs.

**Materials and methods**

This study is based mainly in the *Atom study*, a systematic review of clinical trials followed by a meta-regression.

A cost-effectiveness study has been completed through the application of the concept of *Law et al*. and by the ICER analysis.

**Results**

This work compares the effectiveness and cost-effectiveness of different antihypertensive drugs commonly used in clinical practice. According to the data analysed, the most cost-effectiveness treatments are (depending on the blood pressure reduction interval): *Enalapril 10*, *Amlodipine 5*, *Enalapril 20 + Amlodipine 5, Bisoprolol 5, Enalapril 20 + Indapamide 1.25, Enalapril 20 + HCTZ 12.5, Olmesartan 40 + Amlodipine 10 + HCTZ 25* and *Enalapril 20 + HCTZ 12.5 + Amlodipine 10.* Also, it has been proven that the results of the study are in agreement with the antihypertensive treatments prescribed in the current clinical practice in the sanitary region of Girona.

**Conclusions**

The effectiveness analysis and the pharmacoeconomic study provide new information about antihypertensive active ingredients, with the objective of being able to apply it in the usual clinical practice. This knowledge would potentially help the clinician to choose the most adequate treatment and improve the health of patients.

**Key words:** hypertension, antihypertensive agents, effectiveness, cost-effectiveness, incremental cost-effectiveness ratio.

# 3. INTRODUCTION

## 3.1. Definition and classification of hypertension

The hypertension is defined as the persistent elevation of SBP ≥ 140 and/or DBP ≥ 90 mmHg in people over 18 years (1,2).

In the field of primary health care is considered that the elevation of the BP is persistent if the average of two determinations performed at each visit, a total of three visits, is always high (1).

Hypertension can be classified based on two parameters (1):

- According to the etiology:
  - Essential or primary hypertension.
  - Secondary hypertension.

- According to severity. Although the continuous relationship between BP and CV and renal events makes the distinction between normotension and hypertension difficult when based on cut-off BP values. In practice, however, cut-off BP values are universally used arbitrarily(3), both to simplify the diagnostic approach and to facilitate the decision about treatment (2). See ***Table 1.***

**Table 1: Definitions and classification of office blood pressure levels (mmHg). Adapted from '*2013 ESH-ESC Guidelines for the management of arterial hypertension*'**(2)**.**

| CATEGORY | SYSTOLIC | | DIASTOLIC |
|---|---|---|---|
| **Optimal** | <120 | and | <80 |
| **Normal** | 120-129 | and/or | 80-84 |
| **High normal** | 130-139 | and/or | 85/89 |
| **Grade 1 hypertension** | 140-159 | and/or | 90-99 |
| **Grade 2 hypertension** | 160-179 | and/or | 100-109 |
| **Grade 3 hypertension** | ≥180 | and/or | ≥110 |
| **Isolated systolic hypertension** | ≥140 | | <90 |

## 3.2. Epidemiology of hypertension

Hypertension is a worldwide epidemic event that already affects one billion people (4). According to "*2013 ESH/ESC Guidelines for the management of arterial hypertension*" the prevalence of hypertension is about 30–45% in the general population, with a steep increase with ageing (2).

In Catalonia, the prevalence varies between 19.7% and 48.4% of the population over 14 years depending on the age bracket considered; the overall prevalence is 16.9% (1).

In addition, the prevalence is increasing due to, among other factors, the progressive aging of the population (5,6).

### 3.3. Evaluation of hypertension

The initial evaluation of a patient with hypertension should confirm the diagnosis of hypertension (***Table 1***), detect causes of secondary hypertension and assess CV risk, OD and concomitant clinical conditions (1,2).

This evaluation will be based on three main points:

- Anamnesis: personal and family medical history.
- Physical examination.
- Complementary explorations. See the following ***Table 2.***

**Table 2: Tests in Hypertension evaluation.**(1,2)

| ROUTINE TESTS | ADDITIONAL TESTS | EXTENDED EVALUATION |
|---|---|---|
| Haemoglobin, haematocrit.<br>Fasting plasma glucose.<br>Serum total cholesterol, LDL, HDL.<br>Fasting serum triglycerides.<br>Serum potassium and sodium.<br>Serum uric acid.<br>Serum creatinine (with estimation of GFR).<br>Urine analysis: microscopic examination; urinary protein by dipstick test; test for microalbuminuria.<br>ECG. | Haemoglobin A1c (if fasting plasma glucose is >5.6 mmol/L (102 mg/dL) or previous diagnosis of diabetes).<br>Quantitative proteinuria (if dipstick test is positive); urinary potassium and sodium concentration and their ratio.<br>Home and 24-h ambulatory BP monitoring.<br>Echocardiogram.<br>Exercise testing.<br>Holter monitoring in case of arrhythmias.<br>Carotid ultrasound.<br>Peripheral artery/abdominal ultrasound.<br>Pulse wave velocity.<br>Ankle-brachial index.<br>Fundoscopy. | Further search for cerebral, cardiac, renal, and vascular damage, mandatory in resistant and complicated hypertension.<br>Search for secondary hypertension when suggested by history, physical examination, or routine and additional tests. |

### 3.4. Stratification of CV risk and decision making on antihypertensive treatment

For a long time, hypertension guidelines focused on BP values as the only or main variable to determine the need for, and the type of, treatment (2).

Subsequently, it has been proven that the risk of having a cardiovascular event, and therefore the decisions about starting antihypertensive drugs, depends not only on the BP values, but also on the presence or absence of other cardiovascular risk factors (CVRF), asymptomatic organ damage and the presence or absence of clinical cardiovascular or renal disease (1,7). See ***Figure 1***.

| Other risk factors, asymptomatic organ damage or disease | Blood Pressure (mmHg) | | | |
|---|---|---|---|---|
| | High normal SBP 130–139 or DBP 85–89 | Grade 1 HT SBP 140–159 or DBP 90–99 | Grade 2 HT SBP 160–179 or DBP 100–109 | Grade 3 HT SBP ≥180 or DBP ≥110 |
| No other RF | | Low risk | Moderate risk | High risk |
| 1–2 RF | Low risk | Moderate risk | Moderate to high risk | High risk |
| ≥3 RF | Low to Moderate risk | Moderate to high risk | High Risk | High risk |
| OD, CKD stage 3 or diabetes | Moderate to high risk | High risk | High risk | High to very high risk |
| Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs | Very high risk | Very high risk | Very high risk | Very high risk |

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

**Figure 1: Total CV Risk. Adapted from *'2013 ESH-ESC Guidelines for the management of arterial hypertension'*(2)**

It is necessary to choose antihypertensive treatment with criterion because the benefit of hypertension treatment is derived from the correct control of BP values and a faster control of it may reduce the risk of cardiovascular complications (8).

Lowering systolic blood pressure by 10 mmHg or diastolic blood pressure by 5 mmHg reduces the risk of stroke by about 35% and that of ischaemic heart disease events by about 25% at age 65 (9).

## 3.5. Hypertension treatment

### 3.5.1. Blood pressure treatment targets

The overall objective is BP <140/90 mmHg (1,2,10). In certain groups of patients with diabetes, chronic kidney disease and cardiovascular disease, achieve a major reduction can provide additional benefits (1).

There is no international consensus established related to the BP objectives required in each situation. For this reason, the ***Table 3*** has been drawn up to show the main features of the reference guidelines.

**Table 3: BP treatment targets summary.**

| | **ICS GUIDELINE** [1] **(mmHg)** (1) | **2013 ESH/ESC GUIDELINES FOR THE MANAGEMENT OF ARTERIAL HYPERTENSION (mmHg)** (2) | **JNC 8 (mmHg)** (10) |
|---|---|---|---|
| **Overall objective** | <140/90 | <140/90 | <140/90 |
| **Elderly >60 years** | <140/90 | Between 150-140 | <150/90 |
| **Elderly >80 years** | <150 | Between 150-140 | <150/90 |
| **Diabetics** | <140/90 mmHg and the closest possible to 130/80 mmHg. | <140/85 | <140/90 |
| **Chronic kidney disease** | <130/80 mmHg, or even lower values (125/75 mmHg) if there is proteinuria. | <140/90 mmHg, or even lower values (130/90 mmHg) if there is proteinuria. | <140/90 |

[1] "*Guies de pràctica clínica Hipertensió Arterial*"(1)

### 3.5.2. Treatment strategies

There is a general agreement about the two main therapeutic approaches in hypertension:

- **Lifestyle changes:** moderation of alcohol consumption, high consumption of vegetables, fruits and low-fat diet, salt restriction, weight reduction and maintenance , regular physical exercise and smoking cessation (2).

Appropriate lifestyle changes are the cornerstone for the prevention of hypertension, nonetheless they are also important for its treatment, although they should never delay the initiation of drug therapy in patients at a high level of risk (2).

- **Pharmacological therapy:** there are different pharmacological groups of which the following drugs have been highlighted in the ***Table 4*** (in relation to this study – see ***Table 15***):

**Table 4: Pharmacological antihypertensive groups** (1)**.**

| BETA-BLOCKERS | DIURETICS | CALCIUM ANTAGONISTS DIHYDROPYRIDINE | CALCIUM ANTAGONISTS NON-DIHYDROPYRIDINE | ANGIOTENSIN-CONVERTING ENZYME INHIBITORS | ANGIOTENSIN RECEPTOR BLOCKERS | RENIN INHIBITORS |
|---|---|---|---|---|---|---|
| Atenolol | HCTZ | Amlodipine | Verapamil | Enalapril | Losartan | Aliskiren |
| Bisoprolol | Indapamide | - | Diltiazem | Lisinopril | Olmesartan | - |
| Nebivolol | - | - | - | Ramipril | Valsartan | - |

### 3.5.3. Should antihypertensive agents be ranked in order of choice?

- The major benefit of antihypertensive therapy is lowering BP *per se*, independently of the mechanism of action of the selected drug (2).
- All classes of antihypertensive agents have their advantages but also contra-indications.
- Physicians should pay attention to adverse drug effects because they are powerful deterrents to treatment adherence.
- The type of outcome in a given patient is unpredictable (2).
- Drugs to be considered in specific conditions. However, no evidence is available that different choices should be made based on age or gender (except for caution in using RAS blockers in women with child bearing potential because of possible teratogenic effects) (2).

### 3.5.4. Monotherapy and combination therapy

The decision to choose between monotherapy or combination therapy at the beginning is not easy. There are no strict criteria that will solve this decision. However, the hypertension guidelines, and in this case the *2013 ESH/ESC* (2) (see ***Figure 2***), has proposed a logical and simple process to know what type of treatment to offer at all time, according to CV risk (***Figure 1***).

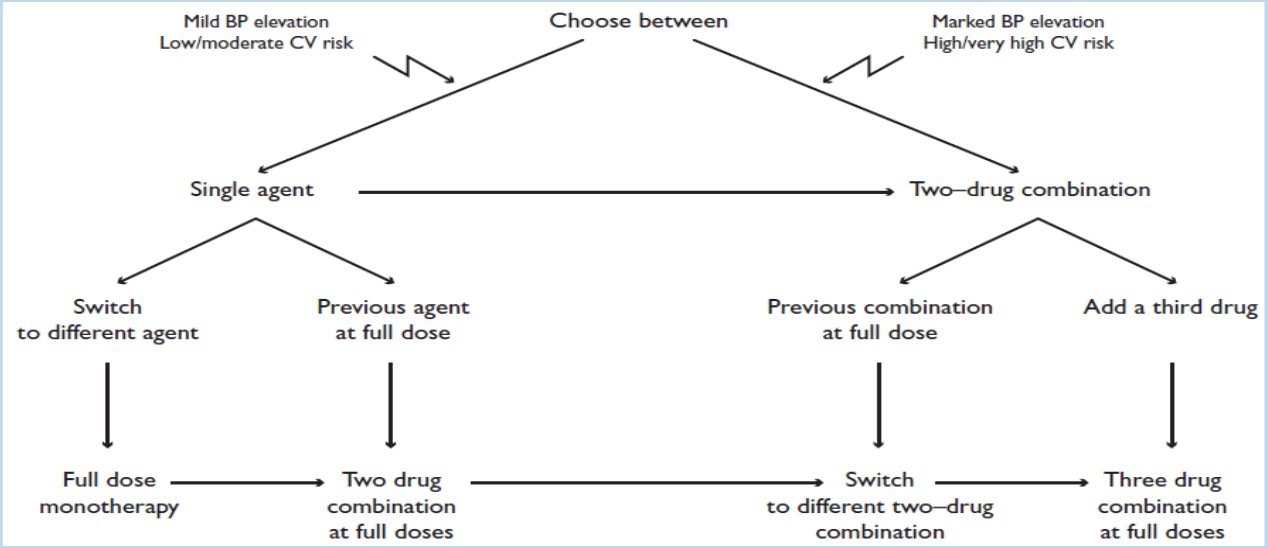



**Figure 2: Process of choice the treatment. Adapted from *'2013 ESH-ESC Guidelines for the management of arterial hypertension'*(2).**

Then it has been done a comparative table (***Table 5***) of pros and cons of both treatment strategies:

**Table 5: Pros and cons of the two approaches** (2)**.**

| | MONOTHERAPY | COMBINATION THERAPY |
|---|---|---|
| **Pros** | Be able to ascribe effectiveness and adverse effects to that agent. | The combination of two agents from any two classes of antihypertensive drugs increases the BP reduction much more than increasing the dose of one agent.<br>The advantages of initiating with combination therapy are:<br>– a prompter response in a larger number of patients (potentially beneficial in high-risk patients)<br>– a greater probability of achieving the target BP in patients with higher BP values<br>– a lower probability of discouraging patient adherence with many treatment changes<br>Patients receiving combination therapy have a lower drop-out rate than patients given any monotherapy.<br>There are physiological and pharmacological synergies between different classes of agents that may not only justify a greater BP reduction but also cause fewer side effects and may provide larger benefits than those offered by a single agent. |
| **Cons** | When monotherapy with one agent is ineffective or insufficiently effective, finding an alternative monotherapy that is more effective or better tolerated maybe a painstaking process and discourage adherence. | One of the drugs may be ineffective. |

### 3.5.5. Preferred drug combinations

When it is already known that combined treatment is needed, it is time to know which drugs will combine to achieve the desired goals. Following the instructions of the guides (***Figure 3***), the best combinations will be between:

- Thiazide diuretics + Angiotension-receptor blockers
- Thiazide diuretics + Calcium antagonists
- Thiazide diuretics + ACE inhibitors
- Angiotension-receptor blockers + Calcium antagonists
- Calcium antagonists + ACE inhibitors

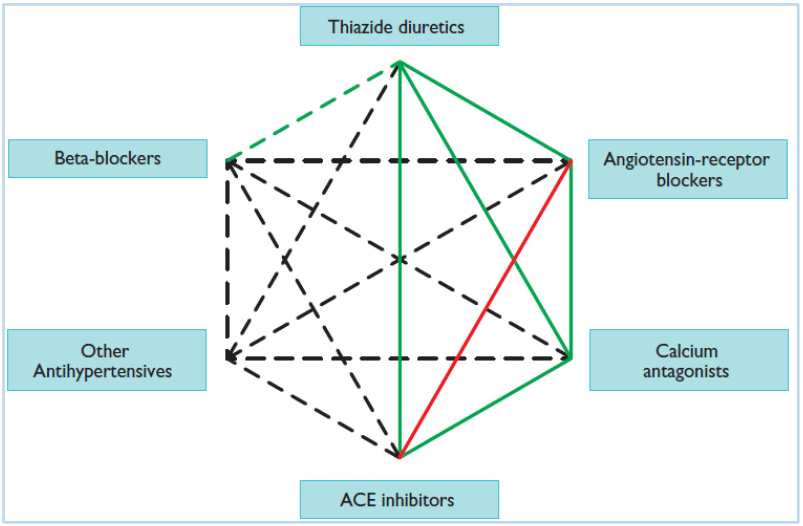



**Figure 3: Antihypertensive drug combinations. Adapted from *'2013 ESH-ESC Guidelines for the management of arterial hypertension'*** (2)**.**

These recommendations should be taken into account at the time of choosing the treatments of each patient. In this work, these recommendations have been applied to formulate the different therapeutic alternatives (***Table 15***).

## 3.6. Hypertension and pharmacoeconomics

An important part of the study is to relate the efficacy of the drugs to the cost of antihypertensive treatment, therefore, the topic of economics in health and pharmacoeconomics has to be tackled.

Health economics is the application of the theories, tools and concepts of the discipline of economics to the topics of health and health care (11). Its usefulness is because health care resources available for medical procedures, including pharmaceuticals, are limited all over the world (12).

The economic burden of health care is a significant concern for all sectors of society and for that researchers and policy makers are increasingly interested in examining the comparative costs and effectiveness of health care interventions (13).

Economic evaluations help to alleviate this burden of scarce resources by improving the allocative efficiency of health care financing (12) and its aim is to inform decisions regarding the best way to use limited resources (14), to promote a sustainable health system.

Pharmacoeconomic analysis identifies, measures and compares the costs and the clinical outcomes of diseases, drug therapies and programmes directed to these diseases (15), for example in hypertension. Accordingly, full economic evaluations compare at least two alternative medical technologies by examining both costs and consequences (12). The current economic situation and the constant increase in the consumption of health resources force to use this type of studies as a priority in the health system.

Additionally, hypertension is the most common condition seen in primary care (5,10). In Spain, in particular, approximately 7% of the outpatient visits are due to hypertension (16). On average, a hypertensive patient would cost twice that of a normotensive individual. In Spain, in 2006, the annual gross unit cost of each hypertensive patient was 1,321.1€, about double that of the same non-hypertensive patient (17). The reason is that hypertension is a risk factor for other diseases. Thus, to know the hypertension cost it is necessary to estimate the cost of each diseases due to risk factor.

The total cost due to hypertension rise to 2.805,6 million of annual euros in 2002, it means between 5.6 and 7.5% of health expenditure (17).

However, it must be taken into account that the cost of treating hypertension represents the sum of different costs, not just medical treatment. See ***Table 6***.

**Table 6: Comparative table of different costs in economic assessment** (5,7,11)**.**

| DIRECT MEDICAL COSTS | DIRECT NON-MEDICAL COSTS | INDIRECT COSTS |
|---|---|---|
| Pharmacological treatment. | Transportation: for outpatient visits, for daily activities. | Sick leave. |
| Hospitalisation: days of hospitalisation. | Services: home help, meals on wheels, social assistance. | Reduced productivity while at work. |
| Outpatient visits: outpatient clinic attendance and visit to private practitioner. | Devices and investments: adaptation to house or car, special kitchen and bathroom utensils. | Early retirement due to illness. |
| Procedures (surgical interventions) and tests (blood analysis, X-ray, scans, gastroscopies, etc.). | Informal care: care by relatives. | Premature death (years to normal retirement). |
| Medical devices (wheelchairs, hearing aid, pacemakers, etc.). | - | - |
| Services: home care and nursing care. | - | - |

Although the percentages of the different costs may vary from year to year or in different countries, those published in *Saez and Barceló* (16) may be taken as a reference. In relation to this, 56% are indirect costs and 44% direct costs. Regarding direct costs, in 2006, 69.4% of these corresponded to medication and 20% to the visits (16). In fact, the percentage corresponding to medication doubled, going from 33.46% of direct costs in 1992 to 69.4% of them in 2006 (16).

Moreover, cost caused by complications of AHT is also very important. Thus, in 2006, a hypertensive subject with high morbidity had a cost which was 3.65 times more than one with mild disease. In addition, the average annual cost per patient was almost triple in those with metabolic syndrome than without it and multiplied by six in hypertensive patients with the five diagnostic criteria for metabolic syndrome (16,17).

However, costs per patient of the hypertension not only varied according to the diseases associated to it, but also the control obtained in the hypertension treatment. It has been estimated that the lack of control increases the unit cost by 13.05 (16).

### 3.7. Pharmacoeconomic studies

Before proceeding to explain the different pharmacoeconomic types of studies, it is important to keep in mind some assessment criteria (***Table 7***) for new therapies (11), as it may generate relevant doubts.

**Table 7: Assessment criteria for new therapies** (11)**.**

| ASSESSMENT CRITERIA | WHAT DOES IT ASSESS? |
|---|---|
| **Safety** | Does it have side effects and are these acceptable and manageable? |
| **Efficacy** | Does it work in a controlled environment (clinical trials)? |
| **Effectiveness** | Does it work in normal clinical practice? |
| **Cost effectiveness/ efficiency** | Is it an efficient use of resources, i.e. is an additional benefit worth an additional cost? |

Their knowledge makes it easier to understand the following studies:

**Cost minimization studies:** are used when the strategies being compared differ only in the costs they incur (18). The health benefit (therapeutic efficacy and consequences) of competing medical technologies has to be equal (12). The lowest-cost strategy is sought.

**Cost-effectiveness studies:** examine the costs and health outcomes of alternative strategies (19). It compares the expenditure and outcomes of two or more strategies for performing the same task (18) and the health benefit should be measured in the same health dimension (12). They are used to identify the strategy that will produce the maximum effectiveness for a given cost or, vice versa, to achieve a given objective at the

lowest cost (20). The purpose of these analyses is to provide information on the additional effectiveness obtained from an extra cost and to help decision makers allocate health care resources efficiently (21).

**Cost-utility studies:** are a generalisation of cost-effectiveness studies for the result obtained. Their theoretical interest lies in their ability to provide a summary indicator of results. This type of analysis requires a knowledge of patient preferences. Cost-utility analysis is used particularly when impacts on survival/quality of life are important criteria for judging the effects of health care strategies (12,18).

**Cost-benefit studies:** is applicable to compare any health technologies even with non-medical investment opportunities (12).

Then, a summary is shown in ***Table 8***:

**Table 8: Pharmacoeconomic studies** (12).

| TYPE OF EVALUATION | MEASUREMENT OF HEALTH GAIN | MEASUREMENT OF COSTS | APPLICABILITY |
|---|---|---|---|
| **Cost minimization studies** | Non-specified (equal health gain) | Monetary value | Comparison of medical procedures with equal health gain |
| **Cost-effectiveness studies** | Natural units | Monetary value | Comparison of medical procedures with non-equal health gain measurable in the same health dimension. |
| **Cost-utility studies** | Quality-adjusted life-years | Monetary value | Comparison of any medical procedures |
| **Cost-benefit studies** | Monetary value | Monetary value | Comparison of any medical and non-medical procedures and investment options |

## 4. JUSTIFICATION

According to the *World Health Organization*, hypertension currently kills nine million people every year around the world (4). Furthermore, it is a global health problem by having a high population attributable risk (22). Hypertension is a key risk factor for the development of cardiovascular diseases (3). For instance, in 2013, 45% of heart disease and 51% of strokes were due to hypertension (4).

The relationship between BP values and CV and renal morbid- and fatal events has been addressed in a large number of observational studies. The results can be summarized as follows:

- Office BP bears an independent continuous relationship with the incidence of several CV events like: stroke, myocardial infarction, sudden death, heart failure and peripheral artery disease (PAD); as well as of end-stage renal disease.
- A continuous relationship with events is also exhibited by out-of-office BP values, such as those obtained by ABPM and HBPM.
- The relationship with BP extends from high BP levels to relatively low values of 110–115 mmHg for SBP and 70–75 mmHg for DBP.
- The relationship between BP and CV morbidity and mortality is modified by the concomitance of other CV risk factors. Metabolic risk factors are more common when BP is high than when it is low.

In addition, HT is the leading cause of loss of quality adjusted life years (QALY's) both in developed countries and those in developing countries (23).

Most of the studies published to date have been made by theoretical models to calculate QUALY's cardiovascular (CV) disease and considering as patient characteristics, age and gender along with the CV risk. They consider antihypertensive therapy in general as equipotent providing a similar degree of control to different drugs. However, the blood pressure as an intermediate variable of interest, at the time of diagnosis and initiation of treatment is considered in broad intervals of 20 mmHg for systolic and 10 mmHg for diastolic BP (7,13,24–26) nor takes into account a patient characteristics such as body mass index. Only one contemplates the ethnicity as a variable of interest (27) and another is based on the recommendations of the NICE guidelines considering only the cost of treatment in hypertension grade 1 without establishing any outcome as controlling blood pressure or morbidity and mortality (3).

Apart from this aspect more related to the morbi-mortality of hypertension, there is another important part related to the pharmacoeconomic issues.

This study is intended to provide additional data in support to the growing opinion that cost-effectiveness information should be included in practical guides (6), although it is already known that the use of economic evaluation of new medical technologies has expanded to an increasing number of countries (11) to promote a more sustainable health system.

Besides that, the comparison of the relative antihypertensive effect of several drugs, or that of the most common combinations, is not well known. There are only few studies comparing the efficacy of the most commonly used antihypertensive drugs (22).

Hypertension guidelines recommend antihypertensive drug classes, without detailing specific drugs (22,24). However, despite all antihypertensive drug groups lower blood pressure similarly, different antihypertensive drugs in each group do not have the same capacity to reduce blood pressure neither the cost is the same, both as monotherapy and in combination.

This knowledge would potentially help the clinician to choose the most adequate treatment, since the response to a specific drug could be better predicted and there is an enormous potential for improving health by expanding control and treatment (6).

## 5. HYPOTESIS

Based on the *Atom study* results, there will be a difference in the cost-effectiveness of the different pharmacological antihypertensive treatment strategies.

## 6. OBJECTIVES

### 6.1. Main objective

To calculate the cost-effectiveness (or efficiency) of the reduction and control of hypertension using antihypertensive drugs according to the initial BP at the time of treatment.

### 6.2. Secondary objectives

To build a useful comparative effectiveness table to facilitate the decision-making in clinical practice.

To build a useful comparative cost-effectiveness table to facilitate the decision-making in clinical practice.

## *7.* MATERIAL AND METHODS

### 7.1. Study design

This study is mainly based on two distinct parts:

- Firstly, a translational study has been realized based on data from the *Atom study* (22).

A translational study refers to translate research into practice, “bench-to-bedside”. To provide a practical and useful application to the data from *Atom study* (22,28,29).

- Secondly, a pharmacoeconomic evaluation has been developed with the information that has been analysed previously.

The pharmacoeconomic evaluation is made based on cost-effectiveness study, to identify the strategy that will achieve a given objective at the lowest cost (20). The results of the cost-effectiveness study are expressed by the incremental cost-effectiveness ratio to assess the cost of the different pharmacological treatments (30). The ICER indicates the cost (€ per day) of producing one extra unit of benefit (mmHg) (11).

In conclusion, a cost-effectiveness or efficiency study is carried out with the aim of being able to apply the results to the usual clinical practice.

### 7.2. Target population

To determine the target population to which this economic evaluation is addressed, the data from *Atom study* (22) has been analysed. The characteristics of the included patients are in the ***Table 9***:

**Table 9: Characteristics of total patients included in *Atom Study*. Adapted from *Atom Study* (22).**

| | **n= 94305** |
|---|---|
| **Age, y** | 54,5±1,9 |
| **Sex: women (%)** | 45,2 (43,8; 46,6) |
| **Type 2 diabetes (%)** | 10,6 (9,4; 11,9) |
| **Caucasians (%)** | 82,9 (86,0; 79,7) |
| **Afro-Americans or Afro-Caribbeans (%)** | 17,1 (14,0; 20,3) |
| **SBP, mmHg** | 155,2±5,7 |
| **DBP, mmHg** | 99,3±1,8 |

Thus, the results can be extrapolated to a wide variety of hypertensive patients, regardless of dosage, the baseline BP and age. Therefore can become a tool that could be used in the majority of hypertensive patients in clinical practice.

However, it must be taken into account that the variability in the response to different treatments depends largely on individual aspects of the patient, with different phenotypic variables that determine a greater or lesser decrease in BP with the use of a specific treatment (24). *Atom study* expose these conclusions (22):

- Women and obese (BMI≥30kg/$m^2$) respond, in general, better.
- The black ethnicity is associated with a worse response.
- Those over 65 years respond better, in general, and to ACE inhibitors in particular.

### 7.3. ATOM Study

As it has been said, this study is based mainly in *Paz et al*. (22).

The first aim of *Atom study* (22) consisted in determining the BP reduction attributed to the drugs of common use for hypertension treatment, adjusted for the most relevant variables in the clinical practice.

A systematic review of clinical trials was carried out followed by a meta-regression.


**Figure 4: Hierarchy of evidence. Adapted from "*Delgado-Rodríguez M. Glosario de metanálisis*."** (32)

Meta-analysis are a statistical procedure that integrates the results of several independent studies synthesizing summaries and conclusions. Related with the hierarchy of evidence (***Figure 4***), where clinical evidence is ranked according to the strength of the freedom from various biases that beset medical research, meta-analyses are in the top (31,32).

In primary studies, multiple-regression is the statistical technique employed to assess the relationship between covariates and a dependent variable. In these studies the unit of analysis is the subject, with covariates and the outcome measured for each subject. With a few modifications, the same technique can be used in meta-analysis. In this case, the unit of analysis is the study, with covariates and outcomes measured for each study (33–35).

The systematic search for clinical trials assessing the efficacy of antihypertensive drugs was conducted following a triple strategy:

- Search in the MEDLINE database.
- Search in the Cochrane Central Register of Controlled Trials database.
- Review of selected papers which had not been found with the 2 previous strategies.

The initial selection of the studies was performed according to the following inclusion and exclusion criteria (see ***Table 10***):

**Table 10: Inclusion and exclusion criteria in *Atom study*** (22)**.**

| **INCLUSION CRITERIA** | **EXCLUSION CRITERIA** |
|---|---|
| Double-blind | Clinical trials conducted exclusively in specific populations of hypertensive patients: diabetic, patients with resistant hypertension or who did not respond to a previous treatment with a specific drug in the same study, chronic kidney disease |
| Randomized clinical trial with a study population ≥50 patients or ≥25 if the study had a crossover design | Clinical trials missing relevant information about the BP reduction obtained or about the dose administered in the different treatment periods |
| Follow-up of at least 8 weeks | Clinical trials whose main reported outcomes were total mortality, cardiovascular morbidity and mortality, or evolution of the subclinical vascular disease |
| Data needed to carry out the meta-analysis had to be available | - |

The meta-analysis was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Finally, a total of 779 studies were reviewed, of which 208 fulfilled the conditions for their analysis, with 94.305 participants. The procedure is represented in ***Figure 5.***

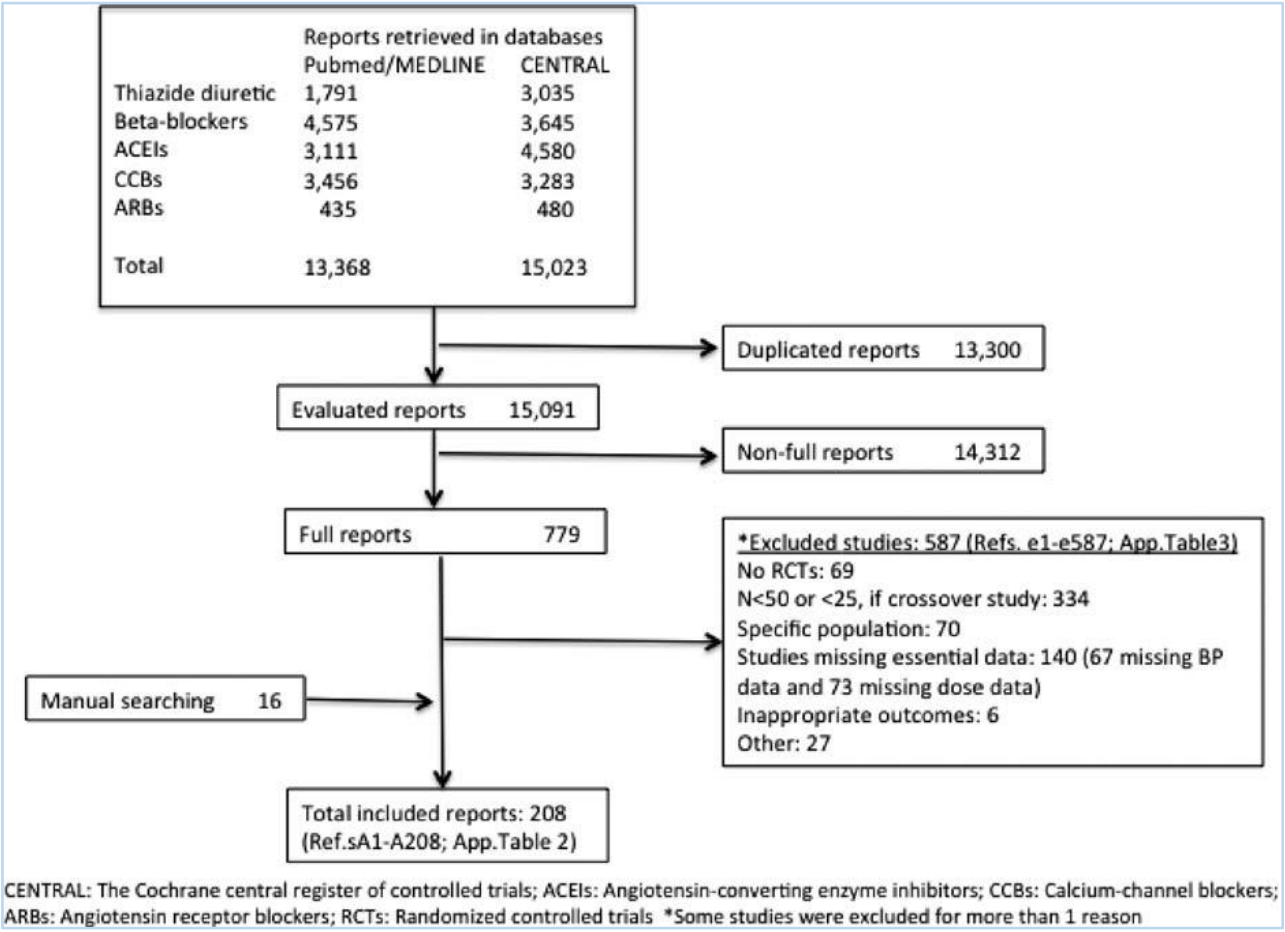



**Figure 5: *Atom study* procedure. Adapted from *Atom study*** (22)**.**

### 7.4. Application of the concept of *Law et al.*

Furthermore, in the current study the average dose of the trials that have been meta-analysed are used for each ingredient, both for monotherapy and for combination, as well as reductions in blood pressure, systolic and diastolic, estimated in meta-regression.

However, the actual dose (of each active ingredient) prescribed in clinical practice does not match the average dose used in these calculations (remember that it was obtained by averaging the dose of the trials meta-analysed).

The problem is that the relationship between dose and reduction in blood pressure is far from being linear. Therefore, when the actual rate is, for instance, half (twice) of the average dose, the reduction is not half (or twice), as it would be if the relation was linear. With half of the standard dose, the reduction of SBP and DBP is about 20% less than the standard dose.

For this reason, the reductions calculated in ***Table 11*** and in ***Table 12*** (using the average doses and the reductions from *Atom study* (22)) are adjusted by means of the results provided by *Law et al*. (9).

**Table 11: Example of the application of *Law et al.* in monotherapy. To see the complete table go to *Annex 2* .**

| Active ingredient | Actual dose (mg) | Average dose (mg) | Reductions (mmHg) | | Adjusted reductions (mmHg) | |
|---|---|---|---|---|---|---|
| | | | Systolic | Diastolic | Systolic | Diastolic |
| Indapamide | 1,5 | 1,90 | 9,71 | 6,55 | 8,89 | 6,00 |
| HCTZ | 25 | 19,10 | 14,93 | 11,90 | 15,85 | 12,64 |
| Atenolol | 50 | 59,20 | 12,00 | 7,75 | 11,25 | 7,26 |
| | 100 | | | | 13,65 | 8,82 |

In the combinations, the situation is slightly different. According to *Law et al*. (9) the sum of the average reductions in blood pressure is close to the observed effect of the two drugs used in combination, indicating an additive effect.

**Table 12: Example of the application of *Law et al.* in combination. To see the complete table go to *Annex 3*.**

| Active ingredient | Actual dose (mg) | Average dose (mg) | Reductions (mmHg) | | Adjusted reductions (mmHg) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Systolic | Diastolic | Systolic | | Diastolic | |
| Indapamide | 1,5 | 1,90 | 9,71 | 6,55 | 8,89 | 12,41 | 6,00 | 8,59 |
| Lisinopril | 10 | 17,60 | 4,26 | 3,13 | 3,52 | | 2,59 | |
| Valsartan | 80 | 137,50 | 12,40 | 9,40 | 10,33 | 19,69 | 7,83 | 15,10 |
| Amlodipine | 10 | 6,60 | 8,49 | 6,59 | 9,36 | | 7,27 | |
| Indapamide | 1,25 | 1,90 | 9,71 | 6,55 | 8,38 | 12,76 | 5,65 | 8,87 |
| Lisinopril | 20 | 17,60 | 4,26 | 3,13 | 4,38 | | 3,22 | |

According to these, when actual dose was higher than the average dose, the reductions (in blood pressure) were 19.78% (in the case of SBP) and 18.18% (DBP) lower than those expected (i.e, if the relationship between dose and reduction was linear). When the actual dose was lower than the average dose, the reductions were 21.98% (systolic) and 20.00% (diastolic) higher than expected.

The temporal horizon expected to obtain the calculated BP reduction with all therapeutic alternatives is 1-2 months, at which time the first follow-up visit will be made to assess the need to adjust the dosage or change the treatment (36).

The results obtained in the *Atom study* (22) correspond to ***efficacy*** data. Nonetheless, applying the concept of *law et al.* (9), what is achieved is to approximate the results to reality. For this reason, it can be considered that the data used in this study correspond to ***effectiveness*** data.

Effectiveness is defined as a clinically meaningful event experienced by a patient such as survival time, quality-adjusted life years (QALYs), or symptom-reduced days (19). In this study, effectiveness is measured by the reduction of SBP and DBP (mmHg).

In this way, what is achieved is to translate the theoretical results into results adapted to the clinical practice.

### 7.5. Treatments cost

Then, these adjusted BP reductions by dose of each active ingredient are compared with the actual cost of these treatments. The prices published by the *Spanish General Council of Official Colleges of Pharmacy* are used to calculate the cost of the active ingredients used in Spain (37).

The prices correspond to the year 2016. These will have to be updated annually in order to be able to apply the results every year.

It has been decided to compare the prices of the drugs per day, because the number of tablets per box varies from one drug to another. The formula used in ***Equation 1*** is this:

**Equation 1: Cost per day (€) in monotherapy**

$$Cost\ per\ day\ (€) = \frac{cost\ per\ box\ (€)}{number\ of\ tablets\ per\ box} \times number\ of\ tablets\ per\ day$$

The results are represented in the ***Table 13***:

**Table 13: Study of the costs of the treatments in monotherapy. To see the complete table go to *Annex 4.***

| Active ingredient | Dose (mg) | Cost per box (€) | Nº of units | Cost x day (€) |
|---|---|---|---|---|
| **Indapamide** | **1,5** | **2,50** | **30** | **0,08** |
| **HCTZ** | **25** | **2,34** | **20** | **0,12** |
| **Atenolol** | **50** | **2,50** | **30** | **0,08** |
| **Atenolol** | **100** | **4,93** | **60** | **0,08** |

Thus, for the active ingredients combinations, the cost of individual presentations has been added up, following the above procedure. The formula used in ***Equation 2*** is:

**Equation 2: Cost per day (€) in combinations**

$$Cost\ per\ day\ (€) = \left(\frac{cost\ per\ box1(€)}{number\ of\ tablets\ per\ box1} \times number\ of\ tablets1\ per\ day\right) + \left(\frac{cost\ per\ box2(€)}{number\ of\ tablets\ per\ box2} \times number\ of\ tablets2\ per\ day\right)$$

And the results are showed in ***Table 14***:

**Table 14: Study of the costs of the treatments in combination. To see the complete table go to *Annex 4.***

| Active Ingredient | Dose (mg) | Cost per box (€) | | Nº of units | Cost x day (€) |
|---|---|---|---|---|---|
| Indapamide | 1,5 | 2,50 | 5,75 | 30 | 0,14 |
| Lisinopril | 10 | 3,25 | | 60 | |
| Valsartan | 80 | 8,15 | 10,65 | 28 | 0,37 |
| Amlodipine | 10 | 2,50 | | 30 | |
| Indapamide | 1,25 | 3,12 | 9,47 | 60 | 0,28 |
| Lisinopril | 20 | 6,35 | | 28 | |

With all the above information, the ***Table 15*** has been built to integrate the list of drugs included in the study, with the main variables:

**Table 15: Active ingredients analysis. To see the complete table go to *Annex 5*.**

| Active Ingredient | Dose (mg) | Cost per day (€) | Systolic BP reduction (mmHg) | Diastolic BP Reduction (mmHg) |
|---|---|---|---|---|
| Indapamide | 1,5 | 0,08 | 8,89 | 6,00 |
| HCTZ | 25 | 0,12 | 15,85 | 12,64 |
| Atenolol | 50 | 0,08 | 11,25 | 7,26 |
| Atenolol | 100 | 0,08 | 13,65 | 8,82 |
| Bisorpolol | 5 | 0,05 | 10,59 | 7,31 |
| Bisorpolol | 10 | 0,11 | 12,95 | 8,94 |
| Nevibolol | 5 | 0,28 | 14,96 | 10,40 |

## 7.6. Blood pressure reduction intervals

It is well known that antihypertensive treatments significantly lowered BP from all pretreatment BP levels, although the reduction was greater from a higher level (9).

According with ***Figure 6***, for each 10 mmHg increase in pretreatment BP, the reduction in BP with one drug at standard dose increased on average by 1.0 (95% confidence interval 0.7 to 1.2) mmHg systolic and 1.1 (0.8 to 1.4) mmHg diastolic (9).

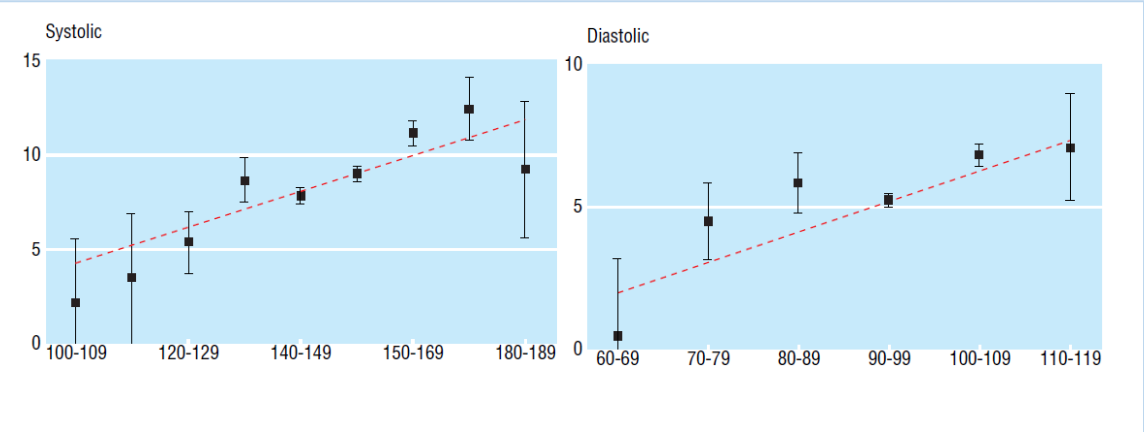



**Figure 6: BP reduction related with pre-treatment BP levels. Adapted from "*Law MR, Wald NJ, Morris JK, Jordan RE, MacMahon S, Peto R, et al. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials.*"**(9)

For this reason, the next step is to sort all different treatments at intervals of blood pressure reduction, both SBP and DBP.

The intervals used in ***Table 16*** and in ***Table 17*** have been chosen following a logical order and trying to reproduce the mental schema of the health professional in clinical practice according to the expert's opinion.

**Table 16: SBP reductions at intervals. To see the complete table go to *Annex 6.***

| Active Ingredient | Dose (mg) | Systolic blood pressure reduction (mmHg) | | | | |
|---|---|---|---|---|---|---|
| | | ≤10,00 | 10,01-15,00 | 15,01-20,00 | 20,01-25,00 | >25,00 |
| Lisinopril | 20 | 4,38 | | | | |
| Verapamil | 240 | 6,56 | | | | |
| Enalapril | 10 | 7,30 | | | | |
| Amlodipine | 5 | 7,67 | | | | |
| Indapamide | 1,5 | 8,89 | | | | |
| Enalapril | 20 | 8,93 | | | | |

**Table 17: DBP reduction at intervals. To see the complete table go to *Annex 7.***

| Active Ingredient | Dose (mg) | Diastolic blood pressure reduction (mmHg) | | | |
|---|---|---|---|---|---|
| | | ≤10,00 | 10,01-15,00 | 15,01-20,00 | >20,00 |
| Lisinopril | 20 | 3,22 | | | |
| Amlodipine | 5 | 5,95 | | | |
| Indapamide | 1,5 | 6,00 | | | |
| Verapamil | 240 | 6,56 | | | |

Taking the BP target of treatment "<140/90 mmHg" as the reference (although the values should be adapted to the treatment objective of each patient –see ***Table 3***), a correlation between the degrees of hypertension and the different intervals exposed can be seen in the ***Table 18***:

**Table 18: BP reduction intervals and Hypertension grades.**

| Category | Systolic (mmHg) | SBP reduction interval (mmHg) | | Diastolic (mmHg) | DBP reduction interval (mmHg) |
|---|---|---|---|---|---|
| **Grade 1 hypertension** | 140-159 | ≤10,00<br>10,01-15,00<br>15,01-20,00 | and/or | 90-99 | ≤10,00 |
| **Grade 2 hypertension** | 160-179 | 20,01-25,00<br>>25,00 | and/or | 100-109 | 10,01-15,00<br>15,01-20,00 |
| **Grade 3 hypertension** | ≥180 | >25,00 | and/or | ≥110 | >20,00 |

As can be seen, to make these interval tables and for the whole procedure that will come hereinafter, some treatments have been eliminated, which by their characteristics were not useful. The following exclusion criteria have been used:

- Use of Lisinopril 10mg, alone or in combination.
- Use of enalapril 10mg in combination.
- Use of valsartan 80mg in combination.

The treatments eliminated are in ***Table 19***:

**Table 19: Treatments eliminated.**

| Active Ingredient | Dose (mg) | Cost per day (€) | Systolic BP reduction (mmHg) | Diastolic BP Reduction (mmHg) |
|---|---|---|---|---|
| **Lisinopril** | **10** | **0,05** | **3,52** | **2,59** |
| **Indapamide** | **1,5** | **0,14** | **12,41** | **8,59** |
| **Lisinopril** | **10** | | | |
| **Valsartan** | **80** | **0,37** | **19,69** | **15,10** |
| **Amlodipine** | **10** | | | |
| **Indapamide** | **1,5** | **0,13** | **16,19** | **12,71** |
| **Enalapril** | **10** | | | |
| **Indapamide** | **1,25** | **0,09** | **15,68** | **12,36** |
| **Enalapril** | **10** | | | |
| **Lisinopril** | **10** | **0,17** | **19,37** | **15,23** |
| **HCTZ** | **25** | | | |
| **Amlodipine** | **10** | **0,14** | **12,88** | **9,86** |
| **Lisinopril** | **10** | | | |
| **Diltiazem** | **240** | **0,67** | **21,76** | **15,28** |
| **Lisinopril** | **10** | | | |
| **Diltiazem** | **240** | **0,65** | **25,54** | **19,40** |
| **Enalapril** | **10** | | | |
| **Valsartan** | **80** | **0,35** | **23,19** | **18,09** |
| **HCTZ** | **12,5** | | | |
| **Valsartan** | **80** | **0,33** | **18,00** | **13,78** |
| **Amlodipine** | **5** | | | |

### 7.7. Cost-effectiveness analysis. Incremental cost-effectiveness ratio

As it was said in section ***3.7***, a cost-effectiveness study examine the costs and health outcomes of alternative strategies (19). In this study the ICER is used for its analysis.

The ICER is expressed as the ratio of the difference in costs between two strategies to the difference in effectiveness (see ***Equation 3***).

**Equation 3: ICER formula**

$$ICER = \frac{Cost\ of\ treatment\ B\ (€) - Cost\ of\ treatment\ A\ (€)}{BP\ reduction\ B\ (mmHg) - BP\ reduction\ A\ (mmHg)}$$

Or

$$\frac{Difference\ in\ Cost}{Difference\ in\ Effect}$$

It provides information on whether additional costs, caused by a change in the treatment A to treatment B, can be justified through their balance with the additional clinical benefits (30).

The first step in this analysis is to select the comparator. It is usually the most used therapeutic alternative in clinical practice (30).

To obtain this information, the results of the prescription of the antihypertensive agents most used in the sanitary region of Girona have been obtained, thanks to the *"Pharmaceutical Care Unit of the Catalan Health Service (CatSalut)".* These results correspond to the medical prescription of the year 2015, therefore these can be used nowadays. See ***Annex 13***.

The most prescribed antihypertensive agents in the sanitary region of Girona are the following showed in ***Table 20***, ***Table 21*** and ***Table 22***:

**Table 20: Most prescribed drugs in monotherapy.**

| MONOTHERAPY |
|---|
| 1. Enalapril |
| 2. Furosemide |
| 3. HCTZ |
| 4. Amlodipine |
| 5. Bisoprolol |

**Table 21: Most prescribed drugs in double combinations.**

| DOUBLE COMBINATIONS |
|---|
| 1. Enalapril + diuretic |
| 2. Losartan + diuretic |
| 3. Lisinopril + diuretic |
| 4. Valsartan + diuretic |
| 5. Candesartan + diuretic |

**Table 22: Most prescribed drugs in triple combinations.**

| TRIPLES COMBINATIONS |
|---|
| 1. Olmesartan + amlodipine + HCTZ |
| 2. Valsartan + amlodipine + diuretic |

The only drawback is that the dosage for each drug is not available. Therefore, standard doses would be used as comparator. To see standard doses go to ***Annex 1***.

Moreover, it should be noted that in the combinations it is not indicated which diuretic is the most used. In this study, the HCTZ is the diuretic applied.

The following procedure has been performed based on the BP intervals, both systolic and diastolic, established in ***Table 16*** and ***Table 17***.

For each interval the most commonly used drug in the clinical practice has been searched to take it as the comparator. One trouble is that it is not known for which initial BP values each of them is used in clinical practice. Therefore, in this study the treatments have been adapted to the established intervals. (See ***Table 23*** and ***Table 24***).

**Table 23: SBP comparators for ICER analysis.**

| SBP INTERVAL | COMPARATOR |
|---|---|
| **≤10,00** | Enalapril 10 |
| **10,01-15,00** | Bisorpolol 5 |
| **15,01-20,00** | HCTZ 25 |
| **20,01-25,00** | Enalapril 20 + HCTZ 12,5 |
| **>25,00** | Olmesartan 40 + Amlodipine 10 + HCTZ 25 |

**Table 24: DBP comparators for ICER analysis.**

| DBP | COMPARATOR |
|---|---|
| **≤10,00** | Enalapril 10 |
| **10,01-15,00** | HCTZ 25 |
| **15,01-20,00** | Enalapril 20 + HCTZ 12,5 |
| **>20,00** | Olmesartan 40 + Amlodipine 10 + HCTZ 25 |

Then, the increase of the cost and effectiveness of the therapeutic alternatives is calculated using ***Equation 3***.

As it can be seen in ***Figure 7***, if a treatment is both more effective and less costly, it is the "dominant" alternative and the decision is straightforward. When the choice is between treatments where one is more effective, but also more costly, the relevant information for making the decision is the additional cost of achieving the additional outcome. The decision maker can then decide whether or not to choose the more costly option based on a consideration of whether the extra cost is justified by the additional benefit obtained (11).

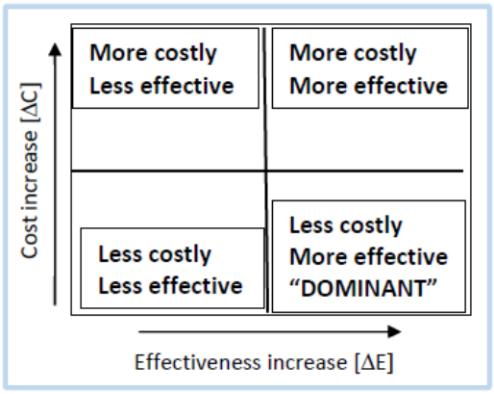



**Figure 7: ICER analysis**

### 7.8. Variables

In *Atom study* (22) were evaluated different variables in each study analysed, summarized in ***Table 25***:

**Table 25: Variables of the study.**

| VARIABLES | CHARACTERISTICS OF THE VARIABLE | MEASUREMENT UNIT |
|---|---|---|
| **Number of included patients** | Quantitative discrete variable | n |
| **Age** | Quantitative continuous variable | Years |
| **Sex** | Qualitative nominal dichotomous variable | Male or female |
| **Ethnicity** | Qualitative nominal variable | Caucasians, afro-americans or afro-caribbeans |
| **Baseline systolic blood pressure** | Quantitative continuous variable | mmHg |
| **Baseline diastolic blood pressure** | Quantitative continuous variable | mmHg |
| **Final SBP at the end of each period** | Quantitative continuous variable | mmHg |
| **Final DBP at the end of each period** | Quantitative continuous variable | mmHg |
| **Baseline heart rate** | Quantitative discrete variable | Beats per minute |
| **Final heart rate** | Quantitative discrete variable | Beats per minute |
| **Drug's dose in each study phase** | Quantitative continuous variable | mg |
| **Body mass index (BMI)** | Quantitative continuous variable | $Kg/m^2$ |
| **Total duration of study** | Quantitative discrete variable | Weeks |
| **Presence or absence of diabetes** | Qualitative nominal dichotomous variable | Diabetes or not diabetes |

In addition, a sensitivity analysis was performed to determine the minimum number of variables to control that, in turn, would allow controlling the heterogeneity in the majority of cases.
The variables finally included in the meta-regression were:

- **Baseline BP (mmHg)**
- **Dose (mg)**
- **Age (years)**
- Number of treated individuals (n)

The number of treated individuals does not affect the analysis, thus the other three variables will be covariates that could affect our dependent and independent variables, which are the following ones:

**Independent variable (exposure):** active ingredients. The different therapeutic alternatives are the variables that will modify the blood pressure levels of the patients. It is considered a **qualitative nominal variable**.

**Dependent variable$_1$ (outcome$_1$):** reduction of systolic blood pressure, measured in mmHg. It is considered a **quantitative continuous variable**.

**Dependent variable$_2$ (outcome$_2$):** reduction of diastolic blood pressure, measured in mmHg. It is considered a **quantitative continuous variable**.

**Dependent variable$_3$ (outcome$_3$):** cost of the treatments, measured in cost (€) per day. It is considered a **quantitative continuous variable.**

### 7.9. Statistical analysis

The statistical analysis of this study is based mainly on two parts:

- The application of the concept of *Law et al*.(9).
- The analysis of the ICER to assess the cost-effectiveness of the antihypertensive pharmacological treatments.

Their study can be seen in the section ***7.***

# 8. RESULTS

## 8.1. Comparative effectiveness table

According to the effectiveness from ***Table 15*** and related to one of the most important objectives of the study, the main tables of the analysis have been built (***Table 26*** and ***Table 27***). Based on *Massana's table* (38) (see ***Annex 8***), it tries to be a simple, useful and up-to-date tool to help the health professional to make decisions related to the treatment of hypertension.

As it can be seen in ***Figure 8***, the tables are mainly made up of three parts (the same procedure was used for the SBP and the DBP):

1. The first column deals with the pretreatment BP values. In the case of SBP, the lowest value is 125 mmHg, which coincides with the lowest target systolic pressure value. The values are increased 5 by 5 until 195 mmHg, point in which no treatment is useful. Then, in the case of DBP, the lowest value is 75 mmHg, which coincides with the lowest target diastolic pressure value. The values also are increased 5 by 5 until 125 mmHg.
2. The second part consists in the BP values that you want to achieve, the goal. Taking reference ***Table 3***, these values are based on the *ICS guideline* (1). According on the pre-treatment BP values and the target BP values, reduction values of the BP are obtained, which can be expressed in both *mmHg* and *percentage (%).* The reason for showing it in these two ways is that this table is based on the *Massana's table* (38) which is represented in *percentages (%)* as well. However, it has been thought that for the treatment of hypertension it will be more useful to show the results in *mmHg*.
3. The third part corresponds to the different pharmacological treatments used, according to the *Atom study* (22) and *Law et al*. (9), explained above. As explained, and as can be seen, the drugs are grouped basically at different intervals. In this table all treatments are arranged in order of lowest to highest BP reduction, both in SBP and DBP. The abbreviations of the active ingredients can be seen in ***Annex 9***.

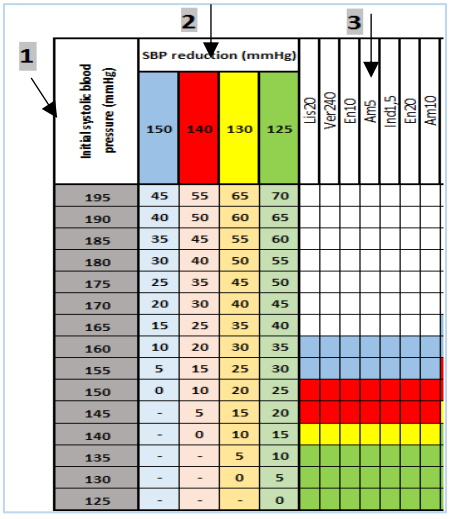



**Figure 8: Part of SBP effectiveness table.**

**Table 26: SBP effectiveness table. BP reduction *(mmHg)*. To see the table with BP reduction in *(%)* go to *Annex 10*.**

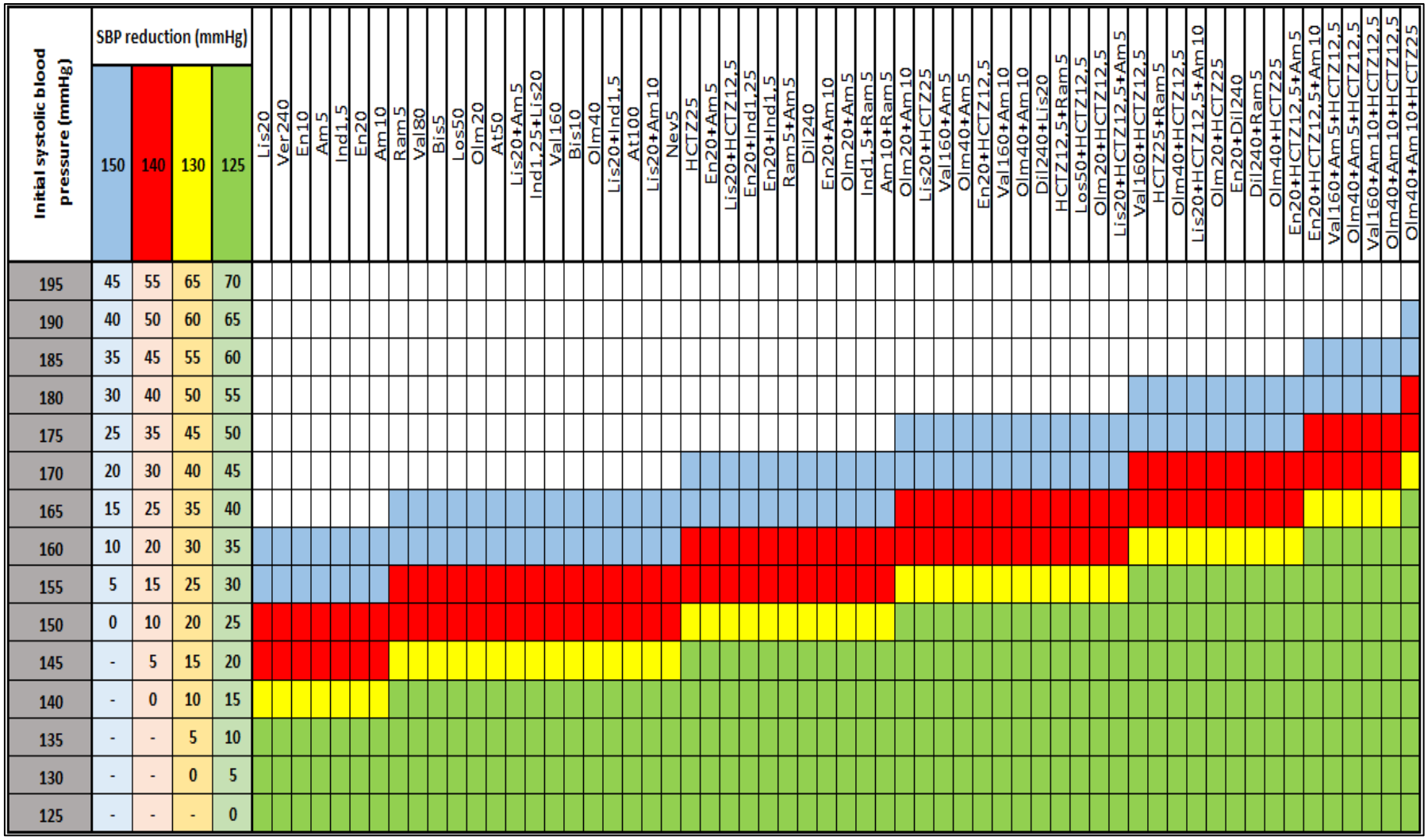
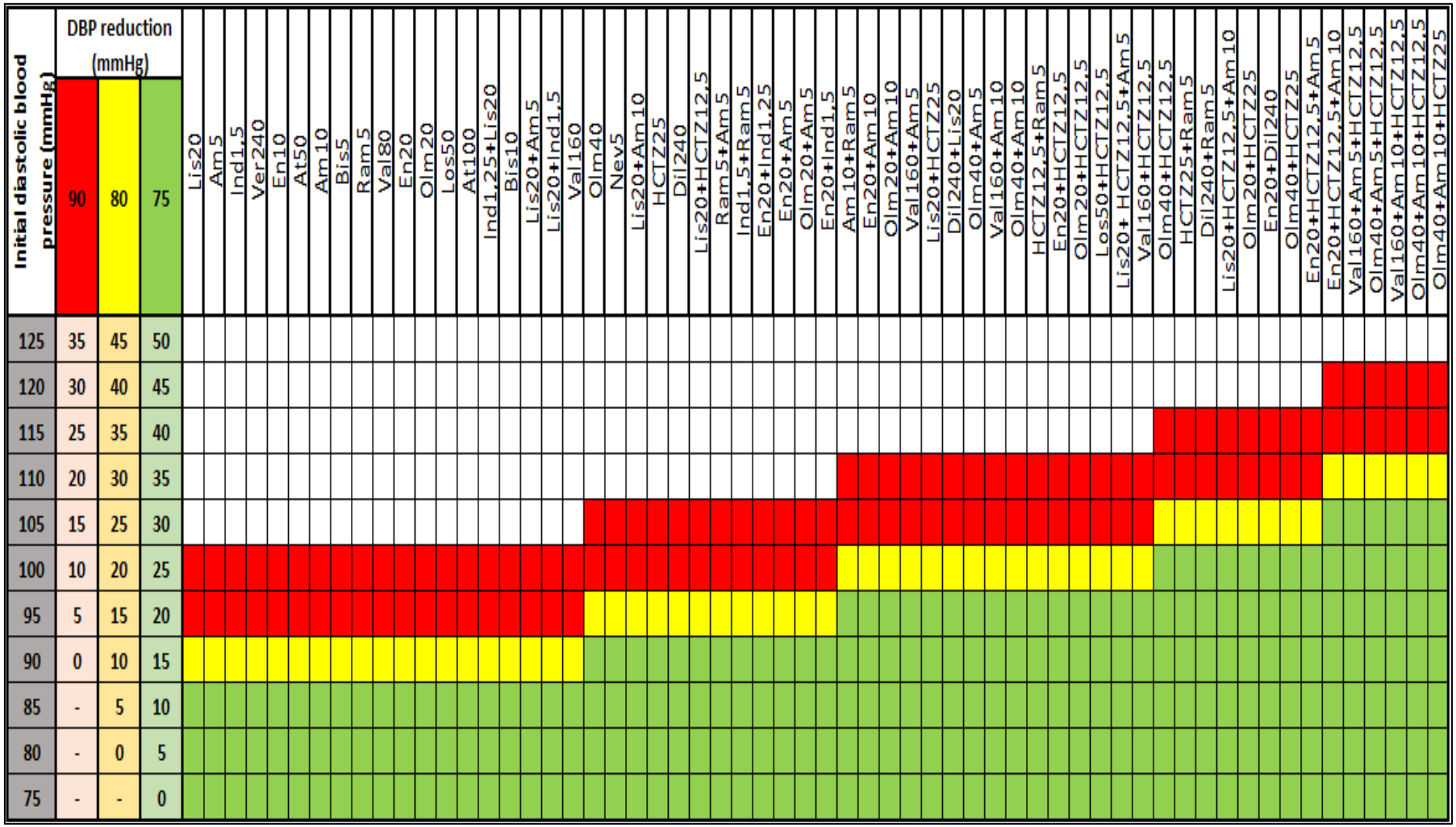


**Table 27: DBP effectiveness table. BP reduction *(mmHg)*. To see the table with BP reduction in *(%)*, go to *Annex 11*.**



The method of use these tables is the following:

In the case of systolic blood pressure:

1. Find the initial systolic BP value in column 1. It corresponds to the pretreatment SBP.
2. Find the SBP target in the adjacent columns 2, 3, 4 or 5. Depending on the current situation of each patient it will be <150, <140, <130 or <125 mmHg. Then check the SBP reduction (*mmHg* and/or *%*) required to achieve the BP target.
3. Follow the row to the right.
4. The cells in blue indicate the therapies that will achieve the target <150 mmHg.
5. The cells in red indicate the therapies that will reach the target <140 mmHg.
6. The cells in yellow indicate the therapies that will reach the target <130 mmHg.
7. The cells in green indicate the therapies that will achieve the target <125 mmHg.
8. Eliminate treatments that do not meet the stated goals.
9. The rest will be your therapeutic alternatives.
10. In agreement with ***Figure 6***, although all "non-eliminated" therapeutic alternatives would be useful in reducing SBP to the desired levels, treatments falling within the appropriate reduction BP interval should preferably be selected.
11. Finally, you can use the "*cost of treatment per day*" or the "*ICER analysis*" to choose the most cost-effectiveness option within the selected alternatives. See section ***7.5***.

In the case of diastolic blood pressure: (the procedure will be exactly the same, it only defers in the values of the blood pressure)

1. Find the initial diastolic BP value in column 1. It corresponds to the pretreatment DBP.
2. Find the DBP target in the adjacent columns 2, 3 or 4. Depending on the current situation of each patient it will be <90 <80 or <75 mmHg. Then check the DBP reduction (*mmHg* and/or *%*) required to achieve the BP target.
3. Follow the row to the right.
4. The cells in red indicate the therapies that will achieve the target <90 mmHg.
5. The cells in yellow indicate the therapies that will reach the target <80 mmHg.
6. The cells in green indicate the therapies that will reach the target <75 mmHg.
7. Eliminate treatments that do not meet the stated goals.
8. The rest will be your therapeutic alternatives.
9. In agreement with ***Figure 6***, although all "non-eliminated" therapeutic alternatives would be useful in reducing DBP to the desired levels, treatments falling within the appropriate reduction BP interval should preferably be selected.
10. Finally, you can use the "*cost of treatment per day*" or the "*ICER analysis*" to choose the most cost-effectiveness option within the selected alternatives. See section ***7.5***.

To understand better the procedure ***Annex 12*** shows examples of the method of using the tables.

**SBP results according to *Atom study*:**

As mentioned before in section ***7.6***, the different antihypertensive treatments are grouped in intervals.

The pharmacological treatments that reduce SBP less are, for example, *Lisinopril 20, Verapamil 240*, *Enalapril 10*, *Amlodipine 5*, and *Indapamide 1.5*. With them SBP can be reduced up to 10 mmHg, but no more.

In the second interval is when double drug combinations begin to appear. For example, to highlight the combination of *Lisinopril 20 + Amlodipine 5* or *Lisinopril 20 + Indapamide 1,25*.

Then, there is a group of therapeutic alternatives that can reduce SBP to about 20 mmHg, according to these data. In this group the most effectiveness monotherapy active ingredients can be seen, such as *HCTZ 25* or *Diltiazem 240*.

After it, there is a fourth therapeutic interval where triple drug combinations begin to appear, for example: *Lisinopril 20 + HCTZ12.5 + Amlodipine 5*.

Finally, there are a heterogeneous group of treatments, most of which are triple combinations, which can reduce the pressure up to 30 mmHg, and highlight *Olmesartan 40 + Amlodipine 10 + HCTZ 25* which can reduce the pressure up to 40 mmHg according to the study results.

**DBP results according to *Atom study*:**

Pharmacological treatments are grouped basically into four groups:

The first group is the one that reduces DBP up to 10 mmHg, to emphasize, *Enalapril 10, Enalapril 20* or *Indapamide 1.25 + Lisinopril 20*, among others.

Second, there are treatments that reduce DBP to 15 mmHg. Most are combinations of two drugs, such as: *Lisinopril 20 + HCTZ 12.5*.

The third group is a large group of doubles and even triple combinations that reduce the pressure to 20 mmHg. For example: *Enalapril 20 + HCTZ 12.5* or *Enalapril 20 + Indapamide 1.5*.

Finally, another group is also quite heterogeneous, formed mainly by triple combinations. The combination that most reduces DBP (according to this study data) is *Olmesartan 40 + Amlodipine 10 + HCTZ 25*.

A practical application can be given at these intervals, summarizing the treatments that could be used in the different grades of hypertension in ***Table 28***:

**Table 28: Examples of treatments for each grade of hypertension.**

| **Category** | **Systolic (mmHg)** | **SBP reduction interval (mmHg)** | **Active ingredient. Examples.** | | **Diastolic (mmHg)** | **DBP reduction interval (mmHg)** | **Active ingredient. Examples.** |
|---|---|---|---|---|---|---|---|
| **Grade 1 hypertension** | 140-159 | ≤10,00<br>10,01-15,00<br>15,01-20,00 | Enalapril 20 | and/or | 90-99 | ≤10,00 | Enalapril 10 |
| **Grade 2 hypertension** | 160-179 | 20,01-25,00<br>>25,00 | Enalapril 20 + HCTZ 12.5 | and/or | 100-109 | 10,01-15,00<br>15,01-20,00 | Lisinopril 20 + HCTZ 12,5 |
| **Grade 3 hypertension** | ≥180 | >25,00 | Olmesartan 40 + Amlodipine 10 + HCTZ 25 | and/or | ≥110 | >20,00 | Enalapril 20 + HCTZ 12,5 + Amlodipine10 |

The treatments shown are only examples of drugs useful for treating the selected degrees of hypertension, there are evidently many other drugs available in this study. The results should be adapted to the needs of each patient.

### 8.2. Comparative cost-effectiveness tables

In relation to the cost-effectiveness analysis, and before proceeding to the ICER results study, two tables (***Table 29*** and ***Table 30***) have been elaborated to relate the effectiveness and the cost of pharmacological treatment per day (taking into account the use of a single tablet per day). The data are based on the ***Annex 4.***

These tables have been developed to be a complement to the effectiveness tables (***Table 26*** and ***Table 27***). The objective is that when there are different alternatives to choose that are useful to achieve the desired target, taking into account information of indications, contraindications, side effects and interactions, the cheapest alternative has to be selected. Achieve a given objective at the lowest cost (20).

**Table 29: SBP efficiency analysis.**

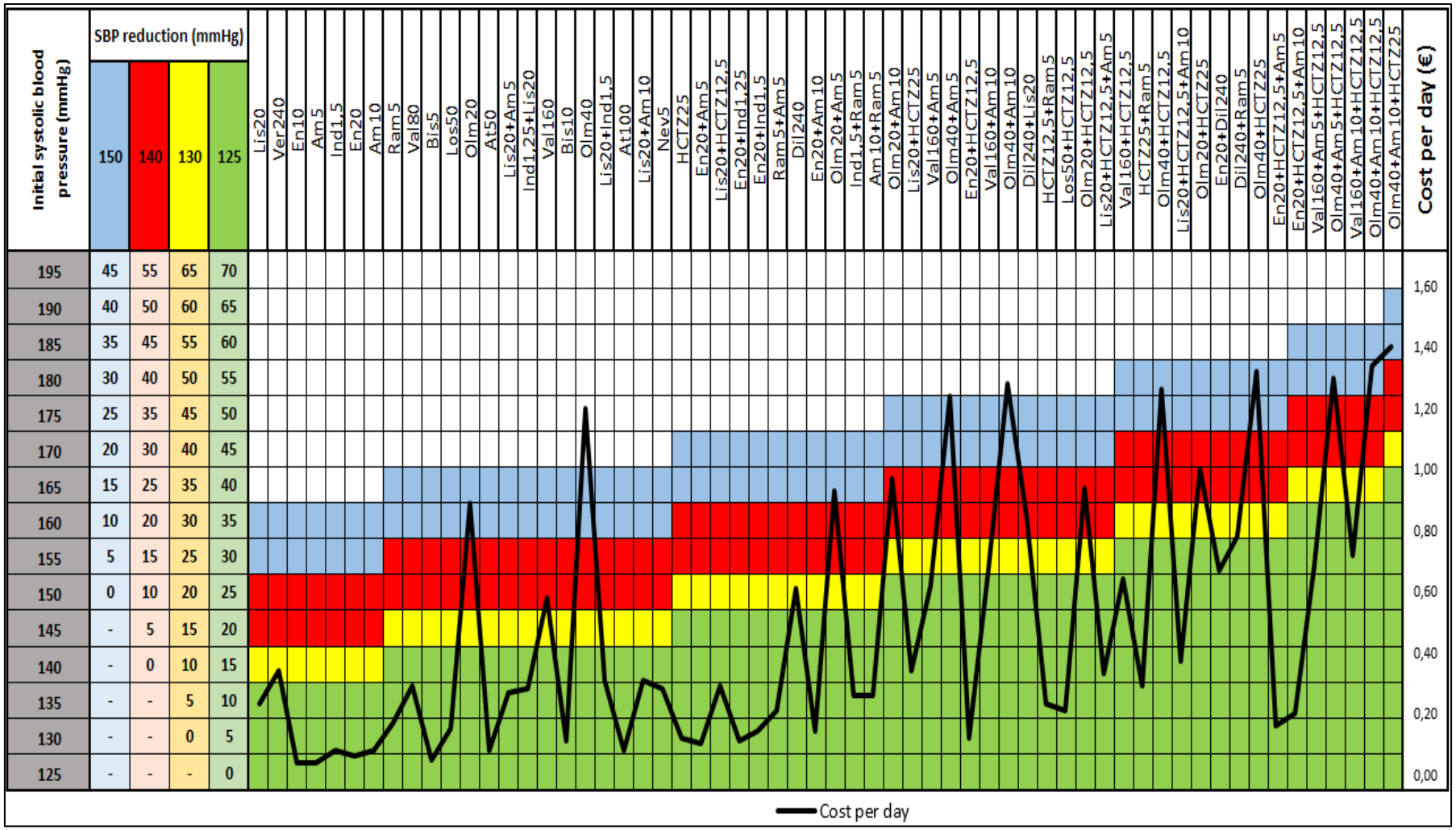
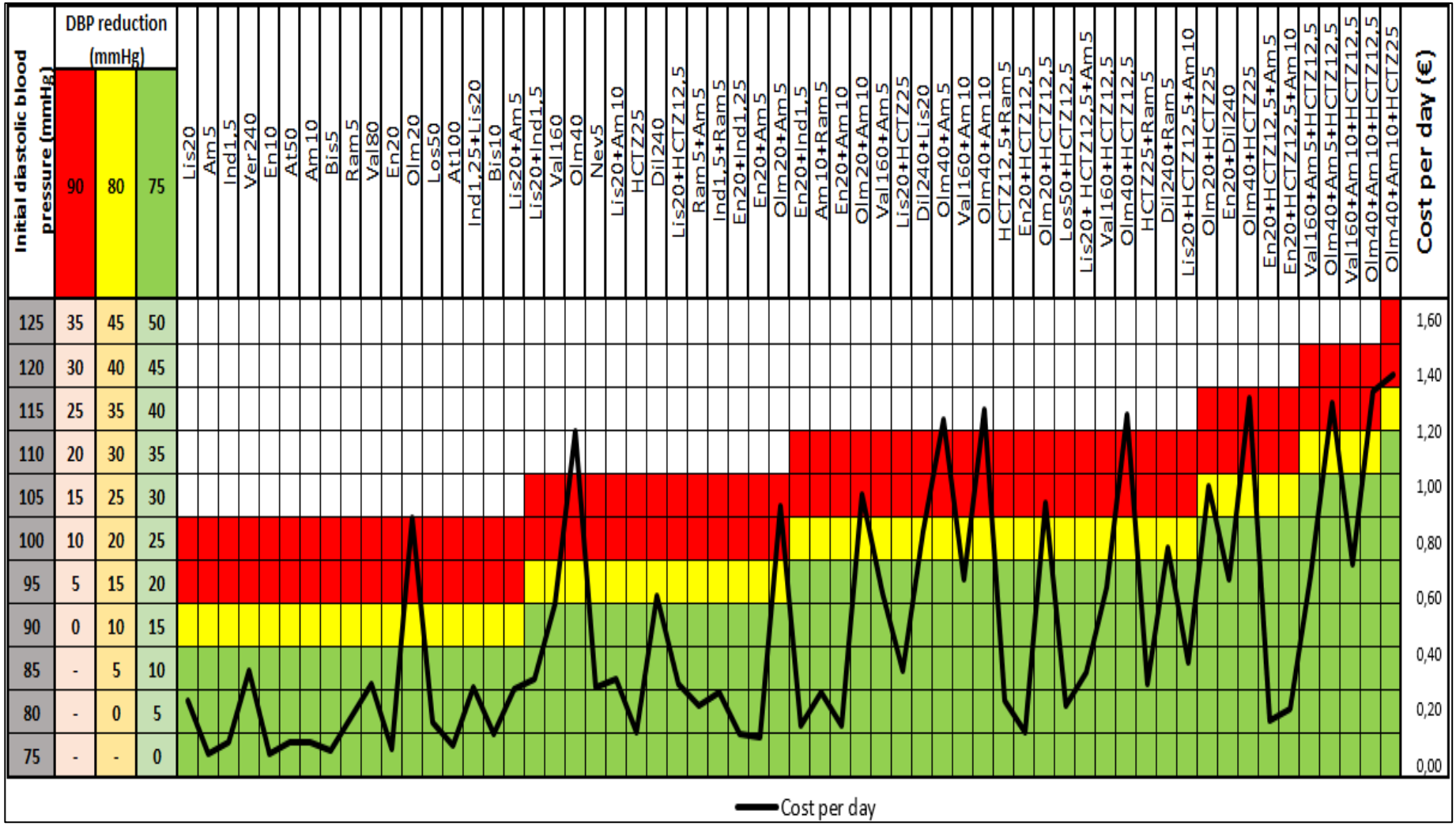


**Table 30: DBP efficiency analysis.**



### 8.3. ICER results

Using the procedure explained in section ***7.7***, the following tables contain the ICER analysis.

The tables are formed by six columns (see ***Table 31***):

- In the first columns there are the active ingredients used in the analysis. The antihypertensive agents have been sorted from less to greater effectiveness.
- The second and third columns show the cost (€ per day) and the effectiveness (BP reduction – mmHg) of the different treatments.
- In the fourth and fifth columns there are the increase of the cost and effectiveness of each treatment concerned in relation to the treatment that each of them have above.
- And finally, in the sixth column the ICER is calculated based on its [$\Delta$C] and [$\Delta$E].

**Table 31: Example. ICER. SBP reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **Lisinopril 20** | **0,23** | **4,38** | **0,23** | **4,38** | **0,05** |
| **Verapamil 240** | **0,34** | **6,56** | **0,11** | **2,18** | **0,05** |

In this section, the ICER analysis of the SBP reduction interval "≤10 mmHg" can be seen in ***Table 32, Table 33, Table 34*** and ***Table 35***. To see the analysis of the other SBP and DBP intervals go to ***Annex 14*** and ***Annex 15.***

In the SBP reduction interval "≤10 mmHg" (***Table 32***) Enalapril 10 is the comparator because, as it can be seen in ***Table 20*** and ***Table 23***, it is the most prescribed antihypertensive drug in monotherapy in Girona.

To determine the most cost-effectiveness therapeutic alternatives there are two processes of exclusion:

- **Dominated therapies:**

As has been said, therapies are sorted from less to greater effectiveness. For this reason, the fact that *Enalapril 10* has a negative ICER implies that it is an alternative treatment with lower cost and greater effectiveness than *Verapamil 240*. Consequently, *Verapamil 240* can be excluded. The same happens between *Indapamide 1.5* and *Enalapril 20*.

**Table 32: ICER-Exclusion of dominated therapies. Systolic blood pressure reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| Lisinopril 20 | 0,23 | 4,38 | 0,23 | 4,38 | 0,05 |
| Verapamil 240 | 0,34 | 6,56 | 0,11 | 2,18 | 0,05 |
| Enalapril 10 | 0,04 | 7,30 | -0,30 | 0,74 | -0,41 |
| Amlodipine 5 | 0,04 | 7,67 | 0,00 | 0,37 | 0,00 |
| Indapamide 1,5 | 0,08 | 8,89 | 0,04 | 1,22 | 0,03 |
| Enalapril 20 | 0,06 | 8,93 | -0,02 | 0,04 | -0,50 |
| Amlodipine 10 | 0,08 | 9,36 | 0,02 | 0,43 | 0,05 |

From these results, ***Table 32*** can be simplified in ***Table 33***:

**Table 33: ICER-Exclusion of dominated therapies. Systolic blood pressure reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| Lisinopril 20 | 0,23 | 4,38 | 0,23 | 4,38 | 0,05 |
| Enalapril 10 | 0,04 | 7,30 | -0,19 | 2,92 | -0,07 |
| Amlodipine 5 | 0,04 | 7,67 | 0,00 | 0,37 | 0,00 |
| Enalapril 20 | 0,06 | 8,93 | 0,02 | 1,26 | 0,02 |
| Amlodipine 10 | 0,08 | 9,36 | 0,02 | 0,43 | 0,05 |

There comes a moment of the analysis in which there are no therapies with negative ICER (dominants), therefore another process is used to exclude the less cost-effectiveness alternatives.

- **Therapies with higher ICER:**

In ***Table 34,*** *Amlodipine 10* is now excluded because the ICER are so high compared to the other alternatives.

**Table 34: ICER- Exclusion of therapies with higher ICER. Systolic blood pressure reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| Enalapril 10 | 0,04 | 7,30 | 0,04 | 7,30 | 0,01 |
| Amlodipine 5 | 0,04 | 7,67 | 0,00 | 0,37 | 0,00 |
| Enalapril 20 | 0,06 | 8,93 | 0,02 | 1,26 | 0,02 |
| Amlodipine 10 | 0,08 | 9,36 | 0,02 | 0,43 | 0,05 |

Finally, according to ***Table 35***, it can be said that *Enalapril 10*, *Amlodipine 5* and *Enalapril 20* are the most cost-effectiveness treatments for this SBP interval.

**Table 35: ICER- Exclusion of therapies with higher ICER. Systolic blood pressure reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **Enalapril 10** | **0,04** | **7,30** | **0,04** | **7,30** | **0,01** |
| **Amlodipine 5** | **0,04** | **7,67** | **0,00** | **0,37** | **0,00** |
| **Enalapril 20** | **0,06** | **8,93** | **0,02** | **1,26** | **0,02** |

Although *Amlodipine 5* has a lower ICER than the other treatments, the decision must be made with caution and the circumstances that surround the analysis must be evaluated (See ***Figure 7***). In all the tables, the treatments excluded by dominants therapies are marked in yellow and the most cost-effectiveness treatments are marked in red.

Finally, two tables (***Table 36*** and ***Table 37***) have been developed to summarize the main features of the results of the ICER study.

**Table 36: SBP ICER summary.**

| SBP reduction interval (mmHg) | Most used treatment in clinical practice | More effectiveness/Less cost (DOMINANT) |
|---|---|---|
| ≤10,00 | Enalapril 10 | Enalapril 10, Amlodipine 5, Enalapril 20 |
| 10,01-15,00 | Bisorpolol 5 | Bisoprolol 5, Atenolol 100 |
| 15,01-20,00 | HCTZ 25 | Enalapril 20 + Amlodipine 5, Enalapril 20 + Indapamide 1,25 |
| 20,01-25,00 | Enalapril 20 + HCTZ 12,5 | Enalapril 20 + HCTZ 12,5 |
| >25 | Olmesartan 40 + Amlodipine 10 + HCTZ 25 | Enalapril 20 + HCTZ 12,5 + Amlodipine 5, Enalapril 20 + HCTZ 12,5 + Amlodipine 10 |

**Table 37: DBP ICER summary.**

| DBP reduction interval (mmHg) | Most used treatment in clinical practice | More effectiveness/Less cost (DOMINANT) |
|---|---|---|
| ≤10,00 | Enalapril 10 | Enalapril 10, Amlodipine 5, Enalapril 20 |
| 10,01-15,00 | HCTZ 25 | Enalapril 20 + Amlodipine 5 |
| 15,01-20,00 | Enalapril 20 + HCTZ 12,5 | Enalapril 20 + HCTZ 12,5 |
| >20,00 | Olmesartan 40 + Amlodipine 10 + HCTZ 25 | Enalapril 20 + HCTZ 12,5 + Amlodipine 5 |

For each BP interval, both SBP and DBP, it has been assessed if the treatments that are prescribed nowadays in the clinical practice (according to ***Annex 13***) are the most cost-effectiveness ones. It is observed that even though there is no exact match in some of the intervals, it can be seen that almost all the comparators treatments belong to the therapeutic alternatives with a good cost-effectiveness.

In addition, a concordance can be seen between the results obtained with the reduction of SBP and DBP, thus these selected antihypertensive treatments will be cost-effectiveness for both SBP and DBP.

## 8.4. Sensitivity analysis

In addition to all of the above procedure, a sensitivity analysis has been carried out.

Sensitivity analysis is a method to determine the robustness of an assessment by examining the extent to which results are affected by changes in methods, models, values of unmeasured variables, or assumptions. It has also been defined as "a series of analyses of a data set to assess whether altering any of the assumptions made leads to different final interpretations or conclusions" (39). The aim of this analysis is to identifying the results that are most dependent on questionable or unsupported assumptions (40).

In this study the sensitivity analysis was performed to appraise if a change in the representation of the ICER values shows the same results of cost-effectiveness.

Treatments will be sorted from lowest to highest effectiveness, setting the comparator above the whole. Then, the increase in cost and effectiveness of each therapeutic alternative in relation to the comparator will be calculated. See ***Table 38***.

**Table 38: Sensitivity analysis. ICER. SBP reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **Enalapril 10** | **0,04** | **7,30** | **0,04** | **7,30** | **0,01** |
| **Lisinopril 20** | **0,23** | **4,38** | **0,19** | **-2,92** | **-0,07** |
| **Verapamil 240** | **0,34** | **6,56** | **0,30** | **-0,74** | **-0,41** |
| **Amlodipine 5** | **0,04** | **7,67** | **0,00** | **0,37** | **0,00** |
| **Indapamide 1,5** | **0,08** | **8,89** | **0,04** | **1,59** | **0,03** |
| **Enalapril 20** | **0,06** | **8,93** | **0,02** | **1,63** | **0,01** |
| **Amlodipine 10** | **0,08** | **9,36** | **0,04** | **2,06** | **0,02** |

After analysing the ICER tables, a second part consists in the figures that follow each table. They try to show the relationship between all the therapeutic alternatives in each interval, as explained in ***Figure 7***.

The ***Figure 9*** has been made to assess the relation between *Enalapril 10* to the other therapeutic alternatives available in this BP reduction interval.

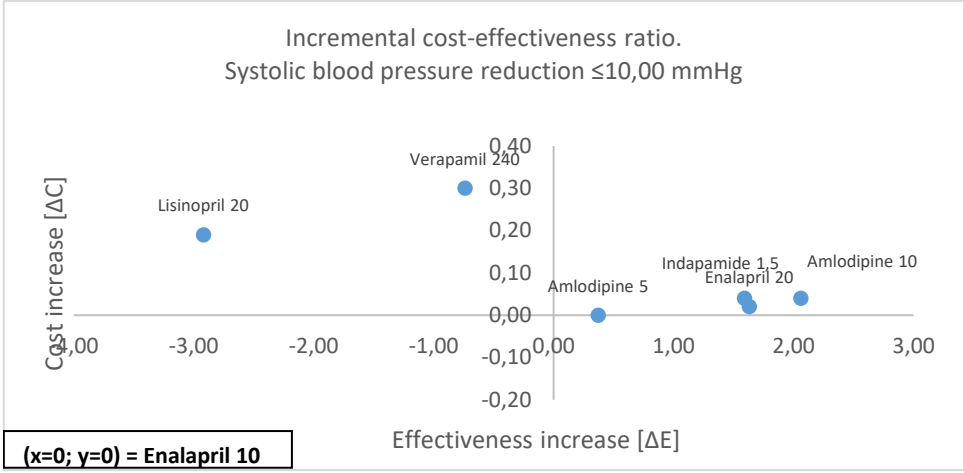



**Figure 9: Sensitivity analysis. ICER. SBP ≤10,00 mmHg.**

In the point (x=0; y=0) of the figures always will appear the comparator (the most used pharmacological treatment in clinical practice). In this case is *Enalapril 10.*

Then, the other active ingredients in the interval can be represented depending on their increase in cost [ΔC] and effectiveness [ΔE]. Treatments that reduce BP more and are cheaper than the comparator will be more cost-effectiveness treatments (dominant) than the treatments that are used in the clinical practice.

Furthermore, do not forget the treatments that, although more expensive, can reduce the BP more than the comparator. In these cases, it should be assessed if the benefit obtained with the reduction of BP is higher than the additional cost of treatment.

This procedure has been performed for each BP interval in ***Annex 16*** and ***Annex 17***.

The last step (***Table 39*** and ***Table 40***) is to compare the results of the ICER analysis (***8.3***) with the results of the sensitivity analysis (***8.4***).

**Table 39: Analysis of ICER results. SBP.**

| SBP reduction interval (mmHg) | Most used treatment in clinical practice | ICER analysis (DOMINANT) | Sensitivity analysis (DOMINANT) |
|---|---|---|---|
| ≤10,00 | Enalapril 10 | Enalapril 10<br>Amlodipine 5<br>Enalapril 20 | Amlodipine 5 |
| 10,01-15,00 | Bisorpolol 5 | Bisoprolol 5, Atenolol 100 | Bisorpolol 5 |
| 15,01-20,00 | HCTZ 25 | Enalapril 20 + Amlodipine 5<br>Enalapril 20 + Indapamide 1,25 | Enalapril 20 + Amlodipine 5<br>Enalapril 20 + Indapamide 1,25 |
| 20,01-25,00 | Enalapril 20 + HCTZ 12,5 | Enalapril 20 + HCTZ 12,5 | Enalapril 20 + HCTZ 12,5 |
| >25 | Olmesartan 40 + Amlodipine 10 + HCTZ 25 | Enalapril 20 + HCTZ 12,5 + Amlodipine 5<br>Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | Olmesartan 40 + Amlodipine 10 + HCTZ 25 |

**Table 40: Analysis of ICER results. DBP.**

| DBP reduction interval (mmHg) | Most used treatment in clinical practice | ICER analysis (DOMINANT) | Sensitivity analysis (DOMINANT) |
|---|---|---|---|
| 5,01-10,00 | Enalapril 10 | Enalapril 10<br>Amlodipine 5<br>Enalapril 20 | Enalapril 10 |
| 10,01-15,00 | HCTZ 25 | Enalapril 20 + Amlodipine 5 | Enalapril 20 + Indapamide 1,25<br>Enalapril 20 + Amlodipine 5 |
| 15,01-20,00 | Enalapril 20 + HCTZ 12,5 | Enalapril 20 + HCTZ 12,5 | Enalapril 20 + HCTZ 12,5 |
| >20,00 | Olmesartan 40 + Amlodipine 10 + HCTZ 25 | Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | Olmesartan 40 + Amlodipine 10 + HCTZ 25 |

In all SBP and DBP reduction intervals, except in SBP reduction >25,00 mmHg and DBP >20,00 mmHg, the values of both analyses agree. The reason for this slight difference in these two intervals is because the treatment most used in clinical practice, comparator, is the one that has greater effectiveness. Therefore, it is not possible that any treatment has less cost and more effectiveness than it. For this reason, it is said that the results should be assessed with caution according to ***Figure 7***.

According to this analysis, it can be said that the results of the ICER analysis are robust and reliable.

## 9. ETHICAL ASPECTS

This study intends to focus in different perspectives:

First, the patient. With this pharmacoeconomic study the purpose is to give the best antihypertensive treatment at lower cost. Thus, the health resources will be better distributed and then they will can be allocated more fair and reasonable, fulfilling the principle of justice.
When a physician indicates a therapy for a patient, this means that at the end of the day another patient will miss the appropriate treatment due to the scarcity of resources. If in the latter case the missed treatment would have resulted in more health benefit than for the former patient, the opportunity cost of the decision (the amount of the missed health gain) is greater than the proceeds of the decision (12).

Second, the health professionals. Health professionals with this study will have access to the pharmacoeconomic information of the antihypertensive treatments, and then they will can use it as an important tool in making decisions in clinical practice.

Finally, the public health. Also, it could be a tool to improve the distribution of health resources and promote a more sustainable health system. It would be desirable that in future this type of information will be adopted in the national and international reference hypertension guidelines.

Apart from this, all study data are impersonal. Remember that the study is mainly based on three types of data:

- Efficacy data, from *Atom Study* (22).
- Antihypertensive agents cost details, from *Spanish General Council of Official Colleges of Pharmacy* (37).
- Antihypertensive agents prescribed in Girona, from *Pharmaceutical Care Unit of the Catalan Health Service (CatSalut).*

Furthermore, there are no conflicts of interest for any of the authors.

## 10. STUDY LIMITATIONS

The main limitations of the study are derived from the *Atom study* (22), as all the content of the work depends directly on these data. These limitations are:

- Data used in *Atom study* (22) were collected in 2008 and 2009. However, the researchers are confident that the prevalence estimates are still relevant today.
- Data are not individual but correspond to those obtained in each of the included trials.
- The estimation was performed using the mean administered does, which do not exactly match those of the available drug formats, although they are very close.
- The analysis of the combinations is limited to the most recent ones, there are not enough studies performed with other commonly used combinations. It is possible that there are other treatment strategies that could be used in practice that do not appear in the tables. For these antihypertensive agents the study will not be useful.

In addition, one limitation stems from the use of Law et al (9). The paper, as previously indicated in this work, linearized relations that are essentially non-linear. As a consequence, the further away from the actual relation from the linearized (i.e the difference of the prescribed dose and the mean dose), the greater the difference can be obtained in the adjustment (i.e. the adjusted reduction will be furthest from the actual reduction). This could greatly distort the results if the prescribed dose were very far from the theoretical (i.e. mean) dose. Fortunately, the doses used in clinical practice do not deviate excessively from the mean doses used in the meta-analyzed clinical trials in the *Atom study* (22).

Another limitation refers to the pharmacoeconomic study. Although the cost-effectiveness studies are a key tool in the context of decision-making, the results should be interpreted with caution. Careful in interpreting whether one treatment is more cost-effectiveness than another. Pharmacoeconomists usually present the results and refrain from unbalancing the balance on one side or the other. In this type of decisions the circumstances that surround the analysis must be evaluated, such as budgetary, clinical objectives, patient preferences, degree of patient compliance, etc.

Moreover, another important limitation is that the prices of the treatments studied are based in the prices in Spain in 2016. Therefore, the results should be updated annually. In addition, the estimated prices must be modified according to the prices of each country, as the intention of the study is to have national and international impact.

Finally, it should be noted that the work of the present author has been mainly the management and the analysis of the data. The author would like to thanks the work team that provided the data of efficacy from the *Atom study* (22) that have served to realize all the study.

## 11. CONCLUSIONS

1. The effectiveness in a series of antihypertensive drugs has been obtained based on the efficacy data from the *Atom study* and the application of the concept of *Law et al*.

2. Effectiveness tables have been built to provide a practical application to the results of the *Atom study* in order to become an easy and useful tool in the clinical practice.

3. Cost effectiveness tables (including the cost per day as the cost reference) have been made to be a complement of the effectiveness tables, and permit in a quick, easy and visual way choose the best therapeutic option based on both criteria.

4. A cost-effectiveness study, using the ICER method, has been applied to evaluate the different therapeutic options. *Amlodipine 5*, *Enalapril 10*, *Enalapril 20+Amlodipine 5*, *Enalapril 20+HCTZ 12.5*, *Enalapril 20+HCTZ 12.5+Amlodipine 5*, are examples of cost-effectiveness antihypertensive strategies.

5. In Girona, this study has shown that cost-effectiveness pharmacological treatments are being prescribed in clinical practice.

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# ANNEXES

## Annex 1

**Table 41: Oral antihypertensive drugs. Adapted from *ICS Guideline* (1).**

| Grups farmacològics | Dosi inicial *mg/dia* | Dosi estàndard *mg/dia* | Dosi màxima *mg/dia* | Grups farmacològics | Dosi inicial *mg/dia* | Dosi estàndard *mg/dia* | Dosi màxima *mg/dia* |
|---|---|---|---|---|---|---|---|
| ANTAGONISTES DELS RECEPTORS DE L'ANGIOTENSINA 2 (ARA-2) | | | | DIURÈTICS | | | |
| Candesartan | 8 | 8-16 | 32 | D. tiazídics i anàlegs | | | |
| Eprosartan | 600 | 600 | 1.200 | Clortalidona | 12,5 | 25 | 50 |
| Irbesartan | 150 | 150-300 | 300 | Hidroclorotiazida | 12,5 | 25 | 50 |
| Losartan | 50 | 50-100 | 100 | Indapamida | 2,5 | 2,5 | 5 |
| Olmesartan | 10 | 20 | 40 | Indapamida retard | 1,5 | 1,5 | 2,5 |
| Telmisartan | 40 | 40-80 | 80 | Xipamida | 10 | 20 | 20 |
| Valsartan | 80 | 80-160 | 320 | *D. de nansa:* | | | |
| | | | | Furosemida | 20 | 20-40 | 80 |
| BLOCADORS ALFA ADRENÈRGICS | | | | Torasemida | 2,5 | 5 | 10 |
| Doxazosina | 1 | 2-4 | 16 | *D. estalviadors de K* | | | |
| | | | | Amilorida (2) | 2,5-5 | 10 | 20 |
| BLOCADORS ALFA-BETA ADRENÈRGICS | | | | Espironolactona | 50 | 50-100 | 100 |
| Carvedilol | 12,5 | 25 | 50 | | | | |
| Labetalol | 200* | 400-800* | 2.400** | INHIBIDORS DE L'ENZIM CONVERSOR DE L'ANGIOTENSINA (IECA) | | | |
| | | | | | | | |
| BLOCADORS BETA ADRENÈRGICS (BB) | | | | Benazepril | 10 | 10-20 | 40 |
| *Cardioselectius* | | | | Captopril* | 25* | 50* | 150* |
| Atenolol | 50 | 50-100 | 100 | Cilazapril | 1,25 | 2,5 | 5 |
| Bisoprolol | 5 | 10 | 20 | Delapril | 30* | 60* | 120* |
| Metoprolol | 100 | 200 | 200 | Enalapril | 5 | 10-20 | 40 |
| Nebivolol | 5 | 5 | 5 | Espirapril | 3 | 6 | 6 |
| *No cardioselectius*: | | | | Fosinopril | 10 | 20 | 40 |
| Nadolol | 40 | 80-160 | 320 | Lisinopril | 10 | 20 | 80 |
| Propanolol retard | 80 | 160 | 320 | Perindopril | 4 | 4 | 8 |
| | | | | Quinapril | 10 | 20-40 | 80 |
| | | | | Ramipril | 2,5 | 2,5-5 | 10 |
| | | | | Trandolapril | 2 | 2 | 4 |
| | | | | Zofenopril | 15 | 30 | 60 |

| Grups farmacològics | Dosi inicial *mg/dia* | Dosi estàndard *mg/dia* | Dosi màxima *mg/dia* | Grups farmacològics | Dosi inicial *mg/dia* | Dosi estàndard *mg/dia* | Dosi màxima *mg/dia* |
|---|---|---|---|---|---|---|---|
| BLOCADORS CANALS CALCI (BCC) | | | | SIMPATICOLÍTICS D'ACCIÓ CENTRAL | | | |
| *Dihidropiridínic* | | | | Clonidina* | 0,1* | 0,2-0,8* | 1,2* |
| Amlodipina | 5 | 5-10 | 10 | Metildopa* | 250-500* | 1000* | 3000* |
| Barnidipina | 10 | 10 | 20 | Moxonidina* | 0,2 | 0,4 | 0,6 |
| Felodipina | 5 | 5-10 | 10 | | | | |
| Lacidipina | 2 | 4 | 4 | VASODILATADORS | | | |
| Lercanidipina | 10 | 10 | 20 | Hidralazina* | 25* | 50* | 100* |
| Manidipina | 10 | 10-20 | 20 | Minoxidil* | 5* | 10-20* | 100* |
| Nifedipina oros | 30 | 30-60 | 120 | | | | |
| Nitrendipina | 10 | 20 | 40** | INHIBIDORS DIRECTES DE LA RENINA | | | |
| *No dihidropiridínics* | | | | Aliskirèn | 150 | 150-300 | 300 |
| Verapamil SR | 120 | 240 | 480** | | | | |
| Diltiazem SR | 120 | 180-240 | 360 | | | | |

ASI: activitat simpaticomimètica intrínseca.

* Dosi dividida en dues o tres preses dia.

** Dosi dividida en dues o tres preses si s'arriba a la dosi màxima.

(1) Alliberament sostingut.

(2) Només es presenten associats amb diürètics.

## Annex 2

**Table 42: BP reductions adjusted by *Law et al.***

| Active ingredient | Actual dose (mg) | Average dose (mg) | Reductions (mmHg) | | Adjusted reductions (mmHg) | |
|---|---|---|---|---|---|---|
| | | | Systolic | Diastolic | Systolic | Diastolic |
| Indapamide | 1,5 | 1,90 | 9,71 | 6,55 | 8,89 | 6,00 |
| HCTZ | 25 | 19,10 | 14,93 | 11,90 | 15,85 | 12,64 |
| Atenolol | 50 | 59,20 | 12,00 | 7,75 | 11,25 | 7,27 |
| | 100 | | | | 13,65 | 8,82 |
| Bisoprolol | 5 | 6,70 | 11,79 | 8,14 | 10,59 | 7,31 |
| | 10 | | | | 12,95 | 8,94 |
| Nevibolol | 5 | 4,60 | 14,46 | 10,22 | 14,96 | 10,40 |
| Amlodipine | 5 | 6,60 | 8,49 | 6,59 | 7,67 | 5,95 |
| | 10 | | | | 9,36 | 7,27 |
| Nifedipine | 20 | 23,80 | 11,94 | 8,82 | 11,18 | 8,26 |
| Diltiazem | 240 | 159,30 | 16,56 | 11,52 | 18,24 | 12,69 |
| Verapamil | 240 | 226,10 | 6,48 | 6,48 | 6,56 | 6,56 |
| Enalapril | 10 | 13,60 | 8,16 | 7,50 | 7,30 | 6,71 |
| | 20 | | | | 8,93 | 8,21 |
| Lisinopril | 10 | 17,60 | 4,26 | 3,13 | 3,52 | 2,59 |
| | 20 | | | | 4,38 | 3,22 |
| Ramipril | 5 | 5,50 | 10,55 | 8,09 | 10,17 | 7,80 |
| Olmesartan | 20 | 25,70 | 11,90 | 9,02 | 10,84 | 8,22 |
| | 40 | | | | 13,22 | 10,02 |
| Valsartan | 80 | 137,50 | 12,40 | 9,40 | 10,33 | 7,83 |
| | 160 | | | | 12,81 | 9,71 |
| Losartan | 50 | 62,50 | 11,60 | 9,10 | 10,67 | 8,37 |

## Annex 3

**Table 43: BP reduction ajusted by *Law et al*.**

| Active ingredient | Actual dose (mg) | Average dose (mg) | Reductions (mmHg) | | Adjusted reductions (mmHg) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Systolic | Diastolic | Systolic | | Diastolic | |
| Indapamide | 1,5 | 1,90 | 9,71 | 6,55 | 8,89 | 12,41 | 6,00 | 8,59 |
| Lisinopril | 10 | 17,60 | 4,26 | 3,13 | 3,52 | | 2,59 | |
| Valsartan | 80 | 137,50 | 12,40 | 9,40 | 10,33 | 19,69 | 7,83 | 15,10 |
| Amlodipine | 10 | 6,60 | 8,49 | 6,59 | 9,36 | | 7,27 | |
| Indapamide | 1,25 | 1,90 | 9,71 | 6,55 | 8,38 | 12,76 | 5,65 | 8,87 |
| Lisinopril | 20 | 17,60 | 4,26 | 3,13 | 4,38 | | 3,22 | |
| Indapamide | 1,5 | 1,90 | 9,71 | 6,55 | 8,89 | 19,06 | 6,00 | 13,80 |
| Ramipril | 5 | 5,50 | 10,55 | 8,09 | 10,17 | | 7,80 | |
| Indapamide | 1,5 | 1,90 | 9,71 | 6,55 | 8,89 | 16,19 | 6,00 | 12,71 |
| Enalapril | 10 | 13,60 | 8,16 | 7,50 | 7,30 | | 6,71 | |
| Indapamide | 1,25 | 1,90 | 9,71 | 6,55 | 8,38 | 15,68 | 5,65 | 12,36 |
| Enalapril | 10 | 13,60 | 8,16 | 7,50 | 7,30 | | 6,71 | |
| Lisinopril | 20 | 17,60 | 4,26 | 3,13 | 4,38 | 13,27 | 3,22 | 9,22 |
| Indapamide | 1,5 | 1,90 | 9,71 | 6,55 | 8,89 | | 6,00 | |
| Lisinopril | 10 | 17,60 | 4,26 | 3,13 | 3,52 | 19,37 | 2,59 | 15,23 |
| HCTZ | 25 | 19,10 | 14,93 | 11,90 | 15,85 | | 12,64 | |
| Lisinopril | 20 | 17,60 | 4,26 | 3,13 | 4,38 | 17,24 | 3,22 | 13,48 |
| HCTZ | 12,5 | 19,10 | 14,93 | 11,90 | 12,86 | | 10,26 | |
| HCTZ | 12,5 | 19,10 | 14,93 | 11,90 | 12,86 | 23,03 | 10,26 | 18,06 |
| Ramipril | 5 | 5,50 | 10,55 | 8,09 | 10,17 | | 7,80 | |
| Amlodipine | 10 | 6,60 | 8,49 | 6,59 | 9,36 | 12,88 | 7,27 | 9,86 |
| Lisinopril | 10 | 17,60 | 4,26 | 3,13 | 3,52 | | 2,59 | |
| Lisinopril | 20 | 17,60 | 4,26 | 3,13 | 4,38 | 12,05 | 3,22 | 9,17 |
| Amlodipine | 5 | 6,60 | 8,49 | 6,59 | 7,67 | | 5,95 | |
| Lisinopril | 20 | 17,60 | 4,26 | 3,13 | 4,38 | 13,74 | 3,22 | 10,49 |
| Amlodipine | 10 | 6,60 | 8,49 | 6,59 | 9,36 | | 7,27 | |
| Ramipril | 5 | 5,50 | 10,55 | 8,09 | 10,17 | 17,84 | 7,80 | 13,75 |
| Amlodipine | 5 | 6,60 | 8,49 | 6,59 | 7,67 | | 5,95 | |
| Diltiazem | 240 | 159,30 | 16,56 | 11,52 | 18,24 | 21,76 | 12,69 | 15,28 |
| Lisinopril | 10 | 17,60 | 4,26 | 3,13 | 3,52 | | 2,59 | |
| Diltiazem | 240 | 159,30 | 16,56 | 11,52 | 18,24 | 22,62 | 12,69 | 15,91 |
| Lisinopril | 20 | 17,60 | 4,26 | 3,13 | 4,38 | | 3,22 | |
| Diltiazem | 240 | 159,30 | 16,56 | 11,52 | 18,24 | 25,54 | 12,69 | 19,40 |
| Enalapril | 10 | 13,60 | 8,16 | 7,50 | 7,30 | | 6,71 | |
| Olmesartan | 20 | 25,70 | 11,90 | 9,02 | 10,84 | 23,70 | 8,22 | 18,48 |
| HCTZ | 12,5 | 19,10 | 14,93 | 11,90 | 12,86 | | 10,26 | |
| Olmesartan | 20 | 25,70 | 11,90 | 9,02 | 10,84 | 18,51 | 8,22 | 14,17 |
| Amlodipine | 5 | 6,60 | 8,49 | 6,59 | 7,67 | | 5,95 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Losartan | 50 | 62,50 | 11,60 | 9,10 | 10,67 | 23,53 | 8,37 | 18,63 |
| HCTZ | 12,5 | 19,10 | 14,93 | 11,90 | 12,86 | | 10,26 | |
| Valsartan | 80 | 137,50 | 12,40 | 9,40 | 10,33 | 23,19 | 7,83 | 18,09 |
| HCTZ | 12,5 | 19,10 | 14,93 | 11,90 | 12,86 | | 10,26 | |
| Valsartan | 80 | 137,50 | 12,40 | 9,40 | 10,33 | 18,00 | 7,83 | 13,78 |
| Amlodipine | 5 | 6,60 | 8,49 | 6,59 | 7,67 | | 5,95 | |
| Valsartan | 160 | 137,50 | 12,40 | 9,40 | 12,81 | 22,17 | 9,71 | 16,98 |
| Amlodipine | 10 | 6,60 | 8,49 | 6,59 | 9,36 | | 7,27 | |
| Enalapril | 20 | 13,60 | 8,16 | 7,50 | 8,93 | 17,31 | 8,21 | 13,86 |
| Indapamide | 1,25 | 1,90 | 9,71 | 6,55 | 8,38 | | 5,65 | |
| Lisinopril | 20 | 17,60 | 4,26 | 3,13 | 4,38 | 20,23 | 3,22 | 15,86 |
| HCTZ | 25 | 19,10 | 14,93 | 11,90 | 15,85 | | 12,64 | |
| HCTZ | 25 | 19,10 | 14,93 | 11,90 | 15,85 | 26,02 | 12,64 | 20,44 |
| Ramipril | 5 | 5,50 | 10,55 | 8,09 | 10,17 | | 7,80 | |
| Enalapril | 20 | 13,60 | 8,16 | 7,50 | 8,93 | 21,79 | 8,21 | 18,47 |
| HCTZ | 12,5 | 19,10 | 14,93 | 11,90 | 12,86 | | 10,26 | |
| Amlodipinde | 10 | 6,60 | 8,49 | 6,59 | 9,36 | 19,53 | 7,27 | 15,07 |
| Ramipril | 5 | 5,50 | 10,55 | 8,09 | 10,17 | | 7,80 | |
| Enalapril | 20 | 13,60 | 8,16 | 7,50 | 8,93 | 16,60 | 8,21 | 14,16 |
| Amlodipinde | 5 | 6,60 | 8,49 | 6,59 | 7,67 | | 5,95 | |
| Diltiazem | 240 | 159,30 | 16,56 | 11,52 | 18,24 | 28,41 | 12,69 | 20,49 |
| Ramipril | 5 | 5,50 | 10,55 | 8,09 | 10,17 | | 7,80 | |
| Enalapril | 20 | 13,60 | 8,16 | 7,50 | 8,93 | 27,17 | 8,21 | 20,90 |
| Diltiazem | 240 | 159,30 | 16,56 | 11,52 | 18,24 | | 12,69 | |
| Enalapril | 20 | 13,60 | 8,16 | 7,50 | 8,93 | 17,82 | 8,21 | 14,21 |
| Indapamide | 1,5 | 1,90 | 9,71 | 6,55 | 8,89 | | 6,00 | |
| Enalapril | 20 | 13,60 | 8,16 | 7,50 | 8,93 | 18,29 | 8,21 | 15,48 |
| Amlodipine | 10 | 6,60 | 8,49 | 6,59 | 9,36 | | 7,27 | |
| Olmesartan | 20 | 25,70 | 11,90 | 9,02 | 10,84 | 26,69 | 8,22 | 20,86 |
| HCTZ | 25 | 19,10 | 14,93 | 11,90 | 15,85 | | 12,64 | |
| Olmesartan | 40 | 25,70 | 11,90 | 9,02 | 13,22 | 26,08 | 10,02 | 20,28 |
| HCTZ | 12,5 | 19,10 | 14,93 | 11,90 | 12,86 | | 10,26 | |
| Olmesartan | 20 | 25,70 | 11,90 | 9,02 | 10,84 | 20,20 | 8,22 | 15,49 |
| Amlodipine | 10 | 6,60 | 8,49 | 6,59 | 9,36 | | 7,27 | |
| Olmesartan | 40 | 25,70 | 11,90 | 9,02 | 13,22 | 20,89 | 10,02 | 15,97 |
| Amlodipine | 5 | 6,60 | 8,49 | 6,59 | 7,67 | | 5,95 | |
| Valsartan | 160 | 137,50 | 12,40 | 9,40 | 12,81 | 25,67 | 9,71 | 19,97 |
| HCTZ | 12,5 | 19,10 | 14,93 | 11,90 | 12,86 | | 10,26 | |
| Valsartan | 160 | 137,50 | 12,40 | 9,40 | 12,81 | 20,48 | 9,71 | 15,66 |
| Amlodipine | 5 | 6,60 | 8,49 | 6,59 | 7,67 | | 5,95 | |
| Olmesartan | 40 | 25,70 | 11,90 | 9,02 | 13,22 | 29,07 | 10,02 | 22,66 |
| HCTZ | 25 | 19,10 | 14,93 | 11,90 | 15,85 | | 12,64 | |
| Olmesartan | 40 | 25,70 | 11,90 | 9,02 | 13,22 | 22,58 | 10,02 | 17,29 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Amlodipine** | **10** | **6,60** | **8,49** | **6,59** | **9,36** | | **7,27** | |
| **Lisinopril** | **20** | **17,60** | **4,26** | **3,13** | **4,38** | | **3,22** | |
| **HCTZ** | **12,5** | **19,10** | **14,93** | **11,90** | **12,86** | **24,91** | **10,26** | **19,43** |
| **Amlodipine** | **5** | **6,60** | **8,49** | **6,59** | **7,67** | | **5,95** | |
| **Lisinopril** | **20** | **17,60** | **4,26** | **3,13** | **4,38** | | **3,22** | |
| **HCTZ** | **12,5** | **19,10** | **14,93** | **11,90** | **12,86** | **26,60** | **10,26** | **20,75** |
| **Amlodipine** | **10** | **6,60** | **8,49** | **6,59** | **9,36** | | **7,27** | |
| **Enalapril** | **20** | **13,60** | **8,16** | **7,50** | **8,93** | | **8,21** | |
| **HCTZ** | **12,5** | **19,10** | **14,93** | **11,90** | **12,86** | **29,46** | **10,26** | **24,42** |
| **Amlodipine** | **5** | **6,60** | **8,49** | **6,59** | **7,67** | | **5,95** | |
| **Enalapril** | **20** | **13,60** | **8,16** | **7,50** | **8,93** | | **8,21** | |
| **HCTZ** | **12,5** | **19,10** | **14,93** | **11,90** | **12,86** | **31,15** | **10,26** | **25,74** |
| **Amlodipine** | **10** | **6,60** | **8,49** | **6,59** | **9,36** | | **7,27** | |
| **Olmesartan** | **40** | **25,70** | **11,90** | **9,02** | **13,22** | | **10,02** | |
| **Amlodipine** | **10** | **6,60** | **8,49** | **6,59** | **9,36** | **38,43** | **7,27** | **29,93** |
| **HCTZ** | **25** | **19,10** | **14,93** | **11,90** | **15,85** | | **12,64** | |
| **Olmesartan** | **40** | **25,70** | **11,90** | **9,02** | **13,22** | | **10,02** | |
| **Amlodipine** | **10** | **6,60** | **8,49** | **6,59** | **9,36** | **35,44** | **7,27** | **27,55** |
| **HCTZ** | **12,5** | **19,10** | **14,93** | **11,90** | **12,86** | | **10,26** | |
| **Olmesartan** | **40** | **25,70** | **11,90** | **9,02** | **13,22** | | **10,02** | |
| **Amlodipino** | **5** | **6,60** | **8,49** | **6,59** | **7,67** | **33,75** | **5,95** | **26,23** |
| **HCTZ** | **12,5** | **19,10** | **14,93** | **11,90** | **12,86** | | **10,26** | |
| **Valsartan** | **160** | **137,50** | **12,40** | **9,40** | **12,81** | | **9,71** | |
| **Amlodipine** | **5** | **6,60** | **8,49** | **6,59** | **7,67** | **33,34** | **5,95** | **25,92** |
| **HCTZ** | **12,5** | **19,10** | **14,93** | **11,90** | **12,86** | | **10,26** | |
| **Valsartan** | **160** | **137,50** | **12,40** | **9,40** | **12,81** | | **9,71** | |
| **Amlodipine** | **10** | **6,60** | **8,49** | **6,59** | **9,36** | **35,03** | **7,27** | **27,24** |
| **HCTZ** | **12,5** | **19,10** | **14,93** | **11,90** | **12,86** | | **10,26** | |

## Annex 4

**Table 44: Treatments cost analysis.**

| Active Ingredient | Dose (mg) | Cost per box (€) | | Nº of units | Cost x day (€) |
|---|---|---|---|---|---|
| Indapamide | 1,5 | 2,50 | | 30 | 0,08 |
| HCTZ | 25 | 2,34 | | 20 | 0,12 |
| Atenolol | 50 | 2,50 | | 30 | 0,08 |
| Atenolol | 100 | 4,93 | | 60 | 0,08 |
| Bisorpolol | 5 | 3,29 | | 60 | 0,05 |
| Bisorpolol | 10 | 6,57 | | 60 | 0,11 |
| Nevibolol | 5 | 7,88 | | 28 | 0,28 |
| Amlodipine | 5 | 1,25 | | 30 | 0,04 |
| Amlodipine | 10 | 2,50 | | 30 | 0,08 |
| Diltiazem | 240 | 12,19 | | 20 | 0,61 |
| Verapamil | 240 | 10,26 | | 30 | 0,34 |
| Enalapril | 10 | 2,50 | | 60 | 0,04 |
| Enalapril | 20 | 1,61 | | 28 | 0,06 |
| Lisinopril | 10 | 3,25 | | 60 | 0,05 |
| Lisinopril | 20 | 6,35 | | 28 | 0,23 |
| Ramipril | 5 | 4,84 | | 28 | 0,17 |
| Olmesartan | 20 | 24,82 | | 28 | 0,89 |
| Olmesartan | 40 | 33,64 | | 28 | 1,20 |
| Losartan | 50 | 4,17 | | 28 | 0,15 |
| Valsartan | 80 | 8,15 | | 28 | 0,29 |
| Valsartan | 160 | 16,30 | | 28 | 0,58 |
| Indapamide | 1,5 | 2,50 | 5,75 | 30 | 0,14 |
| Lisinopril | 10 | 3,25 | | 60 | |
| Valsartan | 80 | 8,15 | 10,65 | 28 | 0,37 |
| Amlodipine | 10 | 2,50 | | 30 | |
| Indapamide | 1,25 | 3,12 | 9,47 | 60 | 0,28 |
| Lisinopril | 20 | 6,35 | | 28 | |
| Indapamide | 1,5 | 2,50 | 7,34 | 30 | 0,26 |
| Ramipril | 5 | 4,84 | | 28 | |
| Indapamide | 1,5 | 2,50 | 5,00 | 30 | 0,13 |
| Enalapril | 10 | 2,50 | | 60 | |
| Indapamide | 1,25 | 3,12 | 5,62 | 60 | 0,09 |
| Enalapril | 10 | 2,50 | | 60 | |
| Lisinopril | 20 | 6,35 | 8,85 | 28 | 0,31 |
| Indapamide | 1,5 | 2,50 | | 30 | |
| Lisinopril | 10 | 3,25 | 5,59 | 60 | 0,17 |

| | | | | | |
|---|---|---|---|---|---|
| **HCTZ** | **25** | **2,34** | | **20** | |
| **Lisinopril** | **20** | **6,35** | **8,69** | **28** | **0,29** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **HCTZ** | **12,5** | **2,34** | **7,18** | **40** | **0,23** |
| **Ramipril** | **5** | **4,84** | | **28** | |
| **Amlodipine** | **10** | **2,50** | **5,75** | **30** | **0,14** |
| **Lisinopril** | **10** | **3,25** | | **60** | |
| **Lisinopril** | **20** | **6,35** | **7,60** | **28** | **0,27** |
| **Amlodipine** | **5** | **1,25** | | **30** | |
| **Lisinopril** | **20** | **6,35** | **8,85** | **28** | **0,31** |
| **Amlodipine** | **10** | **2,50** | | **30** | |
| **Ramipril** | **5** | **4,84** | **6,09** | **28** | **0,21** |
| **Amlodipine** | **5** | **1,25** | | **30** | |
| **Diltiazem** | **240** | **12,19** | **15,44** | **20** | **0,66** |
| **Lisinopril** | **10** | **3,25** | | **60** | |
| **Diltiazem** | **240** | **12,19** | **18,54** | **20** | **0,84** |
| **Lisinopril** | **20** | **6,35** | | **28** | |
| **Diltiazem** | **240** | **12,19** | **14,69** | **20** | **0,65** |
| **Enalapril** | **10** | **2,50** | | **60** | |
| **Olmesartan** | **20** | **24,82** | **27,16** | **28** | **0,94** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Olmesartan** | **20** | **24,82** | **26,07** | **28** | **0,93** |
| **Amlodipine** | **5** | **1,25** | | **30** | |
| **Losartan** | **50** | **4,17** | **6,51** | **28** | **0,21** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Valsartan** | **80** | **8,15** | **10,49** | **28** | **0,35** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Valsartan** | **80** | **8,15** | **9,40** | **28** | **0,33** |
| **Amlodipine** | **5** | **1,25** | | **30** | |
| **Valsartan** | **160** | **16,30** | **18,80** | **28** | **0,67** |
| **Amlodipine** | **10** | **2,50** | | **30** | |
| **Enalapril** | **20** | **1,61** | **4,73** | **28** | **0,11** |
| **Indapamide** | **1,25** | **3,12** | | **60** | |
| **Lisinopril** | **20** | **6,35** | **8,69** | **28** | **0,34** |
| **HCTZ** | **25** | **2,34** | | **20** | |
| **HCTZ** | **25** | **2,34** | **7,18** | **20** | **0,29** |
| **Ramipril** | **5** | **4,84** | | **28** | |
| **Enalapril** | **20** | **1,61** | **3,95** | **28** | **0,12** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Amlodipine** | **10** | **2,50** | **7,34** | **30** | **0,26** |
| **Ramipril** | **5** | **4,84** | | **28** | |

| | | | | | |
|---|---|---|---|---|---|
| **Enalapril** | **20** | **1,61** | **2,86** | **28** | **0,10** |
| **Amlodipine** | **5** | **1,25** | | **30** | |
| **Diltiazem** | **240** | **12,19** | **17,03** | **20** | **0,78** |
| **Ramipril** | **5** | **4,84** | | **28** | |
| **Enalapril** | **20** | **1,61** | **13,80** | **28** | **0,67** |
| **Diltiazem** | **240** | **12,19** | | **20** | |
| **Enalapril** | **20** | **1,61** | **4,11** | **28** | **0,14** |
| **Indapamide** | **1,5** | **2,50** | | **30** | |
| **Enalapril** | **20** | **1,61** | **4,11** | **28** | **0,14** |
| **Amlodipine** | **10** | **2,50** | | **30** | |
| **Olmesartan** | **20** | **24,82** | **27,16** | **28** | **1,00** |
| **HCTZ** | **25** | **2,34** | | **20** | |
| **Olmesartan** | **40** | **33,64** | **35,98** | **28** | **1,26** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Olmesartan** | **20** | **24,82** | **27,32** | **28** | **0,97** |
| **Amlodipine** | **10** | **2,50** | | **30** | |
| **Olmesartan** | **40** | **33,64** | **34,89** | **28** | **1,24** |
| **Amlodipine** | **5** | **1,25** | | **30** | |
| **Valsartan** | **160** | **16,30** | **18,64** | **28** | **0,64** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Valsartan** | **160** | **16,30** | **17,55** | **28** | **0,62** |
| **Amlodipine** | **5** | **1,25** | | **30** | |
| **Olmesartan** | **40** | **33,64** | **35,98** | **28** | **1,32** |
| **HCTZ** | **25** | **2,34** | | **20** | |
| **Olmesartan** | **40** | **33,64** | **36,14** | **28** | **1,28** |
| **Amlodipine** | **10** | **2,50** | | **30** | |
| **Lisinopril** | **20** | **6,35** | **9,94** | **28** | **0,33** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Amlodipine** | **5** | **1,25** | | **30** | |
| **Lisinopril** | **20** | **6,35** | **11,19** | **28** | **0,37** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Amlodipine** | **10** | **2,5** | | **30** | |
| **Enalapril** | **20** | **1,61** | **5,20** | **28** | **0,16** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Amlodipine** | **5** | **1,25** | | **30** | |
| **Enalapril** | **20** | **1,61** | **6,45** | **28** | **0,20** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Amlodipine** | **10** | **2,5** | | **30** | |
| **Olmesartan** | **40** | **33,64** | **38,48** | **28** | **1,40** |
| **Amlodipine** | **10** | **2,5** | | **30** | |
| **HCTZ** | **25** | **2,34** | | **20** | |

| | | | | | |
|---|---|---|---|---|---|
| **Olmesartan** | **40** | **33,64** | | **28** | |
| **Amlodipine** | **10** | **2,5** | **38,48** | **30** | **1,34** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Olmesartan** | **40** | **33,64** | | **28** | |
| **Amlodipine** | **5** | **1,25** | **37,23** | **30** | **1,30** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Valsartan** | **160** | **16,3** | | **28** | |
| **Amlodipine** | **5** | **1,25** | **19,89** | **30** | **0,68** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |
| **Valsartan** | **160** | **16,3** | | **28** | |
| **Amlodipine** | **10** | **2,5** | **21,14** | **30** | **0,72** |
| **HCTZ** | **12,5** | **2,34** | | **40** | |

## Annex 5

**Table 45: Active ingredients analysis.**

| Active Ingredient | Dose (mg) | Cost per day (€) | Systolic BP reduction (mmHg) | Diastolic BP Reduction (mmHg) |
|---|---|---|---|---|
| Indapamide | 1,5 | 0,08 | 8,89 | 6,00 |
| HCTZ | 25 | 0,12 | 15,85 | 12,64 |
| Atenolol | 50 | 0,08 | 11,25 | 7,27 |
| Atenolol | 100 | 0,07 | 13,65 | 8,82 |
| Bisorpolol | 5 | 0,05 | 10,59 | 7,31 |
| Bisorpolol | 10 | 0,11 | 12,95 | 8,94 |
| Nevibolol | 5 | 0,28 | 14,96 | 10,40 |
| Amlodipine | 5 | 0,04 | 7,67 | 5,95 |
| Amlodipine | 10 | 0,08 | 9,36 | 7,27 |
| Diltiazem | 240 | 0,61 | 18,24 | 12,69 |
| Verapamil | 240 | 0,34 | 6,56 | 6,56 |
| Enalapril | 10 | 0,04 | 7,30 | 6,71 |
| Enalapril | 20 | 0,06 | 8,93 | 8,21 |
| Lisinopril | 10 | 0,05 | 3,52 | 2,59 |
| Lisinopril | 20 | 0,23 | 4,38 | 3,22 |
| Ramipril | 5 | 0,17 | 10,17 | 7,80 |
| Olmesartan | 20 | 0,89 | 10,84 | 8,22 |
| Olmesartan | 40 | 1,2 | 13,22 | 10,02 |
| Losartan | 50 | 0,15 | 10,67 | 8,37 |
| Valsartan | 80 | 0,29 | 10,33 | 7,83 |
| Valsartan | 160 | 0,58 | 12,81 | 9,71 |
| Indapamide | 1,5 | 0,14 | 12,41 | 8,59 |
| Lisinopril | 10 | | | |
| Valsartan | 80 | 0,37 | 19,69 | 15,10 |
| Amlodipine | 10 | | | |
| Indapamide | 1,25 | 0,28 | 12,76 | 8,87 |
| Lisinopril | 20 | | | |
| Indapamide | 1,5 | 0,26 | 19,06 | 13,80 |
| Ramipril | 5 | | | |
| Indapamide | 1,5 | 0,13 | 16,19 | 12,71 |
| Enalapril | 10 | | | |
| Indapamide | 1,25 | 0,09 | 15,68 | 12,36 |
| Enalapril | 10 | | | |
| Lisinopril | 20 | 0,31 | 13,27 | 9,22 |
| Indapamide | 1,5 | | | |
| Lisinopril | 10 | 0,17 | 19,37 | 15,23 |

| | | | | |
|---|---|---|---|---|
| **HCTZ** | **25** | | | |
| **Lisinopril** | **20** | **0,29** | **17,24** | **13,48** |
| **HCTZ** | **12,5** | | | |
| **HCTZ** | **12,5** | **0,23** | **23,03** | **18,06** |
| **Ramipril** | **5** | | | |
| **Amlodipine** | **10** | **0,14** | **12,88** | **9,86** |
| **Lisinopril** | **10** | | | |
| **Lisinopril** | **20** | **0,27** | **12,05** | **9,17** |
| **Amlodipine** | **5** | | | |
| **Lisinopril** | **20** | **0,31** | **13,74** | **10,49** |
| **Amlodipine** | **10** | | | |
| **Ramipril** | **5** | **0,21** | **17,84** | **13,75** |
| **Amlodipine** | **5** | | | |
| **Diltiazem** | **240** | **0,67** | **21,76** | **15,28** |
| **Lisinopril** | **10** | | | |
| **Diltiazem** | **240** | **0,84** | **22,62** | **15,91** |
| **Lisinopril** | **20** | | | |
| **Diltiazem** | **240** | **0,65** | **25,54** | **19,40** |
| **Enalapril** | **10** | | | |
| **Olmesartan** | **20** | **0,94** | **23,70** | **18,48** |
| **HCTZ** | **12,5** | | | |
| **Olmesartan** | **20** | **0,93** | **18,51** | **14,17** |
| **Amlodipine** | **5** | | | |
| **Losartan** | **50** | **0,21** | **23,53** | **18,63** |
| **HCTZ** | **12,5** | | | |
| **Valsartan** | **80** | **0,35** | **23,19** | **18,09** |
| **HCTZ** | **12,5** | | | |
| **Valsartan** | **80** | **0,33** | **18,00** | **13,78** |
| **Amlodipine** | **5** | | | |
| **Valsartan** | **160** | **0,67** | **22,17** | **16,98** |
| **Amlodipine** | **10** | | | |
| **Enalapril** | **20** | **0,11** | **17,31** | **13,86** |
| **Indapamide** | **1,25** | | | |
| **Lisinopril** | **20** | **0,34** | **20,23** | **15,86** |
| **HCTZ** | **25** | | | |
| **HCTZ** | **25** | **0,29** | **26,02** | **20,44** |
| **Ramipril** | **5** | | | |
| **Enalapril** | **20** | **0,12** | **21,79** | **18,47** |
| **HCTZ** | **12,5** | | | |
| **Amlodipinde** | **10** | **0,26** | **19,53** | **15,07** |
| **Ramipril** | **5** | | | |

| | | | | |
|---|---|---|---|---|
| **Enalapril** | **20** | **0,10** | **16,60** | **14,16** |
| **Amlodipinde** | **5** | | | |
| **Diltiazem** | **240** | **0,78** | **28,41** | **20,49** |
| **Ramipril** | **5** | | | |
| **Enalapril** | **20** | **0,67** | **27,17** | **20,90** |
| **Diltiazem** | **240** | | | |
| **Enalapril** | **20** | **0,14** | **17,82** | **14,21** |
| **Indapamide** | **1,5** | | | |
| **Enalapril** | **20** | **0,14** | **18,29** | **15,48** |
| **Amlodipine** | **10** | | | |
| **Olmesartan** | **20** | **1,00** | **26,69** | **20,86** |
| **HCTZ** | **25** | | | |
| **Olmesartan** | **40** | **1,26** | **26,08** | **20,28** |
| **HCTZ** | **12,5** | | | |
| **Olmesartan** | **20** | **0,97** | **20,20** | **15,49** |
| **Amlodipine** | **10** | | | |
| **Olmesartan** | **40** | **1,24** | **20,89** | **15,97** |
| **Amlodipine** | **5** | | | |
| **Valsartan** | **160** | **0,64** | **25,67** | **19,97** |
| **HCTZ** | **12,5** | | | |
| **Valsartan** | **160** | **0,62** | **20,48** | **15,66** |
| **Amlodipine** | **5** | | | |
| **Olmesartan** | **40** | **1,32** | **29,07** | **22,66** |
| **HCTZ** | **25** | | | |
| **Olmesartan** | **40** | **1,28** | **22,58** | **17,29** |
| **Amlodipine** | **10** | | | |
| **Lisinopril** | **20** | **0,33** | **24,91** | **19,43** |
| **HCTZ** | **12,5** | | | |
| **Amlodipine** | **5** | | | |
| **Lisinopril** | **20** | **0,37** | **26,60** | **20,75** |
| **HCTZ** | **12,5** | | | |
| **Amlodipine** | **10** | | | |
| **Enalapril** | **20** | **0,16** | **29,46** | **24,42** |
| **HCTZ** | **12,5** | | | |
| **Amlodipine** | **5** | | | |
| **Enalapril** | **20** | **0,20** | **31,15** | **25,74** |
| **HCTZ** | **12,5** | | | |
| **Amlodipine** | **10** | | | |
| **Olmesartan** | **40** | **1,40** | **38,43** | **29,93** |
| **Amlodipine** | **10** | | | |
| **HCTZ** | **25** | | | |

| | | | | |
|---|---|---|---|---|
| **Olmesartan** | **40** | **1,34** | **35,44** | **27,55** |
| **Amlodipine** | **10** | | | |
| **HCTZ** | **12,5** | | | |
| **Olmesartan** | **40** | **1,30** | **33,75** | **26,23** |
| **Amlodipino** | **5** | | | |
| **HCTZ** | **12,5** | | | |
| **Valsartan** | **160** | **0,68** | **33,34** | **25,92** |
| **Amlodipine** | **5** | | | |
| **HCTZ** | **12,5** | | | |
| **Valsartan** | **160** | **0,72** | **35,03** | **27,24** |
| **Amlodipine** | **10** | | | |
| **HCTZ** | **12,5** | | | |

## Annex 6

**Table 46: SBP reduction at intervals.**

| Active Ingredient | Dose (mg) | Systolic blood pressure reduction (mmHg) | | | | |
|---|---|---|---|---|---|---|
| | | ≤10,00 | 10,01-15,00 | 15,01-20,00 | 20,01-25,00 | >25,00 |
| Lisinopril | 20 | 4,38 | | | | |
| Verapamil | 240 | 6,56 | | | | |
| Enalapril | 10 | 7,30 | | | | |
| Amlodipine | 5 | 7,67 | | | | |
| Indapamide | 1,5 | 8,89 | | | | |
| Enalapril | 20 | 8,93 | | | | |
| Amlodipine | 10 | 9,36 | | | | |
| Ramipril | 5 | | 10,17 | | | |
| Valsartan | 80 | | 10,33 | | | |
| Bisorpolol | 5 | | 10,59 | | | |
| Losartan | 50 | | 10,67 | | | |
| Olmesartan | 20 | | 10,84 | | | |
| Atenolol | 50 | | 11,25 | | | |
| Lisinopril | 20 | | 12,05 | | | |
| Amlodipine | 5 | | | | | |
| Indapamide | 1,25 | | 12,76 | | | |
| Lisinopril | 20 | | | | | |
| Valsartan | 160 | | 12,81 | | | |
| Bisorpolol | 10 | | 12,95 | | | |
| Olmesartan | 40 | | 13,22 | | | |
| Lisinopril | 20 | | 13,27 | | | |
| Indapamide | 1,5 | | | | | |
| Atenolol | 100 | | 13,65 | | | |
| Lisinopril | 20 | | 13,74 | | | |
| Amlodipine | 10 | | | | | |
| Nevibolol | 5 | | 14,96 | | | |
| HCTZ | 25 | | | 15,85 | | |
| Enalapril | 20 | | | 16,60 | | |
| Amlodipinde | 5 | | | | | |
| Lisinopril | 20 | | | 17,24 | | |
| HCTZ | 12,5 | | | | | |
| Enalapril | 20 | | | 17,31 | | |
| Indapamide | 1,25 | | | | | |
| Enalapril | 20 | | | 17,82 | | |
| Indapamide | 1,5 | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Ramipril** | **5** | | | **17,84** | | |
| **Amlodipine** | **5** | | | | | |
| **Diltiazem** | **240** | | | **18,24** | | |
| **Enalapril** | **20** | | | **18,29** | | |
| **Amlodipine** | **10** | | | | | |
| **Olmesartan** | **20** | | | **18,51** | | |
| **Amlodipine** | **5** | | | | | |
| **Indapamide** | **1,5** | | | **19,06** | | |
| **Ramipril** | **5** | | | | | |
| **Amlodipinde** | **10** | | | **19,53** | | |
| **Ramipril** | **5** | | | | | |
| **Olmesartan** | **20** | | | | **20,20** | |
| **Amlodipine** | **10** | | | | | |
| **Lisinopril** | **20** | | | | **20,23** | |
| **HCTZ** | **25** | | | | | |
| **Valsartan** | **160** | | | | **20,48** | |
| **Amlodipine** | **5** | | | | | |
| **Olmesartan** | **40** | | | | **20,89** | |
| **Amlodipine** | **5** | | | | | |
| **Enalapril** | **20** | | | | **21,79** | |
| **HCTZ** | **12,5** | | | | | |
| **Valsartan** | **160** | | | | **22,17** | |
| **Amlodipine** | **10** | | | | | |
| **Olmesartan** | **40** | | | | **22,58** | |
| **Amlodipine** | **10** | | | | | |
| **Diltiazem** | **240** | | | | **22,62** | |
| **Lisinopril** | **20** | | | | | |
| **HCTZ** | **12,5** | | | | **23,03** | |
| **Ramipril** | **5** | | | | | |
| **Losartan** | **50** | | | | **23,53** | |
| **HCTZ** | **12,5** | | | | | |
| **Olmesartan** | **20** | | | | **23,70** | |
| **HCTZ** | **12,5** | | | | | |
| **Lisinopril** | **20** | | | | **24,91** | |
| **HCTZ** | **12,5** | | | | | |
| **Amlodipine** | **5** | | | | | |
| **Valsartan** | **160** | | | | | **25,67** |
| **HCTZ** | **12,5** | | | | | |
| **HCTZ** | **25** | | | | | **26,02** |
| **Ramipril** | **5** | | | | | |
| **Olmesartan** | **40** | | | | | **26,08** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **HCTZ** | **12,5** | | | | | |
| **Lisinopril** | **20** | | | | | |
| **HCTZ** | **12,5** | | | | | **26,60** |
| **Amlodipine** | **10** | | | | | |
| **Olmesartan** | **20** | | | | | |
| **HCTZ** | **25** | | | | | **26,69** |
| **Enalapril** | **20** | | | | | |
| **Diltiazem** | **240** | | | | | **27,17** |
| **Diltiazem** | **240** | | | | | |
| **Ramipril** | **5** | | | | | **28,41** |
| **Olmesartan** | **40** | | | | | |
| **HCTZ** | **25** | | | | | **29,07** |
| **Enalapril** | **20** | | | | | |
| **HCTZ** | **12,5** | | | | | **29,46** |
| **Amlodipine** | **5** | | | | | |
| **Enalapril** | **20** | | | | | |
| **HCTZ** | **12,5** | | | | | **31,15** |
| **Amlodipine** | **10** | | | | | |
| **Valsartan** | **160** | | | | | |
| **Amlodipine** | **5** | | | | | **33,34** |
| **HCTZ** | **12,5** | | | | | |
| **Olmesartan** | **40** | | | | | |
| **Amlodipino** | **5** | | | | | **33,75** |
| **HCTZ** | **12,5** | | | | | |
| **Valsartan** | **160** | | | | | |
| **Amlodipine** | **10** | | | | | **35,03** |
| **HCTZ** | **12,5** | | | | | |
| **Olmesartan** | **40** | | | | | |
| **Amlodipine** | **10** | | | | | **35,44** |
| **HCTZ** | **12,5** | | | | | |
| **Olmesartan** | **40** | | | | | |
| **Amlodipine** | **10** | | | | | **38,43** |
| **HCTZ** | **25** | | | | | |

## Annex 7

**Table 47: DBP reductions at intervals.**

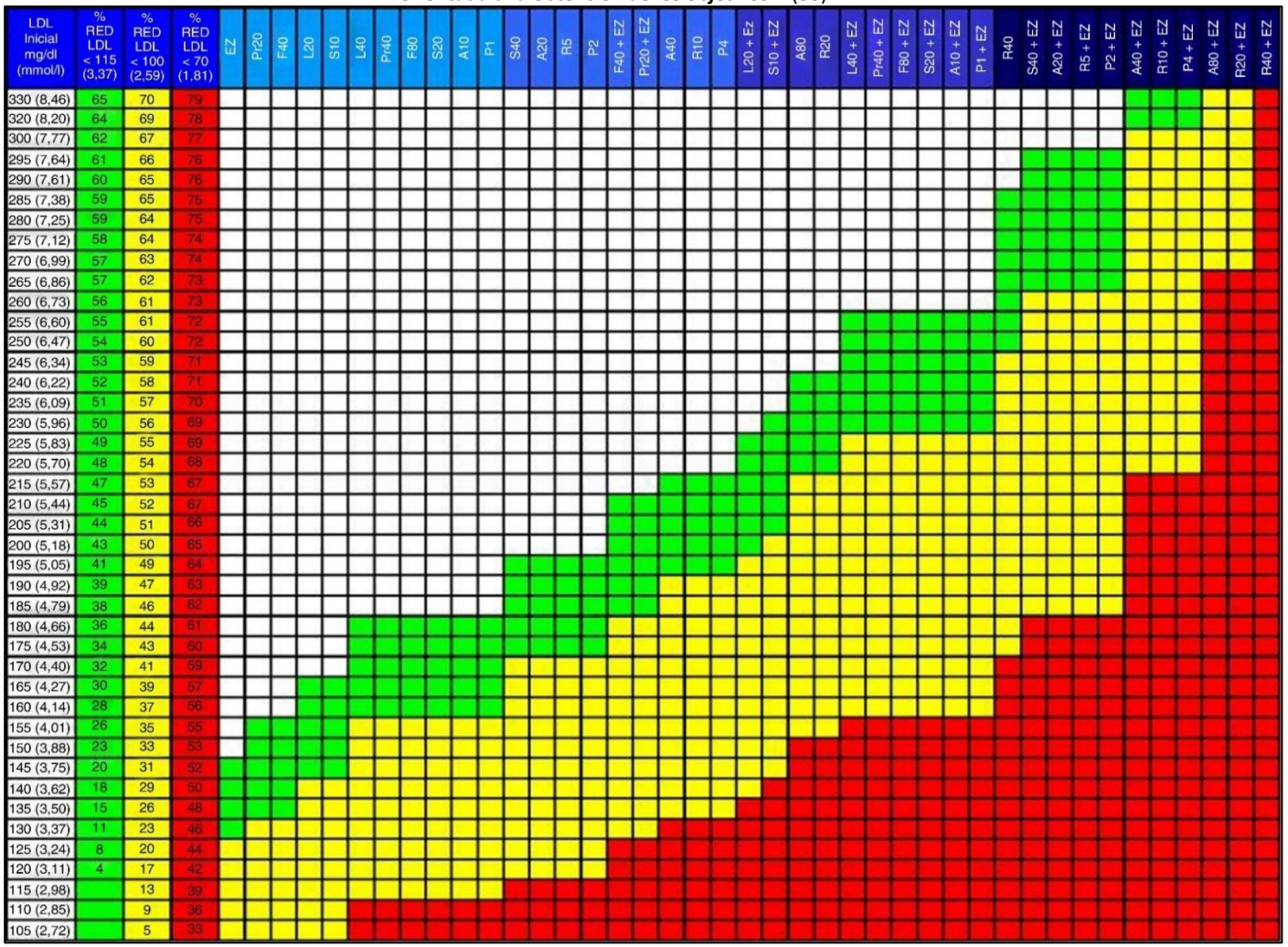
| Active Ingredient | Dose (mg) | Diastolic blood pressure reduction (mmHg) | | | |
|---|---|---|---|---|---|
| | | ≤10,00 | 10,01-15,00 | 15,01-20,00 | >20,00 |
| Lisinopril | 20 | 3,22 | | | |
| Amlodipine | 5 | 5,95 | | | |
| Indapamide | 1,5 | 6,00 | | | |
| Verapamil | 240 | 6,56 | | | |
| Enalapril | 10 | 6,71 | | | |
| Atenolol | 50 | 7,27 | | | |
| Amlodipine | 10 | 7,27 | | | |
| Bisorpolol | 5 | 7,31 | | | |
| Ramipril | 5 | 7,80 | | | |
| Valsartan | 80 | 7,83 | | | |
| Enalapril | 20 | 8,21 | | | |
| Olmesartan | 20 | 8,22 | | | |
| Losartan | 50 | 8,37 | | | |
| Atenolol | 100 | 8,82 | | | |
| Indapamide | 1,25 | 8,87 | | | |
| Lisinopril | 20 | | | | |
| Bisorpolol | 10 | 8,94 | | | |
| Lisinopril | 20 | 9,17 | | | |
| Amlodipine | 5 | | | | |
| Lisinopril | 20 | 9,22 | | | |
| Indapamide | 1,5 | | | | |
| Valsartan | 160 | 9,71 | | | |
| Olmesartan | 40 | | 10,02 | | |
| Nevibolol | 5 | | 10,40 | | |
| Lisinopril | 20 | | 10,49 | | |
| Amlodipine | 10 | | | | |
| HCTZ | 25 | | 12,64 | | |
| Diltiazem | 240 | | 12,69 | | |
| Lisinopril | 20 | | 13,48 | | |
| HCTZ | 12,5 | | | | |
| Ramipril | 5 | | 13,75 | | |
| Amlodipine | 5 | | | | |
| Indapamide | 1,5 | | 13,80 | | |
| Ramipril | 5 | | | | |
| Enalapril | 20 | | 13,86 | | |

| | | | | | |
|---|---|---|---|---|---|
| **Indapamide** | **1,25** | | | | |
| **Enalapril** | **20** | | **14,16** | | |
| **Amlodipinde** | **5** | | | | |
| **Olmesartan** | **20** | | **14,17** | | |
| **Amlodipine** | **5** | | | | |
| **Enalapril** | **20** | | **14,21** | | |
| **Indapamide** | **1,5** | | | | |
| **Amlodipinde** | **10** | | | **15,07** | |
| **Ramipril** | **5** | | | | |
| **Enalapril** | **20** | | | **15,48** | |
| **Amlodipine** | **10** | | | | |
| **Olmesartan** | **20** | | | **15,49** | |
| **Amlodipine** | **10** | | | | |
| **Valsartan** | **160** | | | **15,66** | |
| **Amlodipine** | **5** | | | | |
| **Lisinopril** | **20** | | | **15,86** | |
| **HCTZ** | **25** | | | | |
| **Diltiazem** | **240** | | | **15,91** | |
| **Lisinopril** | **20** | | | | |
| **Olmesartan** | **40** | | | **15,97** | |
| **Amlodipine** | **5** | | | | |
| **Valsartan** | **160** | | | **16,98** | |
| **Amlodipine** | **10** | | | | |
| **Olmesartan** | **40** | | | **17,29** | |
| **Amlodipine** | **10** | | | | |
| **HCTZ** | **12,5** | | | **18,06** | |
| **Ramipril** | **5** | | | | |
| **Enalapril** | **20** | | | **18,47** | |
| **HCTZ** | **12,5** | | | | |
| **Olmesartan** | **20** | | | **18,48** | |
| **HCTZ** | **12,5** | | | | |
| **Losartan** | **50** | | | **18,63** | |
| **HCTZ** | **12,5** | | | | |
| **Lisinopril** | **20** | | | **19,43** | |
| **HCTZ** | **12,5** | | | | |
| **Amlodipine** | **5** | | | | |
| **Valsartan** | **160** | | | **19,97** | |
| **HCTZ** | **12,5** | | | | |
| **Olmesartan** | **40** | | | | **20,28** |
| **HCTZ** | **12,5** | | | | |
| **HCTZ** | **25** | | | | **20,44** |

| | | | | | |
|---|---|---|---|---|---|
| **Ramipril** | **5** | | | | |
| **Diltiazem** | **240** | | | | **20,49** |
| **Ramipril** | **5** | | | | |
| **Lisinopril** | **20** | | | | **20,75** |
| **HCTZ** | **12,5** | | | | |
| **Amlodipine** | **10** | | | | |
| **Olmesartan** | **20** | | | | **20,86** |
| **HCTZ** | **25** | | | | |
| **Enalapril** | **20** | | | | **20,90** |
| **Diltiazem** | **240** | | | | |
| **Olmesartan** | **40** | | | | **22,66** |
| **HCTZ** | **25** | | | | |
| **Enalapril** | **20** | | | | **24,42** |
| **HCTZ** | **12,5** | | | | |
| **Amlodipine** | **5** | | | | |
| **Enalapril** | **20** | | | | **25,74** |
| **HCTZ** | **12,5** | | | | |
| **Amlodipine** | **10** | | | | |
| **Valsartan** | **160** | | | | **25,92** |
| **Amlodipine** | **5** | | | | |
| **HCTZ** | **12,5** | | | | |
| **Olmesartan** | **40** | | | | **26,23** |
| **Amlodipino** | **5** | | | | |
| **HCTZ** | **12,5** | | | | |
| **Valsartan** | **160** | | | | **27,24** |
| **Amlodipine** | **10** | | | | |
| **HCTZ** | **12,5** | | | | |
| **Olmesartan** | **40** | | | | **27,55** |
| **Amlodipine** | **10** | | | | |
| **HCTZ** | **12,5** | | | | |
| **Olmesartan** | **40** | | | | **29,93** |
| **Amlodipine** | **10** | | | | |
| **HCTZ** | **25** | | | | |

## Annex 8

**Table 48: Massana's Table. From *"Masana L. Actualización de las tablas de planificación terapéutica hipocolesterolemiante orientada a la obtención de los objetivos."*** (38)



## Annex 9

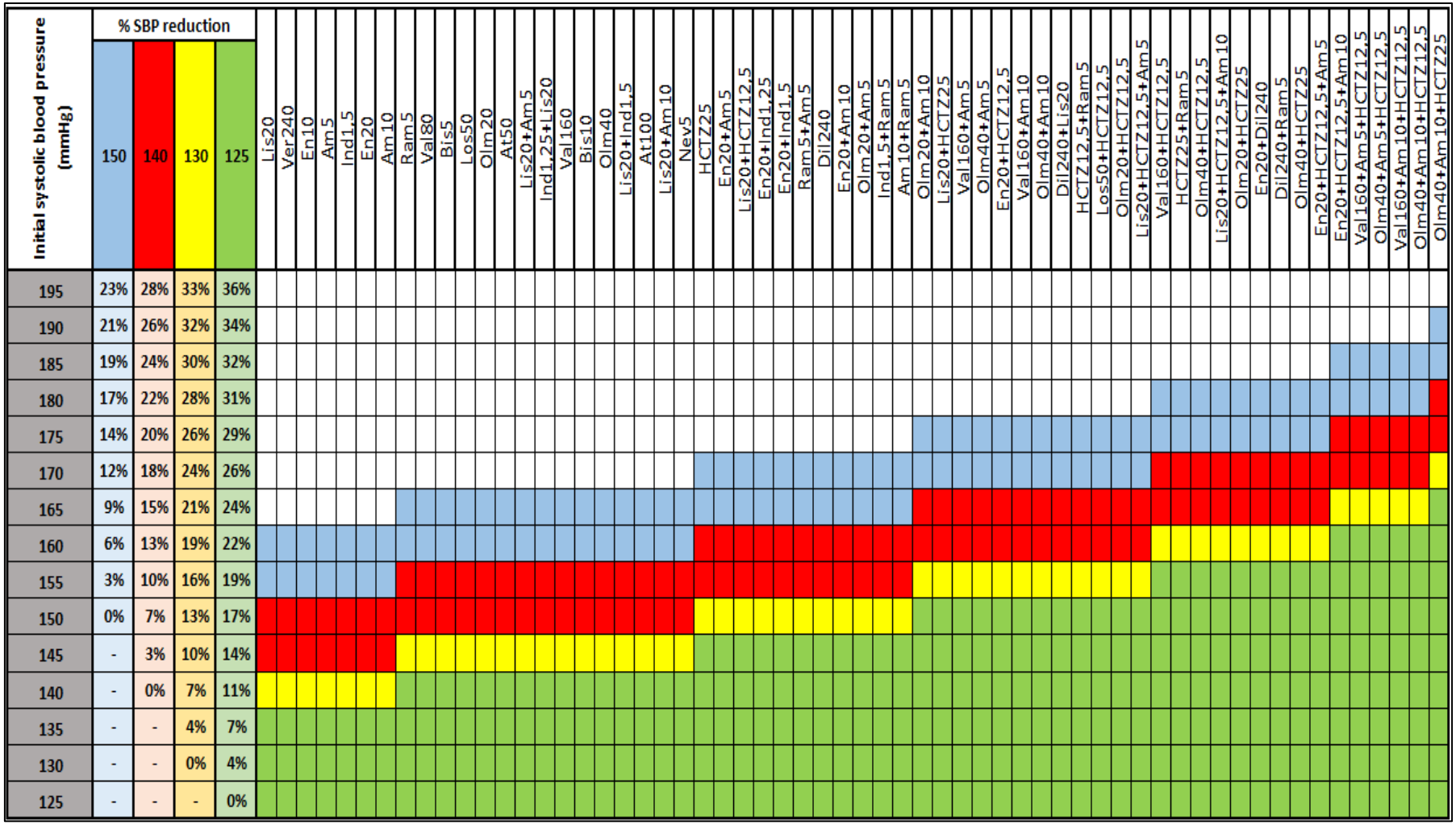
**Table 49: Abbreviations of the efficiency and effectiveness study tables.**

| | |
|---|---|
| Ver240 | Verapamil 240 |
| En10 | Enalapril 10 |
| Am5 | Amlodipine 5 |
| Lis20 | Lisinopril 20 |
| Ind1,5 | Indapamide 1,5 |
| Val80 | Valsartan 80 |
| Ram5 | Ramipril 5 |
| Bis5 | Bisorpolol 5 |
| Los50 | Losartan 50 |
| Olm20 | Olmesartan 20 |
| At50 | Atenolol 50 |
| Val160 | Valsartan 160 |
| Dil240 | Diltiazem 240 |
| En20 | Enalapril 20 |
| Am10 | Amlodipine 10 |
| HCTZ25 | Hydrochlorothiazide 25 |
| Nev5 | Nevibolol 5 |
| At100 | Atenolol 100 |
| Ind1,25+Lis20 | Indapamide 1,25 + Lisinopril 20 |
| Lis20+Am5 | Lisinopril 20 + Amlodipine 5 |
| Olm40 | Olmesartan 40 |
| Lis20+Ind1,5 | Lisinopril 20 + Indapamide 1,5 |
| Bis10 | Bisorpolol 10 |
| Lis20+HCTZ12,5 | Lisinopril 20 + Hydrochlorothiazide 12,5 |
| Ram5+Am5 | Ramipril 5 + Amlodipine 5 |
| Olm20+Am5 | Olmesartan 20 + Amlodipine 5 |
| En20+Ind1,25 | Enalapril 20 + Indapamide 1,25 |
| Val160+Am5 | Valsartan 160 + Amlodipine 5 |
| Ind1,5+Ram5 | Indapamide 1,5 + Ramipril 5 |
| En20+Am5 | Enalapril 20 + Amlodipine 5 |
| Dil240+Lis20 | Diltiazem 240 + Lisinopril 20 |
| Lis20+Am10 | Lisinopril 20 + Amlodipine 10 |
| HCTZ12,5+Ram5 | Hydrochlorothiazide 12,5 + Ramipril 5 |
| Lis20+HCTZ25 | Lisinopril 20 + Hydrochlorothiazide 25 |
| Los50+HCTZ12,5 | Losartan 50 + Hydrochlorothiazide 12,5 |
| Olm20+HCTZ12,5 | Olmesartan 20 + Hydrochlorothiazide 12,5 |
| En20+Ind1,5 | Enalapril 20 + Indapamide 1,5 |

| | |
|---|---|
| Val160+HCTZ12,5 | Valsartan 160 + Hydrochlorothiazide 12,5 |
| En20+HCTZ12,5 | Enalapril 20 + Hydrochlorothiazide 12,5 |
| Dil240+Ram5 | Diltiazem 240 + Ramipril 5 |
| Am10+Ram5 | Amlodipine 10 + Ramipril 5 |
| HCTZ25+Ram5 | Hydrochlorothiazide 25 + Ramipril 5 |
| Olm20+Am10 | Olmesartan 20 + Amlodipine 10 |
| Olm20+HCTZ25 | Olmesartan 20 + Hydrochlorothiazide 25 |
| Val160+Am10 | Valsartan 160 + Amlodipine 10 |
| En20+Dil240 | Enalapril 20 + Diltiazem 240 |
| Olm40+Am5 | Olmesartan 40 + Amlodipine 5 |
| En20+Am10 | Enalapril 20 + Amlodipine 10 |
| Lis20+HCTZ12,5+Am5 | Lisinopril 20 + Hydrochlorothiazide 12,5 + Amlodipine 5 |
| Olm40+HCTZ12,5 | Olmesartan 40 + Hydrochlorothiazide 12,5 |
| Olm40+Am10 | Olmesartan 40 + Amlodipine 10 |
| Olm40+HCTZ25 | Olmesartan 40 + Hydrochlorothiazide 25 |
| Val160+Am5+HCTZ12,5 | Valsartan 160 + Amlodipine 5 + Hydrochlorothiazide 12,5 |
| En20+HCTZ12,5+Am5 | Enalapril 20 + Hydrochlorothiazide 12,5 + Amlodipine 5 |
| Lis20+HCTZ12,5+Am10 | Lisinopril 20 + Hydrochlorothiazide 12,5 + Amlodipine 10 |
| Val160+Am10+HCTZ12,5 | Valsartan 160 + Amlodipine 10 + Hydrochlorothiazide 12,5 |
| Olm40+Am5+HCTZ12,5 | Olmesartan 40 + Amlodipine 5 + Hydrochlorothiazide 12,5 |
| En20+HCTZ12,5+Am10 | Enalapril 20 + Hydrochlorothiazide 12,5 + Amlodipine 10 |
| Olm40+Am10+HCTZ12,5 | Olmesartan 40 + Amlodipine 10 + Hydrochlorothiazide 12,5 |
| Olm40+Am10+HCTZ25 | Olmesartan 40 + Amlodipine 10 + Hydrochlorothiazide 25 |

## Annex 10

**Table 50: SBP effectiveness table. BP reduction (%).**

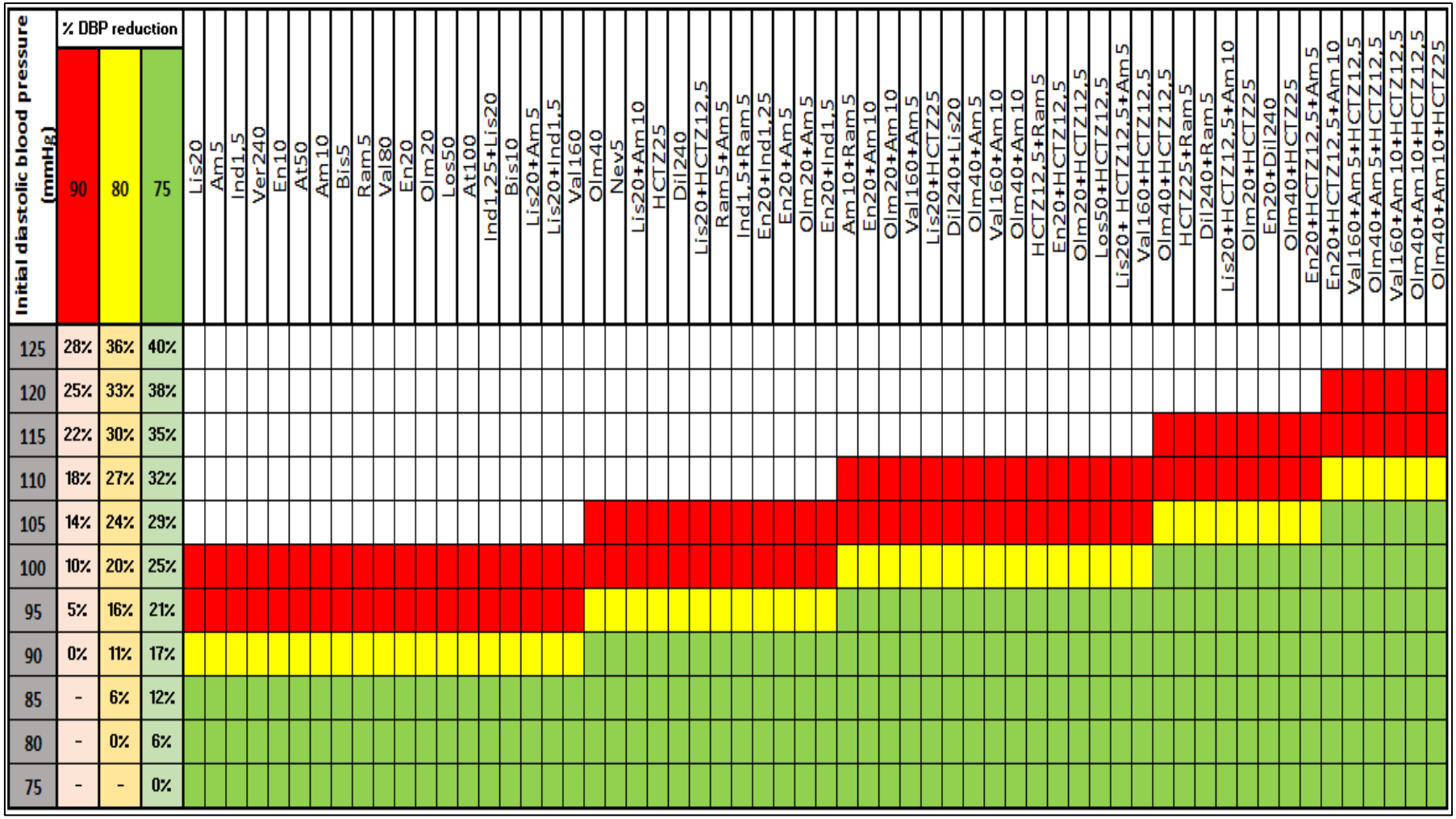


| Initial systolic blood pressure (mmHg) | % SBP reduction | | | |
|---|---|---|---|---|
| | 150 | 140 | 130 | 125 |
| 195 | 23% | 28% | 33% | 36% |
| 190 | 21% | 26% | 32% | 34% |
| 185 | 19% | 24% | 30% | 32% |
| 180 | 17% | 22% | 28% | 31% |
| 175 | 14% | 20% | 26% | 29% |
| 170 | 12% | 18% | 24% | 26% |
| 165 | 9% | 15% | 21% | 24% |
| 160 | 6% | 13% | 19% | 22% |
| 155 | 3% | 10% | 16% | 19% |
| 150 | 0% | 7% | 13% | 17% |
| 145 | - | 3% | 10% | 14% |
| 140 | - | 0% | 7% | 11% |
| 135 | - | - | 4% | 7% |
| 130 | - | - | 0% | 4% |
| 125 | - | - | - | 0% |

Lis20, Ver240, En10, Am5, Ind1,5, En20, Am10, Ram5, Val80, Bis5, Los50, Olm20, At50, Lis20+Am5, Ind1,25+Lis20, Val160, Bis10, Olm40, Lis20+Ind1,5, At100, Lis20+Am10, Nev5, HCTZ25, En20+Am5, Lis20+HCTZ12,5, En20+Ind1,25, En20+Ind1,5, Ram5+Am5, Dil240, En20+Am10, Olm20+Am5, Ind1,5+Ram5, Am10+Ram5, Olm20+Am10, Lis20+HCTZ25, Val160+Am5, Olm40+Am5, En20+HCTZ12,5, Val160+Am10, Olm40+Am10, Dil240+Lis20, HCTZ12,5+Ram5, Los50+HCTZ12,5, Olm20+HCTZ12,5, Lis20+HCTZ12,5+Am5, Val160+HCTZ12,5, HCTZ25+Ram5, Olm40+HCTZ12,5, Lis20+HCTZ12,5+Am10, Olm20+HCTZ25, En20+Dil240, Dil240+Ram5, Olm40+HCTZ25, En20+HCTZ12,5+Am5, En20+HCTZ12,5+Am10, Val160+Am5+HCTZ12,5, Olm40+Am5+HCTZ12,5, Val160+Am10+HCTZ12,5, Olm40+Am10+HCTZ12,5, Olm40+Am10+HCTZ25

## Annex 11

**Table 51: DBP effectiveness table. BP reduction (%).**



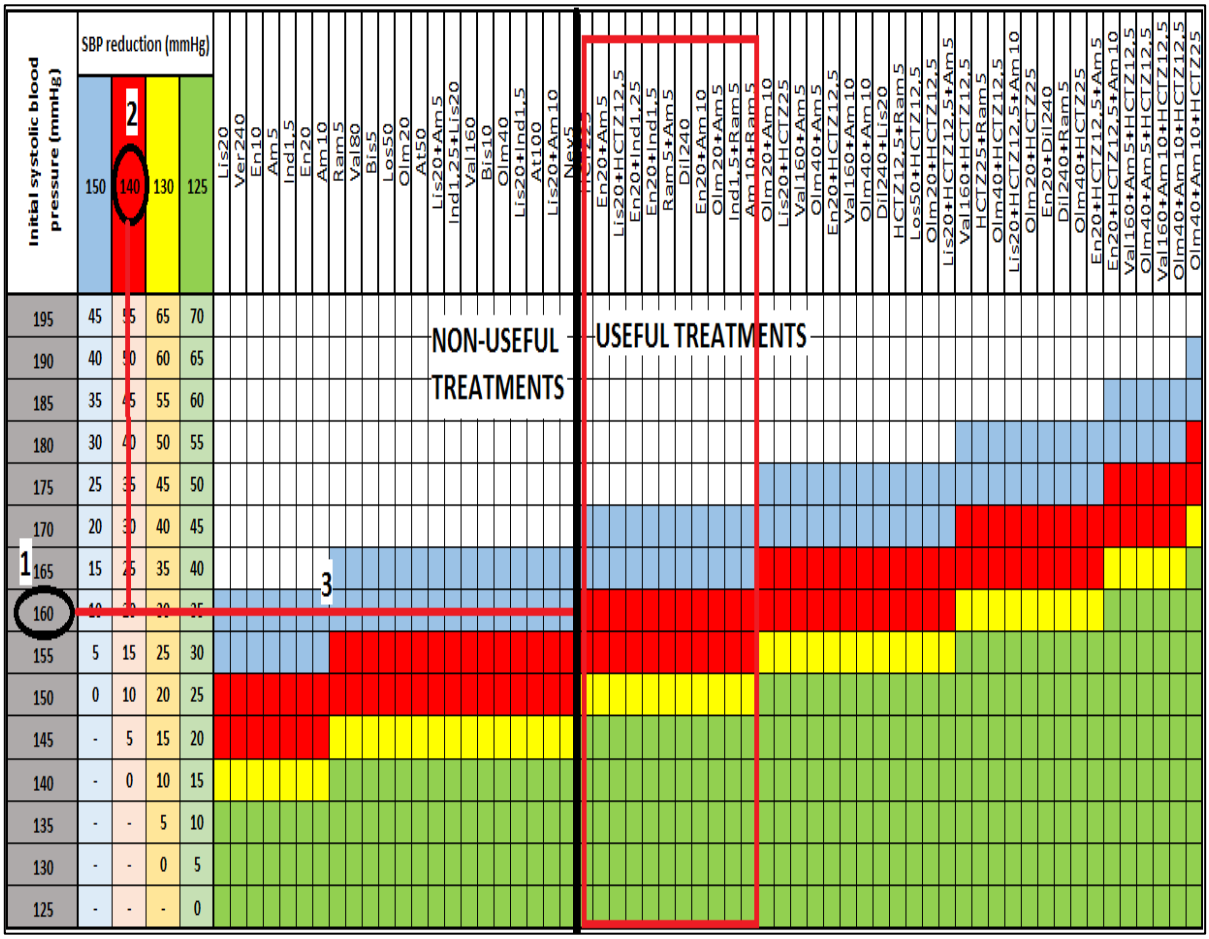
## Annex 12

To understand the procedure better, see following examples:

Patient 1 (***Table 52***):

- 55 years.
- No history of interest.
- No associated diseases.
- BP target value: <140/90 mmHg.
- Pre-treatment BP value: 158/85 mmHg.
- SBP reduction: 18 mmHg. SBP interval: 15,01-20,00 mmHg.

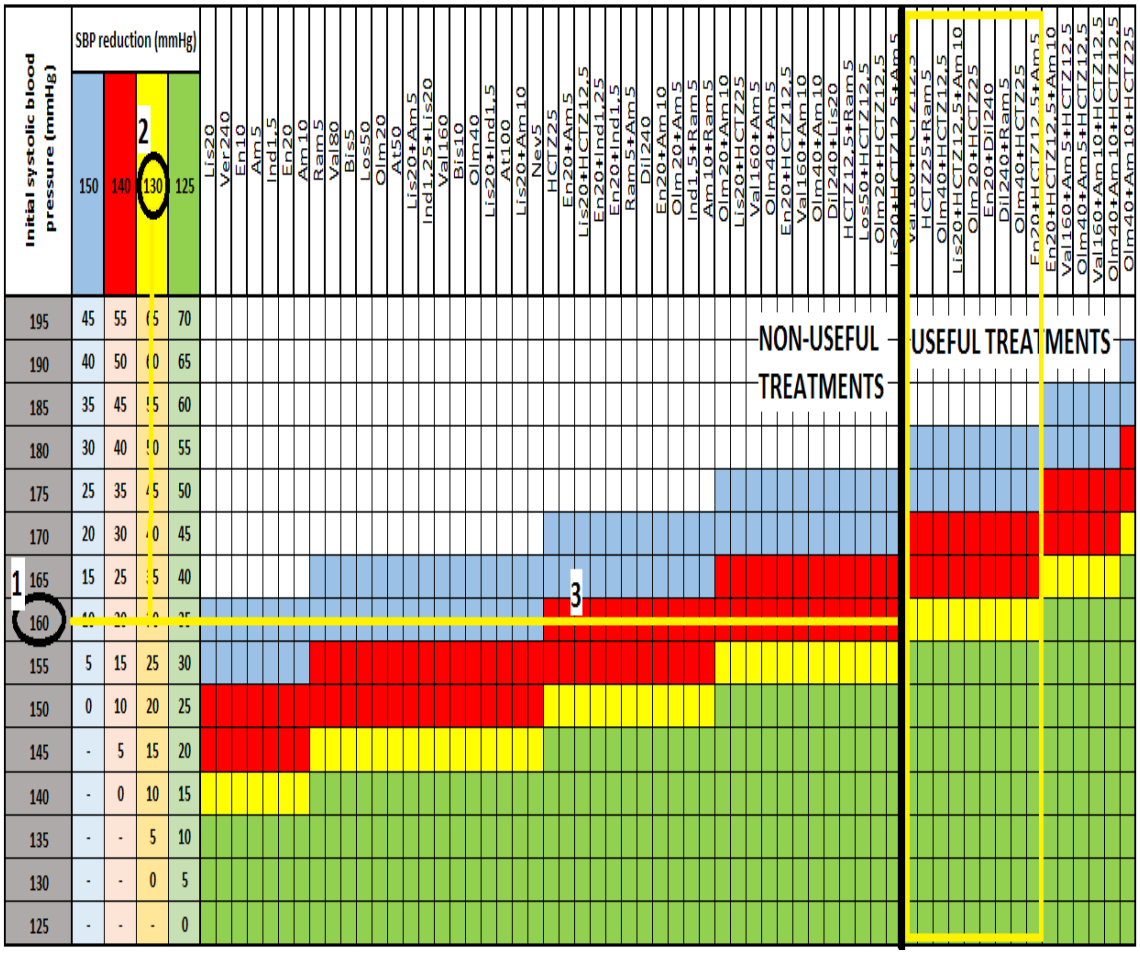
**Table 52: Example 1.**



Patient 2 (***Table 53***):

- 75 years.
- Diabetic and chronic kidney disease without proteinuria.
- BP target value: <130/80 mmHg.
- Pre-treatment BP value: 158/90 mmHg.
- SBP reduction: 28 mmHg. SBP interval: >25,00 mmHg.

**Table 53: Example 2.**




All drugs selected within the box "*Non-useful treatments*" are not efficient enough to reduce the SBP to the desired levels. For this reason, we would like to select one of the other treatments available in "*useful treatments*", preferably one of the treatments that are within the established BP reduction interval.

## Annex 13

**Table 54: Pharmacy data 1.**

| GRUPS C02 i C03 - ANY 2015 - RS GIRONA | | | |
|---|---|---|---|
| (HIS) | Principi Actiu Principal (PAP) | Nombre envasos | Import PVP |
| MI0809 | ESPIRONOLACTONA | 27.154 | 77.135,83 |
| MI0810 | CLORTALIDONA | 6.053 | 19.853,10 |
| MI1112 | BUMETANIDA | 179 | 458,24 |
| MI1459 | MINOXIDIL | 173 | 1.098,55 |
| MI1867 | PRAZOSINA CLORHIDRAT | 122 | 468,57 |
| MI2150 | HIDROCLOROTIAZIDA | 181.014 | 423.572,76 |
| MI2548 | FUROSEMIDA | 182.524 | 407.784,52 |
| MI2691 | HIDRALAZINA, CLORHIDRAT D' | 5.460 | 15.868,43 |
| MI2774 | INDAPAMIDA | 20.640 | 56.474,44 |
| MI2986 | METILDOPA | 446 | 2.416,84 |
| MI3869 | XIPAMIDA | 471 | 2.536,08 |
| RE0108 | PIRETANIDA | 288 | 1.569,60 |
| RE0312 | DOXAZOSINA, MESILAT DE | 44.616 | 417.366,06 |
| RE0467 | TORASEMIDA | 40.788 | 147.279,21 |
| RE2619 | CLORTALIDONA+ESTALVIADOR DE POTASSI | 396 | 1.619,64 |
| RE2620 | HIDROCLOROTIAZIDA+ESTALVIADOR DE POTASSI | 10.040 | 39.125,96 |
| RE2631 | FUROSEMIDA +ESTALVIADOR DE POTASSI | 707 | 4.054,68 |
| RE2709 | DOXAZOSINA | 3.053 | 19.066,25 |
| RE2976 | EPLERENONA | 9.157 | 282.539,20 |
| **Total** | | **533.281** | **1.920.287,96** |

**Table 55: Pharmacy data 2.**

| GRUP C07 - ANY 2015 - RS GIRONA | | | |
|---|---|---|---|
| (HIS) | Principi Actiu Principal (PAP) | Nombre envasos | Import PVP |
| 2218B | PROPANOLOL | 10.454 | 14.774,76 |
| MI0851 | ATENOLOL | 50.916 | 143.474,42 |
| MI0855 | METOPROLOL TARTRAT | 960 | 4.012,80 |
| MI0859 | SOTALOL CLORHIDRAT | 2.835 | 8.845,20 |
| MI1147 | NADOLOL | 2.869 | 19.392,02 |
| MI1586 | LABETALOL CLORHIDRAT | 1.512 | 5.343,84 |
| RE0126 | CELIPROLOL, CLORHIDRAT | 54 | 945,00 |
| RE0127 | BISOPROLOL, FUMARAT | 113.815 | 320.149,22 |
| RE0128 | PROPRANOLOL, CLORHIDRAT | 13.466 | 24.208,25 |
| RE0380 | CARVEDILOL | 75.633 | 297.329,53 |
| RE0454 | NEBIVOLOL, CLORHIDRAT | 25.042 | 197.330,96 |
| RE0546 | METOPROLOL SUCCINAT | 1.424 | 4.581,26 |
| RE2614 | BISOPROLOL+DIURETIC | 3.978 | 27.518,92 |
| RE2638 | ATENOLOL+DIURETIC | 4.845 | 55.424,06 |
| RE2892 | METOPROLOL+BLOQUEJANT CANALS CALCI | 2.893 | 50.858,94 |
| RE3285 | NEBIVOLOL + DIURETIC | 2.787 | 28.336,24 |
| RE3401 | BISOPROLOL HEMIFUMARAT | 27.325 | 72.029,81 |
| **Total** | | **340.808** | **1.274.555,23** |

**Table 56: Pharmacy data 3.**

| GRUP C08 - ANY 2015 - RS GIRONA | | | |
|---|---|---|---|
| **(HIS)** | **Principi Actiu Principal (PAP)** | **Nombre envasos** | **Import PVP** |
| FM0625 | NIMODIPINA | 2.363 | 32.130,78 |
| FM0629 | NITRENDIPINA | 1.218 | 11.412,66 |
| MI0294 | NICARDIPINA, CLORHIDRAT DE | 1.421 | 19.436,85 |
| MI0364 | AMLODIPINA, BESILAT D' | 173.128 | 285.579,22 |
| MI3806 | VERAPAMIL, CLORHIDRAT DE | 7.335 | 64.169,62 |
| MI3859 | NIFEDIPINA | 14.847 | 64.882,86 |
| MI4263 | DILTIAZEM, CLORHIDRAT DE | 32.625 | 440.717,50 |
| RE0364 | FELODIPINA | 585 | 5.177,25 |
| RE0371 | LACIDIPINO | 2.488 | 28.238,80 |
| RE0378 | LERCANIDIPINA, CLORHIDRAT | 14.880 | 127.128,66 |
| RE0414 | NISOLDIPINO | 178 | 2.972,64 |
| RE2051 | BARNIDIPINA CLORHIDRAT | 1.566 | 42.576,34 |
| RE2512 | MANIDIPI HIDROCLORUR DE | 21.551 | 212.169,47 |
| RE2959 | AMLODIPINA MESILAT MONOHIDRAT | 7.686 | 12.690,00 |
| RE3017 | AMLODIPINA | 7 | 10,00 |
| RE3317 | MANIDIPINA DIHIDROCLORUR | 1.722 | 17.681,82 |
| **Total** | | **283.600** | **1.366.974,47** |

**Table 57: Pharmacy data 4.**

| GRUP C09 - GENER a MARÇ 2015 - RS GIRONA | | | |
|---|---|---|---|
| **(HIS)** | **Principi Actiu Principal (PAP)** | **Nombre envasos** | **Import PVP** |
| MI0036 | IRBESARTAN | 3.821 | 40.349,41 |
| MI4359 | CAPTOPRIL | 1.183 | 4.175,99 |
| RE0105 | ENALAPRIL, MALEAT | 69.455 | 129.860,61 |
| RE0356 | LISINOPRIL, DIHIDRAT | 10.902 | 65.336,65 |
| RE0359 | QUINAPRIL, CLORHIDRAT DE | 692 | 4.487,50 |
| RE0373 | LISINOPRIL | 5.686 | 33.362,60 |
| RE0390 | BENAZEPRIL | 39 | 467,35 |
| RE0392 | CILAZAPRIL | 72 | 484,68 |
| RE0394 | RAMIPRIL | 17.951 | 92.792,00 |
| RE0417 | FOSINOPRIL SODIC | 247 | 2.005,64 |
| RE0439 | VALSARTAN | 12.606 | 184.587,99 |
| RE0441 | CANDESARTAN | 1.515 | 19.296,98 |
| RE0456 | TRANDOLAPRIL | 50 | 299,52 |
| RE0489 | LOSARTAN | 25.824 | 136.497,60 |
| RE2000 | TELMISARTAN | 3.011 | 47.110,76 |
| RE2006 | EPROSARTAN | 621 | 14.767,38 |
| RE2140 | IMIDAPRIL, HIDROCLORUR | 679 | 10.422,84 |
| RE2601 | LOSARTAN+DIURETIC | 18.034 | 80.121,88 |
| RE2602 | VALSARTAN+DIURETIC | 12.925 | 169.445,12 |
| RE2604 | CAPTOPRIL+DIURETIC | 631 | 4.656,78 |
| RE2607 | ENALAPRIL+DIURETIC | 40.993 | 75.600,04 |
| RE2608 | FOSINOPRIL+DIURETIC | 145 | 1.423,90 |

| | | | |
|---|---|---|---|
| RE2609 | TRANDOLAPRIL+BLOQ. CALCI | 612 | 13.617,00 |
| RE2610 | CILAZAPRIL+DIURETIC | 115 | 1.867,60 |
| RE2612 | LISINOPRIL+DIURETIC | 13.278 | 97.858,86 |
| RE2613 | QUINAPRIL+DIURETIC | 288 | 875,52 |
| RE2624 | IRBESARTAN+DIURETIC | 3.355 | 55.994,00 |
| RE2635 | CANDESARTAN+DIURETIC | 3.825 | 53.784,32 |
| RE2646 | TELMISARTAN+DIURETIC | 2.692 | 46.086,48 |
| RE2655 | EPROSARTAN MESILAT DIHIDRATAT | 42 | 998,76 |
| RE2721 | ENALAPRIL | 6.861 | 11.046,21 |
| RE2933 | PERINDOPRIL+DIURETIC | 774 | 13.282,92 |
| RE2961 | OLMESARTAN MEDOXOMIL | 4.269 | 116.332,40 |
| RE2962 | RAMIPRIL+BLOQ. CALCI | 37 | 921,30 |
| RE2982 | BENAZEPRIL+DIURETIC | 5 | 69,70 |
| RE3001 | EPROSARTAN+DIURETIC | 804 | 19.955,28 |
| RE3071 | OLMESARTAN MEDOXOMIL + DIURETIC | 3.561 | 103.060,50 |
| RE3119 | RAMIPRIL +DIURÈTIC | 1.339 | 8.217,90 |
| RE3124 | ALISKIREN | 246 | 7.937,75 |
| RE3140 | PERINDOPRIL ERBUMINA | 388 | 2.999,87 |
| RE3143 | VALSARTAN + BLOQ CANALS CALCI | 2.365 | 54.011,12 |
| RE3219 | OLMESARTAN MEDOXOMIL+ BLOQ. CANALS CALCI | 2.557 | 88.604,96 |
| RE3254 | CANDESARTAN CILEXETIL | 3.393 | 37.657,00 |
| RE3269 | ALISKIREN + DIURETIC | 113 | 4.368,45 |
| RE3295 | DELAPRIL + MANIDIPINO | 445 | 9.376,15 |
| RE3322 | VALSARTAN+AMLODIPINA+DIURÈTIC | 1.771 | 40.610,00 |
| RE3369 | TELMISARTAN+AMLODIPINA | 237 | 8.975,70 |
| RE3375 | ENALAPRIL + LERCANIDIPINA | 1.133 | 11.588,44 |
| RE3376 | ENALAPRIL + NITRENDIPINA | 937 | 22.103,83 |
| RE3387 | OLMESARTAN MEDOX+AMLODIP.+HIDROCLORTIAZ. | 2.344 | 82.692,53 |
| **Total** | | **284.868** | **2.032.447,77** |

**Table 58: Pharmacy data 5.**

| GRUP C09 - ABRIL a JUNY 2015 - RS GIRONA | | | |
|---|---|---|---|
| **(HIS)** | **Principi Actiu Principal (PAP)** | **Nombre envasos** | **Import PVP** |
| MI0036 | IRBESARTAN | 3.580 | 37.755,41 |
| MI4359 | CAPTOPRIL | 1.155 | 4.077,15 |
| RE0105 | ENALAPRIL, MALEAT | 69.476 | 129.907,96 |
| RE0333 | PERINDOPRIL | 1 | 6,74 |
| RE0356 | LISINOPRIL, DIHIDRAT | 11.218 | 67.260,65 |
| RE0359 | QUINAPRIL, CLORHIDRAT DE | 666 | 4.361,25 |
| RE0373 | LISINOPRIL | 5.766 | 33.876,50 |
| RE0390 | BENAZEPRIL | 44 | 514,57 |
| RE0392 | CILAZAPRIL | 60 | 385,44 |
| RE0394 | RAMIPRIL | 18.314 | 94.080,58 |
| RE0417 | FOSINOPRIL SODIC | 252 | 2.046,24 |
| RE0439 | VALSARTAN | 12.790 | 187.584,38 |
| RE0441 | CANDESARTAN | 1.489 | 19.070,81 |
| RE0456 | TRANDOLAPRIL | 43 | 262,08 |
| RE0489 | LOSARTAN | 26.280 | 138.519,92 |

| | | | |
|---|---|---|---|
| RE2000 | TELMISARTAN | 2.958 | 46.381,69 |
| RE2006 | EPROSARTAN | 576 | 13.697,28 |
| RE2140 | IMIDAPRIL, HIDROCLORUR | 761 | 11.610,93 |
| RE2601 | LOSARTAN+DIURETIC | 18.583 | 83.024,36 |
| RE2602 | VALSARTAN+DIURETIC | 13.128 | 172.675,02 |
| RE2604 | CAPTOPRIL+DIURETIC | 606 | 4.472,28 |
| RE2607 | ENALAPRIL+DIURETIC | 41.211 | 75.994,56 |
| RE2608 | FOSINOPRIL+DIURETIC | 135 | 1.325,70 |
| RE2609 | TRANDOLAPRIL+BLOQ. CALCI | 603 | 13.416,75 |
| RE2610 | CILAZAPRIL+DIURETIC | 101 | 1.640,24 |
| RE2612 | LISINOPRIL+DIURETIC | 13.854 | 102.103,98 |
| RE2613 | QUINAPRIL+DIURETIC | 278 | 845,12 |
| RE2624 | IRBESARTAN+DIURETIC | 3.297 | 54.749,61 |
| RE2635 | CANDESARTAN+DIURETIC | 3.716 | 52.160,63 |
| RE2646 | TELMISARTAN+DIURETIC | 2.588 | 44.286,00 |
| RE2655 | EPROSARTAN MESILAT DIHIDRATAT | 39 | 927,42 |
| RE2721 | ENALAPRIL | 6.837 | 11.007,57 |
| RE2933 | PERINDOPRIL+DIURETIC | 790 | 13.812,12 |
| RE2961 | OLMESARTAN MEDOXOMIL | 4.189 | 113.851,68 |
| RE2962 | RAMIPRIL+BLOQ. CALCI | 44 | 1.095,60 |
| RE2982 | BENAZEPRIL+DIURETIC | 7 | 97,58 |
| RE3001 | EPROSARTAN+DIURETIC | 779 | 19.334,78 |
| RE3071 | OLMESARTAN MEDOXOMIL + DIURETIC | 3.614 | 104.667,02 |
| RE3119 | RAMIPRIL +DIURÈTIC | 1.404 | 8.673,30 |
| RE3124 | ALISKIREN | 250 | 8.102,79 |
| RE3140 | PERINDOPRIL ERBUMINA | 382 | 2.986,43 |
| RE3143 | VALSARTAN + BLOQ CANALS CALCI | 2.418 | 55.231,80 |
| RE3219 | OLMESARTAN MEDOXOMIL+ BLOQ. CANALS CALCI | 2.435 | 84.712,53 |
| RE3254 | CANDESARTAN CILEXETIL | 3.374 | 37.324,96 |
| RE3269 | ALISKIREN + DIURETIC | 112 | 4.296,25 |
| RE3295 | DELAPRIL + MANIDIPINO | 431 | 9.081,17 |
| RE3322 | VALSARTAN+AMLODIPINA+DIURÈTIC | 1.927 | 45.106,26 |
| RE3369 | TELMISARTAN+AMLODIPINA | 207 | 7.822,35 |
| RE3375 | ENALAPRIL + LERCANIDIPINA | 1.119 | 11.481,66 |
| RE3376 | ENALAPRIL + NITRENDIPINA | 910 | 21.466,90 |
| RE3387 | OLMESARTAN MEDOX+AMLODIP.+HIDROCLORTIAZ. | 2.445 | 86.349,08 |
| | **Total** | **287.242** | **2.045.523,08** |

**Table 59: Pharmacy data 6.**

| GRUP C09 - JULIOL a SETEMBRE 2015 - RS GIRONA | | | |
|---|---|---|---|
| **(HIS)** | **Principi Actiu Principal (PAP)** | **Nombre envasos** | **Import PVP** |
| MI0036 | IRBESARTAN | 3.531 | 37.294,76 |
| MI4359 | CAPTOPRIL | 1.043 | 3.681,79 |
| RE0105 | ENALAPRIL, MALEAT | 69.261 | 129.666,88 |
| RE0333 | PERINDOPRIL | 5 | 40,45 |
| RE0356 | LISINOPRIL, DIHIDRAT | 11.216 | 67.171,25 |
| RE0359 | QUINAPRIL, CLORHIDRAT DE | 648 | 4.219,95 |
| RE0373 | LISINOPRIL | 5.648 | 33.044,60 |

| | | | |
|---|---|---|---|
| RE0390 | BENAZEPRIL | 47 | 536,58 |
| RE0392 | CILAZAPRIL | 61 | 401,46 |
| RE0394 | RAMIPRIL | 18.464 | 95.777,18 |
| RE0417 | FOSINOPRIL SODIC | 237 | 1.924,44 |
| RE0439 | VALSARTAN | 12.912 | 187.231,78 |
| RE0441 | CANDESARTAN | 1.403 | 17.819,93 |
| RE0456 | TRANDOLAPRIL | 44 | 265,20 |
| RE0489 | LOSARTAN | 26.855 | 141.218,90 |
| RE2000 | TELMISARTAN | 2.875 | 45.238,15 |
| RE2006 | EPROSARTAN | 584 | 12.109,15 |
| RE2140 | IMIDAPRIL, HIDROCLORUR | 753 | 11.520,35 |
| RE2601 | LOSARTAN+DIURETIC | 18.994 | 84.980,76 |
| RE2602 | VALSARTAN+DIURETIC | 12.984 | 171.672,60 |
| RE2604 | CAPTOPRIL+DIURETIC | 569 | 4.199,22 |
| RE2607 | ENALAPRIL+DIURETIC | 40.736 | 75.119,90 |
| RE2608 | FOSINOPRIL+DIURETIC | 144 | 1.414,08 |
| RE2609 | TRANDOLAPRIL+BLOQ. CALCI | 563 | 12.526,75 |
| RE2610 | CILAZAPRIL+DIURETIC | 101 | 1.640,24 |
| RE2612 | LISINOPRIL+DIURETIC | 13.865 | 102.185,05 |
| RE2613 | QUINAPRIL+DIURETIC | 279 | 848,16 |
| RE2624 | IRBESARTAN+DIURETIC | 3.098 | 51.489,30 |
| RE2635 | CANDESARTAN+DIURETIC | 3.619 | 51.115,10 |
| RE2645 | ENALAPRIL+BLOQ. CANALS CALCI | 1 | 11,24 |
| RE2646 | TELMISARTAN+DIURETIC | 2.497 | 42.979,20 |
| RE2655 | EPROSARTAN MESILAT DIHIDRATAT | 39 | 775,26 |
| RE2721 | ENALAPRIL | 6.759 | 10.881,99 |
| RE2933 | PERINDOPRIL+DIURETIC | 783 | 14.138,46 |
| RE2961 | OLMESARTAN MEDOXOMIL | 4.091 | 111.013,32 |
| RE2962 | RAMIPRIL+BLOQ. CALCI | 45 | 1.120,50 |
| RE2982 | BENAZEPRIL+DIURETIC | 5 | 69,70 |
| RE3001 | EPROSARTAN+DIURETIC | 755 | 18.739,10 |
| RE3071 | OLMESARTAN MEDOXOMIL + DIURETIC | 3.529 | 102.354,46 |
| RE3119 | RAMIPRIL +DIURÈTIC | 1.510 | 9.297,75 |
| RE3124 | ALISKIREN | 230 | 7.447,76 |
| RE3140 | PERINDOPRIL ERBUMINA | 400 | 3.168,50 |
| RE3143 | VALSARTAN + BLOQ CANALS CALCI | 2.334 | 53.210,02 |
| RE3219 | OLMESARTAN MEDOXOMIL+ BLOQ. CANALS CALCI | 2.368 | 82.574,72 |
| RE3254 | CANDESARTAN CILEXETIL | 3.292 | 36.258,55 |
| RE3269 | ALISKIREN + DIURETIC | 123 | 4.549,00 |
| RE3295 | DELAPRIL + MANIDIPINO | 414 | 8.722,98 |
| RE3322 | VALSARTAN+AMLODIPINA+DIURÈTIC | 2.000 | 46.993,32 |
| RE3369 | TELMISARTAN+AMLODIPINA | 228 | 8.625,60 |
| RE3375 | ENALAPRIL + LERCANIDIPINA | 1.135 | 11.644,64 |
| RE3376 | ENALAPRIL + NITRENDIPINA | 854 | 20.145,86 |
| RE3387 | OLMESARTAN MEDOX+AMLODIP.+HIDROCLORTIAZ. | 2.372 | 83.502,80 |
| | **Total** | **286.303** | **2.024.578,69** |

**Table 60: Pharmacy data 7.**

| GRUP C09 - OCTUBRE a DESEMBRE 2015 - RS GIRONA | | | |
|---|---|---|---|
| (HIS) | Principi Actiu Principal (PAP) | Nombre envasos | Import PVP |
| MI0036 | IRBESARTAN | 3.492 | 36.675,17 |
| MI4359 | CAPTOPRIL | 1.071 | 3.780,63 |
| RE0105 | ENALAPRIL, MALEAT | 70.586 | 132.395,54 |
| RE0333 | PERINDOPRIL | 7 | 67,43 |
| RE0356 | LISINOPRIL, DIHIDRAT | 11.503 | 68.716,40 |
| RE0359 | QUINAPRIL, CLORHIDRAT DE | 633 | 4.136,60 |
| RE0373 | LISINOPRIL | 5.938 | 34.620,60 |
| RE0390 | BENAZEPRIL | 41 | 461,78 |
| RE0392 | CILAZAPRIL | 64 | 474,42 |
| RE0394 | RAMIPRIL | 18.953 | 97.502,62 |
| RE0417 | FOSINOPRIL SODIC | 227 | 1.843,24 |
| RE0439 | VALSARTAN | 13.110 | 189.448,19 |
| RE0441 | CANDESARTAN | 1.374 | 17.421,66 |
| RE0456 | TRANDOLAPRIL | 50 | 299,52 |
| RE0489 | LOSARTAN | 27.666 | 145.036,28 |
| RE2000 | TELMISARTAN | 2.814 | 43.925,17 |
| RE2006 | EPROSARTAN | 569 | 8.119,63 |
| RE2140 | IMIDAPRIL, HIDROCLORUR | 816 | 12.375,85 |
| RE2601 | LOSARTAN+DIURETIC | 19.810 | 88.773,84 |
| RE2602 | VALSARTAN+DIURETIC | 13.315 | 175.681,25 |
| RE2604 | CAPTOPRIL+DIURETIC | 593 | 4.376,34 |
| RE2607 | ENALAPRIL+DIURETIC | 41.477 | 76.485,32 |
| RE2608 | FOSINOPRIL+DIURETIC | 142 | 1.394,44 |
| RE2609 | TRANDOLAPRIL+BLOQ. CALCI | 546 | 12.148,50 |
| RE2610 | CILAZAPRIL+DIURETIC | 92 | 1.494,08 |
| RE2612 | LISINOPRIL+DIURETIC | 14.499 | 106.857,63 |
| RE2613 | QUINAPRIL+DIURETIC | 264 | 802,56 |
| RE2624 | IRBESARTAN+DIURETIC | 3.076 | 51.026,36 |
| RE2635 | CANDESARTAN+DIURETIC | 3.635 | 51.327,83 |
| RE2645 | ENALAPRIL+BLOQ. CANALS CALCI | 47 | 528,28 |
| RE2646 | TELMISARTAN+DIURETIC | 2.516 | 43.046,96 |
| RE2655 | EPROSARTAN MESILAT DIHIDRATAT | 34 | 485,18 |
| RE2721 | ENALAPRIL | 6.969 | 11.220,09 |
| RE2933 | PERINDOPRIL+DIURETIC | 843 | 15.823,08 |
| RE2961 | OLMESARTAN MEDOXOMIL | 3.983 | 107.749,16 |
| RE2962 | RAMIPRIL+BLOQ. CALCI | 46 | 1.145,40 |
| RE2982 | BENAZEPRIL+DIURETIC | 8 | 111,52 |
| RE3001 | EPROSARTAN+DIURETIC | 751 | 18.639,82 |
| RE3071 | OLMESARTAN MEDOXOMIL + DIURETIC | 3.521 | 102.455,78 |
| RE3119 | RAMIPRIL +DIURÈTIC | 1.633 | 10.122,30 |
| RE3124 | ALISKIREN | 227 | 7.277,57 |
| RE3140 | PERINDOPRIL ERBUMINA | 396 | 3.161,79 |
| RE3143 | VALSARTAN + BLOQ CANALS CALCI | 2.382 | 54.329,51 |
| RE3219 | OLMESARTAN MEDOXOMIL+ BLOQ. CANALS CALCI | 2.386 | 83.296,02 |

| | | | |
|---|---|---|---|
| RE3254 | CANDESARTAN CILEXETIL | 3.357 | 36.876,60 |
| RE3269 | ALISKIREN + DIURETIC | 106 | 3.955,87 |
| RE3295 | DELAPRIL + MANIDIPINO | 372 | 7.838,04 |
| RE3322 | VALSARTAN+AMLODIPINA+DIURÈTIC | 2.038 | 48.491,45 |
| RE3369 | TELMISARTAN+AMLODIPINA | 217 | 8.227,80 |
| RE3375 | ENALAPRIL + LERCANIDIPINA | 1.168 | 11.818,86 |
| RE3376 | ENALAPRIL + NITRENDIPINA | 898 | 21.183,82 |
| RE3387 | OLMESARTAN MEDOX+AMLODIP.+HIDROCLORTIAZ. | 2.433 | 85.618,47 |
| | **Total** | **292.694** | **2.051.072,25** |

## Annex 14

**Table 61: ICER. Exclusion of dominated therapies. SBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Ramipril 5 | 0,17 | 10,17 | 0,17 | 10,17 | 0,02 |
| Valsartan 80 | 0,29 | 10,33 | 0,12 | 0,16 | 0,75 |
| Bisorpolol 5 | 0,05 | 10,59 | -0,24 | 0,26 | -0,92 |
| Losartan 50 | 0,15 | 10,67 | 0,10 | 0,08 | 1,25 |
| Olmesartan 20 | 0,89 | 10,84 | 0,74 | 0,17 | 4,35 |
| Atenolol 50 | 0,08 | 11,25 | -0,81 | 0,41 | -1,98 |
| Lisinopril 20 + Amlodipine 5 | 0,27 | 12,05 | 0,19 | 0,80 | 0,24 |
| Indapamide 1,25 + Lisinopril 20 | 0,28 | 12,76 | 0,01 | 0,71 | 0,01 |
| Valsartan 160 | 0,58 | 12,81 | 0,30 | 0,05 | 6,00 |
| Bisorpolol 10 | 0,11 | 12,95 | -0,47 | 0,14 | -3,36 |
| Olmesartan 40 | 1,20 | 13,22 | 1,09 | 0,27 | 4,04 |
| Lisinopril 20 + Indapamide 1,5 | 0,31 | 13,27 | -0,89 | 0,05 | -17,80 |
| Atenolol 100 | 0,08 | 13,65 | -0,23 | 0,38 | -0,61 |
| Lisinopril 20 + Amlodipine 10 | 0,31 | 13,74 | 0,23 | 0,09 | 2,56 |
| Nevibolol 5 | 0,28 | 14,96 | -0,03 | 1,22 | -0,02 |

**Table 62: ICER. Exclusion of dominated therapies. SBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Ramipril 5 | 0,17 | 10,17 | 0,17 | 10,17 | 0,02 |
| Bisorpolol 5 | 0,05 | 10,59 | -0,12 | 0,42 | -0,29 |
| Losartan 50 | 0,15 | 10,67 | 0,10 | 0,08 | 1,25 |
| Atenolol 50 | 0,08 | 11,25 | -0,07 | 0,58 | -0,12 |
| Lisinopril 20 + Amlodipine 5 | 0,27 | 12,05 | 0,19 | 0,80 | 0,24 |
| Indapamide 1,25 + Lisinopril 20 | 0,28 | 12,76 | 0,01 | 0,71 | 0,01 |
| Bisorpolol 10 | 0,11 | 12,95 | -0,17 | 0,19 | -0,89 |
| Atenolol 100 | 0,08 | 13,65 | -0,03 | 0,70 | -0,04 |
| Nevibolol 5 | 0,28 | 14,96 | 0,20 | 1,31 | 0,15 |

**Table 63: ICER. Exclusion of dominated therapies. SBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Bisorpolol 5 | 0,05 | 10,59 | 0,05 | 10,59 | 0,00 |
| Atenolol 50 | 0,08 | 11,25 | 0,03 | 0,66 | 0,05 |
| Lisinopril 20 + Amlodipine 5 | 0,27 | 12,05 | 0,19 | 0,80 | 0,24 |
| Atenolol 100 | 0,08 | 13,65 | -0,19 | 1,60 | -0,12 |
| Nevibolol 5 | 0,28 | 14,96 | 0,20 | 1,31 | 0,15 |

**Table 64: ICER. Exclusion of therapies with higher ICER. SBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Bisorpolol 5 | 0,05 | 10,59 | 0,05 | 10,59 | 0,00 |
| Atenolol 50 | 0,08 | 11,25 | 0,03 | 0,66 | 0,05 |
| Atenolol 100 | 0,08 | 13,65 | 0,00 | 2,40 | 0,00 |
| Nevibolol 5 | 0,28 | 14,96 | 0,20 | 1,31 | 0,15 |

**Table 65: ICER. Exclusion of therapies with higher ICER. SBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Bisorpolol 5 | 0,05 | 10,59 | 0,05 | 10,59 | 0,00 |
| Atenolol 100 | 0,08 | 13,65 | 0,03 | 3,06 | 0,01 |

**Table 66: ICER. Exclusion of dominated therapies. SBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| HCTZ 25 | 0,12 | 15,85 | 0,12 | 15,85 | 0,01 |
| Enalapril 20 + Amlodipine 5 | 0,10 | 16,60 | -0,02 | 0,75 | -0,03 |
| Lisinopril 20 + HCTZ 12,5 | 0,29 | 17,24 | 0,19 | 0,64 | 0,30 |
| Enalapril 20 + Indapamide 1,25 | 0,11 | 17,31 | -0,18 | 0,07 | -2,57 |
| Enalapril 20 + Indapamide 1,5 | 0,14 | 17,82 | 0,03 | 0,51 | 0,06 |
| Ramipril 5 + Amlodipine 5 | 0,21 | 17,84 | 0,07 | 0,02 | 3,50 |
| Diltiazem 240 | 0,61 | 18,24 | 0,40 | 0,40 | 1,00 |
| Enalapril 20 + Amlodipine 10 | 0,14 | 18,29 | -0,47 | 0,05 | -9,40 |
| Olmesartan 20 + Amlodipine 5 | 0,93 | 18,51 | 0,79 | 0,22 | 3,59 |
| Indapamide 1,5 + Ramipril 5 | 0,26 | 19,06 | -0,67 | 0,55 | -1,22 |
| Amlodipine 10 + Ramipril 5 | 0,26 | 19,53 | 0,00 | 0,47 | 0,00 |

**Table 67: ICER. Exclusion of dominated therapies. SBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + Amlodipine 5 | 0,10 | 16,60 | 0,10 | 16,60 | 0,01 |
| Enalapril 20 + Indapamide 1,25 | 0,11 | 17,31 | 0,01 | 0,71 | 0,01 |
| Enalapril 20 + Indapamide 1,5 | 0,14 | 17,82 | 0,03 | 0,51 | 0,06 |
| Ramipril 5 + Amlodipine 5 | 0,21 | 17,84 | 0,07 | 0,02 | 3,50 |
| Enalapril 20 + Amlodipine 10 | 0,14 | 18,29 | -0,07 | 0,45 | -0,16 |
| Indapamide 1,5 + Ramipril 5 | 0,26 | 19,06 | 0,12 | 0,77 | 0,16 |
| Amlodipine 10 + Ramipril 5 | 0,26 | 19,53 | 0,00 | 0,47 | 0,00 |

**Table 68: ICER. Exclusion of therapies with higher ICER. SBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + Amlodipine 5 | 0,10 | 16,60 | 0,10 | 16,60 | 0,01 |
| Enalapril 20 + Indapamide 1,25 | 0,11 | 17,31 | 0,01 | 0,71 | 0,01 |
| Enalapril 20 + Indapamide 1,5 | 0,14 | 17,82 | 0,03 | 0,51 | 0,06 |
| Enalapril 20 + Amlodipine 10 | 0,14 | 18,29 | 0,00 | 0,47 | 0,00 |
| Indapamide 1,5 + Ramipril 5 | 0,26 | 19,06 | 0,12 | 0,77 | 0,16 |
| Amlodipine 10 + Ramipril 5 | 0,26 | 19,53 | 0,00 | 0,47 | 0,00 |

**Table 69: ICER. Exclusion of therapies with higher ICER. SBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + Amlodipine 5 | 0,10 | 16,60 | 0,10 | 16,60 | 0,01 |
| Enalapril 20 + Indapamide 1,25 | 0,11 | 17,31 | 0,01 | 0,71 | 0,01 |
| Enalapril 20 + Amlodipine 10 | 0,14 | 18,29 | 0,03 | 0,98 | 0,03 |
| Amlodipine 10 + Ramipril 5 | 0,26 | 19,53 | 0,12 | 1,24 | 0,10 |

**Table 70: ICER. Exclusion of therapies with higher ICER. SBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + Amlodipine 5 | 0,10 | 16,60 | 0,10 | 16,60 | 0,01 |
| Enalapril 20 + Indapamide 1,25 | 0,11 | 17,31 | 0,01 | 0,71 | 0,01 |

**Table 71: ICER. Exclusion of dominated therapies. SBP reduction 20,01-25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 20,01-25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Olmesartan 20 + Amlodipine 10 | 0,97 | 20,20 | 0,97 | 20,20 | 0,05 |
| Lisinopril 20 + HCTZ 25 | 0,34 | 20,23 | -0,63 | 0,03 | -21,00 |
| Valsartan 160 + Amlodipine 5 | 0,62 | 20,48 | 0,28 | 0,25 | 1,12 |
| Olmesartan 40 + Amlodipine 5 | 1,24 | 20,89 | 0,62 | 0,41 | 1,51 |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 21,79 | -1,12 | 0,90 | -1,24 |
| Valsartan 160 + Amlodipine 10 | 0,67 | 22,17 | 0,55 | 0,38 | 1,45 |
| Olmesartan 40 + Amlodipine 10 | 1,28 | 22,58 | 0,61 | 0,41 | 1,49 |
| Diltiazem 240 + Lisinopril 20 | 0,84 | 22,62 | -0,44 | 0,04 | -11,00 |
| HCTZ 12,5 + Ramipril 5 | 0,23 | 23,03 | -0,61 | 0,41 | -1,49 |
| Losartan 50 + HCTZ 12,5 | 0,21 | 23,53 | -0,02 | 0,50 | -0,04 |
| Olmesartan 20 + HCTZ 12,5 | 0,94 | 23,70 | 0,73 | 0,17 | 4,29 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 5 | 0,33 | 24,91 | -0,61 | 1,21 | -0,50 |

**Table 72: ICER. Exclusion of dominated therapies. SBP reduction 20,01-25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 20,01-25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Lisinopril 20 + HCTZ 25 | 0,34 | 20,23 | 0,34 | 20,23 | 0,02 |
| Valsartan 160 + Amlodipine 5 | 0,62 | 20,48 | 0,28 | 0,25 | 1,12 |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 21,79 | -0,50 | 1,31 | -0,38 |
| Valsartan 160 + Amlodipine 10 | 0,67 | 22,17 | 0,55 | 0,38 | 1,45 |
| Losartan 50 + HCTZ 12,5 | 0,21 | 23,53 | -0,46 | 1,36 | -0,34 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 5 | 0,33 | 24,91 | 0,12 | 1,38 | 0,09 |

**Table 73: ICER. Exclusion of dominated therapies. SBP reduction 20,01-25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 20,01-25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Lisinopril 20 + HCTZ 25 | 0,34 | 20,23 | 0,34 | 20,23 | 0,02 |

| | | | | | |
|---|---|---|---|---|---|
| Enalapril 20 + HCTZ 12,5 | 0,12 | 21,79 | -0,22 | 1,56 | -0,14 |
| Losartan 50 + HCTZ 12,5 | 0,21 | 23,53 | 0,09 | 1,74 | 0,05 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 5 | 0,33 | 24,91 | 0,12 | 1,38 | 0,09 |

**Table 74: ICER. Exclusion of therapies with higher ICER. SBP reduction 20,01-25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 20,01-25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 21,79 | 0,12 | 21,79 | 0,01 |
| Losartan 50 + HCTZ 12,5 | 0,21 | 23,53 | 0,09 | 1,74 | 0,05 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 5 | 0,33 | 24,91 | 0,12 | 1,38 | 0,09 |

**Table 75: ICER. Exclusion of therapies with higher ICER. SBP reduction 20,01-25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 20,01-25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 21,79 | 0,12 | 21,79 | 0,01 |

**Table 76: ICER. Exclusion of dominated therapies. SBP reduction >25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction >25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Valsartan 160 + HCTZ 12,5 | 0,64 | 25,67 | 0,64 | 25,67 | 0,02 |
| HCTZ 25 + Ramipril 5 | 0,29 | 26,02 | -0,35 | 0,35 | -1,00 |
| Olmesartan 40 + HCTZ 12,5 | 1,26 | 26,08 | 0,97 | 0,06 | 16,17 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 10 | 0,37 | 26,60 | -0,89 | 0,52 | -1,71 |
| Olmesartan 20 + HCTZ 25 | 1,00 | 26,69 | 0,63 | 0,09 | 7,00 |
| Enalapril 20 + Diltiazem 240 | 0,67 | 27,17 | -0,33 | 0,48 | -0,69 |
| Diltiazem 240 + Ramipril 5 | 0,78 | 28,41 | 0,11 | 1,24 | 0,09 |
| Olmesartan 40 + HCTZ 25 | 1,32 | 29,07 | 0,54 | 0,66 | 0,82 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 29,46 | -1,16 | 0,39 | -2,97 |

| | | | | | |
|---|---|---|---|---|---|
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 31,15 | 0,04 | 1,69 | 0,02 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 33,34 | 0,48 | 2,19 | 0,22 |
| Olmesartan 40 + Amlodipine 5 + HCTZ 12,5 | 1,30 | 33,75 | 0,62 | 0,41 | 1,51 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 35,03 | -0,58 | 1,28 | -0,45 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 35,44 | 0,62 | 0,41 | 1,51 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 38,43 | 0,06 | 2,99 | 0,02 |

**Table 77: ICER. Exclusion of dominated therapies. SBP reduction >25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction >25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| HCTZ 25 + Ramipril 5 | 0,29 | 26,02 | 0,29 | 26,02 | 0,01 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 10 | 0,37 | 26,60 | 0,08 | 0,58 | 0,14 |
| Enalapril 20 + Diltiazem 240 | 0,67 | 27,17 | 0,30 | 0,57 | 0,53 |
| Diltiazem 240 + Ramipril 5 | 0,78 | 28,41 | 0,11 | 1,24 | 0,09 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 29,46 | -0,62 | 1,05 | -0,59 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 31,15 | 0,04 | 1,69 | 0,02 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 33,34 | 0,48 | 2,19 | 0,22 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 35,03 | 0,04 | 1,69 | 0,02 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 35,44 | 0,62 | 0,41 | 1,51 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 38,43 | 0,06 | 2,99 | 0,02 |

**Table 78: ICER. Exclusion of dominated therapies. SBP reduction >25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction >25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| HCTZ 25 + Ramipril 5 | 0,29 | 26,02 | 0,29 | 26,02 | 0,01 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 10 | 0,37 | 26,60 | 0,08 | 0,58 | 0,14 |
| Enalapril 20 + Diltiazem 240 | 0,67 | 27,17 | 0,30 | 0,57 | 0,53 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 29,46 | -0,51 | 2,29 | -0,22 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 31,15 | 0,04 | 1,69 | 0,02 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 33,34 | 0,48 | 2,19 | 0,22 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 35,03 | 0,04 | 1,69 | 0,02 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 35,44 | 0,62 | 0,41 | 1,51 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 38,43 | 0,06 | 2,99 | 0,02 |

**Table 79: ICER. Exclusion of dominated therapies. SBP reduction >25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction >25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| HCTZ 25 + Ramipril 5 | 0,29 | 26,02 | 0,29 | 26,02 | 0,01 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 10 | 0,37 | 26,60 | 0,08 | 0,58 | 0,14 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 29,46 | -0,21 | 2,86 | -0,07 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 31,15 | 0,04 | 1,69 | 0,02 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 33,34 | 0,48 | 2,19 | 0,22 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 35,03 | 0,04 | 1,69 | 0,02 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 35,44 | 0,62 | 0,41 | 1,51 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 38,43 | 0,06 | 2,99 | 0,02 |

**Table 80: ICER. Exclusion of dominated therapies. SBP reduction >25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction >25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| HCTZ 25 + Ramipril 5 | 0,29 | 26,02 | 0,29 | 26,02 | 0,01 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 29,46 | -0,13 | 3,44 | -0,04 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 31,15 | 0,04 | 1,69 | 0,02 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 33,34 | 0,48 | 2,19 | 0,22 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 35,03 | 0,04 | 1,69 | 0,02 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 35,44 | 0,62 | 0,41 | 1,51 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 38,43 | 0,06 | 2,99 | 0,02 |

**Table 81: ICER. Exclusion of therapies with higher ICER. SBP reduction >25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction >25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 29,46 | 0,16 | 29,46 | 0,01 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 31,15 | 0,04 | 1,69 | 0,02 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 33,34 | 0,48 | 2,19 | 0,22 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 35,03 | 0,04 | 1,69 | 0,02 |

| | | | | | |
|---|---|---|---|---|---|
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 35,44 | 0,62 | 0,41 | 1,51 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 38,43 | 0,06 | 2,99 | 0,02 |

**Table 82: ICER. Exclusion of therapies with higher ICER. SBP reduction >25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction >25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 29,46 | 0,16 | 29,46 | 0,01 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 31,15 | 0,04 | 1,69 | 0,02 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 35,03 | 0,52 | 3,88 | 0,13 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 38,43 | 0,68 | 3,40 | 0,20 |

**Table 83: ICER. Exclusion of therapies with higher ICER. SBP reduction >25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction >25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 29,46 | 0,16 | 29,46 | 0,01 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 31,15 | 0,04 | 1,69 | 0,02 |

## Annex 15

**Table 84: ICER. Exclusion of dominated therapies. DBP reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Lisinopril 20 | 0,23 | 3,22 | 0,23 | 3,22 | 0,07 |
| Amlodipine 5 | 0,04 | 5,95 | -0,19 | 2,73 | -0,07 |
| Indapamide 1,5 | 0,08 | 6,00 | 0,04 | 0,05 | 0,80 |
| Verapamil 240 | 0,34 | 6,56 | 0,26 | 0,56 | 0,46 |
| Enalapril 10 | 0,04 | 6,71 | -0,30 | 0,15 | -2,00 |
| Atenolol 50 | 0,08 | 7,26 | 0,04 | 0,55 | 0,07 |
| Amlodipine 10 | 0,08 | 7,27 | 0,00 | 0,01 | 0,00 |
| Bisorpolol 5 | 0,05 | 7,31 | -0,03 | 0,04 | -0,75 |
| Ramipril 5 | 0,17 | 7,80 | 0,12 | 0,49 | 0,24 |
| Valsartan 80 | 0,29 | 7,83 | 0,12 | 0,03 | 4,00 |
| Enalapril 20 | 0,06 | 8,21 | -0,23 | 0,38 | -0,61 |
| Olmesartan 20 | 0,89 | 8,22 | 0,83 | 0,01 | 83,00 |
| Losartan 50 | 0,15 | 8,37 | -0,74 | 0,15 | -4,93 |
| Atenolol 100 | 0,07 | 8,82 | -0,08 | 0,45 | -0,18 |
| Indapamide 1,25 + Lisinopril 20 | 0,28 | 8,87 | 0,21 | 0,05 | 4,20 |
| Bisorpolol 10 | 0,11 | 8,94 | -0,17 | 0,07 | -2,43 |
| Lisinopril 20 + Amlodipine 5 | 0,27 | 9,17 | 0,16 | 0,23 | 0,70 |
| Lisinopril 20 + Indapamide 1,5 | 0,31 | 9,22 | 0,04 | 0,05 | 0,80 |
| Valsartan 160 | 0,58 | 9,71 | 0,27 | 0,49 | 0,55 |

**Table 85: ICER. Exclusion of dominated therapies. DBP reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Amlodipine 5 | 0,04 | 5,95 | 0,04 | 5,95 | 0,01 |
| Indapamide 1,5 | 0,08 | 6,00 | 0,04 | 0,05 | 0,80 |
| Enalapril 10 | 0,04 | 6,71 | -0,04 | 0,71 | -0,06 |
| Atenolol 50 | 0,08 | 7,26 | 0,04 | 0,55 | 0,07 |
| Bisorpolol 5 | 0,05 | 7,31 | -0,03 | 0,05 | -0,60 |
| Ramipril 5 | 0,17 | 7,80 | 0,12 | 0,49 | 0,24 |
| Enalapril 20 | 0,06 | 8,21 | -0,11 | 0,41 | -0,27 |
| Atenolol 100 | 0,07 | 8,82 | 0,01 | 0,61 | 0,02 |

| | | | | | |
|---|---|---|---|---|---|
| Bisorpolol 10 | 0,11 | 8,94 | 0,04 | 0,12 | 0,33 |
| Lisinopril 20 + Amlodipine 5 | 0,27 | 9,17 | 0,16 | 0,23 | 0,70 |
| Lisinopril 20 + Indapamide 1,5 | 0,31 | 9,22 | 0,04 | 0,05 | 0,80 |
| Valsartan 160 | 0,58 | 9,71 | 0,27 | 0,49 | 0,55 |

**Table 86: ICER. Exclusion of therapies with higher ICER. DBP reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Amlodipine 5 | 0,04 | 5,95 | 0,04 | 5,95 | 0,01 |
| Enalapril 10 | 0,04 | 6,71 | 0,00 | 0,76 | 0,00 |
| Bisorpolol 5 | 0,05 | 7,31 | 0,01 | 0,60 | 0,02 |
| Enalapril 20 | 0,06 | 8,21 | 0,01 | 0,90 | 0,01 |
| Atenolol 100 | 0,07 | 8,82 | 0,01 | 0,61 | 0,02 |
| Bisorpolol 10 | 0,11 | 8,94 | 0,04 | 0,12 | 0,33 |
| Lisinopril 20 + Amlodipine 5 | 0,27 | 9,17 | 0,16 | 0,23 | 0,70 |
| Lisinopril 20 + Indapamide 1,5 | 0,31 | 9,22 | 0,04 | 0,05 | 0,80 |
| Valsartan 160 | 0,58 | 9,71 | 0,27 | 0,49 | 0,55 |

**Table 87: ICER. Exclusion of therapies with higher ICER. DBP reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Amlodipine 5 | 0,04 | 5,95 | 0,04 | 5,95 | 0,01 |
| Enalapril 10 | 0,04 | 6,71 | 0,00 | 0,76 | 0,00 |
| Bisorpolol 5 | 0,05 | 7,31 | 0,01 | 0,60 | 0,02 |
| Enalapril 20 | 0,06 | 8,21 | 0,01 | 0,90 | 0,01 |
| Atenolol 100 | 0,07 | 8,82 | 0,01 | 0,61 | 0,02 |

**Table 88: ICER. Exclusion of therapies with higher ICER. DBP reduction ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Amlodipine 5 | 0,04 | 5,95 | 0,04 | 5,95 | 0,01 |
| Enalapril 10 | 0,04 | 6,71 | 0,00 | 0,76 | 0,00 |
| Enalapril 20 | 0,06 | 8,21 | 0,02 | 1,50 | 0,01 |

**Table 89: ICER. Exclusion of dominated therapies. DBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Olmesartan 40 | 1,20 | 10,02 | 1,20 | 10,02 | 0,12 |
| Nevibolol 5 | 0,28 | 10,40 | -0,92 | 0,38 | -2,42 |
| Lisinopril 20 + Amlodipine 10 | 0,31 | 10,49 | 0,03 | 0,09 | 0,33 |
| HCTZ 25 | 0,12 | 12,64 | -0,19 | 2,15 | -0,09 |
| Diltiazem 240 | 0,61 | 12,69 | 0,49 | 0,05 | 9,80 |
| Lisinopril 20 + HCTZ 12,5 | 0,29 | 13,48 | -0,32 | 0,79 | -0,41 |
| Ramipril 5 + Amlodipine 5 | 0,21 | 13,75 | -0,08 | 0,27 | -0,30 |
| Indapamide 1,5 + Ramipril 5 | 0,26 | 13,80 | 0,05 | 0,05 | 1,00 |
| Enalapril 20 + Indapamide 1,25 | 0,11 | 13,86 | -0,15 | 0,06 | -2,50 |
| Enalapril 20 + Amlodipine 5 | 0,10 | 14,16 | -0,01 | 0,30 | -0,03 |
| Olmesartan 20 + Amlodipine 5 | 0,93 | 14,17 | 0,83 | 0,01 | 83,00 |
| Enalapril 20 + Indapamide 1,5 | 0,14 | 14,21 | -0,79 | 0,04 | -19,75 |

**Table 90: ICER. Exclusion of dominated therapies. DBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Nevibolol 5 | 0,28 | 10,40 | 0,28 | 10,40 | 0,03 |
| HCTZ 25 | 0,12 | 12,64 | -0,16 | 2,24 | -0,07 |
| Ramipril 5 + Amlodipine 5 | 0,21 | 13,75 | 0,09 | 1,11 | 0,08 |
| Enalapril 20 + Amlodipine 5 | 0,10 | 14,16 | -0,11 | 0,41 | -0,27 |
| Enalapril 20 + Indapamide 1,5 | 0,14 | 14,21 | 0,04 | 0,05 | 0,80 |

**Table 91: ICER. Exclusion of dominated therapies. DBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| HCTZ 25 | 0,12 | 12,64 | 0,12 | 12,64 | 0,01 |
| Enalapril 20 + Amlodipine 5 | 0,10 | 14,16 | -0,02 | 1,52 | -0,01 |
| Enalapril 20 + Indapamide 1,5 | 0,14 | 14,21 | 0,04 | 0,05 | 0,80 |

**Table 92: ICER. Exclusion of therapies with higher ICER. DBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + Amlodipine 5 | 0,10 | 14,16 | 0,10 | 14,16 | 0,01 |
| Enalapril 20 + Indapamide 1,5 | 0,14 | 14,21 | 0,04 | 0,05 | 0,80 |

**Table 93: ICER. Exclusion of therapies with higher ICER. DBP reduction 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + Amlodipine 5 | 0,10 | 14,16 | 0,10 | 14,16 | 0,01 |

**Table 94: ICER. Exclusion of dominated therapies. DBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Amlodipine 10 + Ramipril 5 | 0,26 | 15,07 | 0,26 | 15,07 | 0,02 |
| Enalapril 20 + Amlodipine 10 | 0,14 | 15,48 | -0,12 | 0,41 | -0,29 |
| Olmesartan 20 + Amlodipine 10 | 0,97 | 15,49 | 0,83 | 0,01 | 83,00 |
| Valsartan 160 + Amlodipine 5 | 0,62 | 15,66 | -0,35 | 0,17 | -2,06 |
| Lisinopril 20 + HCTZ 25 | 0,34 | 15,86 | -0,28 | 0,20 | -1,40 |
| Diltiazem 240 + Lisinopril 20 | 0,84 | 15,91 | 0,50 | 0,05 | 10,00 |
| Olmesartan 40 + Amlodipine 5 | 1,24 | 15,97 | 0,40 | 0,06 | 6,67 |
| Valsartan 160 + Amlodipine 10 | 0,67 | 16,98 | -0,57 | 1,01 | -0,56 |
| Olmesartan 40 + Amlodipine 10 | 1,28 | 17,29 | 0,61 | 0,31 | 1,97 |
| HCTZ 12,5 + Ramipril 5 | 0,23 | 18,06 | -1,05 | 0,77 | -1,36 |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 18,47 | -0,11 | 0,41 | -0,27 |
| Olmesartan 20 + HCTZ 12,5 | 0,94 | 18,48 | 0,82 | 0,01 | 82,00 |
| Losartan 50 + HCTZ 12,5 | 0,21 | 18,63 | -0,73 | 0,15 | -4,87 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 5 | 0,33 | 19,43 | 0,12 | 0,80 | 0,15 |
| Valsartan 160 + HCTZ 12,5 | 0,64 | 19,97 | 0,31 | 0,54 | 0,57 |

**Table 95: ICER. Exclusion of dominated therapies. DBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + Amlodipine 10 | 0,14 | 15,48 | 0,14 | 15,48 | 0,01 |
| Lisinopril 20 + HCTZ 25 | 0,34 | 15,86 | 0,20 | 0,38 | 0,53 |
| Diltiazem 240 + Lisinopril 20 | 0,84 | 15,91 | 0,50 | 0,05 | 10,00 |
| Valsartan 160 + Amlodipine 10 | 0,67 | 16,98 | -0,17 | 1,07 | -0,16 |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 18,47 | -0,55 | 1,49 | -0,37 |
| Losartan 50 + HCTZ 12,5 | 0,21 | 18,63 | 0,09 | 0,16 | 0,56 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 5 | 0,33 | 19,43 | 0,12 | 0,80 | 0,15 |
| Valsartan 160 + HCTZ 12,5 | 0,64 | 19,97 | 0,31 | 0,54 | 0,57 |

**Table 96: ICER. Exclusion of dominated therapies. DBP reduction 15,01-20,00 mmHg..**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + Amlodipine 10 | 0,14 | 15,48 | 0,14 | 15,48 | 0,01 |
| Lisinopril 20 + HCTZ 25 | 0,34 | 15,86 | 0,20 | 0,38 | 0,53 |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 18,47 | -0,22 | 2,61 | -0,08 |
| Losartan 50 + HCTZ 12,5 | 0,21 | 18,63 | 0,09 | 0,16 | 0,56 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 5 | 0,33 | 19,43 | 0,12 | 0,80 | 0,15 |
| Valsartan 160 + HCTZ 12,5 | 0,64 | 19,97 | 0,31 | 0,54 | 0,57 |

**Table 97: ICER. Exclusion of dominated therapies. DBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + Amlodipine 10 | 0,14 | 15,48 | 0,14 | 15,48 | 0,01 |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 18,47 | -0,02 | 2,99 | -0,01 |
| Losartan 50 + HCTZ 12,5 | 0,21 | 18,63 | 0,09 | 0,16 | 0,56 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 5 | 0,33 | 19,43 | 0,12 | 0,80 | 0,15 |
| Valsartan 160 + HCTZ 12,5 | 0,64 | 19,97 | 0,31 | 0,54 | 0,57 |

**Table 98: ICER. Exclusion of therapies with higher ICER. DBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 18,47 | 0,12 | 18,47 | 0,01 |
| Losartan 50 + HCTZ 12,5 | 0,21 | 18,63 | 0,09 | 0,16 | 0,56 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 5 | 0,33 | 19,43 | 0,12 | 0,80 | 0,15 |
| Valsartan 160 + HCTZ 12,5 | 0,64 | 19,97 | 0,31 | 0,54 | 0,57 |

**Table 99: ICER. Exclusion of therapies with higher ICER. DBP reduction 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 | 0,12 | 18,47 | 0,12 | 18,47 | 0,01 |

**Table 100: ICER. Exclusion of dominated therapies. DBP reduction >20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction >20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Olmesartan 40 + HCTZ 12,5 | 1,26 | 20,28 | 1,26 | 20,28 | 0,06 |
| HCTZ 25 + Ramipril 5 | 0,29 | 20,44 | -0,97 | 0,16 | -6,06 |
| Diltiazem 240 + Ramipril 5 | 0,78 | 20,49 | 0,49 | 0,05 | 9,80 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 10 | 0,37 | 20,75 | -0,41 | 0,26 | -1,58 |
| Olmesartan 20 + HCTZ 25 | 1,00 | 20,86 | 0,63 | 0,11 | 5,73 |
| Enalapril 20 + Diltiazem 240 | 0,67 | 20,90 | -0,33 | 0,04 | -8,25 |
| Olmesartan 40 + HCTZ 25 | 1,32 | 22,66 | 0,65 | 1,76 | 0,37 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 24,42 | -1,16 | 1,76 | -0,66 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 25,74 | 0,04 | 1,32 | 0,03 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 25,92 | 0,48 | 0,18 | 2,67 |
| Olmesartan 40 + Amlodipine 5 + HCTZ 12,5 | 1,30 | 26,23 | 0,62 | 0,31 | 2,00 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 27,24 | -0,58 | 1,01 | -0,57 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 27,55 | 0,62 | 0,31 | 2,00 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 29,93 | 0,06 | 2,38 | 0,03 |

**Table 101: ICER. Exclusion of dominated therapies. DBP reduction >20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction >20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| HCTZ 25 + Ramipril 5 | 0,29 | 20,44 | 0,29 | 20,44 | 0,01 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 10 | 0,37 | 20,75 | 0,08 | 0,31 | 0,26 |
| Enalapril 20 + Diltiazem 240 | 0,67 | 20,90 | 0,30 | 0,15 | 2,00 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 24,42 | -0,51 | 3,52 | -0,14 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 25,74 | 0,04 | 1,32 | 0,03 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 25,92 | 0,48 | 0,18 | 2,67 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 27,24 | 0,04 | 1,32 | 0,03 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 27,55 | 0,62 | 0,31 | 2,00 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 29,93 | 0,06 | 2,38 | 0,03 |

**Table 102: ICER. Exclusion of dominated therapies. DBP reduction >20,00 mmHg**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction >20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| HCTZ 25 + Ramipril 5 | 0,29 | 20,44 | 0,29 | 20,44 | 0,01 |
| Lisinopril 20 + HCTZ 12,5 + Amlodipine 10 | 0,37 | 20,75 | 0,08 | 0,31 | 0,26 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 24,42 | -0,21 | 3,67 | -0,06 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 25,74 | 0,04 | 1,32 | 0,03 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 25,92 | 0,48 | 0,18 | 2,67 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 27,24 | 0,04 | 1,32 | 0,03 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 27,55 | 0,62 | 0,31 | 2,00 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 29,93 | 0,06 | 2,38 | 0,03 |

**Table 103: ICER. Exclusion of dominated therapies. DBP reduction >20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction >20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| HCTZ 25 + Ramipril 5 | 0,29 | 20,44 | 0,29 | 20,44 | 0,01 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 24,42 | -0,13 | 3,98 | -0,03 |

| | | | | | |
|---|---|---|---|---|---|
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 25,74 | 0,04 | 1,32 | 0,03 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 25,92 | 0,48 | 0,18 | 2,67 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 27,24 | 0,04 | 1,32 | 0,03 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 27,55 | 0,62 | 0,31 | 2,00 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 29,93 | 0,06 | 2,38 | 0,03 |

**Table 104: ICER. Exclusion of therapies with higher ICER. DBP reduction >20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction >20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 24,42 | 0,16 | 24,42 | 0,01 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 25,74 | 0,04 | 1,32 | 0,03 |
| Valsartan 160 + Amlodipine 5 + HCTZ 12,5 | 0,68 | 25,92 | 0,48 | 0,18 | 2,67 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 27,24 | 0,04 | 1,32 | 0,03 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 12,5 | 1,34 | 27,55 | 0,62 | 0,31 | 2,00 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 29,93 | 0,06 | 2,38 | 0,03 |

**Table 105: ICER. Exclusion of therapies with higher ICER. DBP reduction >20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction >20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 24,42 | 0,16 | 24,42 | 0,01 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 25,74 | 0,04 | 1,32 | 0,03 |
| Valsartan 160 + Amlodipine 10 + HCTZ 12,5 | 0,72 | 27,24 | 0,52 | 1,50 | 0,35 |
| Olmesartan 40 + Amlodipine 10 + HCTZ 25 | 1,40 | 29,93 | 0,68 | 2,69 | 0,25 |

**Table 106: ICER. Exclusion of therapies with higher ICER. DBP reduction >20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction >20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| Active ingredient | Cost (€) [C] | Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E] | Cost increase [ΔC] | Effectiveness increase [ΔE] | ICER [ΔC/ΔE] |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 5 | 0,16 | 24,42 | 0,16 | 24,42 | 0,01 |
| Enalapril 20 + HCTZ 12,5 + Amlodipine 10 | 0,20 | 25,74 | 0,04 | 1,32 | 0,03 |

## Annex 16

**Table 107: Sensitivity analysis. ICER. SBP 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **Bisorpolol 5** | **0,05** | **10,59** | **0,05** | **10,59** | **0,00** |
| **Ramipril 5** | **0,17** | **10,17** | **0,12** | **-0,42** | **-0,29** |
| **Valsartan 80** | **0,29** | **10,33** | **0,24** | **-0,26** | **-0,92** |
| **Losartan 50** | **0,15** | **10,67** | **0,10** | **0,08** | **1,25** |
| **Olmesartan 20** | **0,89** | **10,84** | **0,84** | **0,25** | **3,36** |
| **Atenolol 50** | **0,08** | **11,25** | **0,03** | **0,66** | **0,05** |
| **Lisinopril 20 + Amlodipine 5** | **0,27** | **12,05** | **0,22** | **1,46** | **0,15** |
| **Indapamide 1,25 + Lisinopril 20** | **0,28** | **12,76** | **0,23** | **2,17** | **0,11** |
| **Valsartan 160** | **0,58** | **12,81** | **0,53** | **2,22** | **0,24** |
| **Bisorpolol 10** | **0,11** | **12,95** | **0,06** | **2,36** | **0,03** |
| **Olmesartan 40** | **1,20** | **13,22** | **1,15** | **2,63** | **0,44** |
| **Lisinopril 20 + Indapamide 1,5** | **0,31** | **13,27** | **0,26** | **2,68** | **0,10** |
| **Atenolol 100** | **0,08** | **13,65** | **0,03** | **3,06** | **0,01** |
| **Lisinopril 20 + Amlodipine 10** | **0,31** | **13,74** | **0,26** | **3,15** | **0,08** |
| **Nevibolol 5** | **0,28** | **14,96** | **0,23** | **4,37** | **0,05** |

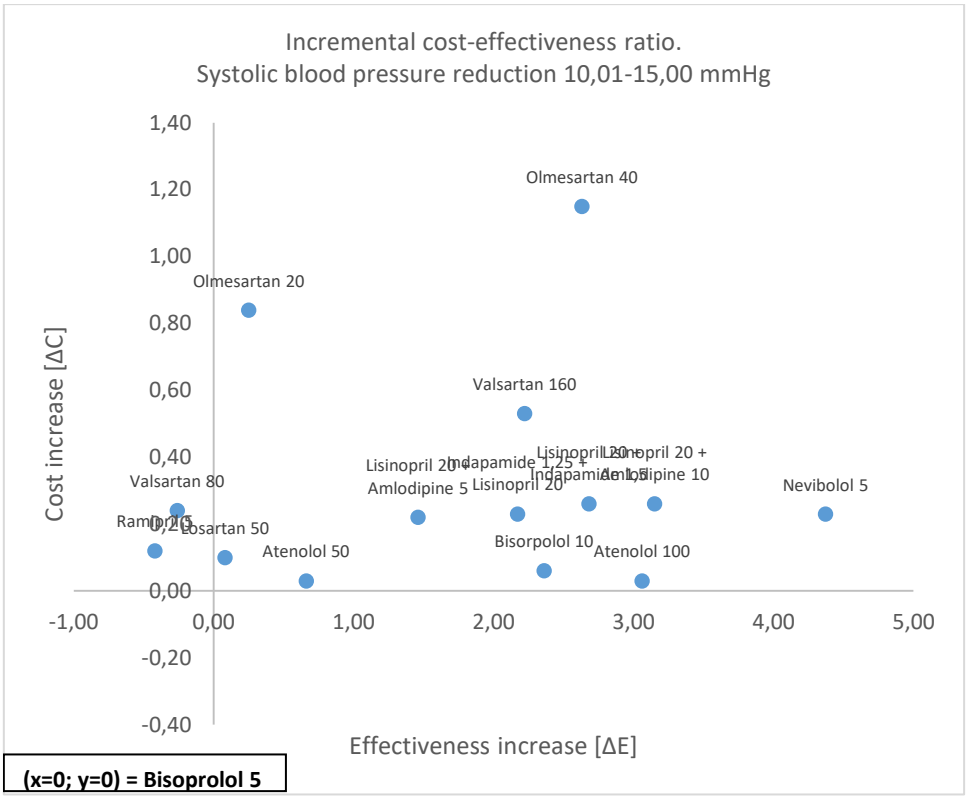



**Figure 10: Sensitivity analysis. ICER. SBP 10,01-15,00 mmHg.**

**Table 108: Sensitivity analysis. ICER. SBP 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **HCTZ 25** | **0,12** | **15,85** | **0,12** | **15,85** | **0,01** |
| **Enalapril 20 + Amlodipine 5** | **0,10** | **16,60** | **-0,02** | **0,75** | **-0,03** |
| **Lisinopril 20 + HCTZ 12,5** | **0,29** | **17,24** | **0,17** | **1,39** | **0,12** |
| **Enalapril 20 + Indapamide 1,25** | **0,11** | **17,31** | **-0,01** | **1,46** | **-0,01** |
| **Enalapril 20 + Indapamide 1,5** | **0,14** | **17,82** | **0,02** | **1,97** | **0,01** |
| **Ramipril 5 + Amlodipine 5** | **0,21** | **17,84** | **0,09** | **1,99** | **0,05** |
| **Diltiazem 240** | **0,61** | **18,24** | **0,49** | **2,39** | **0,21** |
| **Enalapril 20 + Amlodipine 10** | **0,14** | **18,29** | **0,02** | **2,44** | **0,01** |
| **Olmesartan 20 + Amlodipine 5** | **0,93** | **18,51** | **0,81** | **2,66** | **0,30** |
| **Indapamide 1,5 + Ramipril 5** | **0,26** | **19,06** | **0,14** | **3,21** | **0,04** |
| **Amlodipine 10 + Ramipril 5** | **0,26** | **19,53** | **0,14** | **3,68** | **0,04** |

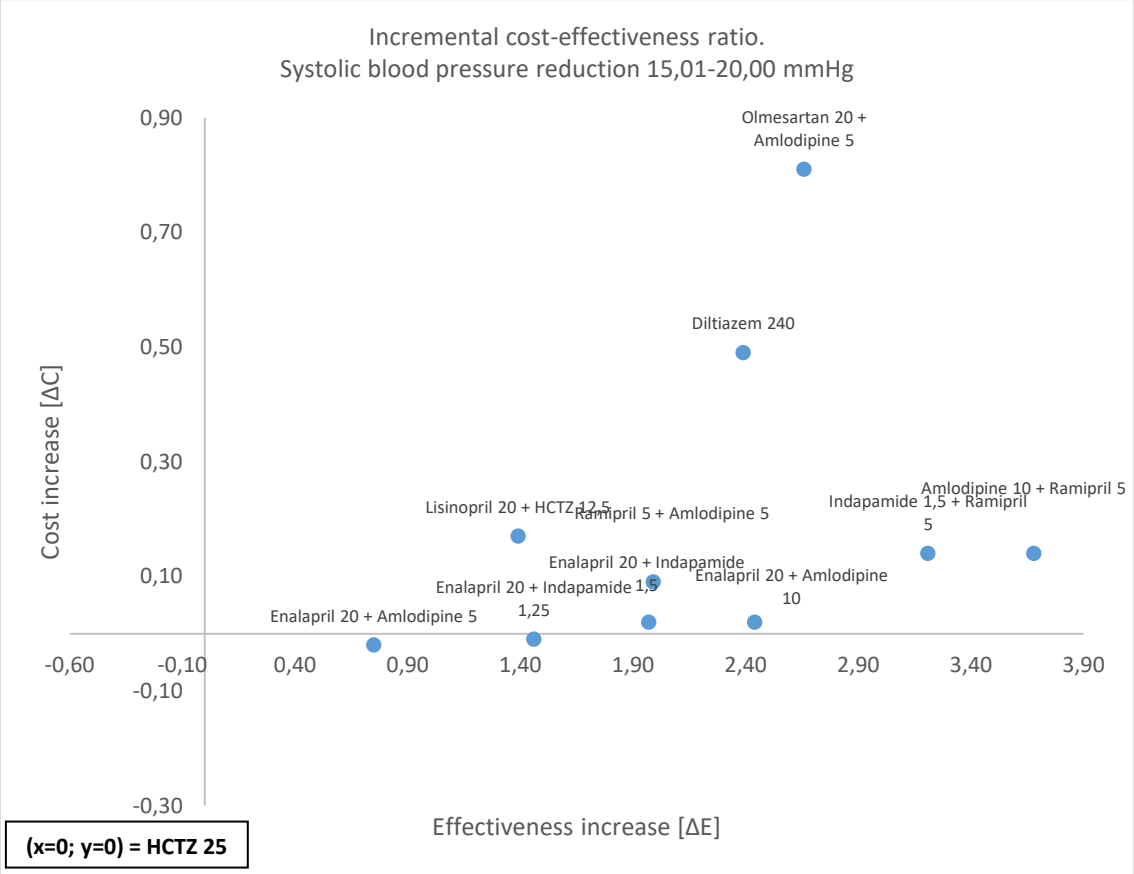



**Figure 11: Sensitivity analysis. ICER. SBP 15,01-20,00 mmHg.**

**Table 109: Sensitivity analysis. ICER. SBP 20,01-25,00**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction 20,01-25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **Enalapril 20 + HCTZ 12,5** | **0,12** | **21,79** | **0,12** | **21,79** | **0,01** |
| **Olmesartan 20 + Amlodipine 10** | **0,97** | **20,20** | **0,85** | **-1,59** | **-0,53** |
| **Lisinopril 20 + HCTZ 25** | **0,34** | **20,23** | **0,22** | **-1,56** | **-0,14** |
| **Valsartan 160 + Amlodipine 5** | **0,62** | **20,48** | **0,50** | **-1,31** | **-0,38** |
| **Olmesartan 40 + Amlodipine 5** | **1,24** | **20,89** | **1,12** | **-0,90** | **-1,24** |
| **Valsartan 160 + Amlodipine 10** | **0,67** | **22,17** | **0,55** | **0,38** | **1,45** |
| **Olmesartan 40 + Amlodipine 10** | **1,28** | **22,58** | **1,16** | **0,79** | **1,47** |
| **Diltiazem 240 + Lisinopril 20** | **0,84** | **22,62** | **0,72** | **0,83** | **0,87** |
| **HCTZ 12,5 + Ramipril 5** | **0,23** | **23,03** | **0,11** | **1,24** | **0,09** |
| **Losartan 50 + HCTZ 12,5** | **0,21** | **23,53** | **0,09** | **1,74** | **0,05** |
| **Olmesartan 20 + HCTZ 12,5** | **0,94** | **23,70** | **0,82** | **1,91** | **0,43** |
| **Lisinopril 20 + HCTZ 12,5 + Amlodipine 5** | **0,33** | **24,91** | **0,21** | **3,12** | **0,07** |

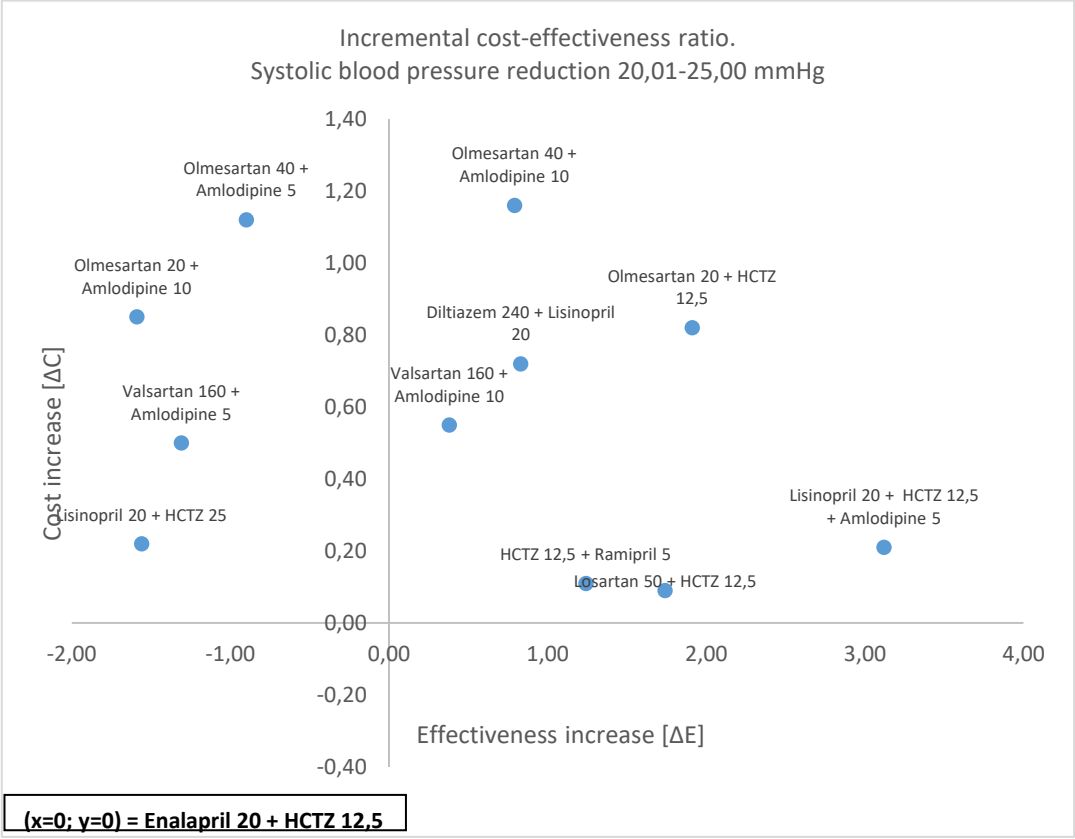



**Figure 12: Sensitivity analysis. ICER. SBP 20,01-25,00**

**Table 110: Sensitivity analysis. ICER. SBP >25,00 mmHg.**

| Incremental cost-effectiveness ratio. Systolic blood pressure reduction >25,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Systolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **Olmesartan 40 + Amlodipine 10 + HCTZ 25** | **1,40** | **38,43** | **1,40** | **38,43** | **0,04** |
| **Valsartan 160 + HCTZ 12,5** | **0,64** | **25,67** | **-0,76** | **-12,76** | **0,06** |
| **HCTZ 25 + Ramipril 5** | **0,29** | **26,02** | **-1,11** | **-12,41** | **0,09** |
| **Olmesartan 40 + HCTZ 12,5** | **1,26** | **26,08** | **-0,14** | **-12,35** | **0,01** |
| **Lisinopril 20 + HCTZ 12,5 + Amlodipine 10** | **0,37** | **26,60** | **-1,03** | **-11,83** | **0,09** |
| **Olmesartan 20 + HCTZ 25** | **1,00** | **26,69** | **-0,40** | **-11,74** | **0,03** |
| **Enalapril 20 + Diltiazem 240** | **0,67** | **27,17** | **-0,73** | **-11,26** | **0,06** |
| **Diltiazem 240 + Ramipril 5** | **0,78** | **28,41** | **-0,62** | **-10,02** | **0,06** |
| **Olmesartan 40 + HCTZ 25** | **1,32** | **29,07** | **-0,08** | **-9,36** | **0,01** |
| **Enalapril 20 + HCTZ 12,5 + Amlodipine 5** | **0,16** | **29,46** | **-1,24** | **-8,97** | **0,14** |
| **Enalapril 20 + HCTZ 12,5 + Amlodipine 10** | **0,20** | **31,15** | **-1,20** | **-7,28** | **0,16** |
| **Valsartan 160 + Amlodipine 5 + HCTZ 12,5** | **0,68** | **33,34** | **-0,72** | **-5,09** | **0,14** |
| **Olmesartan 40 + Amlodipine 5 + HCTZ 12,5** | **1,30** | **33,75** | **-0,10** | **-4,68** | **0,02** |
| **Valsartan 160 + Amlodipine 10 + HCTZ 12,5** | **0,72** | **35,03** | **-0,68** | **-3,40** | **0,20** |
| **Olmesartan 40 + Amlodipine 10 + HCTZ 12,5** | **1,34** | **35,44** | **-0,06** | **-2,99** | **0,02** |

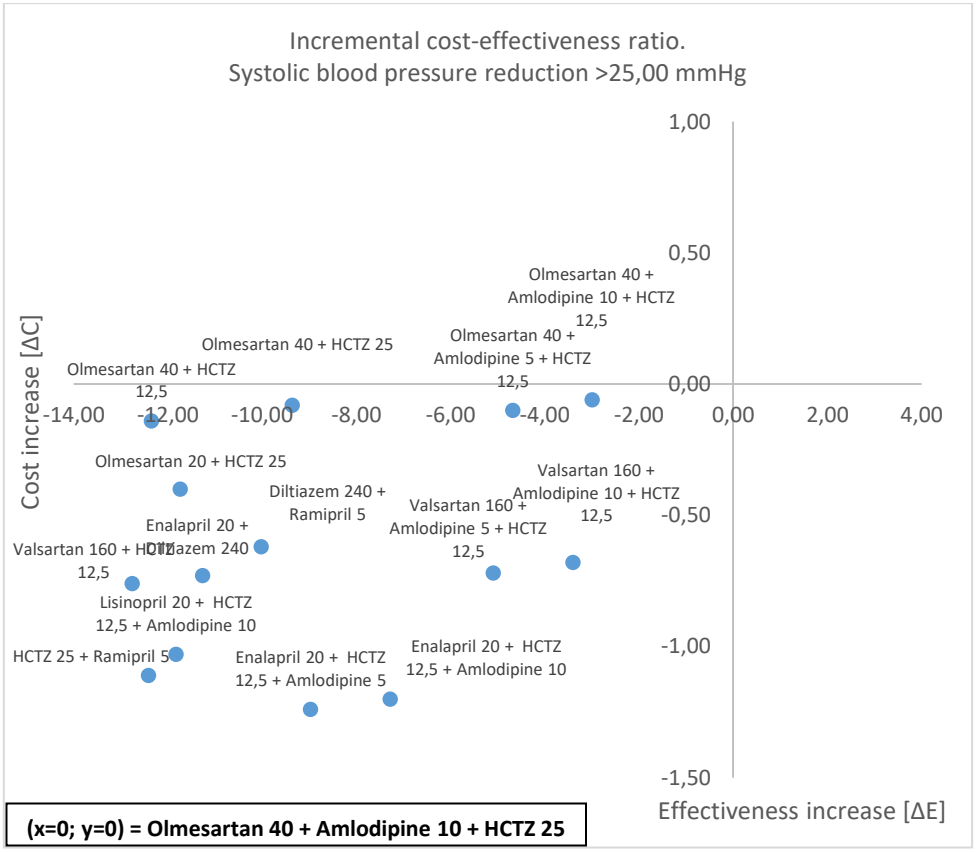



**Figure 13: Sensitivity analysis. ICER. SBP >25,00 mmHg.**

## Annex 17

**Table 111: Sensitivity analysis. ICER. DBP ≤10,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction ≤10,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **Enalapril 10** | **0,04** | **6,71** | **0,04** | **6,71** | **0,01** |
| **Lisinopril 20** | **0,23** | **3,22** | **0,19** | **-3,49** | **-0,05** |
| **Amlodipine 5** | **0,04** | **5,95** | **0,00** | **-0,76** | **0,00** |
| **Indapamide 1,5** | **0,08** | **6,00** | **0,04** | **-0,71** | **-0,06** |
| **Verapamil 240** | **0,34** | **6,56** | **0,30** | **-0,15** | **-2,00** |
| **Atenolol 50** | **0,08** | **7,26** | **0,04** | **0,55** | **0,07** |
| **Amlodipine 10** | **0,08** | **7,27** | **0,04** | **0,56** | **0,07** |
| **Bisorpolol 5** | **0,05** | **7,31** | **0,01** | **0,60** | **0,02** |
| **Ramipril 5** | **0,17** | **7,80** | **0,13** | **1,09** | **0,12** |
| **Valsartan 80** | **0,29** | **7,83** | **0,25** | **1,12** | **0,22** |
| **Enalapril 20** | **0,06** | **8,21** | **0,02** | **1,50** | **0,01** |
| **Olmesartan 20** | **0,89** | **8,22** | **0,85** | **1,51** | **0,56** |
| **Losartan 50** | **0,15** | **8,37** | **0,11** | **1,66** | **0,07** |
| **Atenolol 100** | **0,07** | **8,82** | **0,03** | **2,11** | **0,01** |
| **Indapamide 1,25 + Lisinopril 20** | **0,28** | **8,87** | **0,24** | **2,16** | **0,11** |
| **Bisorpolol 10** | **0,11** | **8,94** | **0,07** | **2,23** | **0,03** |
| **Lisinopril 20 + Amlodipine 5** | **0,27** | **9,17** | **0,23** | **2,46** | **0,09** |
| **Lisinopril 20 + Indapamide 1,5** | **0,31** | **9,22** | **0,27** | **2,51** | **0,11** |
| **Valsartan 160** | **0,58** | **9,71** | **0,54** | **3,00** | **0,18** |

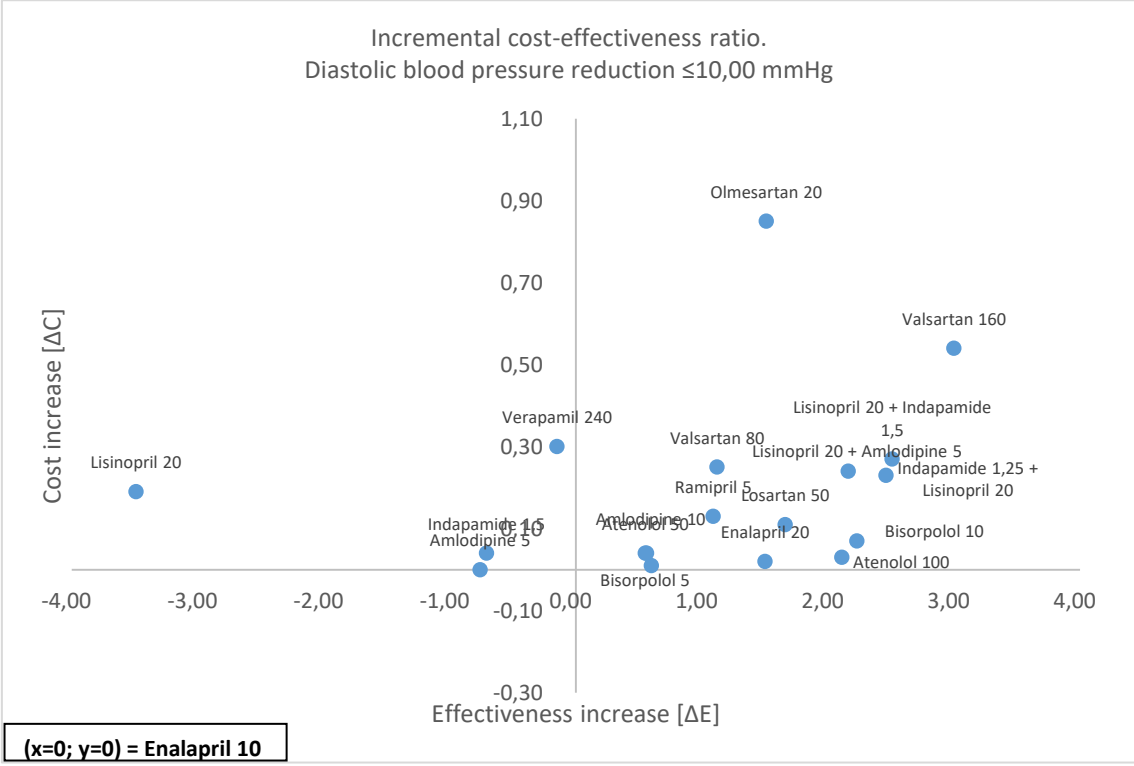



**Figure 14: Sensitivity analysis. ICER. DBP ≤10,00 mmHg.**

**Table 112: Sensitivity analysis. ICER. DBP 10,01-15,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 10,01-15,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **HCTZ 25** | **0,12** | **12,64** | **0,12** | **12,64** | **0,01** |
| **Olmesartan 40** | **1,20** | **10,02** | **1,08** | **-2,62** | **-0,41** |
| **Nevibolol 5** | **0,28** | **10,40** | **0,16** | **-2,24** | **-0,07** |
| **Lisinopril 20 + Amlodipine 10** | **0,31** | **10,49** | **0,19** | **-2,15** | **-0,09** |
| **Diltiazem 240** | **0,61** | **12,69** | **0,49** | **0,05** | **9,80** |
| **Lisinopril 20 + HCTZ 12,5** | **0,29** | **13,48** | **0,17** | **0,84** | **0,20** |
| **Ramipril 5 + Amlodipine 5** | **0,21** | **13,75** | **0,09** | **1,11** | **0,08** |
| **Indapamide 1,5 + Ramipril 5** | **0,26** | **13,80** | **0,14** | **1,16** | **0,12** |
| **Enalapril 20 + Indapamide 1,25** | **0,11** | **13,86** | **-0,01** | **1,22** | **-0,01** |
| **Enalapril 20 + Amlodipine 5** | **0,10** | **14,16** | **-0,02** | **1,52** | **-0,01** |
| **Olmesartan 20 + Amlodipine 5** | **0,93** | **14,17** | **0,81** | **1,53** | **0,53** |
| **Enalapril 20 + Indapamide 1,5** | **0,14** | **14,21** | **0,02** | **1,57** | **0,01** |

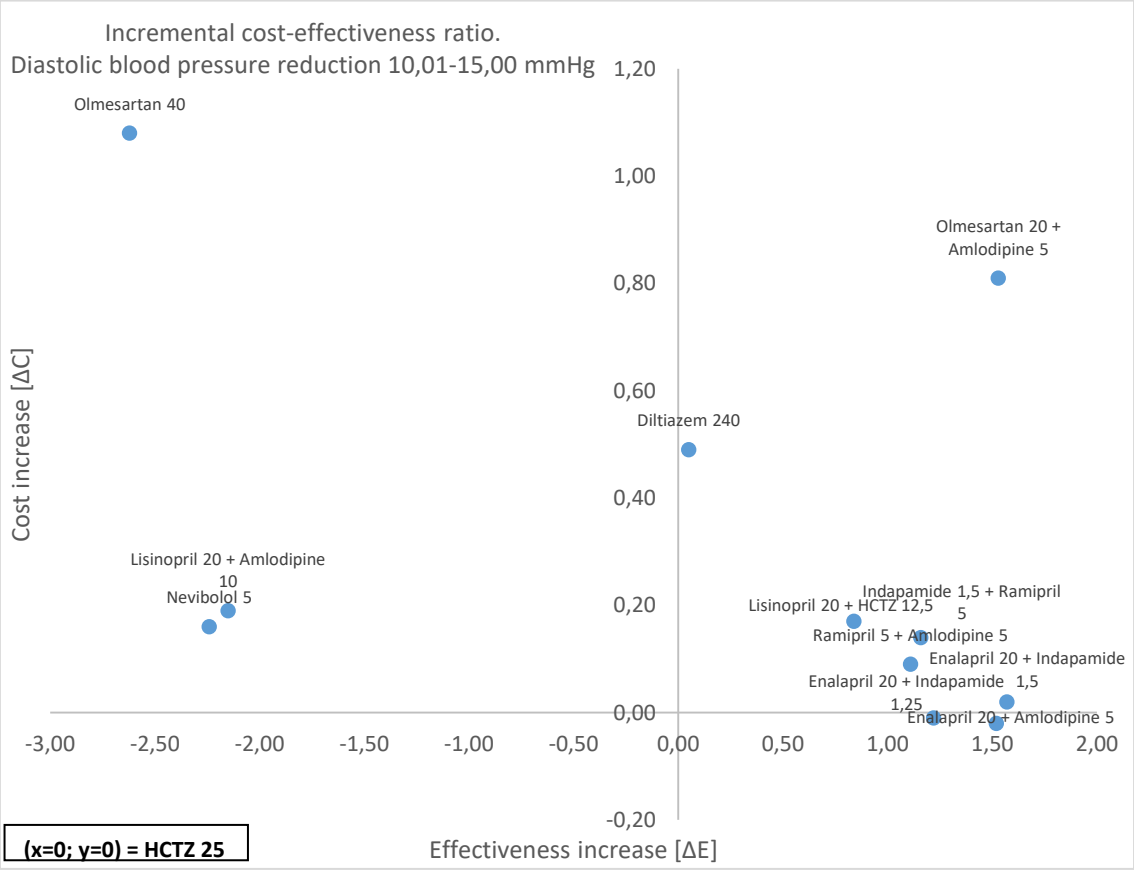



**Figure 15: Sensitivity analysis. ICER. DBP 10,01-15,00 mmHg.**

**Table 113: Sensitivity analysis. ICER. DBP 15,01-20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction 15,01-20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **Enalapril 20 + HCTZ 12,5** | **0,12** | **18,47** | **0,12** | **18,47** | **0,01** |
| **Amlodipine 10 + Ramipril 5** | **0,26** | **15,07** | **0,14** | **-3,40** | **-0,04** |
| **Enalapril 20 + Amlodipine 10** | **0,14** | **15,48** | **0,02** | **-2,99** | **-0,01** |
| **Olmesartan 20 + Amlodipine 10** | **0,97** | **15,49** | **0,85** | **-2,98** | **-0,29** |
| **Valsartan 160 + Amlodipine 5** | **0,62** | **15,66** | **0,50** | **-2,81** | **-0,18** |
| **Lisinopril 20 + HCTZ 25** | **0,34** | **15,86** | **0,22** | **-2,61** | **-0,08** |
| **Diltiazem 240 + Lisinopril 20** | **0,84** | **15,91** | **0,72** | **-2,56** | **-0,28** |
| **Olmesartan 40 + Amlodipine 5** | **1,24** | **15,97** | **1,12** | **-2,50** | **-0,45** |
| **Valsartan 160 + Amlodipine 10** | **0,67** | **16,98** | **0,55** | **-1,49** | **-0,37** |
| **Olmesartan 40 + Amlodipine 10** | **1,28** | **17,29** | **1,16** | **-1,18** | **-0,98** |
| **HCTZ 12,5 + Ramipril 5** | **0,23** | **18,06** | **0,11** | **-0,41** | **-0,27** |
| **Olmesartan 20 + HCTZ 12,5** | **0,94** | **18,48** | **0,82** | **0,01** | **82,00** |
| **Losartan 50 + HCTZ 12,5** | **0,21** | **18,63** | **0,09** | **0,16** | **0,56** |
| **Lisinopril 20 + HCTZ 12,5 + Amlodipine 5** | **0,33** | **19,43** | **0,21** | **0,96** | **0,22** |
| **Valsartan 160 + HCTZ 12,5** | **0,64** | **19,97** | **0,52** | **1,50** | **0,35** |

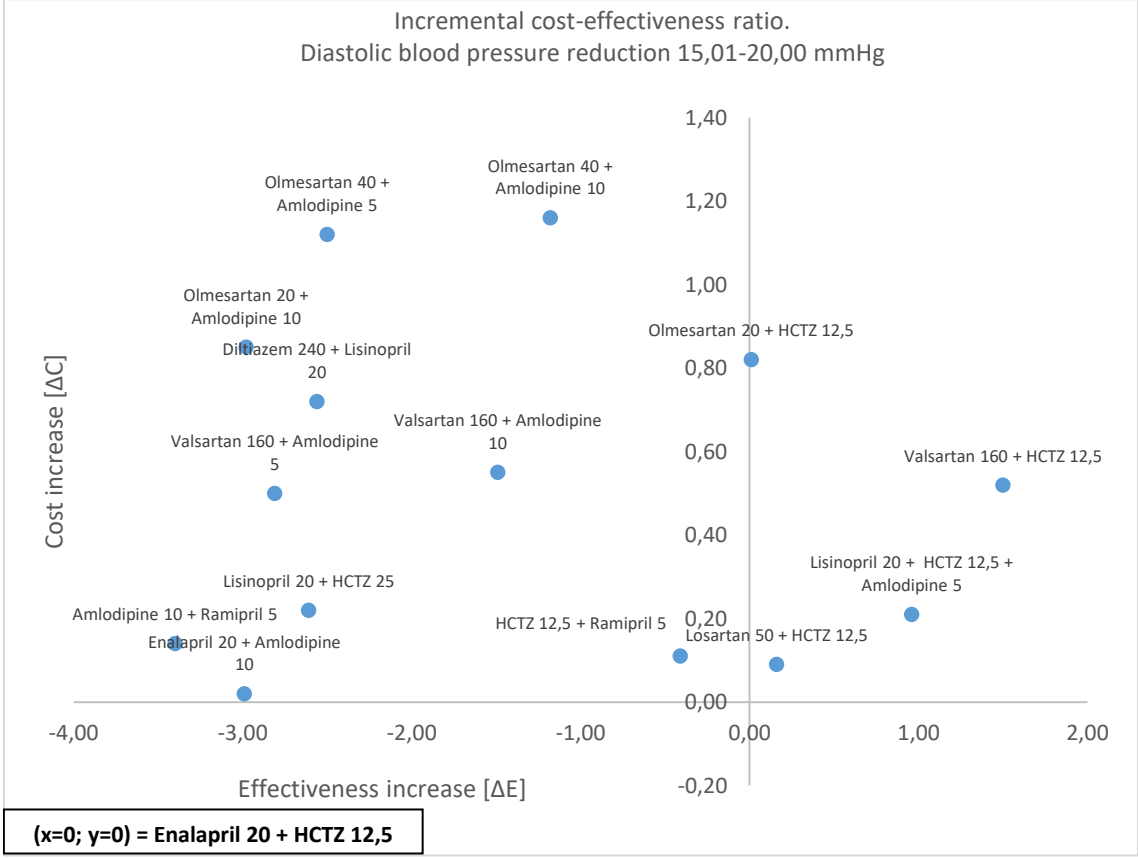



**Figure 16: Sensitivity analysis. ICER. DBP 15,01-20,00 mmHg.**

**Table 114: Sensitivity analysis. ICER. DBP >20,00 mmHg.**

| Incremental cost-effectiveness ratio. Diastolic blood pressure reduction >20,00 mmHg | | | | | |
|---|---|---|---|---|---|
| **Active ingredient** | **Cost (€) [C]** | **Effecttiveness (Adjusted reductions-Diastolic Pressure (mmHg)) [E]** | **Cost increase [ΔC]** | **Effectiveness increase [ΔE]** | **ICER [ΔC/ΔE]** |
| **Olmesartan 40 + Amlodipine 10 + HCTZ 25** | **1,40** | **29,93** | **1,40** | **29,93** | **0,05** |
| **Olmesartan 40 + HCTZ 12,5** | **1,26** | **20,28** | **-0,14** | **-9,65** | **0,01** |
| **HCTZ 25 + Ramipril 5** | **0,29** | **20,44** | **-1,11** | **-9,49** | **0,12** |
| **Diltiazem 240 + Ramipril 5** | **0,78** | **20,49** | **-0,62** | **-9,44** | **0,07** |
| **Lisinopril 20 + HCTZ 12,5 + Amlodipine 10** | **0,37** | **20,75** | **-1,03** | **-9,18** | **0,11** |
| **Olmesartan 20 + HCTZ 25** | **1,00** | **20,86** | **-0,40** | **-9,07** | **0,04** |
| **Enalapril 20 + Diltiazem 240** | **0,67** | **20,90** | **-0,73** | **-9,03** | **0,08** |
| **Olmesartan 40 + HCTZ 25** | **1,32** | **22,66** | **-0,08** | **-7,27** | **0,01** |
| **Enalapril 20 + HCTZ 12,5 + Amlodipine 5** | **0,16** | **24,42** | **-1,24** | **-5,51** | **0,23** |
| **Enalapril 20 + HCTZ 12,5 + Amlodipine 10** | **0,20** | **25,74** | **-1,20** | **-4,19** | **0,29** |
| **Valsartan 160 + Amlodipine 5 + HCTZ 12,5** | **0,68** | **25,92** | **-0,72** | **-4,01** | **0,18** |
| **Olmesartan 40 + Amlodipine 5 + HCTZ 12,5** | **1,30** | **26,23** | **-0,10** | **-3,70** | **0,03** |
| **Valsartan 160 + Amlodipine 10 + HCTZ 12,5** | **0,72** | **27,24** | **-0,68** | **-2,69** | **0,25** |
| **Olmesartan 40 + Amlodipine 10 + HCTZ 12,5** | **1,34** | **27,55** | **-0,06** | **-2,38** | **0,03** |

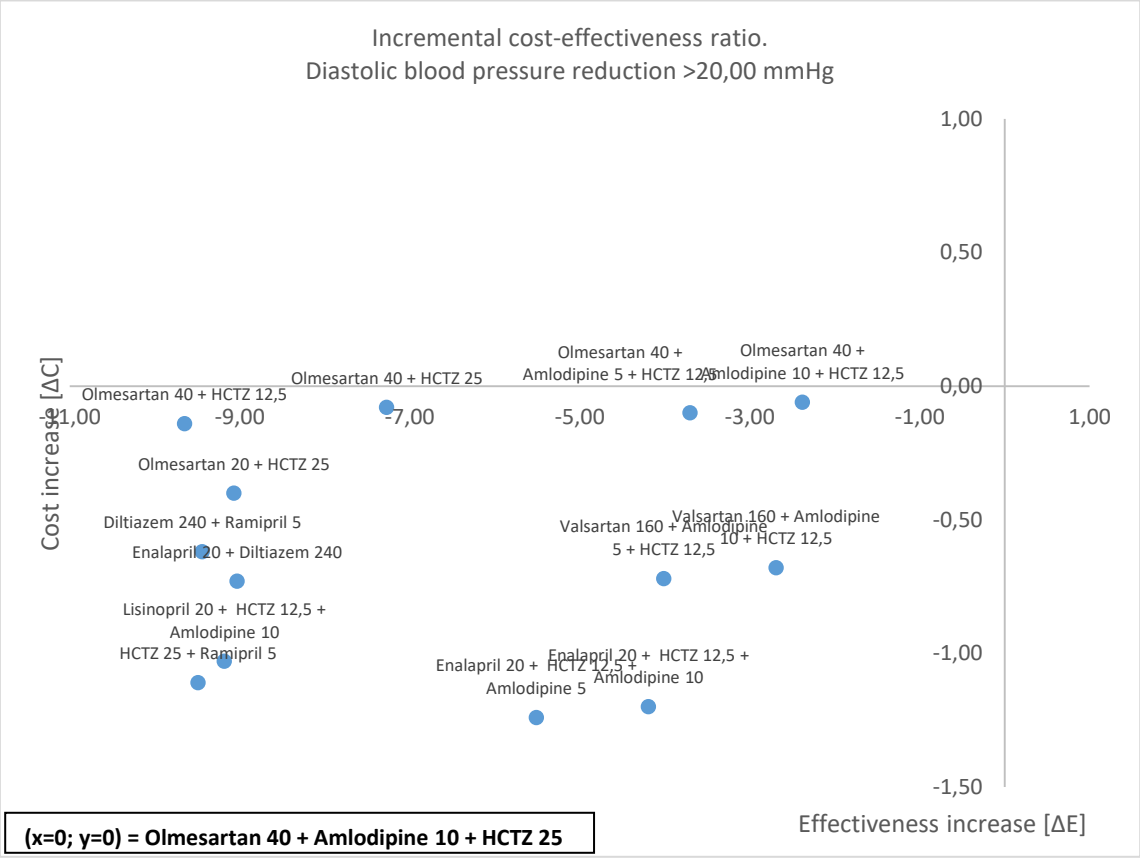



**Figure 17: Sensitivity analysis. ICER. DBP >20,00 mmHg**5