External reference pricing of medicinal products: simulation-based considerations for cross-country coordination

Final Report

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Acknowledgments

The authors would like to thank all country authority representatives (Austria, Belgium, Croatia, Cyprus, Czech Republic, Finland, Hungary, Iceland, Italy, Latvia, Lithuania, Malta, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, and United Kingdom) that kindly responded to this survey with precious information and the following organizations for their support in providing information, inputs and comments to build this report:

- European Federation of Pharmaceutical Industries & Associations (EFPIA)
- European Generic medicines Association (EGA)
- European Self-Medication Industry (AESGP)
- European Patients Forum (EPF)
- Pharmaceutical Group of the European Union (PGEU)
- European Hospital and Healthcare Federation (HOPE)

The authors would like to thank IMS Health, and namely Mr. Per Troein and Mrs Claire Machin, who provided price database for selected drugs.

This report was produced and funded under the EU Health Programme (2008-2013) in the frame of a specific contract with the Executive Agency for Health and Consumers (EAHC) acting under the mandate of the European Commission.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ASMR	Amélioration du Service Médical Rendu (Improvement in Actual Benefit)
AT	Austria
BE	Belgium
BG	Bulgaria
CH	Switzerland
CY	Cyprus
CZ	Czech Republic
DE	Germany
DES	Discrete Event Simulation
DK	Denmark
EE	Estonia
EEA	European Economic Area
EGA	European Generic medicines Association
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association
EHAP	Extraordinary Higher Price
EL	Greece
EMA	European Medicines Agency
ERP	External Reference Pricing
ES	Spain
EU	European Union
FI	Finland
FR	France
GDP	Gross Domestic Product
HAS	Haute Autorité de Santé (French National Authority for Health)
HR	Croatia
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
HU	Hungary
ICER	Incremental Cost-Effectiveness Ratio
IE	Ireland
IS	Iceland

ISPOR	International Society for Pharmacoeconomics and Outcome Research
IT	Italy
LT	Lithuania
LU	Luxembourg
LV	Latvia
MAP	Maximum allowed price
MS	Member State
MT	Malta
NICE	National Institute for Health and Care Excellence
NL	The Netherlands
NO	Norway
OECD	Organisation for Economic Co-operation and Development
PL	Poland
POM	Prescription-only medicines
PPP	Pharmacy purchasing price
PRP	Pharmacy Retail Price
PT	Portugal
QALY	Quality-Adjusted Life Year
RO	Romania
SE	Sweden
SI	Slovenia
SK	Slovakia
SMR	Service Médical Rendu (Actual benefit)
SMC	Scottish Medicines Consortium
UK	United Kingdom
US	United States
VAT	Value Added Tax
VBP	Value-Based Pricing
WHO	World Health Organization

1. Introduction

European Union (EU) Member States (MS) are free to develop their national and regional pharmaceutical pricing and reimbursement policies, as long as they comply with the Transparency Directive.[1] This leads to a large variety in pricing regulation across EU MS due to historical, political, legal and economic development as well as the overall organization and funding of healthcare (Appendix 1). However, these differences in pricing policies are partly responsible for observed price differentials between EU MS in both in- and off-patent markets.[2,3,4]

Since the 1990's, a large number of cost containment measures have been adopted by EU MS to overcome the ever growing pharmaceutical expenditure, in particular the costs borne by public payers. Despite these measures, public pharmaceutical expenditure in the out-patient sector has increased in EU countries by 76 percent between 2000 and 2009 (approximately from €260 to €340 in purchasing power standard per capita).[3]

With the economic crisis of 2008, a major pressure was exercised on most states' budget. Health expenditures became a major target of healthcare cost-containment efforts: from 2010 to 2011, 89 measures were implemented in 23 countries to contain public medicines expenditure.[3] Price reductions, changes in the co-payments, in the value added tax (VAT) rates on medicines and in the distribution margins were among the most common measures. The largest numbers of measures were implemented in Iceland, the Baltic States (Estonia, Latvia, and Lithuania), Greece, Spain and Portugal.[3]

External reference pricing (ERP) (also called "External price referencing", "International price referencing", "International reference pricing", "International price comparison", "International price benchmark", "External price benchmark", "External price linkage", and "International price linkage") has become one of the most common cost-containment tools to reduce prices for in-patent pharmaceuticals in the EU MS.[3,4] ERP is also applied worldwide with EU MS often used as reference countries by non-EU countries (e.g. Brazil, Jordan, South Africa, Japan, Turkey, Canada, and Australia).[2,5]

The WHO Collaborating Centre for Pricing and Reimbursement Policies defines external price referencing as: "*The practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country*".[6] As such, drug price changes in one country will influence the prices in the other countries.

Even if it is a widely accepted and used cost-containment tool, it is also important to remind that ERP has received several critiques. The major arguments raised are in relation to its potential consequences on patient access to medicines and on the level affordability for each country, as well as on industry's revenue and sustainability. [2,4,6,7,8,9,10,11,12,13,14,15]

2. Project objectives

This project was commissioned by the European Commission (Executive Agency for Health and Consumers (EAHC)) to further identify and assess ERP cross-country coordination issues, while acknowledging the need for sustainable public finances and the delivery of high quality healthcare. ERP cross-country coordination issues for the purpose of this study were defined as per the tender specifications by the "Unwanted effects at EU Member States level of ERP schemes that are the result of medicinal product price setting decisions taken in one EU MS that set off dynamic effects in other EU MS and/or in the decision initiating MS itself" such as price instability and suboptimal patient access to medicines.

The assessment was based on a simulation model to identify the main parameters impacting drug price dynamics within ERP systems.

This project is an element of a complex set of objectives as part of the European Commission's activities to support innovation ensuring a high degree of public health while keeping public health expenditure under control, to secure the availability of medicinal products to citizens across EU and to guarantee that EU's pharmaceutical industry evolves into a truly competitive environment.[16]

At European level, several initiatives related to the pharmaceutical sector have been undertaken, including recommendations and directives, among others, on the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems[1] and the Process on Corporate Responsibility in the field of Pharmaceuticals.[17] Additional actions have as objectives the safety and efficacy of medicines with marketing authorization harmonized in the EU,[18] or increasing the assessment of cost-effectiveness of pharmaceutical spending.[19]

The "Joint Report on Health Systems"[20] prepared by the European Commission (Directorate General for Economic and Financial Affairs -DG ECFIN) and the Economic Policy Committee (EPC) (European Commission 2010) has stressed the need to keep public budgets under control through targeted policies promoting the rational use of drugs. This has also been extensively stressed by the High Level Pharmaceutical Forum,[21] the Pharmaceutical Sector Inquiry[22] by DG Competition (European Commission 2009).

In a reflection process as a follow-up to Council conclusions of 2010,[23] EU MS are currently identifying effective ways of investing in health for modern, responsive and sustainable health systems. In this context, the cost-effective use of pharmaceuticals intended for reimbursement by the MS health systems, is being examined by one of the sub-groups of the "Reflection Process on modern, responsive and sustainable health systems" with the participation of six MS and the European Commission. The outcomes of this report are intended to support the work of this sub-group.

Finally, this project will help the European Commission to have an overview of the current ERP policies outcomes and to identify issues to be addressed in view of further policy initiatives (at MS level and / or European Level).

3. Scope of this project

3.1 Countries

This project covered all the 28 EU MS: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

The analysis looked beyond the EU MS to include further OECD member countries into the scope: Australia, Canada, Iceland, Japan, South Korea, Mexico, New Zealand, Norway, Switzerland, Turkey, and United States.

However, only the 28 EU MS, as well as Switzerland, Norway and Iceland were included in the simulation model.

3.2 Products

This project simulated price dynamics within ERP systems of fictitious and real medicinal products.

Real medicinal products selected for this project included:

- Off-patent/in-patent drugs
- Cheap, medium-priced and expensive drugs
- In-patient /out-patient drugs
- Orphan and non-orphan drugs

4. Background and context based on the literature review and stakeholder consultation

4.1 Methodology

The information on ERP systems, both on processes and potential issues related to these systems, as well as the review of existing models related to ERP, was based on data gathered from the literature review conducted according to the methodology described in Appendix 2-Literature Review Methodology and Appendix 3-Literature Review Protocol.

The literature review was completed by two types of stakeholder consultations to validate and complement the literature-based findings as described in Appendix 4-Stakeholder Consultation:

- A written survey, addressed to competent authority representatives of the selected countries, focusing on specific questions related to ERP processes in the 31 countries to be included in the simulation model (28 EU MS, Iceland, Norway and Switzerland).

  Twenty competent authority representatives responded to this survey (Austria, Belgium, Cyprus, Czech Republic, Finland, Hungary, Iceland, Italy, Latvia, Lithuania, Malta, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, and United Kingdom). Nine competent authority representatives did not reply (Bulgaria, Estonia, France, Germany, Greece, Ireland, Luxembourg, the Netherlands, and Romania). Croatia was not in the position to the reply due to local problems in legislation interpretation. Denmark did not accept to participate in the study.

- A written survey, addressed to 14 international organization representatives (industry, patient, doctor, insurance, hospital, wholesaler, and pharmacist representatives), focusing on specific questions related to the perception of their organization of ERP system. Six international organization representatives responded to this survey:

  - European Federation of Pharmaceutical Industries & Associations (EFPIA)
  - European Generic medicines Association (EGA)
  - European Self-Medication Industry (AESGP)
  - European Patients Forum (EPF)
  - Pharmaceutical Group of the European Union (PGEU)
  - European Hospital and Healthcare Federation (HOPE)

  Three international organizations stated that they were not directly involved with ERP regulations. Five international organizations did not reply.

4.2 External reference pricing processes in Europe

The results from the literature review and the stakeholder consultation are presented in Appendix 8-ERP Processes in Europe: Results from the Literature Review and Stakeholder Consultation.

ERP processes in Europe are summarized in Appendix 9-Overview of ERP Processes in Europe.

4.2.1 Application and use

All selected countries apply ERP except the UK and Sweden that is expected to reintroduce it in 2014 (ERP was abolished in 2002 while introducing value-based pricing).[11] Denmark has one of the longest historical experiences with ERP that nonetheless was abandoned in April 2005 to switch to internal reference pricing.[24] ERP was later reintroduced in Denmark in 2009 only for new medicines in the hospital sector.

The majority of the countries (23 out of 31) use ERP as the main systematic criterion when setting the price of a new drug (Figure 1.Overview of ERP across Europe (2013)). ERP is used as supportive criterion in Belgium, Finland, Italy, Poland, Spain and Germany.

For instance, in Italy, ERP is currently used as additional information during price negotiation procedure for all reimbursable pharmaceuticals, whilst in the past it has been used as the main criterion for pricing reimbursed pharmaceuticals.

In Germany, ERP is applied since 2011 and is used as one of the criteria for setting the reimbursement price.

In Belgium, ERP is used as supportive information for the pricing decision, however, pharmaceutical price cuts were introduced in 2013 based on international prices (Austria, Finland, France, Germany, Ireland and the Netherlands) for reimbursed patented medicines, which have been on the market at least five years. For the 2013 exercise, the pharmaceutical company could either accept this price cut or propose another price cut, having the same budget impact.

In Spain, ERP is used to control the price of medicines for which there are no alternatives available on the Spanish market.

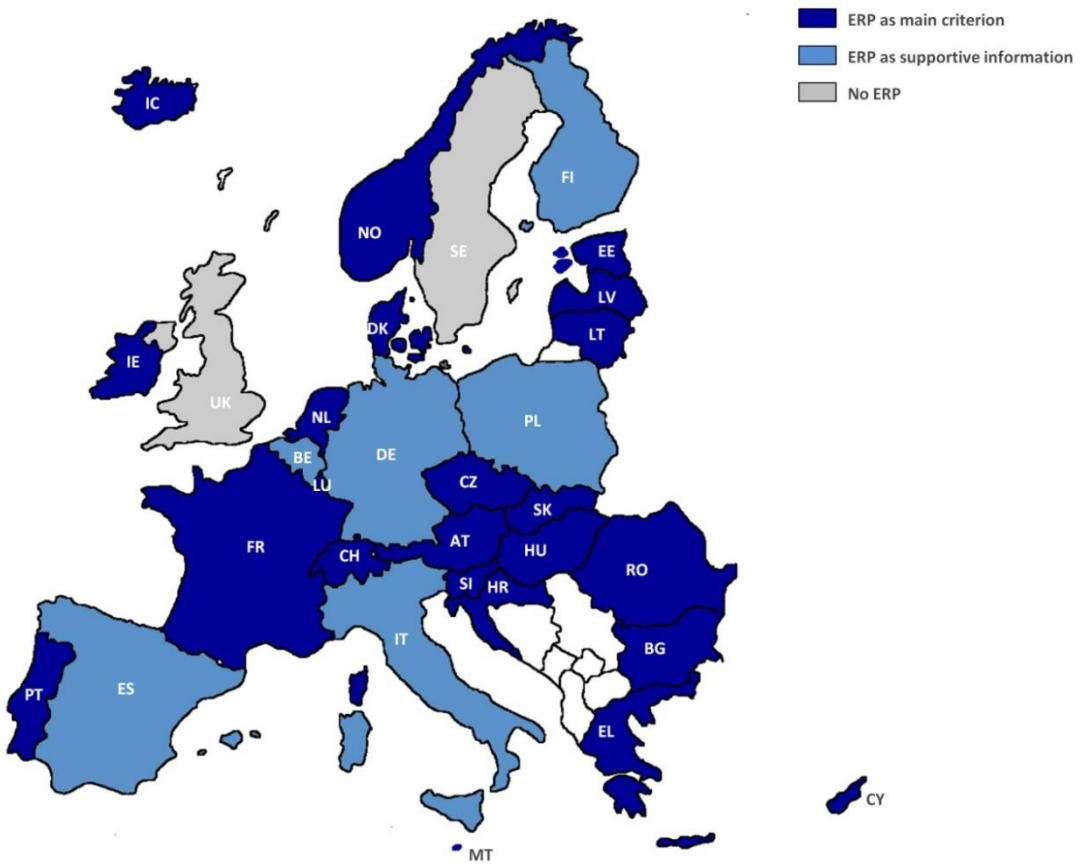


Figure 1.Overview of ERP across Europe (2013)

4.2.2 National legal framework

In the majority of European countries using ERP for setting the price of pharmaceuticals, ERP is based on legislated pricing rules. ERP is sometimes part of agreements, such as in France (Framework agreement between the Healthcare products pricing committee and the pharmaceutical companies) or Ireland (Framework agreement between the Irish Pharmaceutical Healthcare Association Ltd and the Department of Health and the Health Service Executive).

In Spain, ERP was previously regulated by the Royal Decree Law 4/2010. Since 2012, ERP is no longer mentioned in the Law following the Decree law 16/2012. Nevertheless, ERP still conforms to internal criteria of the Interministerial Pricing Committee.

Overall, depending on the country and the use of ERP (main or supportive criterion), ERP methodologies are reported in national pricing legal frameworks with different levels of accuracy. Portugal and Austria are two examples of countries for which ERP procedures are well detailed within their pricing regulations. ERP rules are substantially less detailed for Germany or Estonia.

4.2.3 Scope of external reference pricing

ERP is applied either to all marketed drugs (Luxembourg) or to specific categories of medicines such as publicly reimbursed medicines, prescription-only medicines or innovative medicines.

ERP is mainly used for publicly reimbursed medicines (Austria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia and Switzerland) with some variation for Estonia, France, Germany which apply ERP to reimbursed innovative medicines.

The national legal framework defining ERP pricing rules does not always specify the scope of the products regulated by ERP with accuracy. While it is clearly stated in Denmark that ERP is used for hospital only medicines, for other countries it is not always explicitly indicated if ERP applies only to out-patient sector or both the hospital and out-patient sectors.

The application of ERP for in-patent or off-patent medicines is not always specified. Six countries reported applying ERP to both in- and off-patent drugs (Austria, Croatia, Iceland, Italy, Slovenia, and the Netherlands) and ten countries reported applying ERP to in-patent (or innovative) drugs (Belgium, Cyprus, Estonia, Finland, France, Germany, Greece, Hungary, Norway, and Portugal).

The European Generic medicine Association (EGA) reports that ERP for off-patent drugs is less common than for in-patent drugs and is currently used in Bulgaria, Czech Republic, Slovakia, Slovenia, Latvia, Lithuania, Poland, Romania and Croatia.

4.2.4 Composition of the country basket

Country baskets historically have been defined using as main criteria economic comparability and/or geographic proximity. Over the years, this has evolved toward larger and larger country baskets,[2] without an always explicit rationale for selecting reference countries.[9] The number of reference countries included in the basket varies greatly from one country to another (1 for Luxembourg, 3 for Croatia, Estonia, Portugal and Slovenia to 31 for Hungary and Poland). While most EU MS choose to have only EU countries in their basket, Hungary, Denmark, Poland, and Finland (as well as Malta for the private sector) insert also European Economic Area (EEA) countries. In Hungary and Poland, Switzerland is also used as a reference.

The country of origin (not clearly defined in the literature if considered as the country of manufacture of the drug or the country of the marketing authorization holder in Europe) is used as reference in Luxembourg and in Estonia. In Belgium, where ERP is used as supportive criterion, most common methodologies reported to set ERP prices are average prices of the reference countries (26 EU MS) or the price in the country of origin. The country of origin is also used in Cyprus, Lithuania, and Romania when the price is not available in reference countries.

The most referenced countries are France (19), followed by the UK and Germany (17), Austria, Spain and Slovakia (16), Belgium, Denmark, Finland, the Netherlands, and Italy (15). The least referenced countries are Croatia entered in the EU in July 2013 (5) and non-EU MS: Switzerland (2), Iceland (3) and Norway (6). (Table 1)

Table 1. Overview of country baskets in Europe (2013)

	AT	BE	BU	CH	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HR	HU	IE	IS	IT	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	Add. countries	N. of countries
AT		■			■	■	■	■	■	■	■	■	■		■	■		■	■	■	■	■	■		■	■		■	■	■	■		24
BE	■		■		■	■	■	■	■	■	■	■	■		■	■		■	■	■	■	■	■		■	■	■	■	■	■	■	Or Country of origin	26
BU								■	■	■	■	■	■					■	■							■	■		■	■			12
CH	■						■	■					■										■								■		6
CY	■									■			■															■					4
CZ		■						■		■	■	■	■	■	■	■		■	■		■		■		■	■		■	■	■	■		19
DE	■	■				■		■		■	■	■	■			■		■					■			■		■		■	■		15
DK	■	■					■					■				■							■	■				■			■		9
EE															■				■		■											Country of origin	4
EL	■	■	■		■	■	■				■	■	■		■	■		■	■	■	■		■		■	■	■		■	■	■		22
ES	■	■			■		■		■	■		■	■			■		■		■		■	■			■			■	■		Eurozone but not regulated	16
FI	■	■	■		■	■	■	■	■	■	■		■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	Liechtenstein	29
FR							■				■							■													■		4
HR													■					■												■			3
HU	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	Liechtenstein	31
IE	■	■					■	■			■	■	■										■								■		9
IS								■				■											■	■				■					4
IT	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■			■	■	■	■	■		■	■	■	■	■	■	■		27
LT			■			■			■						■						■				■		■			■			8
LU																																Country of origin	1
LV						■		■	■						■				■								■			■			7
MT					■	■			■		■				■			■	■							■			■	■	■	Public sector*	11
NL		■					■						■																		■		4
NO	■	■					■	■				■				■							■					■			■		9
PL	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	Liechtenstein	31
PT											■		■																	■			3
RO	■	■	■			■	■			■	■				■			■	■						■					■			12
SE																																	n/a
SI	■						■						■																				3
SK	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■		■		27
UK																																	n/a
Reference frequency	16	15	9	2	10	13	17	15	12	13	16	15	19	5	13	13	3	15	14	9	11	8	15	6	10	13	10	13	13	16	17		

*For private sector in Malta, data from 12 European reference countries, classified in a three-tier system, is used for ERP: Low- priced tier: ES; UK; PT; FR/Medium-priced tier: BE; IS; CY; IT/High-priced tier: DK; DE; IE; NO. AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FI, Finland; FR, France; HR, Croatia; HU, Hungary; IE, Ireland; IS, Iceland; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MT, Malta; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SI, Slovenia; SK, Slovakia; UK, United Kingdom

4.2.5 Price calculation and selection of reference products

ERP regulations are usually described in countries' legal frameworks; however the accuracy of this description differs from country to country. The rules that apply to the choice of the reference products are not always clearly described (e.g. generics, non-reimbursed drugs, out-patient/hospital-only drug, different pack size, different dosages, and different pharmaceutical forms).

There is a great variation in calculation methods used to compute the reference price. Rules are not always clearly defined (Germany and Estonia) and can vary within the same country from one type of product to another, such as brand versus generic products (Croatia and Iceland).

One of the main methods is the calculation of the average price of reference countries (Austria, Belgium, Cyprus, Denmark, Iceland, Ireland, Portugal, Switzerland, and the Netherlands). Another method applied is to use the lowest price among all the reference countries (Bulgaria, Hungary, Italy, Romania, Slovenia (for original drugs and biosimilars), and Spain). Some countries such as Greece, Norway, Slovakia and Czech Republic -the latter only to calculate the maximum price- use the average of the 3 or 4 lowest prices of all countries in the basket. France, with only 4 countries in its basket, applies prices that are similar to those in the reference countries. Malta uses 2 ERP systems, one for the private market and one for the public sector medicines. These 2 systems are characterized by different rules; for instance, the average wholesale price of the basket is used for the public sector and an algorithm is used for the private sector for price calculation.

When there is no price available in one or more of the reference countries or when the price is not approved in all reference countries, some MS (Bulgaria, Croatia, and Cyprus) set the price using the same method in alternative reference countries. Other countries like Belgium, Denmark and Latvia estimate the price based on reference countries where the price is approved; the price is revised when a price becomes available in an additional country. In the Netherlands, the price is only set if a comparable drug is marketed in at least 2 of the 4 referenced countries. In Romania, the price from the country of origin shall be considered when no price is set in the 12 countries of the basket.

Prices can be re-evaluated on regular basis after the initial price has been set. The frequency and process of reviewing prices differ between countries. Ireland performed in 2012 a downward price realignment based on the currency-adjusted average ex-factory price of the drug in reference countries. This was carried out according to the framework agreement between the Irish Pharmaceutical Healthcare Association Ltd and the Department of Health and the Health Service Executive on the Supply Terms, Conditions, and Prices of Medicines. The Norwegian Medicines Agency (NOMA) yearly revaluates the maximum price of 250 active ingredients with the highest turnover to ensure that the maximum prices reflect the changes in European prices. In Slovenia, prices are revised twice a year in case changes in the price of reference countries occurred.

Most of the countries compare prices at ex-factory level and use public official price databases. Other prices that are considered to set ERP price are pharmacy purchasing price (PPP) and pharmacy retail price (PRP).

When different dosages and pack sizes are approved in the reference countries at different prices, the same or closest pack size or dosage are generally used as reference. These rules, by generating incorrect measures of price differences across countries, can raise a concern in terms of representativeness. For example, as the

average pack size can vary significantly across countries, basing the price comparisons on identical pack size would imply the exclusion of some reference countries, but also to ignore the representativeness of the matching pack size for the price level in the reference countries.[25,26]

When the pharmaceutical formulation of a drug in the reference country is different from the formulation approved in the referencing country, some countries do not take into account the different formulation for ERP (e.g. Latvia, Portugal, Slovakia), while other countries (Belgium, Hungary, Iceland) consider the different pharmaceutical formulation only if it is similar to the one approved (e.g. oral solid forms such as capsule versus tablet can be compared to each other but not to injectable forms).

A product that is not reimbursed in a reference country can still be used as reference by some countries (e.g. Austria, Belgium, and Portugal). In general, the branded version is selected for reference purposes even if the generic form is available in a reference country.

4.3 External reference pricing processes in non-European countries

Countries outside Europe, such as Australia, Canada, Japan, South Korea, Mexico, New-Zealand, and Turkey, among OECD member countries, also utilize ERP and reference EU prices. It should be noted that total expenditures on pharmaceuticals of these countries are about 80% of total EU pharmaceutical expenditures on pharmaceuticals (Table 2), suggesting a considerable spill-over effect of ERP outside EU countries. In the United States (US), there is no ERP system, as prices of drugs are not controlled.[7] However, the US are referenced by Canada, Japan and South Korea. Total expenditures on pharmaceuticals for all the above cited countries are about 2 times higher than the ones found in European countries (considering EU-25, Switzerland, Norway, Iceland) (Table 2).

Table 2. Expenditure on pharmaceuticals in European and non European countries

	Expenditure on pharmaceuticals per capita (Purchasing Power Parities, Euro)	Total population (million)	Total expenditure on pharmaceuticals, (Purchasing Power Parities, Euro) (billion)
EU -25 (RO, LV, EE, DK, PL, UK, BG, LT, CZ, LU, CY, SI, FI, SE, NL, PT, IT, AT, ES, HU, SK, FR, BE, DE, IE)	349*[27]	472.6[28]	164.9
Switzerland	393*[27]	7.8[28]	3.1
Norway	305*[27]	4.8[28]	1.5
Iceland	327*[27]	0.3[28]	0.1
Total EU-25, Switzerland, Norway, Iceland			**169.6**
Australia	443**[29]	22.3[30]	9.9
Canada	540**[29]	34.1[30]	18.4
Japan	491**[29]	127.5[30]	62.6
Korea	320**[29]	50.5[30]	16.2
Mexico	186**[29]	108.4[30]	20.2
New Zealand	214**[29]	4.4[30]	0.9
Turkey	150 (Last Data in 2000) **[29]	72.7[30]	10.9
United States	715**[29]	309.1[30]	221
Total non Europe			**360.1**

*2010 (or nearest year)** 2011 (or nearest year)/Exchange rate used to convert US dollars in Euros
Available from:
http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&language=en&pcode=tec00033&plugin=

4.3.1 Australia

In Australia, the Pharmaceutical Benefits Pricing Authority (PBPA or Pricing Authority) sets prices for pharmaceuticals listed under the Pharmaceutical Benefits Scheme (PBS). ERP is used as a supportive criterion, among several other criteria, for pricing. Australia references the UK and New Zealand, as reported in PBPA Policies, Procedures and Methods.[7,31]

4.3.2 Canada

The Patented Medicine Prices Review Board (PMPRB) is responsible for regulating the ex-factory prices for prescription and non-prescription patented drugs sold in Canada.[32]

ERP was first adopted in 1987 as part of the price regulation process.[7] It is used as main criterion for the pricing of innovative medicines (categorised as breakthrough, significant improvement or moderate improvement). The country basket includes 7 countries: the US, France, Germany, Italy, Sweden, Switzerland, and the UK. These countries were selected based on economic and geographic similarities to Canada, but are also deemed to share Canada's goals of encouraging research and innovation in the pharmaceutical sector.[7,32] Exchange rates are based on 36-month average exchange rates for each country and are published on the PMPRB website. [32]

The median of the ex-factory prices of the same strength and dosage form of the same patented drug product for each of the seven countries determines the "maximum average potential price" for a new patented drug. [32,33,34]

If the drug is available in less than five countries at the time it is first sold in Canada, the median international price is calculated on an interim basis and re-assessed after three years. If the drug is available in an even number of countries, the median is determined as the average of the two middle prices. [32] If the drug is not available in the countries of the basket, the most similar strengths of comparable dosage forms, of the same patented drug, is considered.[34]

4.3.3 Japan

In Japan, ERP is used to adjust medicine prices upwards or downwards if it differs significantly from the average of the drug's price in France, Germany, the UK and the United States.

If the price of a new drug - with no therapeutic comparators or with a significant therapeutic added value over therapeutic comparators - is three-quarters that of the average overseas price, then the price is increased.

If, on the other hand, the price of a new drug, with or without therapeutic comparators, is found to be 1.5 times greater than the average overseas price, then the price is lowered. As a result, Japan's prices can vary between 150% above or 75% below the reference countries prices. [5,7,10,35]

4.3.4 South Korea

Before 2006, the Republic of South Korea was using the adjusted average of the ex-factory prices of seven countries (US, UK, France, Japan, Germany, Italy, and Switzerland) to negotiate the price of patented drugs. In 2006, the government introduced the "Drug Expenditure Rationalisation Plan" to slow the growth of spending on drugs, establishing price negotiation between the National Health Insurance Corporation (NHIC) and pharmaceutical manufacturers with price-volume consideration. Instead of a formula-based ERP, individual prices in referenced countries (Australia, France, Germany, Italy, Japan, Singapore, Spain, Switzerland, Taiwan, and UK) are used in pricing negotiations with the NHIC. [36,37,38]

4.3.5 Mexico

In Mexico, ERP is based on a weighted average of the ex-factory prices, from the previous quarter, of the six countries where the medicine has the highest sales. The reference prices are reviewed annually and verified by an external auditor. This price is used to determine the reference price for sales to the public (PRVP, Precio de Referencia para Venta al Público) calculated as follows PRVP = ERP × 1.72. The multiplication factor of 1.72 corresponds to what is normally considered the combined average wholesale and retail margins in Mexico.[5,7] Mexico is reported as a country that might refer to the UK.[8]

4.3.6 New Zealand

Comparisons for benchmarking appear to be informal in New Zealand. Countries in the reference basket are: Austria, Canada, and the UK[7]

4.3.7 Turkey

The IEGM (General Directorate of Pharmaceuticals and Pharmacy) is responsible for setting the prices for all human medicinal products. ERP system was introduced in

Turkey in 2004 due to concern over the rapid growth of pharmaceutical expenditure. According to the Turkish rules, the maximum ex-factory price cannot exceed the lowest ex-factory price of the identical product seen in five reference countries (France, Greece, Italy, Portugal, and Spain).

Reference countries are reviewed annually, yet they remain unchanged since ERP's implementation. The reference country selection is based on various criteria: pharmaceutical market's characteristics (product variety, licensing procedures), population and age range distribution and health state status.

When a product is not available in any of the five referenced countries, the lowest ex-factory price in other EU countries is applied. If the product is not authorized in the EU, the country of origin is used as reference.

In addition, when the ex-factory price of a drug in the origin country is lower than in any of the reference countries, the product price is set as the same as in the country of origin.

Negotiations are used to set its price when a product is only available in Turkey. Generics and expired branded drugs are priced at a maximum of 66% of the cheapest originator product seen in the five reference countries. [39,40]

4.4 Concerns related to external reference pricing

In this chapter are reported the main concerns that have been addressed by international organization representatives, competent authority representatives of the selected countries, and that have been found in the literature.

One of the limitations arisen is that ERP is characterized by a "path dependence". This means that the observed price levels are influenced by the rules of the systems itself (e.g. country selection, price taken from the basket, and revisions dates) and ignore other aspects of the market such as health needs, income and healthcare costs and the extent of these aspects' variations between countries.[8,9,14]

As already described, ERP presents different characteristics across EU MS, with methodologies evolving over time and contributing to price variations between countries.

Among limitations of the ERP application are the lacks of available price information, as well as the difficulty to identify and obtain access to relevant data sources of the EU MS.[11]

Other main issues reported by the literature and during the stakeholder consultation were:

- Available prices are often heterogeneous (e.g. ex-factory prices, pharmacy purchasing prices, pharmacy retail prices) making the price comparison difficult.[5,8] For example, in the UK and the Netherlands, the only listed price is the pharmacy purchasing price and this price is often unavailable in other countries, where the ex-factory and retail pharmacy price are available. As ex-factory prices are used for reference pricing in most of the countries, the ex-factory price is derived from calculation in order to be used, becoming therefore a proxy of the true ex-factory price.
- Publicly available prices are often facial prices which do not take into account the managed entry agreements, as these are often confidential.[5,8,10,11,14,41] Such practices have become very common to maintain access at a high facial price while offering a substantial discount that will not be considered in ERP. As a result, the theoretical reference price does not always become the actual market price, especially in case of drugs enjoying a monopolistic position.
- Price reductions in reference countries are not automatically translated into price decreases in referencing countries due to irregular monitoring.[41]

The identification of the same medicine across countries can be difficult due to products being launched with different commercial names, pharmaceutical formulations, dosages and pack sizes. The literature describes this issue as a technique used by manufacturers to limit opportunities for ERP.[5,7,10,41]

It is important to note that ERP is also exposed to exchange rate volatility that can affect prices denominated in local currencies [4,8]:

- In Switzerland, the reference price is based on Eurozone MS (Austria, France, Germany, and the Netherlands) and non-Eurozone MS (Denmark and the UK). Swiss drug prices have fallen rapidly towards the reference basket average over the past five years. The appreciation of the Swiss Franc makes foreign prices cheaper and leads to further downward pressure on Swiss ones.[42]
- Conversely, even if not directly related to ERP but illustrating the impact of exchange rate volatility, the UK, which was known as a high price country and a

target for parallel trade, has become a source country for parallel trade following the Pound depreciation.

- Finally, during the stakeholder consultation, it was reported that countries referring to non-Eurozone countries do not disclose the currency rates used at the time of the calculation which might lead to prices miscalculation in other countries.

4.5 Potential consequences of external reference pricing

The real impact of ERP policy is still not well understood.[11,32] Concerns due to the ERP application have been expressed by industry regarding spill-over effects on other countries.[12] It is often argued that ERP can lead to a (downward) price convergence. ERP seems to lower prices, in particular when a MS uses the lowest price in the country basket rather than the average price, or because of currency fluctuations.

A low price for a new product in one national market might affect manufacturer's pricing strategies elsewhere due to the wide application of ERP and could also lead to parallel trade.[4,5,8,11,14,41] However, two recent studies[43,44] suggested no substantial reduction in international price differences within the EU countries.[11]

In the first study[43], authors looked at over 1,000 prescription drugs in 36 therapeutic categories in 30 countries (European and non-European Union countries) over a 12-year period (1993-2004) to assess whether price dispersion decreased in the EU (where parallel trade is permitted) and non-EU countries (where parallel trade is not permitted). Descriptive and regression analyses showed that about half of the price differentials exceeded 50 percent in both EU and non-EU countries over time, and price distributions among EU did not show a dramatic change with the adoption of parallel trade.

In the second study[44], prices of 10 on-patent medicines of 15 European countries over five years (2007, 2008, 2010, 2011 and 2012) were analysed to assess whether ex-factory prices of on-patented medicines in Western European countries have converged over a recent period of time. A price divergence between 2008 and 2012 was shown. This divergence was driven by two countries, Germany (up to 27% more expensive than the average) and Greece (up to 32% cheaper than the average), whereas all other countries had stable prices, centred on the country average. Thus, this study supported a trend for convergence (price close to the country average), with a substantial difference between the lowest price country and the highest price country. Study authors underlined the need for further research with larger sample size and that include prescribing data and Eastern European countries.

The analysis of these studies suggested that even if ERP is argued to lead to price convergence across Europe, price differences still exist and could result from different methodologies used for ERP, as well as from other pricing policies in place in the countries. These differences could also be driven by only some countries.

4.5.1 Patient access to medicines

ERP has been criticized for its potential to limit patient access to medicines. ERP becomes an incentive for pharmaceutical companies to adopt international pricing strategies. The "launch sequence strategy" is used to delay or avoid launching new drugs in countries with lower prices, especially if these are small markets referenced by countries with larger markets.[4,5,8,10,14]

There is evidence that pharmaceutical companies systematically delayed in the past dossier submission in Belgium in order to avoid the Belgian price, usually in the low EU range, affecting other countries.[45]

It is also reported that the widespread use of ERP can determine a circular pricing (the more countries are used as reference countries, the less clear it becomes which country's prices are the reference). Price revisions in one country may, at least in theory, trigger a sequence of circular price revisions, further contributing to strategic launching of new drugs.[41]

However, it is difficult to assess to which extent strategic launching is delaying launch in low-prices countries. Convergence in international pricing may be due to ERP, but also could be a cause of parallel trade or the fact that these markets are less attractive to suppliers; these factors are usually simultaneously present.[5,8]

In actual fact, the price is frequently based on, an often implicit, multi-criteria decision of which ERP is only one of many criteria. Although pharmaceutical companies try to control ERP, they have little capacity to influence it.

4.5.2 Affordability

Carone et al. (2012) reported that countries with high absolute price levels of pharmaceuticals, such as Germany, Denmark, Ireland and Italy, have low relative price levels (pharmaceutical prices divided by GDP per capita), whereas low price countries, such as Poland, Romania and Bulgaria, pay relatively much compared to GDP per capita. This could be partly explained by the fact that medicinal products are traded on international markets, with parallel exportation as an allowed market practice.

This mechanism leads pharmaceutical companies to look for a price convergence to minimize the occurrence and volume of parallel trade, thus impacting country affordability. Indeed, assuming a price convergence (even if the price varies in a narrow range, and poorest countries tend to have the lowest price), the price related to local purchasing power remains higher in poor countries.[41]

As an example, it was reported during the stakeholder consultation that ERP might lead to product shortage in countries referencing the lowest price, due to discontinuations and parallel export, as illustrated with Bulgaria where about 200 products (strengths, pack sizes and chemical entities) were withdrawn from the market in 2012. Although ERP aims to achieve a better control of price and faster erosion, it might also induce a vicious effect such as increasing target price from pharmaceutical companies to avoid both negative impact on company revenues of ERP and parallel trade.[4,5,41]

4.5.3 Industry revenue and sustainability

Differential pricing, based on Ramsey pricing principles, is reported as an efficient way of paying for the global joint costs of pharmaceutical Research and Development.[46] This concept states that prices should differ across markets according to the demand elasticity with more price-sensitive users charged at a lower price than less-price sensitive users.[11] This economic theory supports the use of differential pricing as a way to achieve pharmaceutical companies' objective, i.e., additional revenues (volume) from poorer countries without losing revenues (sales) in richer and less-price sensitive countries.[47] Applying the Ramsey pricing principles would mean to abandon the value-based pricing, based on effectiveness or cost-effectiveness depending on the

countries, and would require a change in national regulations. ERP is reported as one of the limiting factors of possible beneficial effects of differential pricing. ERP is believed to discourage incremental innovation by reducing revenues for Research and Development, with fewer resources to invest in innovation, or by pushing Research and Development toward "niche markets" (higher price countries).[12,13,14,15,47] However, the full impact of this policy on Research and Development will not be measurable for several years.[13]

From the stakeholder consultation, ERP system appears to have a massive negative impact on the pharmaceutical industry competitiveness (off-patent (generic and biosimilar) or in-patent medicine industry):

- From the European Generic medicine Association (EGA) perspective, and considering the very competitive environment of off-patent medicine market, ERP limits generic medicine industry's potential to enter specific markets by driving down the prices to unsustainable levels. EGA cited the case of generic medicine olanzapine price that dropped by up to 98% in Bulgaria due to the application of ERP from Denmark, thus limiting patient access to this medicine in Bulgaria. EGA emphasized that referencing prices in countries where procurement and tendering systems are in place (driving down the prices to unsustainable levels) would be detrimental for the generic sector, for patients (availability of affordable generic medicines) and for payers (savings for the national health systems).
- From the European Federation of Pharmaceutical Industries and Associations (EFPIA) perspective, ERP causes indirect and adverse effects across Europe and beyond, especially in the context of short-term cost-containment measures. They illustrated their perspective by providing two studies carried out by Charles River Associates investigating the impacts of ERP.

  One study focused on ERP and parallel trade impacts on social welfare and patient access.[48] Based on existing evidence, this study concluded that ERP and parallel trade created spill-over effects from low price to higher price countries leading to patient access issues in low price markets, with limited benefits in terms of cost-savings to payers and patients for high price markets. These spill-over effects were also likely to have negative impact on the willingness/potential/capacity to invest in Research and Development, although it was difficult to directly examine this phenomenon. EFPIA illustrated the potential spill-over impact of ERP, in case of price cut, by estimating industry cost following a 10% price drop in Greece in 2011 if all countries re-referencing Greek prices (formal/informal) were included. It was shown that the price drop would have generated loss for the industry of €299 million in Greece, €799 million in Europe and €2,154 million worldwide.

  The second study looked at the impact of Swiss drug regulation, especially focusing on the international impact of price cuts in Switzerland due to ERP.[49] It was notably assessed the worldwide spill-over effects from a 10% price reduction in Switzerland if all countries re-referencing Swiss prices (formal/informal) were included. It was shown that the price reduction would reduce industry revenue by €430 million in Switzerland and €495.2 million worldwide. In the same study, it was modelled the potential impact of price reduction on patient access, taking the example of the Canadian market. It was shown that delaying drug launch in Switzerland due to price reductions was less expensive on the Canadian market than launching the drug in Switzerland.

Moreover, the EFPIA also reported mistakes in published prices which might distort ERP-based systems such as recently seen in Greece[a] where published prices were miscalculated (lower prices than prices obtained if ERP rules had been properly applied). Greece being referenced by 13 countries, such errors may impact these countries.

4.6 Value-based pricing and external reference pricing

Among other price setting procedures, value-based pricing (VBP) is frequently used in the European countries to set the price of their medicines. As such, it was interesting to put VBP and ERP in perspective.

VBP Concept

VBP can be defined as a business model in which selling prices are set on the perceived value to the costumer. VBP implies to link perceived value and delivered value; value depends on an understanding of how customers appreciate value. The VBP model implies that a better drug deserves a better price. To decide on robust ground, payers ask experts on the difference in value between interventions. Health Technology Assessment (HTA) organizations are the expert bodies that set the added value versus reference therapy, and evidence-based medicine is the tool used for making decision.

Even if the value definition is similar, the use of VBP in one country does not necessarily reflect the value of the drug considered in another country, due to particularities of health care service, medical practice, availability of different comparators, etc. Furthermore, even if the assessment of the value of a drug generally relies on a common set of evidence, it may differ across countries because of the assessment methodology in place such as choice of the criteria to determine the benefit, choice of the comparators, health care inputs used in a model to assess the value, etc.

Each country defines and appreciates value differently. In France, price of drugs is based on the Improvement of Actual Benefit (Amélioration du Service Médical Rendu-ASMR) assessed by the Transparency Committee. The ASMR is based on the level of clinical improvement of the new medicine relative to the existing treatments, and is mainly driven by the difference of absolute effect size of the benefit of the drugs being compared. In Germany, the rate ratio of relevant endpoints is used instead of absolute effect size. The upper 95% confidence interval of the rate ratio is considered to acknowledge the drug value but not the estimate of the rate ratio. In the UK, the National Institute for Health and Care Excellence (NICE) uses the cost per quality-adjusted life year (QALY) to measure the health benefits delivered by a given medicine and defines an Incremental Cost-Effectiveness Ratio (ICER) threshold range. Many other countries use the ICER, among several other criteria, but without defining an ICER threshold for new technology approval.

Therefore different definition of value will lead to different appreciation of the value across countries for the same drug.

[a] Letter sent by EFPIA Director General to the Head of the European Commission's Task Force for Greece-Extra-territorial impact of erroneous medicine prices published on the website of the Greek Government (2013 Mar 20) (communicated by EFPIA)

VBP can be ex-ante (before price setting such as in France or Germany) or ex-post (after price setting such as in Sweden and the UK). VBP assumes that a new product with an additional benefit will enjoy a higher price than an alternative therapy, and implicitly refers to the national reference pricing. One of the issues of VBP is that the relation between the added value and the willingness to pay is not clearly defined, except for the countries having a threshold associated to the ICER.

ERP as an alternative to VBP

ERP makes sense in countries that decided to use benchmarking methods and do not have resources for VBP, do not want to use resources for VBP, or do not recognize VBP as a reasonable tool to set drug prices.

ERP and VBP combination

ERP is mixed to VBP in some countries to allow public health authorities to set a reasonable price as it is very difficult to standardize the relationship between the added value of a drug and the willingness to pay. It should be noted that ERP has not been systematically a strategic choice of public health authorities. For example in France, the manufacturer union requested the health authorities to ensure that French prices would be within EU boundaries and prevent negative impact of French prices within ERP based-systems.

However, the legitimacy to use both VBP and ERP may be questionable. Modulating a value, based on a well-established decision analysis framework, by using willingness to pay of other countries can be disputable since value definitions are obviously different between countries. For example, it looks inconsistent to set a price in a country based on value and then draw that price up or down based on decisions from other countries that use other grounds to assess the value.

On the other hand, providing value assessment is associated to uncertainty and linking value to price is a complex process. As such, it might be reasonable to inform the price decision using assessment performed by other countries to ensure that the value of a new treatment is not dramatically under or over estimated. To this end, ERP used as a supportive tool for modulating the VBP decision seems to make sense. However, performing HTA is not consistent with ERP use as a main criterion since prices are set by benchmarking irrespective of the value assessment. In some cases, ERP only applies for innovative medicines, while internal reference pricing applies for non-innovative medicines. In that case, an HTA agency is necessary to identify innovative product.

4.7 Review of the existing models related to ERP

The review of the main existing models related to ERP, including models analyzing the overall role of price regulations of pharmaceutical markets, showed that there were no publications modelling the whole ERP process.[15,50,51,52,53,54,55,56,57,58,59,60,61,62] Published studies focused only on specific features of price regulation and ERP-based systems, especially on their impact on the launch delay of new drugs. The majority of these models were based on empirical data and did not allow for different scenarios. Only five studies were based on theoretical models[40,41,43,60,62] focusing on specific ERP characteristics, but not on the whole process. An overview of these models is described below and each modelling study is summarized in Appendix 10.

- Several studies focused on the link between ERP and the launch sequences.[15,50,51,52,53,54,55,56,57,58] Most of these studies were based on empirical data;

only two studies were based on theoretical models (Lorenzo et al. 2012[60] and Houy et al. 2013 [58]). All studies concluded that pharmaceutical firms had incentives in launching new drugs in high-price countries first and delaying launch or even not launching new drugs in low-price countries. Richter 2008[56] added that the price regulation had a significant impact on the probability and the delay of launching the drug for high-income countries.

- In 2012, Leopold et al.[59] studied the impact of ERP on drug price with a regression model adjusted on other factors that may affect price levels such as sales volume, exchange rates, gross domestic product (GDP), total pharmaceutical expenditure, and size of the pharmaceutical industry. They concluded that prices were generally lower when the country was applying ERP, even if substantial price differences among countries applying ERP could be identified.
- Garcia-Marinoso et al. (2010)[60] used a mathematical model with three fictitious countries (a home country, a foreign country and a third country where the pharmaceutical firm was based) to analyse the effects of adopting ERP on the pricing mechanisms. They found that a country had incentive to engage in ERP if its co-payment level was high compared to other countries.
- Other models focused on the impact of price regulation on drug price. Using a regression model, Danzon et al. (2000)[61] found that countries with strict price regulation had lower prices than less regulated markets. Similarly, Ackerman et al. (2010)[62] used a mathematical model to show that only small countries might have an incentive to engage in ERP, assuming that bargaining power was positively correlated to country size, and that this incentive shrank if population size grew.

The current project aimed at building a theoretical ERP model based on EU Member States, including the main ERP characteristics, to assess the price dynamics through ERP-based systems while assessing various scenarios simulating changes in ERP policies.

5. Project Methodology

5.1 Simulation model

5.1.1 Model objective

An ERP-based simulation model was built to achieve three primary objectives:

a) To simulate the evolution over time of the price of any given drug;

b) To simulate the impact of various changes in ERP policies;

c) To support policy decision makers by identifying the drivers of the price evolution.

The model applied to the 28 EU Member States, Iceland, Norway and Switzerland.

5.1.2 Choice of modelling approach

The choice of the modelling approach was dictated by the need for a flexible and adaptable model that would allow to account for both fixed ERP rules and a quick dynamic change (such as a decrease in price or exchange rate fluctuation occurring at any moment of time).

In order to meet this need, the model was structured as a **discrete-event simulation** (DES). This modelling technique allows continuous "tracking" of the pathway of an **agent** (here, a country) through a number of pre-defined **events**. Occurrence of events as well as their consequences depend on the country's characteristics (or else **attributes**), such as ERP rules, GDP, etc.

As these attributes change over time, associated probabilities change as well. Unlike a Markov model, a DES model has "memory" and accounts for both a country's present and past events. This is a considerable advantage of DES models compared to Markov models. In the latter, "memory" can only be introduced by increasing the number of Markov states, which can make the model cumbersome.

Another advantage of DES model is its time flexibility as it allows occurring of an event at any moment of time, as opposed to Markov models where events can only occur at fixed moments.

Finally, DES structure makes it relatively simple to add, remove, or modify inputs and assumptions when needed. Therefore, it is a perfect tool for decision-makers faced with the rapidly changing environment of drug pricing.

5.1.3 Model overview

5.1.3.1 Time horizon

The model used a flexible time horizon which can be modified by the user. The user controls the occurrence of events through the **event calendar** (events described in section 5.1.3.3).

5.1.3.2 Attributes

As mentioned above, country's characteristics have an impact on the pathway of the model through a series of events and on their outcomes.

Three groups of attributes were included in the model:

- ERP policy attributes
- Drug attributes
- Economic attributes

5.1.3.2.1 ERP policy attributes

Each country was classified according to what role ERP plays in its decision-making process:

- ERP as the main decision criterion
- ERP as a supportive decision criterion
- No ERP

For countries that use ERP as the main or supportive decision criterion, more attributes were considered in the model:

- Basket of reference countries
- Evaluation interval (time period between two price evaluations)
- Method used for price calculation (see section 5.1.3.4)
- Type of price used for price evaluation: ex-factory price, pharmacy purchasing price or pharmacy retail price
- Basket filtering methods (creating a "sub-basket" consisting of N countries with the lowest prices, or countries where the drug is reimbursed etc.)

5.1.3.2.2 Drug attributes

The following drug attributes were considered in the model:

- Drug characteristics in the country (e.g. reimbursed or not, prescription-only medicine or not, brand or generic product, innovative product or not, out-patient or hospital-only medicine, etc.)
- Drug launch status at the model starting point (already launched or not)
- Drug price at any time (ex-factory price, pharmacy purchasing price and pharmacy retail price)

5.1.3.2.3 Economic attributes

The following economic attributes were considered in the model:

- Country currency and exchange rate with Euro
- Total population per country
- GDP per capita per country
- Purchasing power parity per country

5.1.3.3 Events

Events were considered one-by-one by order of occurrence. The following event types were included in the model:

- **Drug launch and first price setting**

  The model took into account both situations:

  1) When a drug had already been launched before the start of the simulation;
  2) When a drug had not already been launched before the start of the simulation.

  In the latter case, price evolution started on the day of launch. Launch prices were either set manually (in that case the model was forced to accept a given price irrespective of ERP) or calculated based on the ERP policy. Launch dates were defined country by country to reproduce any launch sequence. The model was flexible and allowed for any launch sequence.

- **Pricing decision using ERP**

  This event was driven by country's attributes and is detailed in the section 5.1.3.4.

- **Exchange rate fluctuations**

  The user had the possibility to change the exchange rate between any two currencies at any moment of time. This change was expressed in percentage.

- **Country's attributes modification**

  Any of country's attributes could be modified at any moment in time in order to create a more realistic simulation and to assess the impact of any particular change on price dynamics.

- **Drug price change**

  Drug price in any country could be changed at any moment in time in order to simulate events not explicitly included, such as price decrease in case of generic entry.

Figure 2 provides an example of sequence of events and their impact on price evolution.

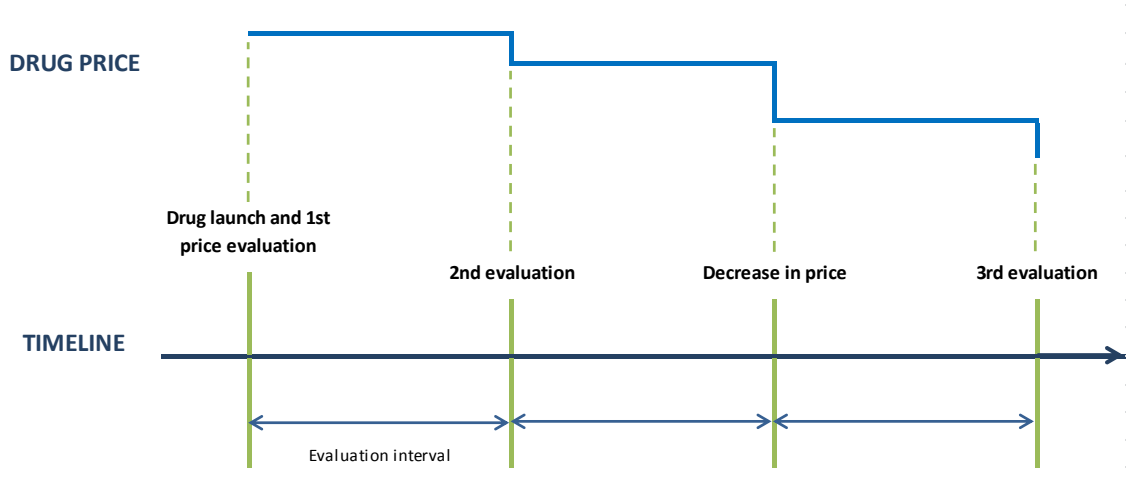


Figure 2. Example of sequence of events and price evolution in the simulation model

5.1.3.4 Price calculation

Each price evaluation event implied the calculation of a new drug price. It depended first of all on the ERP role in a given country. Countries where ERP was the main or a supportive decision criterion had an established set of rules consisting in:

- **Basket price calculation**

  Depending on the country, the basket price was calculated, for instance, as the minimum or the average of the basket. Filtering rules were applied to create a "sub-basket" consisting of N countries with, for example, lowest prices or countries where the drug was reimbursed. Restrictions imposed by some countries on the minimum number of countries in the basket were also taken into account in the model (e.g. a country can require that at least 50% of the countries in its basket have already set a price that can feed the ERP process). If this condition was not satisfied, price evaluation was postponed a later step of the modelling process.

- **Price reduction**

  Some countries apply price reduction to the calculated basket price. In the model, this reduction was expressed in percentage. The ERP price was defined as the basket price minus the reduction.

  Moreover, for countries using ERP as a supportive decision criterion, another price reduction could be applied to the calculated ERP price in order to simulate a change in price following a price negotiation. The discount rate in this case was set arbitrarily, for each country or for groups of countries, depending on their GDP or purchasing power parity (assuming that countries with lower GDP will use higher discount rate and vice versa).

  For countries that did not use ERP, drug prices were set arbitrarily and the user had the possibility to manually reproduce real-life price evolution by creating calendar of changes. This approach yielded sufficiently accurate inputs for ERP-based systems, which were of primary interest in the model.

  All prices of the model were initially set at ex-factory level price. ERP price basis defined per country (i.e. ex-factory price, pharmacy purchasing price or pharmacy retail price) were calculated according to average wholesaler/pharmacy margins which could be modified by the user.

  It was assumed that the drug price could not increase between two evaluation events.

  The process of price calculation is presented in Figure 3.

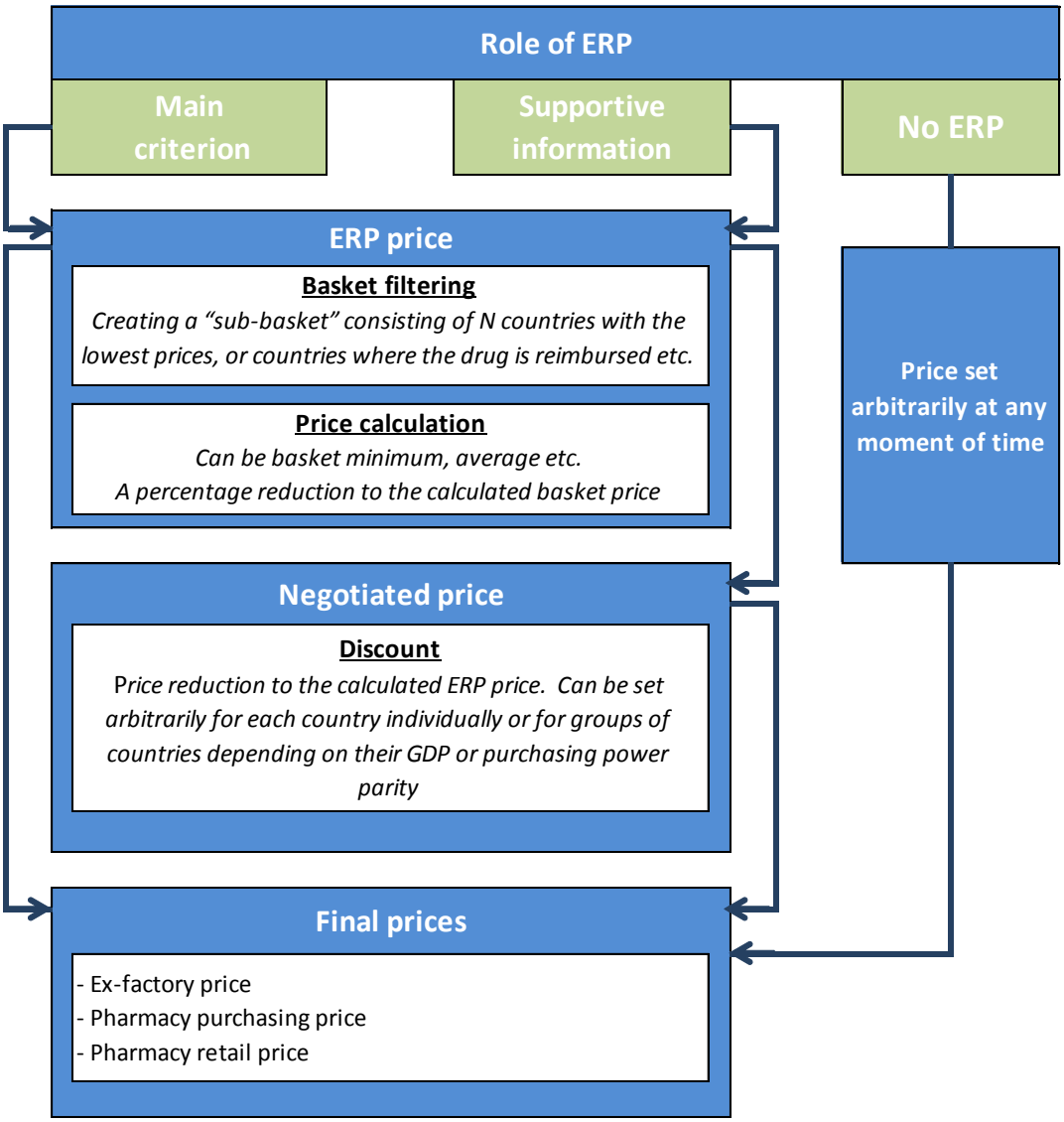


Figure 3. Price calculation process in the simulation model

5.1.3.5 Model outputs

The model generated the following outputs:

- Price evolution in each country over time;
- Minimum, maximum, and average of drug price of all countries;
- Histograms ranking countries by percentage decrease in the price at fixed point of time.

5.2 Analyses

5.2.1 Overview

Two types of simulation were performed. Firstly, in order to gain a better understanding of price dynamics in the context of ERP-based systems, a number of scenarios were simulated with *fictitious drugs* and *fictitious decision rules*. Secondly,

price dynamics were simulated for several *existing drugs*, for which real-life prices were set by the ERP procedure. Model outcomes were then compared to the actual recorded prices.

Appendix 11 presents the simulation model inputs used to assess the current price dynamics of ERP-based systems on which several scenarios were tested. These inputs were obtained from the literature review, as well as consultation with stakeholders. In case of missing data, unclear data, or data that could be complicated to implement in the model, some assumptions, identified by an asterisk, were made. The ex-factory drug price was set for non ERP countries (UK and Sweden) at €100 at simulation start.

Country characteristics taken into account in the simulation model are presented in Appendix 12.

These inputs are summarized in Appendix 13.

5.2.2 Fictitious scenarios

In order to evaluate the impact of each ERP rule, a range of scenarios were implemented.

First, a base case scenario was built based on input data and country characteristics reported in Appendix 11 and Appendix 12, respectively. The base case scenario considered the price evolution only in countries using ERP. ERP was considered as main criterion to set the drug price in all of these countries. In non-ERP countries, the price was considered as fixed in order to assess the impact of ERP independently from other price negotiations.

Various scenarios were tested with all the parameters modified one by one, and the results were compared to the base case.

Time horizon was set at 10 years for all the scenarios to reflect the period of data exclusivity for on-patent medicines as per EU Pharmaceutical Legislation.[63]

The tested scenarios are summarized in Table 3.

Table 3. List of fictitious scenarios tested with ERP simulation model

Scenario 1	Simulation of price revisions each year and every 3 years
Scenario 2	Simulation of drug launch sequence in countries by ascending or descending order of GDP/capita
Scenario 3	Simulation of changes in exchange rates
Scenario 4	Simulation of using ex-factory price or pharmacy purchasing price as price basis taken for reference purpose
Scenario 5	Simulation of the country basket composed of all countries under study
Scenario 6	Simulation of rules on minimum number of countries in basket having approved prices to set the ERP price
Scenario 7	Simulation of calculation methods to set the ERP price
Scenario 8	Simulation of annual price deflation in non ERP countries along with price revisions in ERP countries
Scenario 9	Simulation of price negotiations for country using ERP as supportive criterion and weighted according to GDP/capita
Scenario 10	Simulation of the impact of genericisation
Scenario 11	Simulation of price cuts proportional to government deficit and proportional to pharmaceutical expenditure
Scenario 12	Simulation of historical price cuts
Scenario 13	Simulation of several price cuts on a same year in Greece
Scenario 14	Simulation of adding fixed price in Germany and decreasing fixed price set in UK
Scenario 15	Simulation of various packaging, dosage or formulation of a drug launched in the countries
Scenario 16	Simulation of the use of net drug prices instead of facial prices for reference purposes
Scenario 17	Simulation of price dynamics if all countries leading to important price decreases were removed from the baskets
Scenario 18	Simulation of the increase in the number of countries in the basket
Scenario 19	Simulation of price of one drug available only in the hospital or in the out-patient sector
Scenario 20	Simulation of several scenarios together

5.2.3 Real-life scenarios

In order to evaluate the impact of ERP in the real-life, the ERP model was applied to a selection of drugs.

Real medicinal products selected for this project included:

- Off-patent/in-patent drugs
- Cheap, medium-priced and expensive drugs
- In-patient /out-patient drugs
- Orphan and non-orphan drugs

Real-life cases of medicinal product prices were randomly selected from medicines approved via the European Medicines Agency (EMA) centralised procedure between 2000 and 2012. This sample was completed with additional off-patent products (Table 4).

The IMS price database was selected as one of the most comprehensive source of information since it covered most of the selected products in a large number of countries (26 countries: Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, UK) and included 12 years history data available.

The countries where no prices were available were taken out of the model.

As accurate price could not be obtained for the drugs distributed through the hospital channel due to unknown commercial discounts associated with these drugs, only products distributed via the retail channel were included in the modelling and price analysis. Most countries did not specify if ERP was applied to in- and/or out-patient medicines. Only Denmark reported using ERP only for hospital-only medicines, while Austria, Portugal and the Netherlands reported to use ERP for out-patient medicines. Iceland reported using ERP for in- and out-patient medicines. In general, prices of hospital-only medicines are set through tenders and direct negotiations. As such, analysing ERP impact in real-life using price of drugs distributed *via* the retail channel allows a reasonable overview of price dynamics through ERP-based systems.

To allow comparability among the different case studies, prices were analysed using a price per counting units (e.g. tablet, syringe) or based on milligram of active substance for products (dry powder) and were normalized on the German price (i.e. German price equal to 1).

For each medicine of the database, top selling form/strength available or form/strength available in the highest number of countries was selected. The ex-factory price of this form-strength was used as reference for the real-life scenarios. When this form/strength of the drug was not available in a given country, this country was taken out from the model to avoid a potential price distortion.

The ERP model was used for real drugs as follows:

- The ex-factory drug price was set for non ERP countries (UK and Sweden) as well as for Germany (non-ERP country before AMNOG law).
- The time to uptake of the real drugs was applied as a proxy of launch sequences.

Model outcomes were compared to the actual recorded prices. The unit of analysis was the ex-factory price per unit in constant Euros (to remove the impact of exchange rate). The price data did not include any rebates.

For each drug, the interpretation of the outcomes was enlightened with the HTA assessment reviews of the French National Authority for Health (HAS-Haute Autorité de Santé) and of Scottish Medicine Consortium (SMC), when available, as these HTA agencies publish opinions on all drugs launched in their respective country. This allowed to have two perspectives for each drug; a first perspective with the HAS advice based on the assessment of clinical benefit (actual benefit (SMR-Service Médical Rendu) and improvement of the actual benefit (ASMR-Amélioration du Service Médical Rendu) complemented by the SMC advice providing a second perspective on the incremental cost-effectiveness.

Table 4.List of real medicines selected for the model

Medicine Name	Active Substance	Medicine Name	Active Substance
Abilify	Aripiprazole	**Lexapro ***	Escitalopram
Aerius	Desloratadine	**Lipitor ***	Atorvastatin
Aricept *	Donepezil	**Micardisplus**	Telmisartan/Hydrochlorothiazide
Atripla	Efavirenz/Emtricitabine/Tenofovir Disoproxil	**Neupogen***	Filgrastim
Avastin	Bevacizumab	**Nexium ***	Esomeprazole
Bretaris genuair	Aclidinium Bromide, micronised	**Onbrez breezhaler**	Indacaterol Maleate
Bydureon	Exenatide	**Orencia**	Abatacept
Byetta	Exenatide	**Pravafenix**	Fenofibrate/Pravastatin
Caprelsa	Vandetanib	**Rasilamlo**	Aliskiren/Amlodipine
Cholestagel	Colesevelam	**Rasilez**	Aliskiren
Cimzia	Certolizumab Pegol	**Seebri Breezhaler**	Glycopyrronium Bromide
Crestor	Rosuvastatin	**Simponi**	Golimumab
Daxas	Roflumilast	**Sutent**	Sunitinib
Edurant	Rilpivirine Hydrochloride	**Sycrest**	Asenapine Maleate
Enbrel	Etanercept	**Tamiflu**	Oseltamivir
Erypo *	Epoetin alfa	**Teysuno**	Tegafur/Gimeracil/Oteracil
Erbitux	Cetuximab	**Trajenta**	Linagliptin
Evoltra	Clofarabine	**Truvada**	Emtricitabine/Tenofovir Disoproxil
Exforge	Amlodipine/Valsartan	**Vectibix**	Panitumumab
Galvus	Vildagliptin	**Velcade**	Bortezomib
Glivec	Imatinib	**Victrelis**	Boceprevir
Herceptin	Trastuzumab	**Vidaza**	Azacitidine
Humira	Adalimumab	**Votrient**	Pazopanib
Incivo	Telaprevir	**Votubia**	Everolimus
Invega	Paliperidone	**Xeplion**	Paliperidone Palmitate
Isentress	Raltegravir	**Xolair**	Omalizumab
Januvia	Sitagliptin	**Yervoy**	Ipilimumab
Jevtana	Cabazitaxel	**Zypadhera**	Olanzapine Pamoate
Kaletra	Lopinavir/Ritonavir	**Zyprexa ***	Olanzapine
Keppra *	Levetiracetam		
Lantus	Insulin Glargine	*Specific selected off-patent medicines	

6. Results

6.1 Fictitious scenarios

For the base case, drug price evolution over time was presented per country, and for all countries together with minimum, maximum and average price weighted or not by country population. For the other scenarios, drug price evolution over time was presented for all countries together with average price weighted or not by country population. As too numerous results would have affected the readability of the report, the average drug price evolution over time for all countries weighted by country population were presented in Appendix 14-Average drug price evolution over time for all countries weighted by country population for Scenarios 1 to 20.

Results were also presented as histogram with drug price evolution per country at 10 years for base case and for all the scenarios.

6.1.1 Base case scenario

Assumptions

- Inputs of the base case are reported in Appendix 11 and Appendix 12
- Only price evolution in the countries using ERP was considered
- ERP was considered as the main criterion to set the price of the drug
- The ex-factory drug price was set for non ERP countries (UK and Sweden) at €100
- UK was considered as country of origin
- "Exogenous" price deflation over time was not taken into account
- No general inflation mark-up was assumed over time
- All prices used for reference purpose were facial prices
- The exchange rate remained constant overtime
- It was assumed that Germany applied ERP after one year and that countries referred to German prices one year after launch (taking into account early benefit assessment rules)
- It was assumed that the fictitious drug was:
    - A brand product
    - Reimbursed in all countries
    - Available in out-patient/in-patient sector, with a same pack size/dosage/formulation available in all countries

Figure 4 and Figure 5 present the average minimum and maximum evolution of the drug price over time for all countries (non-weighted by country population and weighted by country population, respectively). Figure 6 presents the evolution of the drug price over time in each of the selected countries.

Average drug price dynamics for all countries (Figure 4 and Figure 5) were characterized by a slight price increase in the first year, explained by the fact that prices at launch were in some countries above €100, depending on the wholesale and pharmacy margins. The price increase was followed by a steady decrease over the

years, with an apparent equilibrium reached about 7-8 years after the simulation and a slow and low decrease after this period of time. The price erosion at 10 years was quite low (about 15%). This observed time-profile was mainly a consequence of mixing various countries with various price revision periodicities.

Stability of prices was observed in countries such as Austria, Belgium, Denmark, Estonia, Luxembourg, Germany Poland, Sweden and the UK (Figure 6) This may be explained by two different factors: two countries do not use ERP (Sweden and the UK) and price re-evaluations were not reported for some countries (Austria, Belgium, Denmark, Estonia, Germany, and Poland). Only ERP could lead to a decrease in price in the base case since it is the unique criterion used to set the price of the drug; as such the above mentioned countries maintained the price level initially set at the time of drug launch. For Luxembourg, the price stability over time was explained by the fact that UK was assumed to be the country of origin (sole country used for ERP) and therefore the reference country of Luxembourg.

To summarize, countries that did not report price revision over time tended to have flat prices on the considered time frame, while countries reporting frequent price revisions had a regular price decline over time. Countries reporting longer interval in price revisions showed long period of flat price, followed by an abrupt price decrease when the price revision was performed.

Initial price reductions did not occur strictly at the same time, thus reflecting the differences between countries in average time to market entry after marketing authorization for a new drug. These various delays in drug launch between countries could also explain the dynamics of the average drug price for all countries (Figure 4 and Figure 5), with (re)-assessment of prices at various time.

There were few impacts on the average minimum and maximum evolution over time of the drug prices when prices were weighted by country population (difference inferior to 3%) (Figure 5).

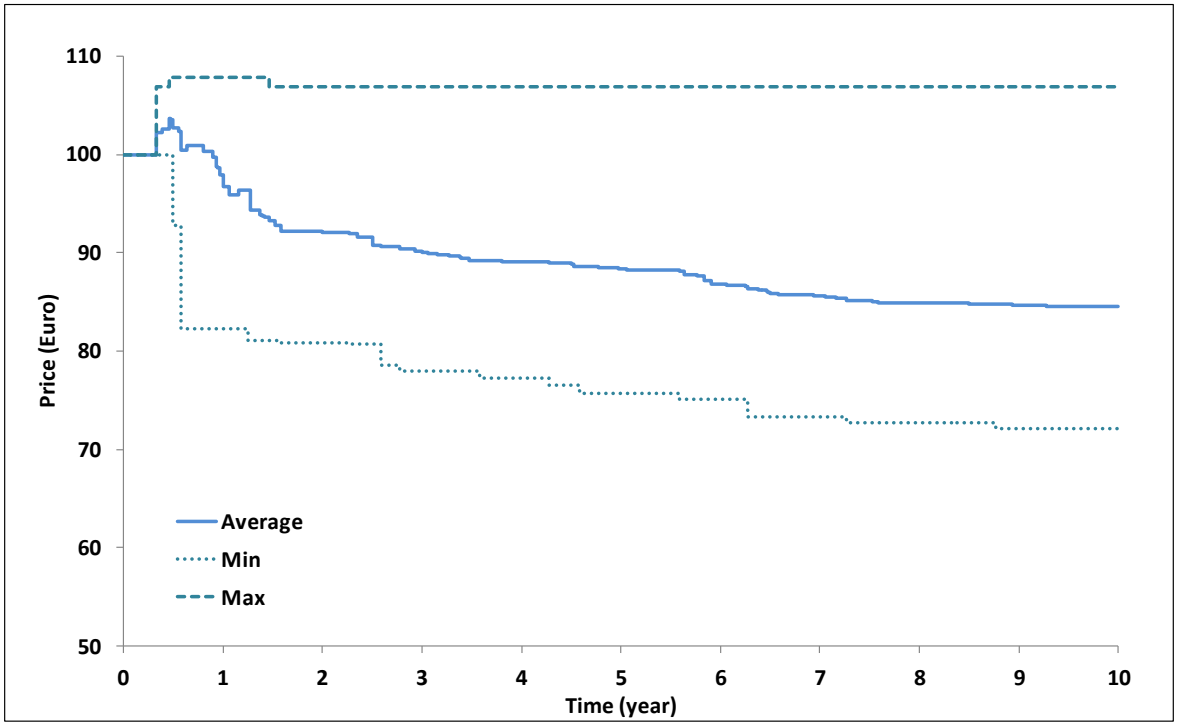


Figure 4. Base case-Evolution of minimum, maximum and average drug price over time

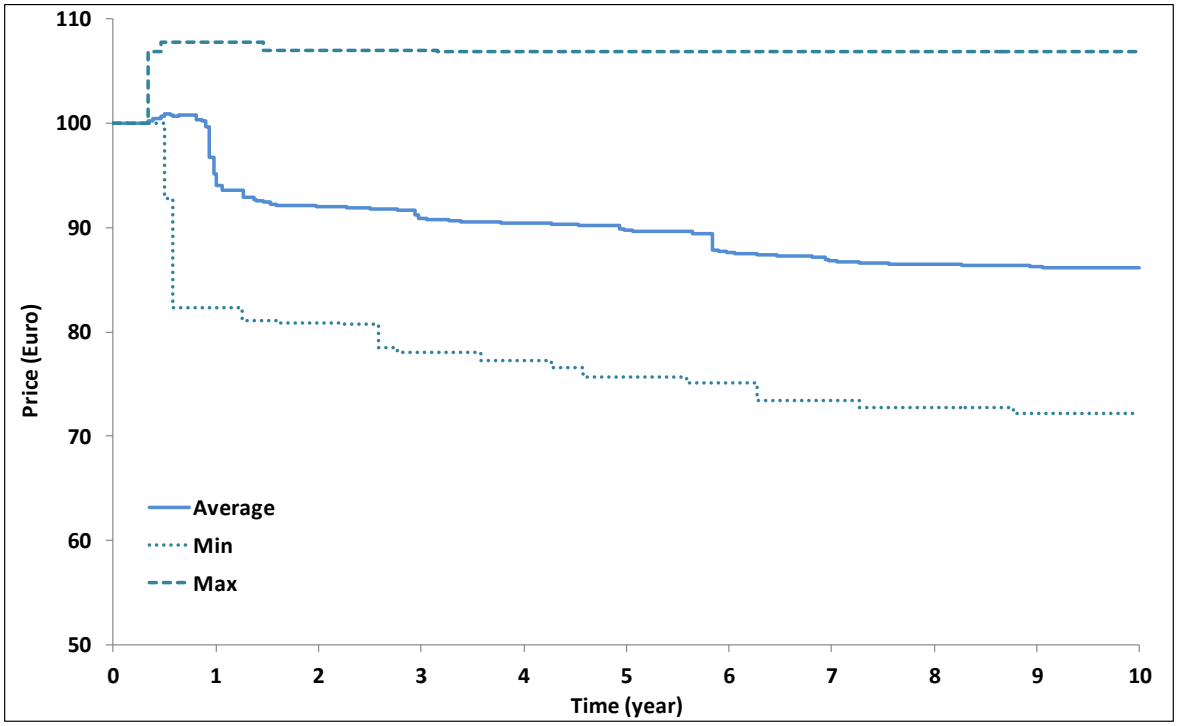
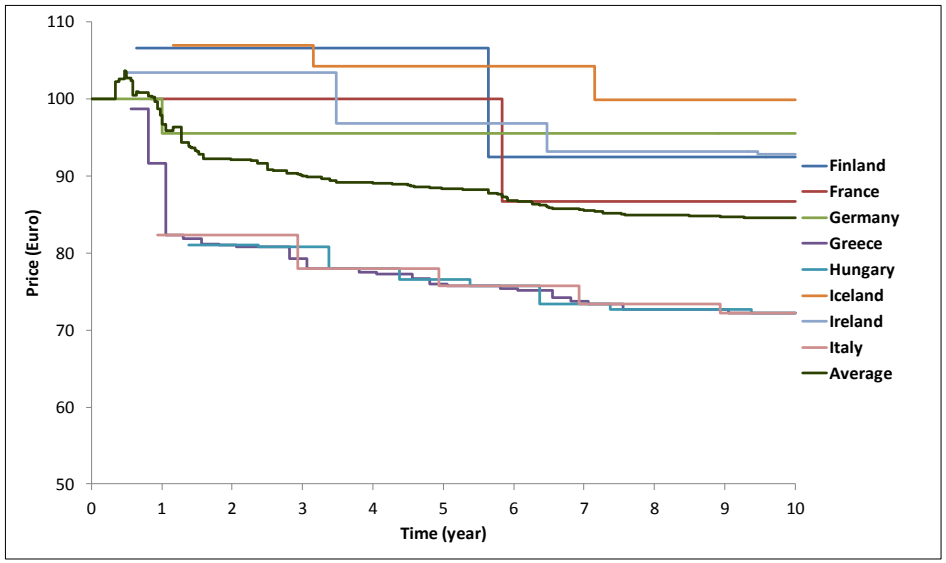
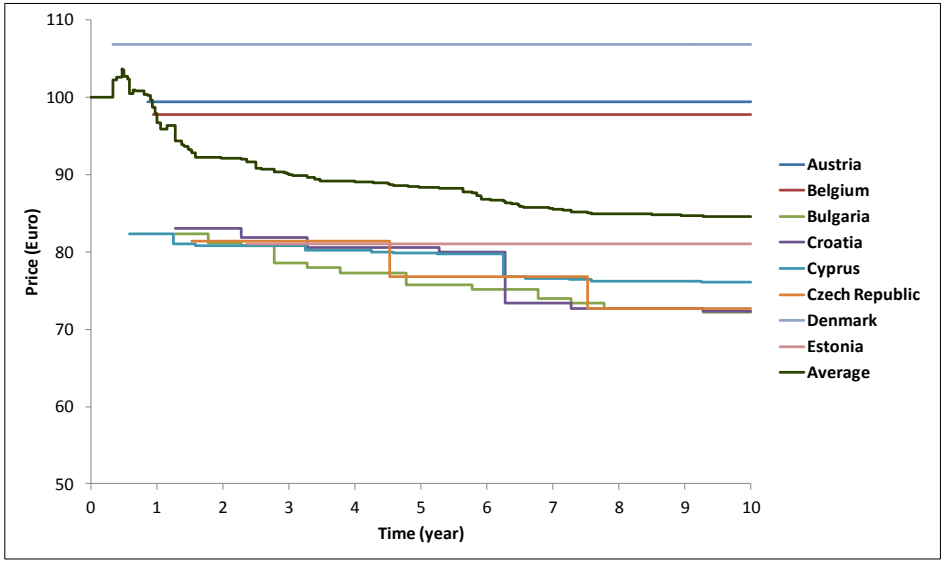
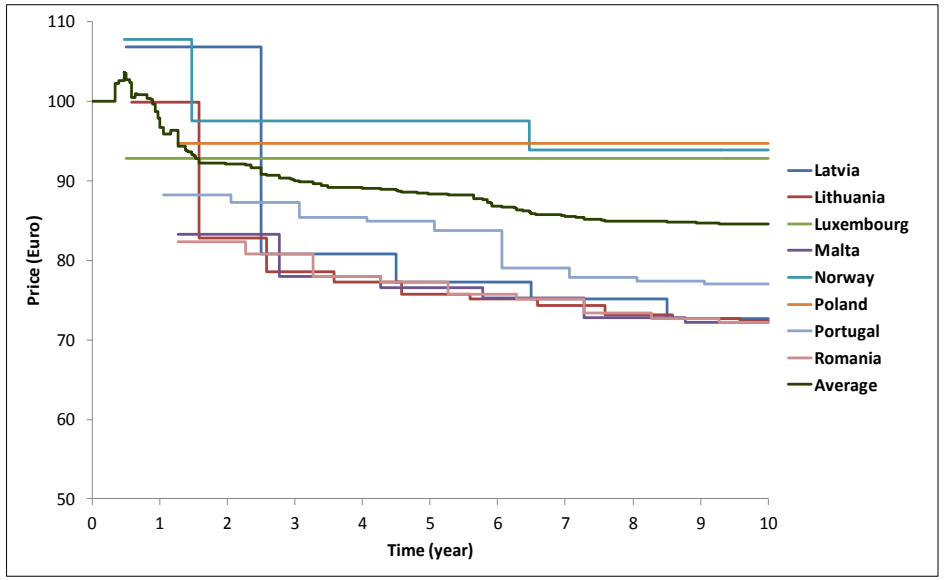


Figure 5. Base case-Evolution of minimum, maximum and average drug price over time weighted by country population







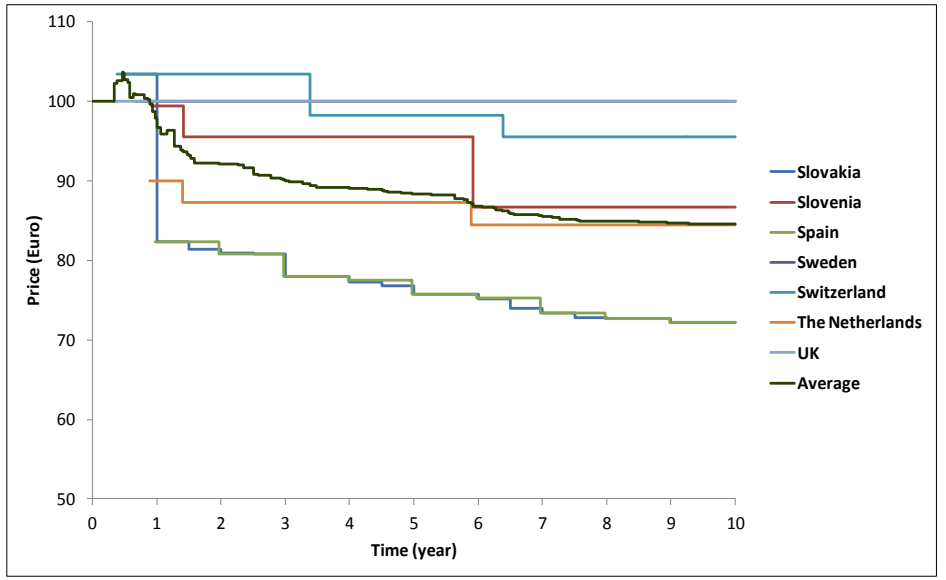


Figure 6. Base case-Evolution of drug price over time per country

Figure 7 represents the drug price evolution in percentage per country at 10 years. The median drug price decrease was around 15%. Countries with the smallest decreases were Austria, Belgium, Cyprus, Denmark, Estonia, Germany, Iceland, Luxembourg, and Poland. The biggest decreases were observed for Greece, Latvia, Lithuania and Slovakia. This was explained by the ERP policies of each country; countries with more frequent price revisions and calculation methods based on the lowest price, the average of the 3 lowest prices, the third lowest price or the average price with additional reduction of the country basket tend to have a faster and more pronounced decrease than the others. These more stringent rules are generally found in the countries with the lowest GDP, which tend to be more cautious in defining their policies in order to achieve the largest price erosion from ERP application.

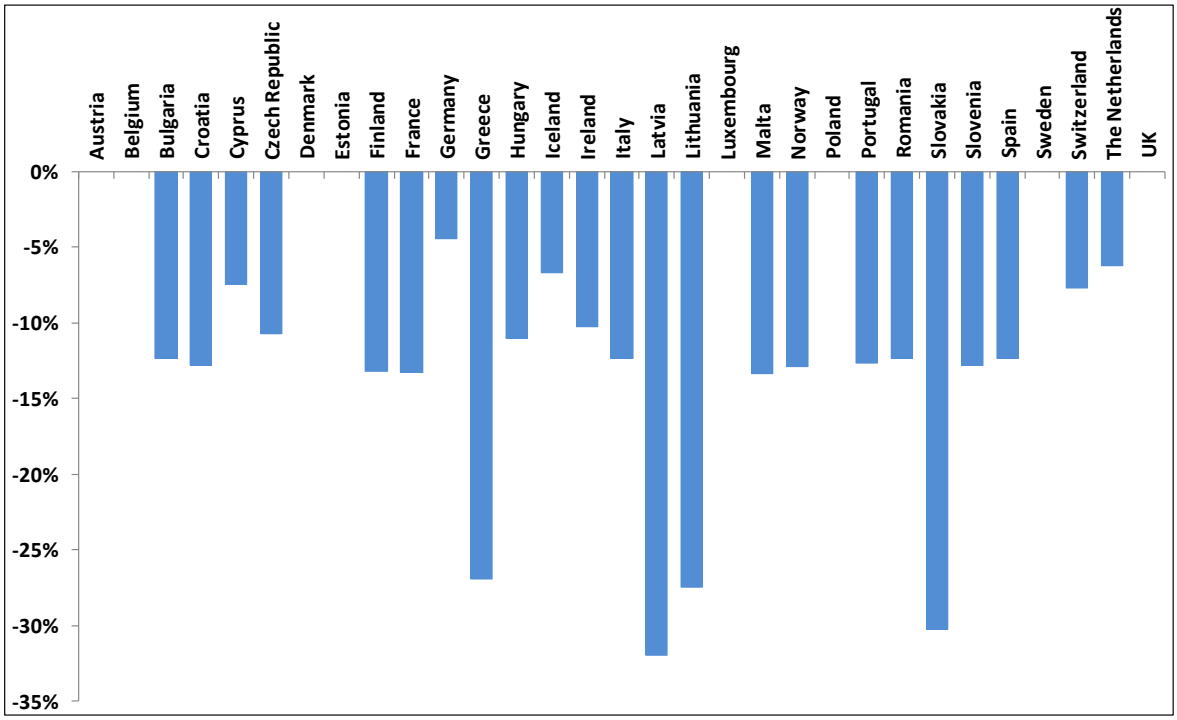


Figure 7. Base case-Evolution of drug price per country at 10 years (in percentage)

6.1.2 Scenario 1. Simulation of price revisions each year and every three years

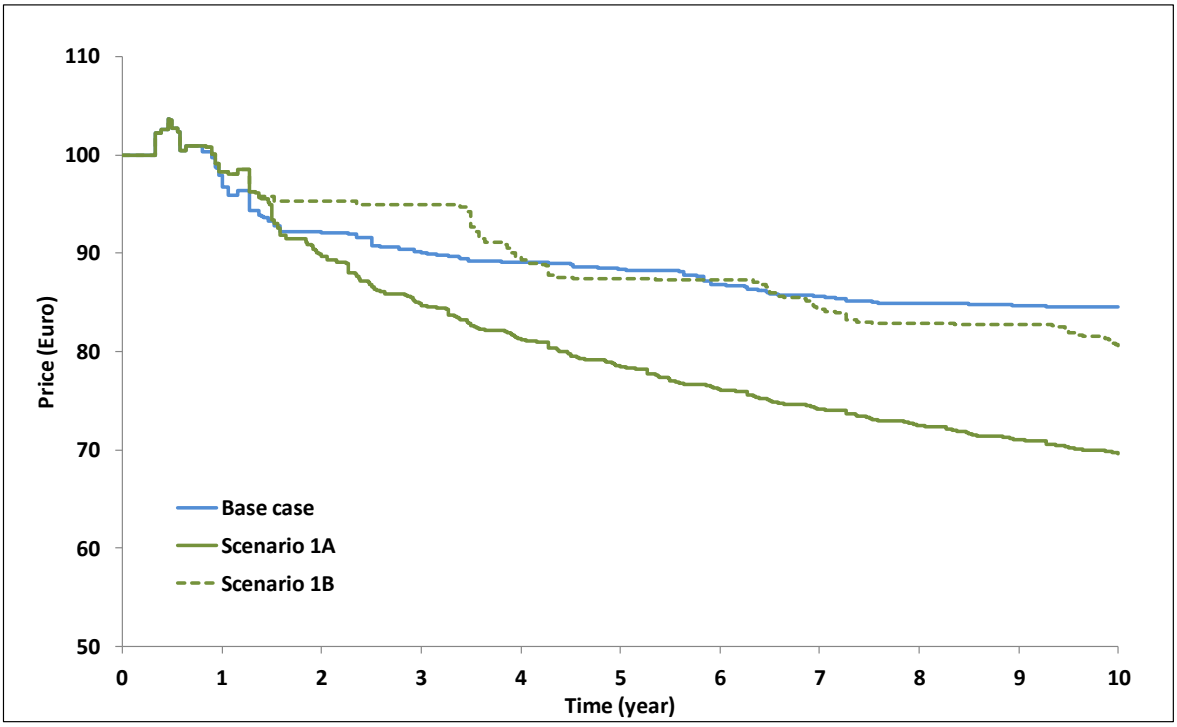
Assumptions

- Base case scenario, except for interval of price revisions

In this scenario, time interval between price revisions was set to one year (**Scenario 1A**) and every 3 years (**Scenario 1B**) following the launch date in all countries using ERP.

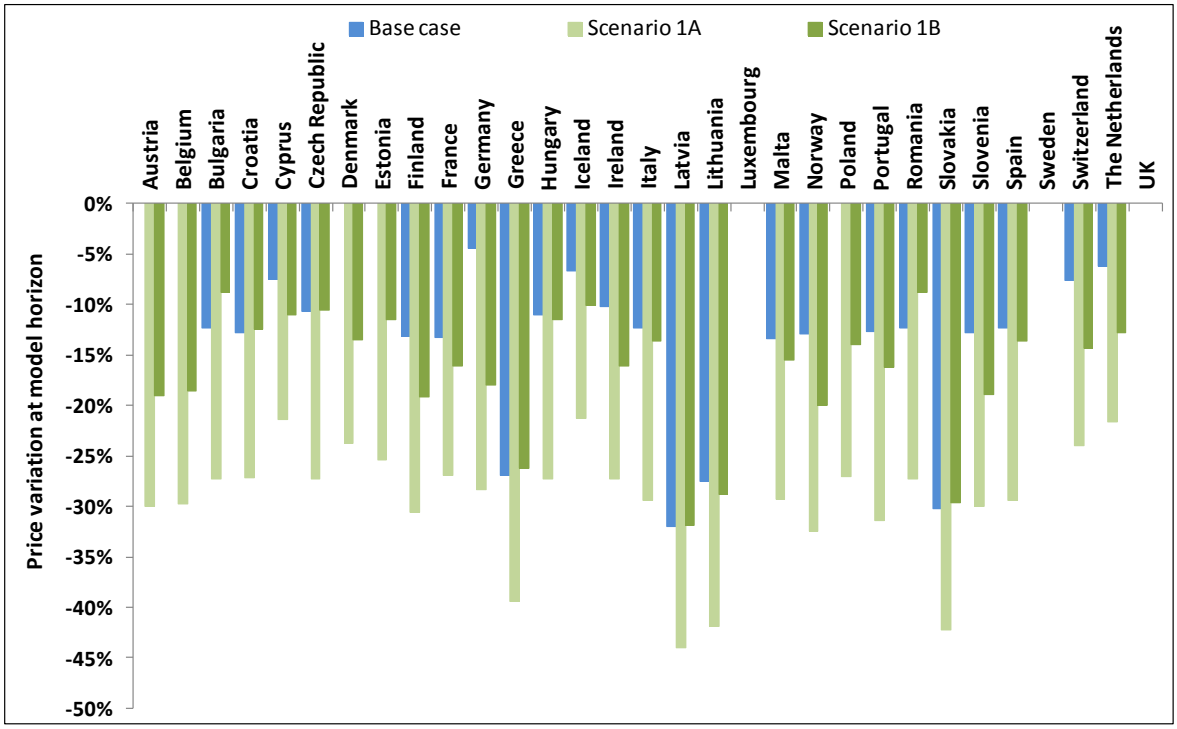
Figure 8 presents the evolution of the average drug price over time for all countries and Figure 9 presents the drug price evolution in percentage per country at 10 years.

This scenario showed that the more frequent the price revisions are, the faster prices decrease. A three-year price revision in all countries induced, compared to the base case, a lower average price decrease up to 4 years, followed by a quite similar average price up to year 7 and by a small average price reduction up to 10 years (-4.67% versus the base case). Applying an annual systematic revision for all countries induced faster average price erosion, up to 30% at 10 years (-17.65% versus the base case at 10 years). Moreover, as all countries undergo the same frequency of price revision, there is no trend to reach equilibrium. This clearly highlighted the weight of infrequent price revision in some countries in reaching apparent equilibrium in the base case. As expected, the drug price decrease at 10 years was higher than base case in countries with less frequent price revisions. However, price decreased in all countries for two reasons; first, because the increased frequency of revision impacted directly the prices of countries with low frequency of revision, and second, those reduced prices impacted the other countries.



Scenario 1A (interval between price revisions set to one year) and Scenario 1B (interval between price revisions set to every 3 years)

Figure 8. Scenario 1- Simulation of price revisions each year and every 3 years-Evolution of average drug price over time



Scenario 1A (interval between price revisions set to one year) and Scenario 1B (interval between price revisions set to every 3 years)

Figure 9. Scenario 1- Simulation of price revisions each year and every 3 years-Evolution of drug price per country at 10 years (in percentage)

6.1.3 Scenario 2. Simulation of drug launch sequence in countries by ascending or descending order of GDP/capita

Assumptions

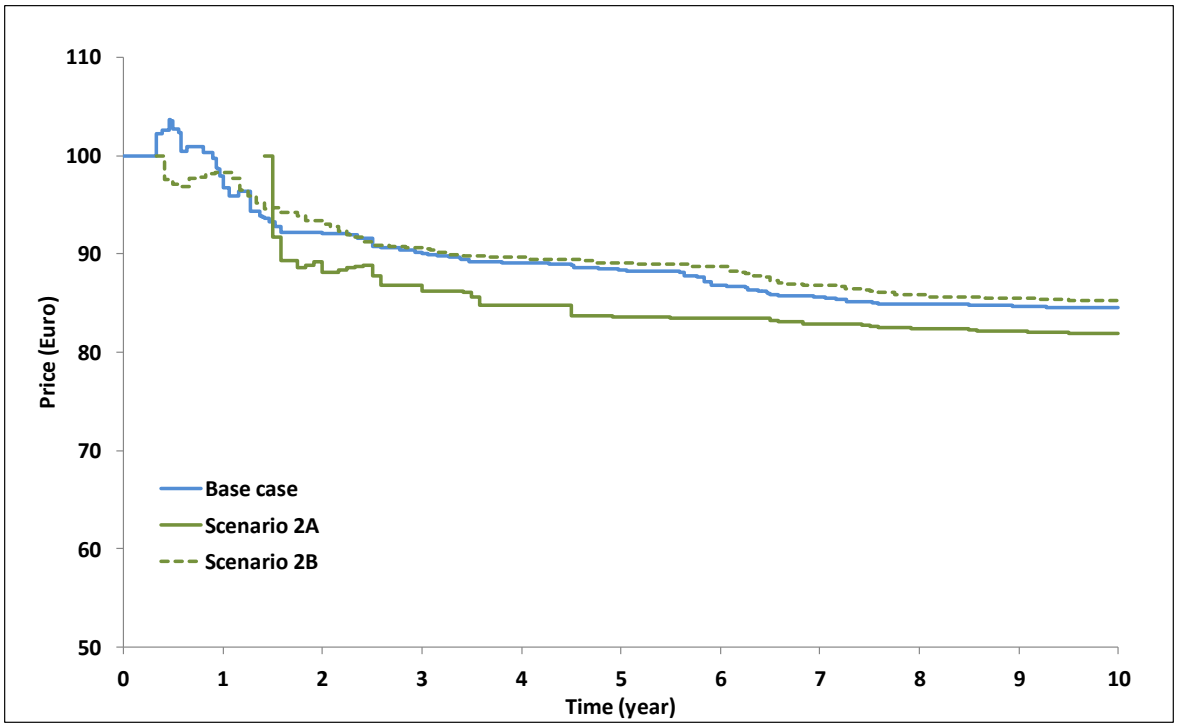
- Base case scenario, except for average time to market entry for new drugs

In this scenario, the sequences of drug launch were performed in the countries by ascending order of GDP/capita (**Scenario 2A**) or descending order of GDP/capita (**Scenario 2B**), with a time interval of one month between each launch in one considered country.

Figure 10 presents the evolution of the average drug price over time for all countries and Figure 11 presents the evolution of the drug price, in percentage per country, at 10 years.

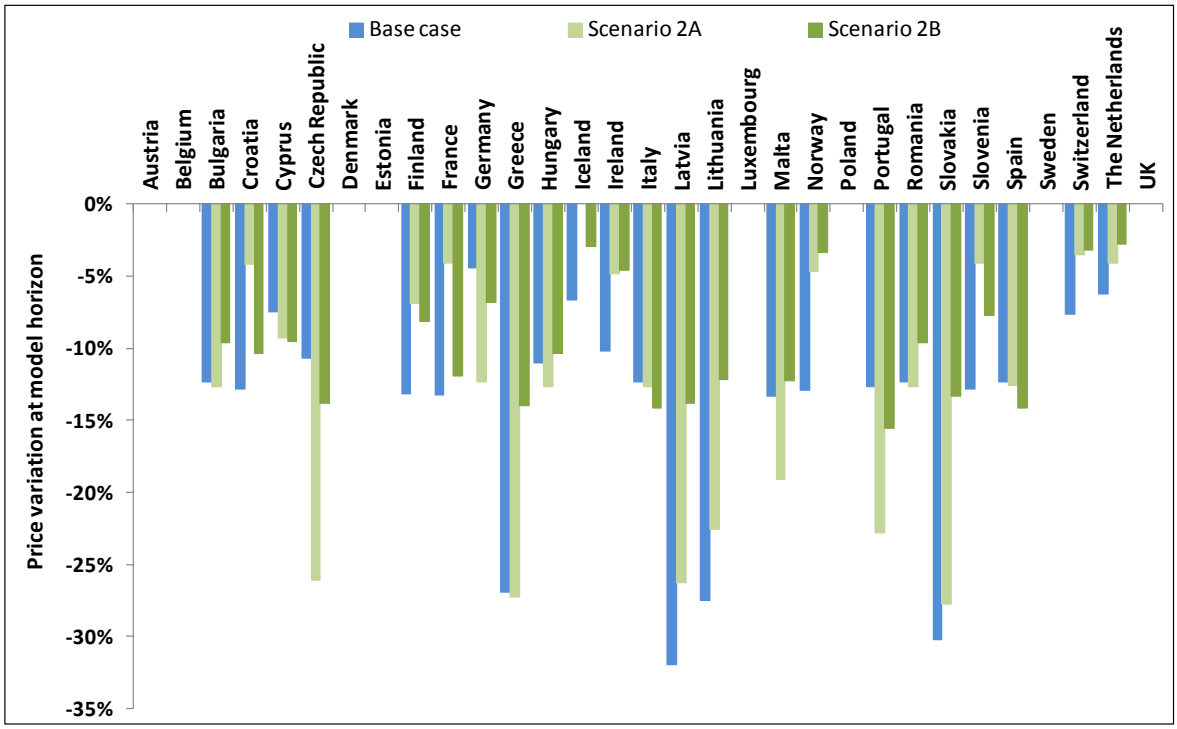
Average erosion of the drug price over time was higher when the drug was first launched in countries with lower GDP per capita (-3.2 % versus the base case at 10 years) compared to a launch initiated in the countries with higher GDP per capita (+0.81% versus the base case at 10 years). This is explained by the fact that, in general, countries with lower GDP per capita apply ERP rules that tend to drive the prices down (e.g. lowest price versus average price used for price calculation, or more frequent price revisions). This scenario clearly implies that countries using more ERP policies that drive down the drug prices might be de-prioritized by market authorisation holders, when a new drug is launched, to minimize the impact on other

country prices. However, in this scenario, the difference looked low in average, as substantial price changes were observed for few countries, while many countries remained unaffected.



Scenario 2A (countries by ascending order of GDP/capita) and Scenario 2B (countries by descending order of GDP/capita)

Figure 10. Scenario 2-Simulation of drug launch sequence in countries by ascending or descending order of GDP/capita-Evolution of average drug price over time



Scenario 2A (countries by ascending order of GDP/capita) and Scenario 2B (countries by descending order of GDP/capita)

Figure 11. Scenario 2-Simulation of drug launch sequence in countries by ascending or descending order of GDP/capita-Evolution of drug price per country at 10 years (in percentage)

6.1.4 Scenario 3. Simulation of changes in exchange rates

Assumptions

- Base case scenario, except for exchange rates

6.1.4.1 Scenario 3A. Simulation of increase or decrease in exchange rate of one local currency

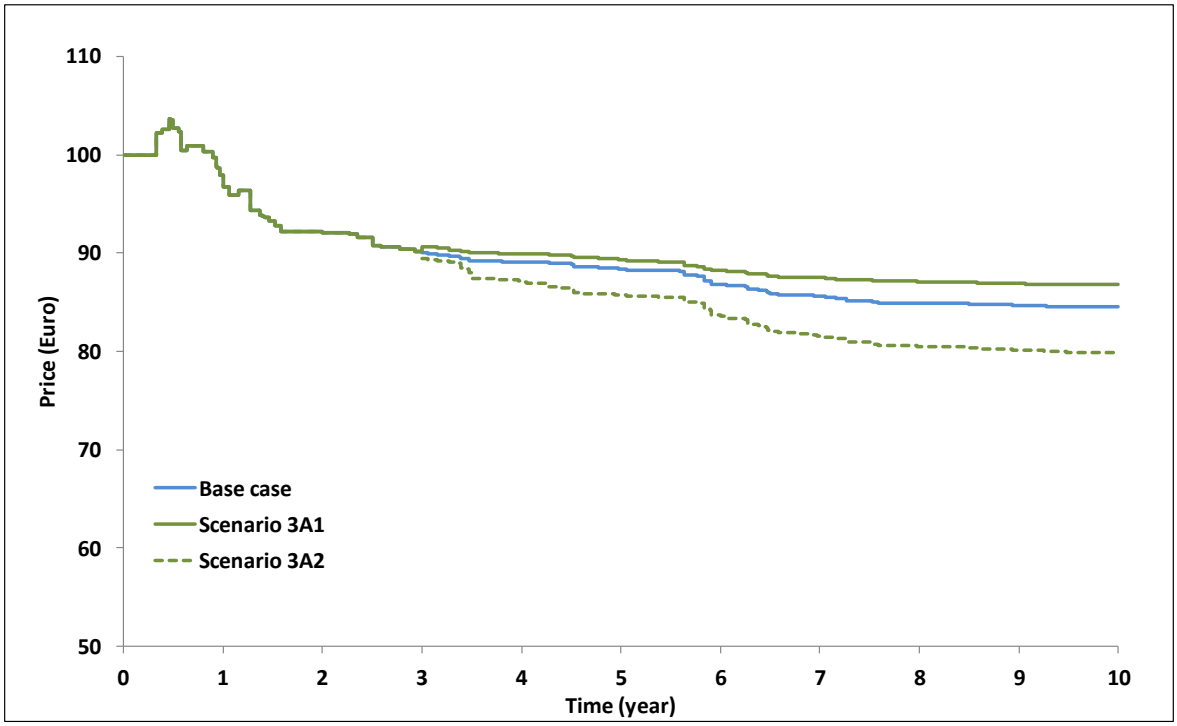
In this scenario, an increase (**Scenario 3A1**) and a decrease (**Scenario 3A2)** of 20% in exchange rate from British Pound to Euro were introduced after the first 3 years of simulation.

Historical fluctuations of exchange rate from British Pound to Euro were also simulated by applying the annual average exchange rate between 2003, for year 0, and 2012, for year 9 [64] (**Scenario 3A3**). (Appendix 15)

Figure 12 and Figure 14 present the evolution of the average drug price over time for all countries. Figure 13 and Figure 15 present the evolution of the drug price in percentage per country at 10 years.

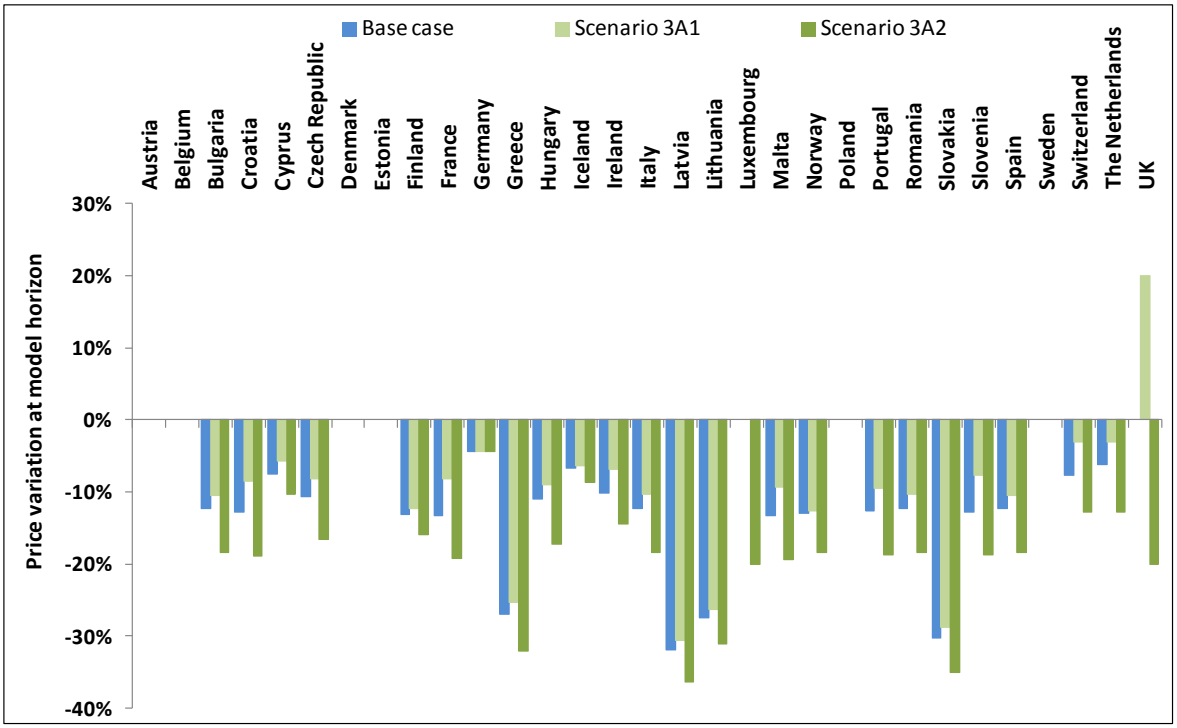
Increase or decrease of 20% in exchange rate from British Pound to Euro introduced after the first 3 years of simulation impacted the average drug price of +2.65% and of -5.48% at 10 years in comparison to base case (Figure 12). It is interesting to note the very limited effect of such scenario and the highest impact of currency depreciation than of appreciation. The limited effect of this scenario is due to the fact that the UK price was considered as the reference price and remained stable over

time. At the same time, the use of a large country basket diluted the impact of the UK price changes despite the fact that the UK is a reference country in most countries using the average price as calculation method for ERP. Moreover, the UK price has no impact on countries that use the lowest price or the average of the three lowest prices as ERP calculation methods, since the UK price was not among the lowest price.



Scenario 3A1 (increase of 20% in exchange rate from British Pound to euro) and Scenario 3A2 (decrease of 20% in exchange rate from British Pound to Euro)

Figure 12. Scenarios 3A1 and 3A2-Simulation of increase or decrease in exchange rate of one local currency-Evolution of average drug price over time



Scenario 3A1 (increase of 20% in exchange rate from British Pound to euro) and Scenario 3A2 (decrease of 20% in exchange rate from British Pound to Euro)

Figure 13. Scenarios 3A1 and 3A2-Simulation of increase or decrease in exchange rate of one local currency-Evolution of drug price per country at 10 years (in percentage)

When using historical fluctuations of exchange rate from British Pound to Euro, an average drug price decrease of -4.20% versus the base case, at 10 years (Figure 15) was introduced. This scenario confirmed that the fluctuation from British Pound to Euro, once isolated, had a small impact. Moreover, it is interesting to note that the exchange rate from British Pound to Euro impacted significantly the average drug price only from 2008 (year 5 in the model) when the British pound saw a sharp decline against Euro.

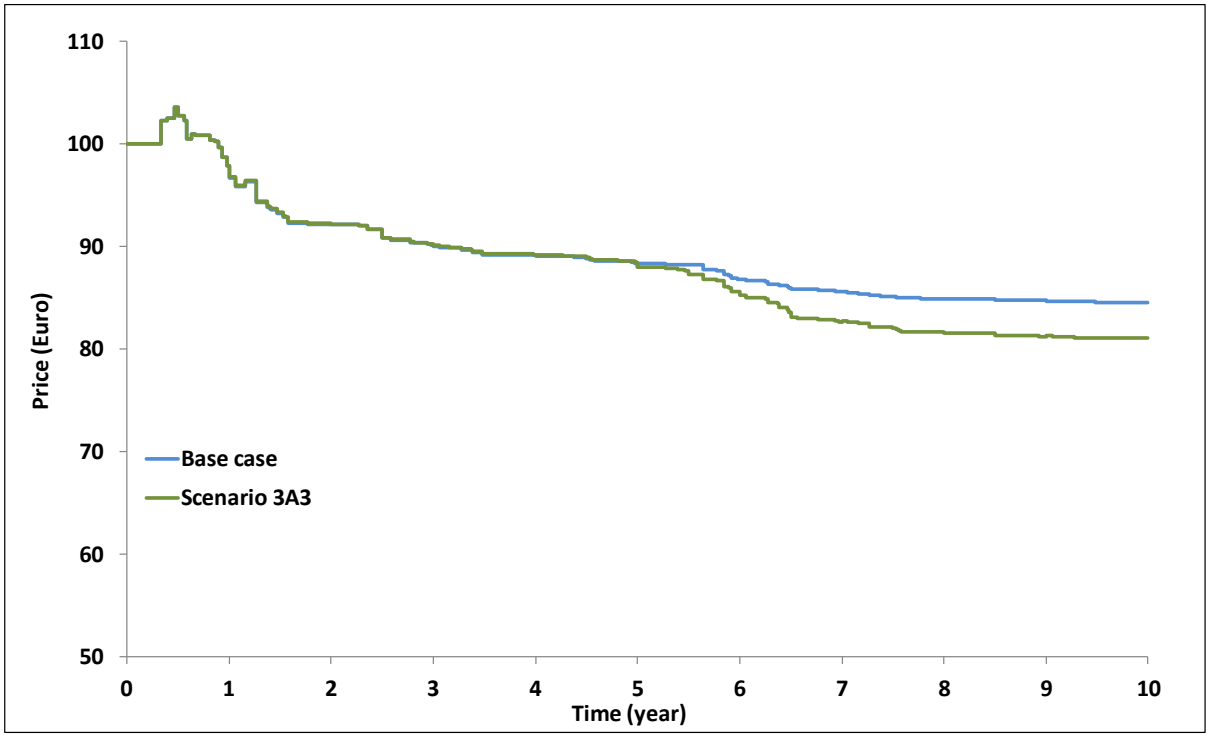


Figure 14. Scenario 3A3-Simulation of historical fluctuations of exchange rate from British Pound to Euro-Evolution of average drug price over time

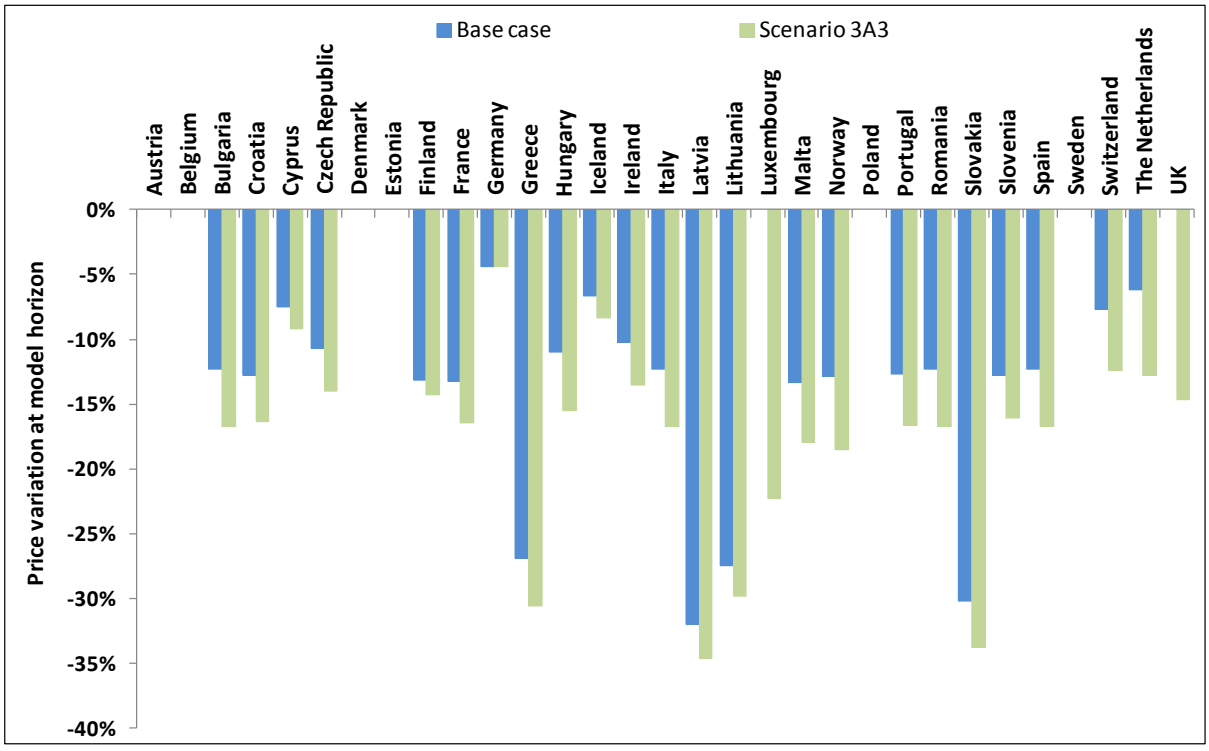


Figure 15. Scenario 3A3-Simulation of historical fluctuations of exchange rate from British Pound to Euro currency- Evolution of drug price per country at 10 years (in percentage)

6.1.4.2 Scenario 3B. Simulation of decrease in exchange rates in Poland and Hungary

In this scenario, a decrease of 10% in exchange rate from Polish Zloty and Hungarian Forint to Euro was introduced after the first 3 years of simulation (**Scenario 3B1**).

Historical fluctuations of exchange rate from Polish Zloty and Hungarian Forint to Euro were also simulated by applying the annual average exchange rate between 2003, for year 0, and 2012, for year 9[64] (**Scenario 3B2**). (Appendix 15)

Figure 16 and Figure 18 present the evolution of the average drug price over time for all countries and Figure 17 and Figure 19 present the evolution of the drug price in percentage per country at 10 years.

The decrease of 10% in exchange rate from Polish Zloty and Hungarian Forint to Euro introduced after the first 3 years of simulation slightly decreased the average drug price of -1.94% versus the base case at 10 years (Figure 16).

This scenario confirmed that, as most countries reference large basket and use average basket price to calculate ERP price, price decrease experienced in 2 countries had a small impact. Moreover, Poland and Hungary are less often referenced than UK: they have fewer opportunities to impact prices. Five countries referencing Hungary do not reference Poland; as such the impact was restricted to a 10% price decrease in only one country, for these countries. This might explain the smaller impact found than in scenario 3A.

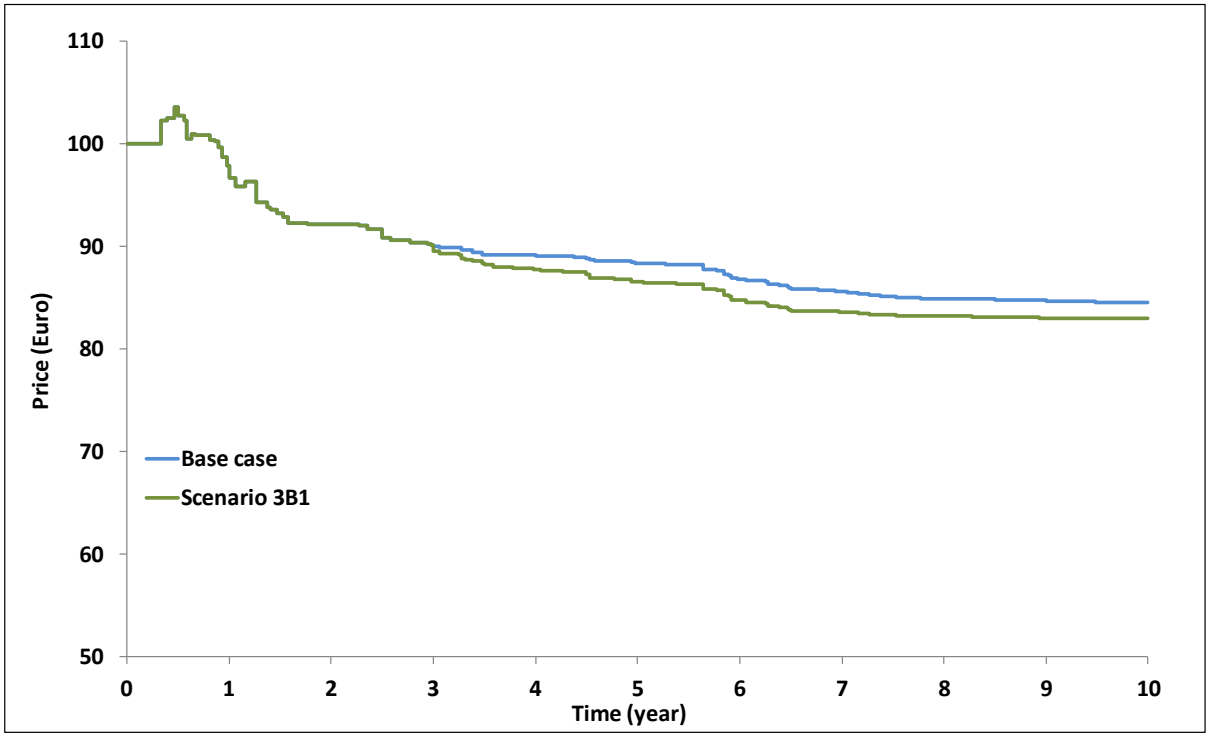


Figure 16. Scenario 3B1-Simulation of decrease of 10% in exchange rate from Polish Zloty and Hungarian Forint to Euro-Evolution of average drug price over time

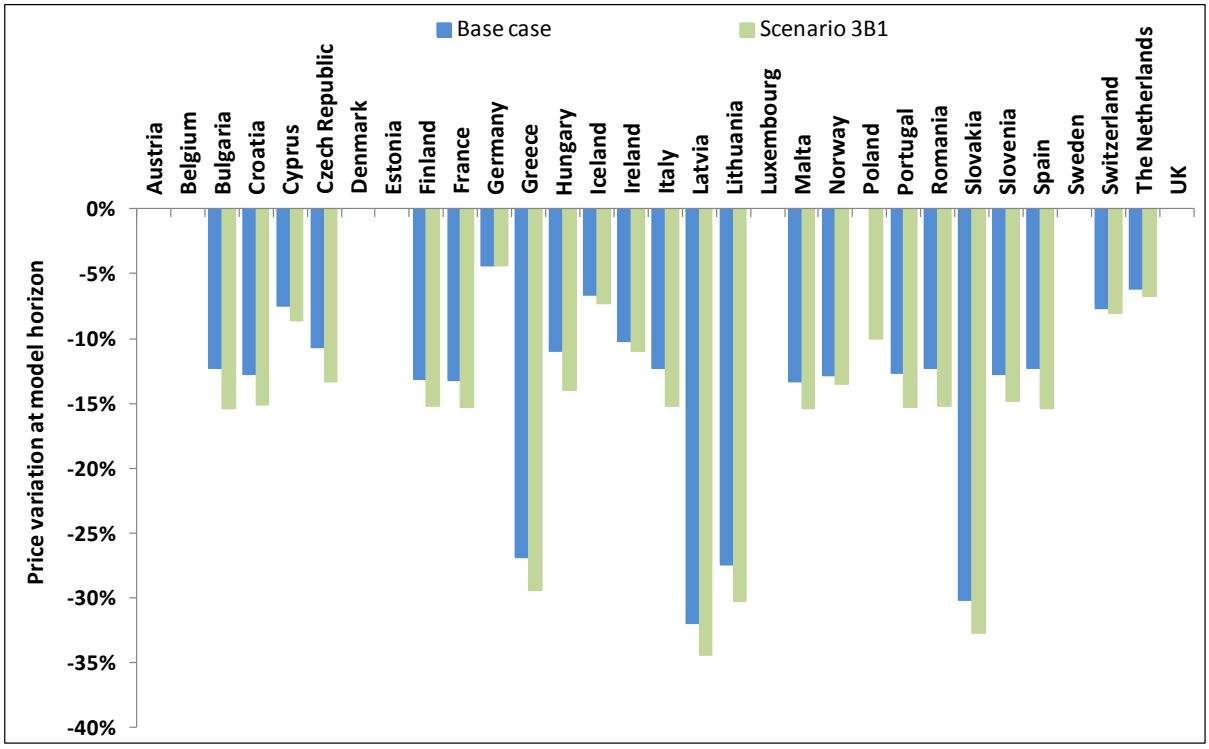


Figure 17. Scenario 3B1-Simulation of decrease of 10% in exchange rate from Polish Zloty and Hungarian Forint to Euro-Evolution of drug price per country at 10 years (in percentage)

Using historical annual average fluctuations of exchange rate from Polish Zloty and Hungarian Forint to Euro confirmed that exchange rate of these two countries had a small impact on price evolution. Results of scenarios 3B1 and 3B2 were very close with an average drug price decrease of -1.94% and of -2.36%, respectively versus the base case at 10 years (Figure 16 and Figure 18).

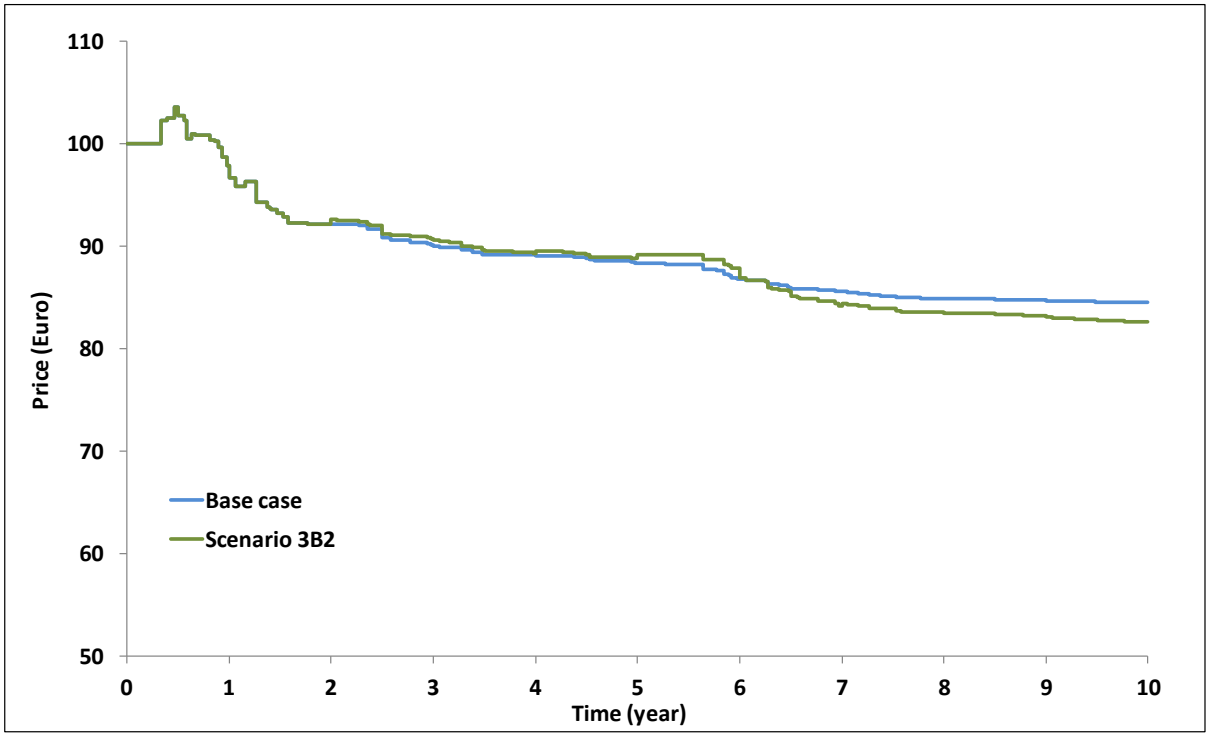


Figure 18. Scenario 3B2-Simulation of historical fluctuations of exchange rate from Polish Zloty and Hungarian Forint to Euro-Evolution of average drug price over time

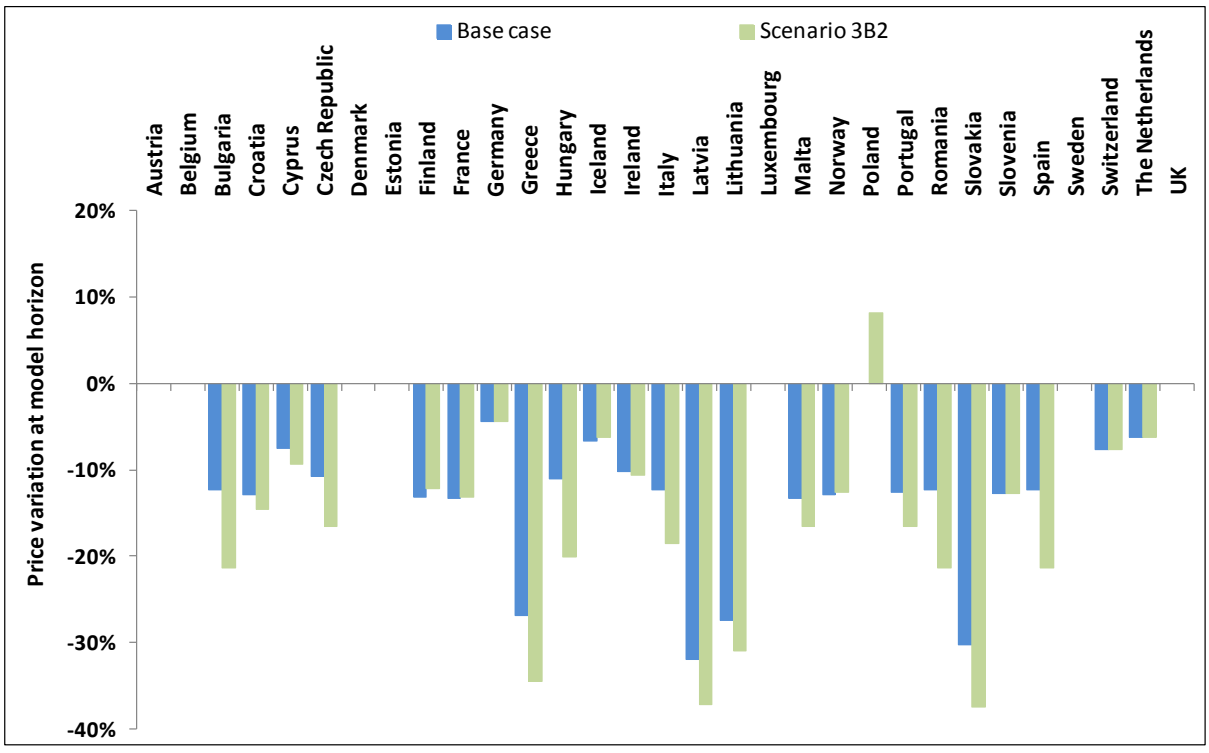


Figure 19. Scenario 3B2-Simulation of historical fluctuations of exchange rate from Polish Zloty and Hungarian Forint to Euro-Evolution of drug price per country at 10 years (in percentage)

6.1.4.3 Scenario 3C. Simulation of decrease in exchange rates in all non-Euro-currency countries

In this scenario, a decrease of 10% in exchange rate from all non-Euro-currencies to Euro was introduced after the first 3 years of simulation (**Scenario 3C1**).

Historical fluctuations of exchange rate from all non-Euro-currencies to Euro were also simulated by applying the annual average exchange rate between 2003, for year 0, and 2012, for year 9[64] (**Scenario 3C2**). (Appendix 15)

Figure 20 and Figure 22 present the evolution of the average drug price over time for all countries and Figure 21 and Figure 23 present the evolution of the drug price in percentage per country at 10 years.

A decrease of 10% in exchange rate from all non-Euro-currencies to Euro, introduced after the first 3 years of simulation, decreased the average drug price of -3.86% versus the base case at 10 years (Figure 20).

As expected, this effect on average price was smaller than the effect of a 20% decrease of Pound exchange rate versus Euro. This underlined the importance of UK as one of the most frequently referenced country.

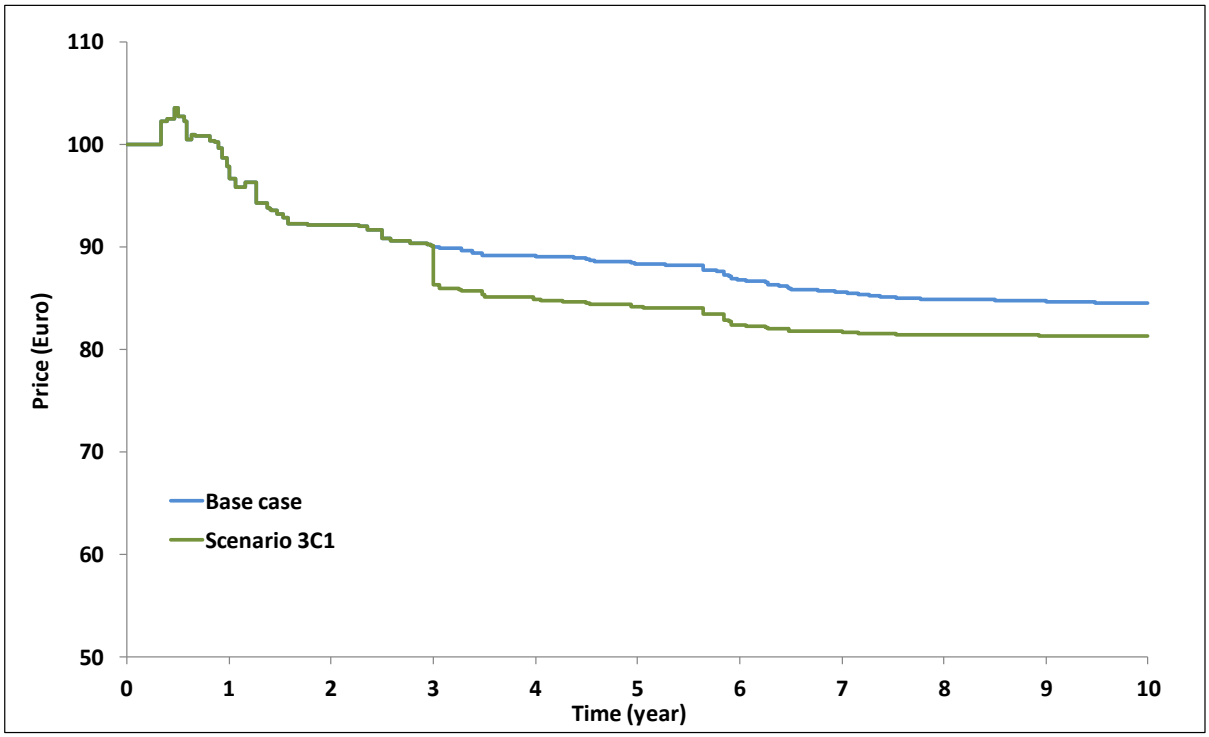


Figure 20. Scenario 3C1-Simulation of decrease of 10% in exchange rate from all non Euro-currencies to Euro-Evolution of average drug price over time

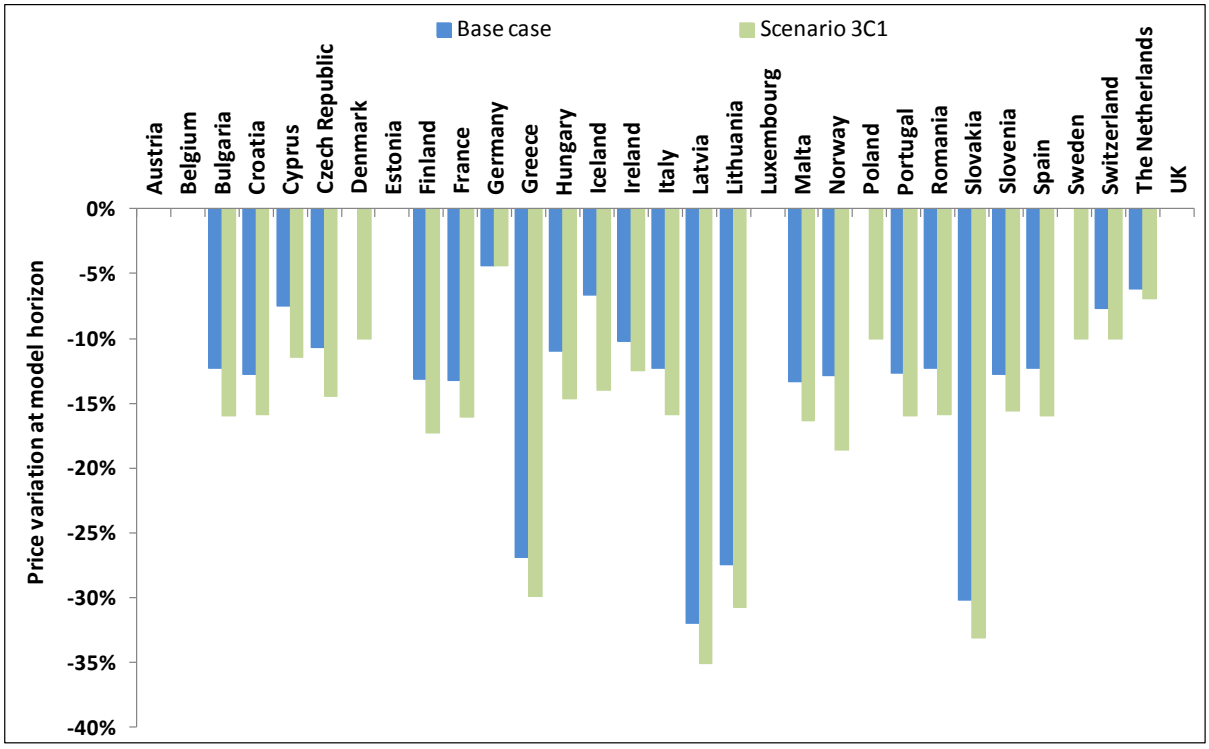


Figure 21. Scenario 3C 1-Simulation of decrease of 10% in exchange rate from all non-Euro-currencies to Euro-Evolution of drug price per country at 10 years (in percentage)

Applying historical annual average fluctuations of exchange rate from all non-Euro-currencies to Euro showed a negative impact on the average drug price, with a decrease of -13.40% versus the base case at 10 years (Figure 22). This decrease was significant from 2008 (year 5 in the model, 3.91% versus 2003), with a peak in 2009 (11.80% versus 2003). The UK, Hungary, Romania and Sweden experienced substantial negative changes in their exchange rates versus Euro from 2008-2009 with decreases of 15.03% in 2008 versus 2003 and of 28.76% in 2009 versus 2003 for the UK, of 10.53%, in Hungary in 2009 versus 2003, of 12.92% for Romania and of 16.39% for Sweden. The UK, Hungary, Romania and Sweden were referenced by 10 to 17 countries and thus drove the average drug price down (Appendix 15).

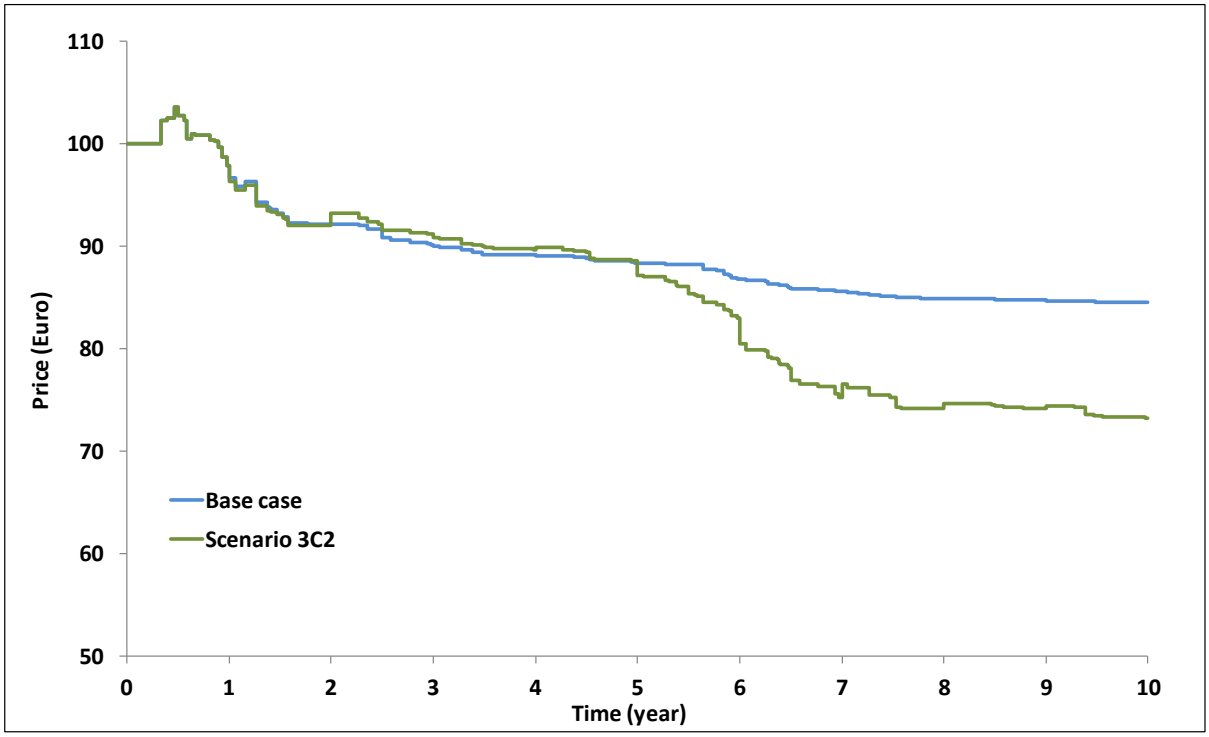


Figure 22. Scenario 3C2-Simulation of historical fluctuations of exchange rate from all non-Euro-currencies to Euro-Evolution of average drug price over time

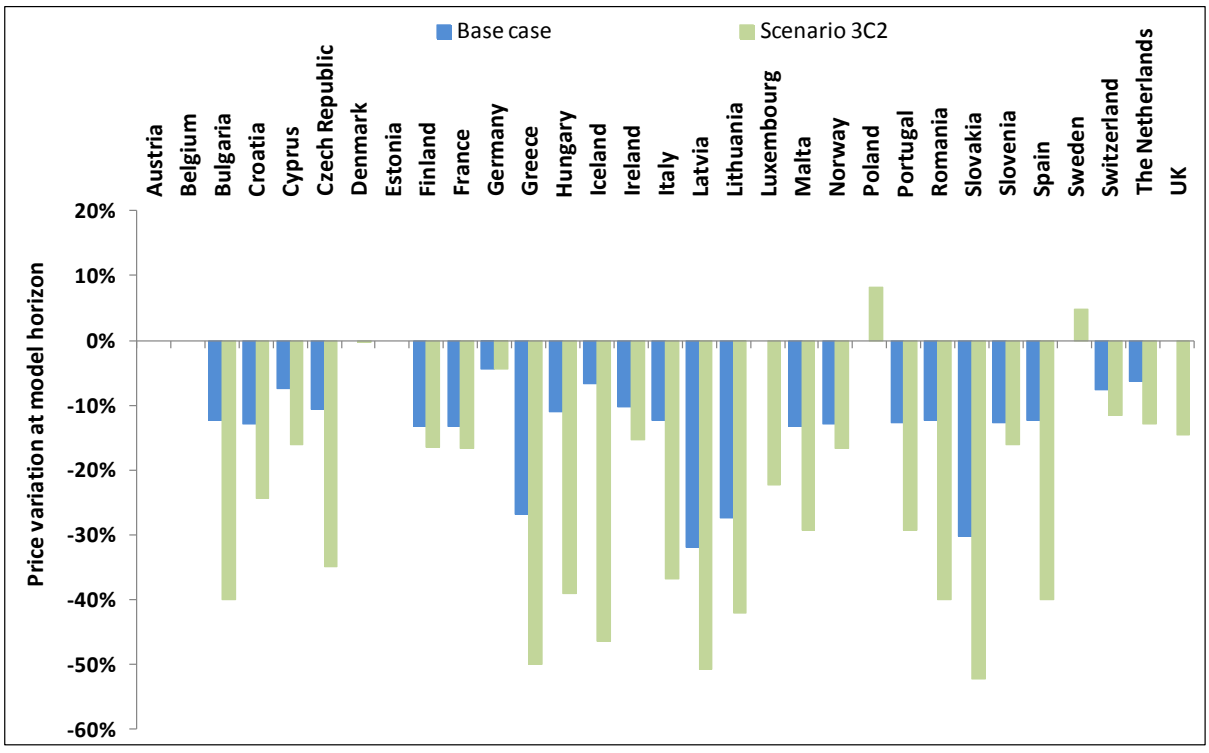


Figure 23. Scenario 3C2-Simulation of historical fluctuations of exchange rate from all non-Euro-currencies to Euro-Evolution of drug price per country at 10 years (in percentage)

6.1.5 Scenario 4. Simulation of using ex-factory price or pharmacy purchasing price as price basis taken for reference purpose

Assumptions

- Base case scenario, except for the type of price level taken into account for reference purpose

In this scenario, the same type of price was taken into account for reference purpose for all countries, i.e., ex-factory price (**Scenario 4A**) or pharmacy purchasing price (**Scenario 4B**).

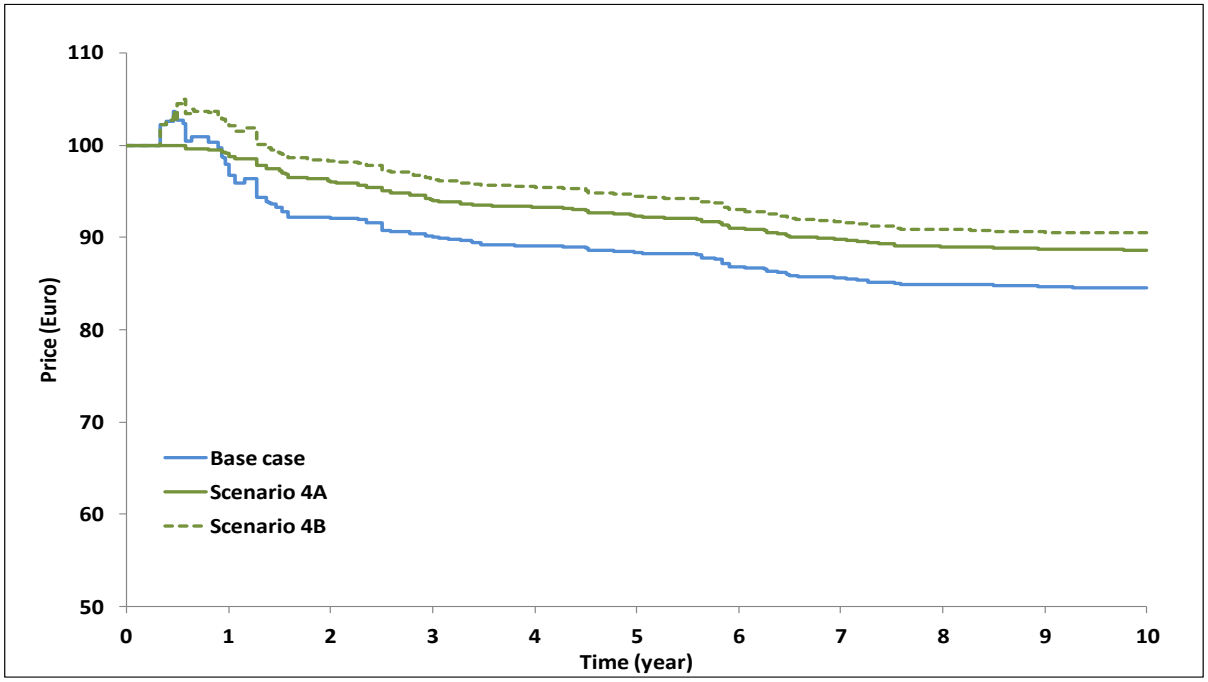
Figure 24 presents the evolution of the average drug price over time for all countries and Figure 25 presents the evolution of the drug price in percentage per country at 10 years.

Applying only ex-factory price or pharmacy purchasing price basis for reference purpose led to an increase in the average drug price over time compared to base case (+4.84% and +7.03% at 10 years, respectively). This scenario showed that having different price levels taken into account for reference purpose (i.e. ex-factory price or pharmacy purchasing price) induced price variability among countries. This is linked to a high heterogeneity in wholesaler and pharmacy margins across countries (Figure 26). The variability in margins between countries is dissociated from GDP and pharmaceutical expenditure level.

Price variability related to the use of various price bases to set ERP price is illustrated in Figure 27. We considered 3 countries A, B, and C:

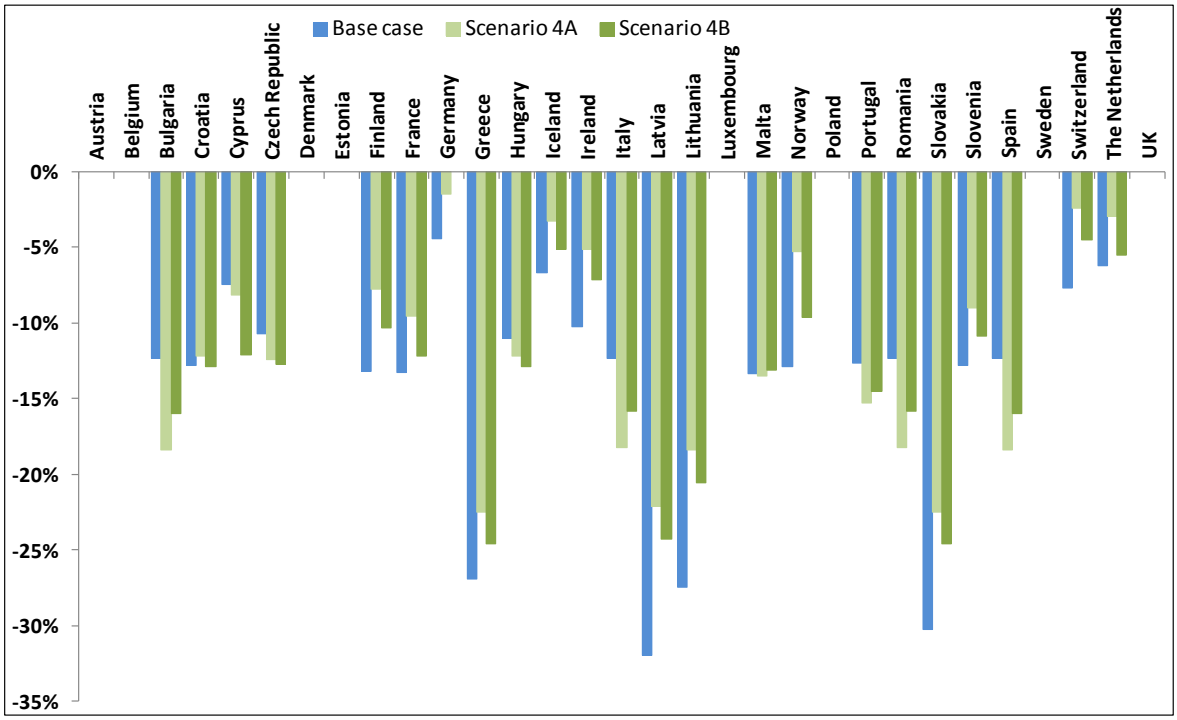
- Country A had a wholesale margin of 12.5% and ex-factory price was set arbitrarily at €100 in country A.
- Country B used the pharmacy purchasing price of country A as reference price and had a wholesale margin of 25%.
- Country C used ex-factory prices' average of countries A and B as reference price.

Mixing countries applying ERP rules based on the ex-factory price with countries using the pharmacy purchasing price led to 3 different ex-factory prices: €100 for country A, €84 for country B, and €92 for country C. This difference between countries would have been avoided when using only ex-factory prices as reference, since the price would have been the same between the 3 countries through ERP-based system.



Scenario 4A (ex-factory price level taken into account for reference purpose) and Scenario 4B (pharmacy purchasing price level taken into account for reference purpose)

Figure 24. Scenario 4-Simulation of using ex-factory price or pharmacy purchasing price as price basis taken for reference purpose-Evolution of average drug price over time



Scenario 4A (ex-factory price level taken into account for reference purpose) and Scenario 4B (pharmacy purchasing price level taken into account for reference purpose)

Figure 25. Scenario 4-Simulation of using ex-factory price or pharmacy purchasing price as price basis taken for reference purpose-Evolution of drug price per country at 10 years (in percentage)

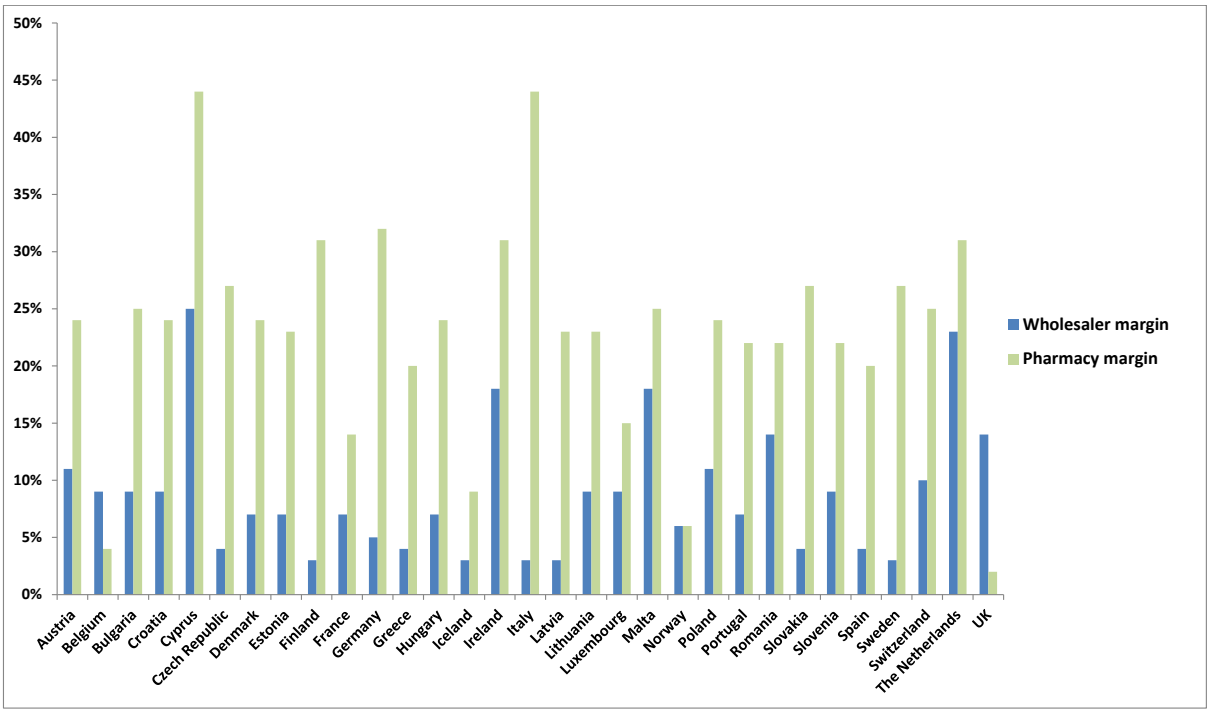


Figure 26. Heterogeneity in wholesaler and pharmacy margins across European countries

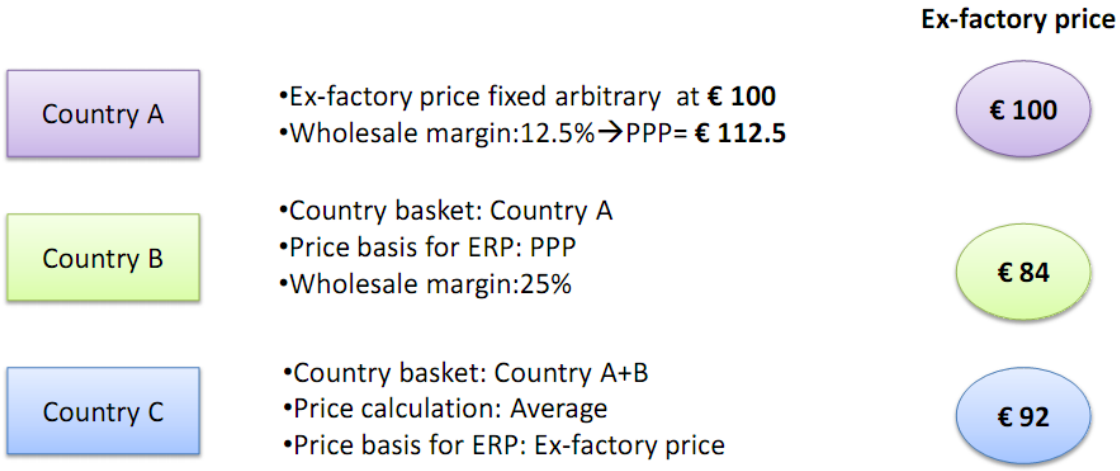


Figure 27. Illustrative representation of the margin effect

6.1.6 Scenario 5. Simulation of the country basket composed of all countries under study

Assumptions

- Base case scenario, except for the country basket

In this scenario, the country basket for each country applying ERP was composed of all countries included in the study (30 countries excluding the initial country).

Figure 28 presents the evolution of the average drug price over time for all countries and Figure 29 presents the evolution of the drug price in percentage per country at 10 years.

A faster and higher decrease in the average drug price over time was observed when all countries were included in the basket (-9.02% versus the base case at 10 years). It can be explained by the fact that more countries that drive the prices down were included in the country baskets. Increasing the number of countries in the basket tended to enhance the price decrease. This was mainly related to the fact that some countries did not include low price countries in their basket at base case, and the prices went down by adding them.

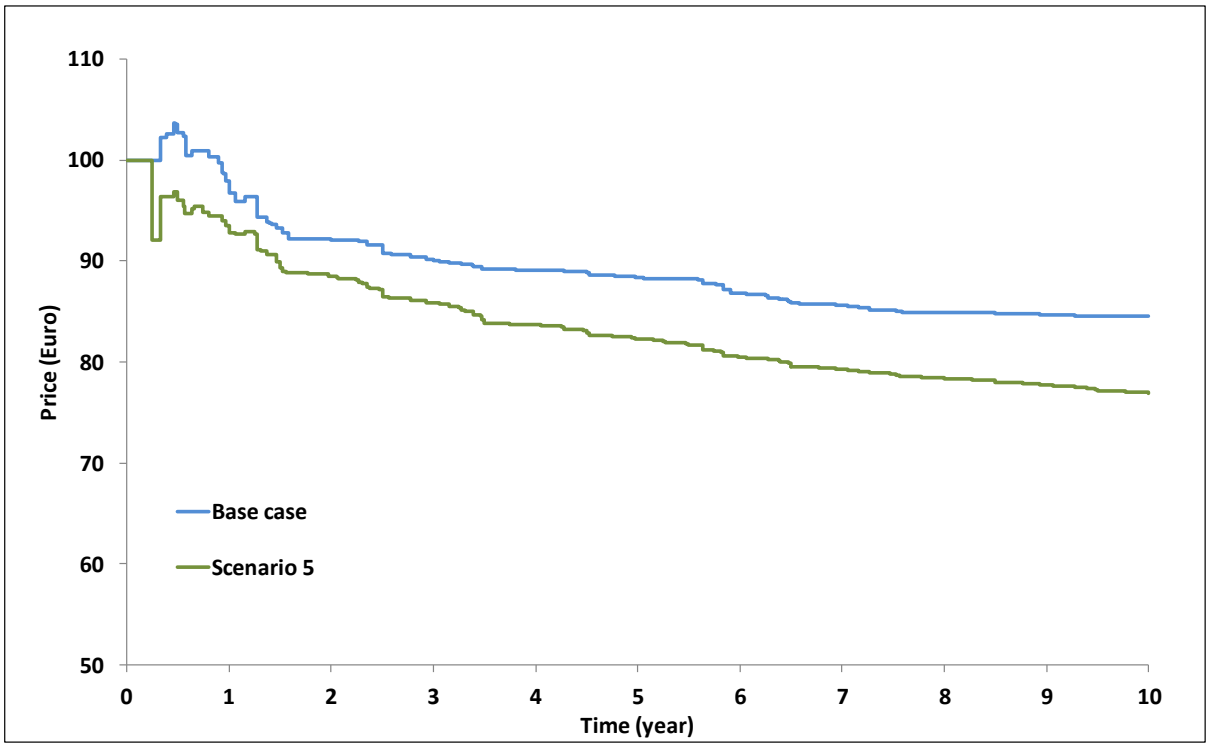


Figure 28. Scenario 5-Simulation of the country basket composed of all countries under study-Evolution of average drug price over time

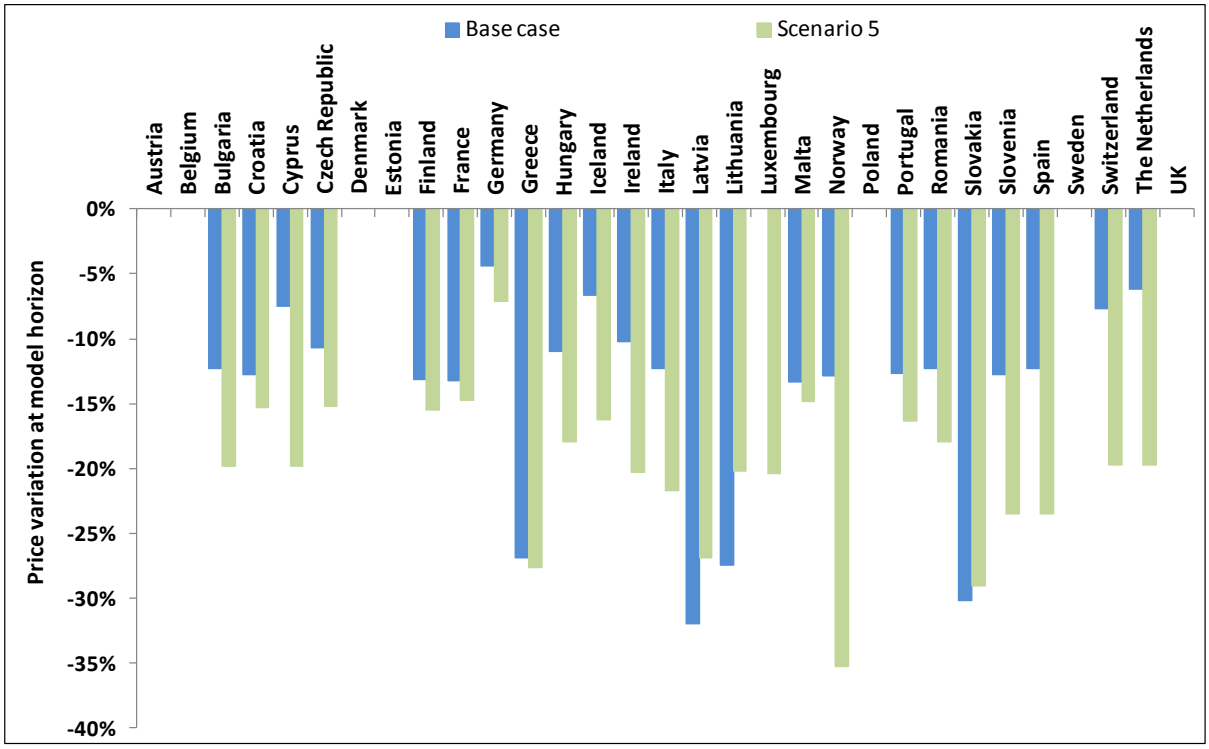


Figure 29. Scenario 5-Simulation of the country basket composed of all countries under study-Evolution of drug price per country at 10 years (in percentage)

6.1.7 Scenario 6. Simulation of rules on minimum number of countries in basket having approved prices to set ERP price

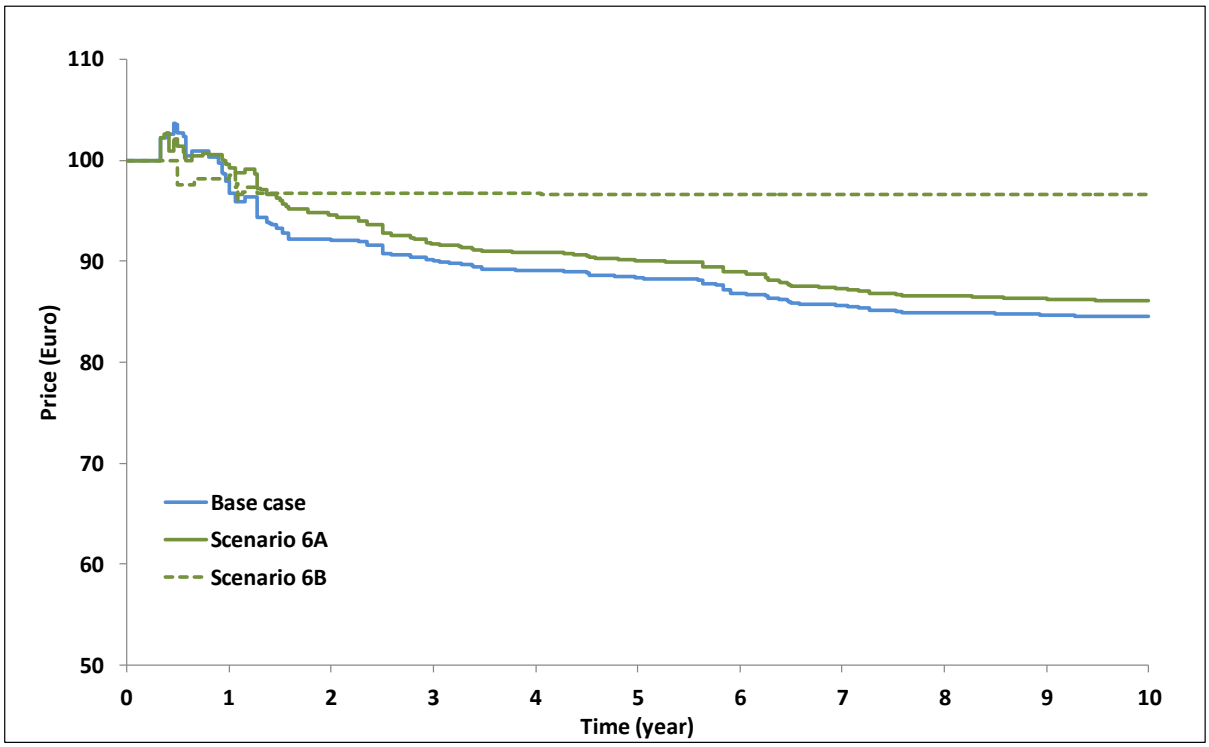
Assumptions

- Base case scenario, except for the minimum number of reference countries needed to set the ERP price

In this scenario, two rules related to the minimum number of reference countries needed to set the ERP price were applied: either one country (**Scenario 6A**) or at least half of countries (**Scenario 6B**) included in the basket having approved price(s) were enough for price evaluation.

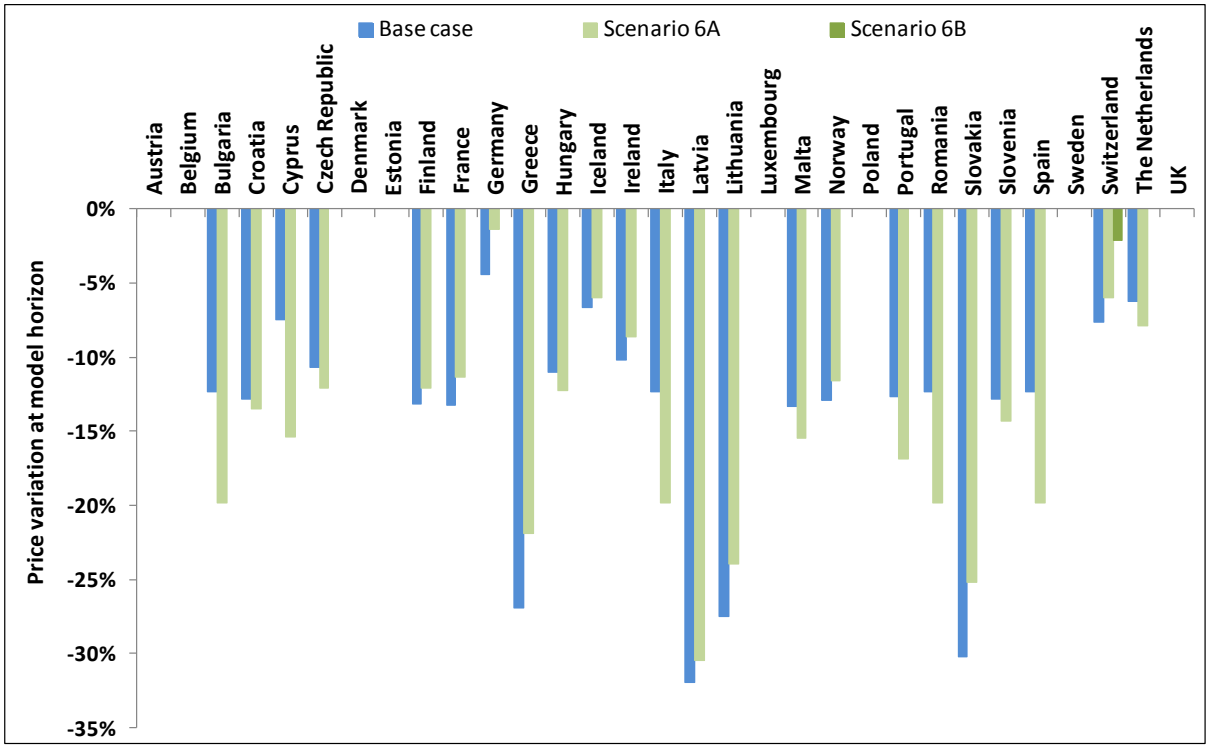
Figure 30 presents the evolution of the average drug price over time for all countries and Figure 31 presents the evolution of the drug price in percentage per country at 10 years.

The evolution of the average drug price over time was slightly higher than the base case (+1.86% at 10 years) when the minimum number of references countries to set ERP prices was one country. However, if at least half of the countries included in the basket having approved price(s) were needed to set the price of the drug, only 25% of countries applying ERP managed to set up a price. This constraint prevented the other countries applying ERP from setting an ERP price. This scenario showed one of the limits of the system; if a country X refers to other countries while other countries refer to country X, and if country X is waiting for others countries to set a price while other countries are waiting for country X to set a price, ERP price will never be set. It highlighted why most of countries started to set ERP price with a limited number of countries, then ensuring updates through periodic revisions.



Scenario 6A (minimum number of reference countries needed to set the ERP price: one country) and Scenario 6B (minimum number of reference countries needed to set the ERP price: at least half of countries)

Figure 30. Scenario 6-Simulation of rules on minimum number of countries in basket having approved prices to set ERP price-Evolution of average drug price over time



Scenario 6A (minimum number of reference countries needed to set the ERP price: one country) and Scenario 6B (minimum number of reference countries needed to set the ERP price: at least half of countries)

Figure 31. Scenario 6-Simulation of rules on minimum number of countries in basket having approved prices to set ERP price-Evolution of drug price per country at 10 years (in percentage)

6.1.8 Scenario 7. Simulation of calculation methods to set the ERP price

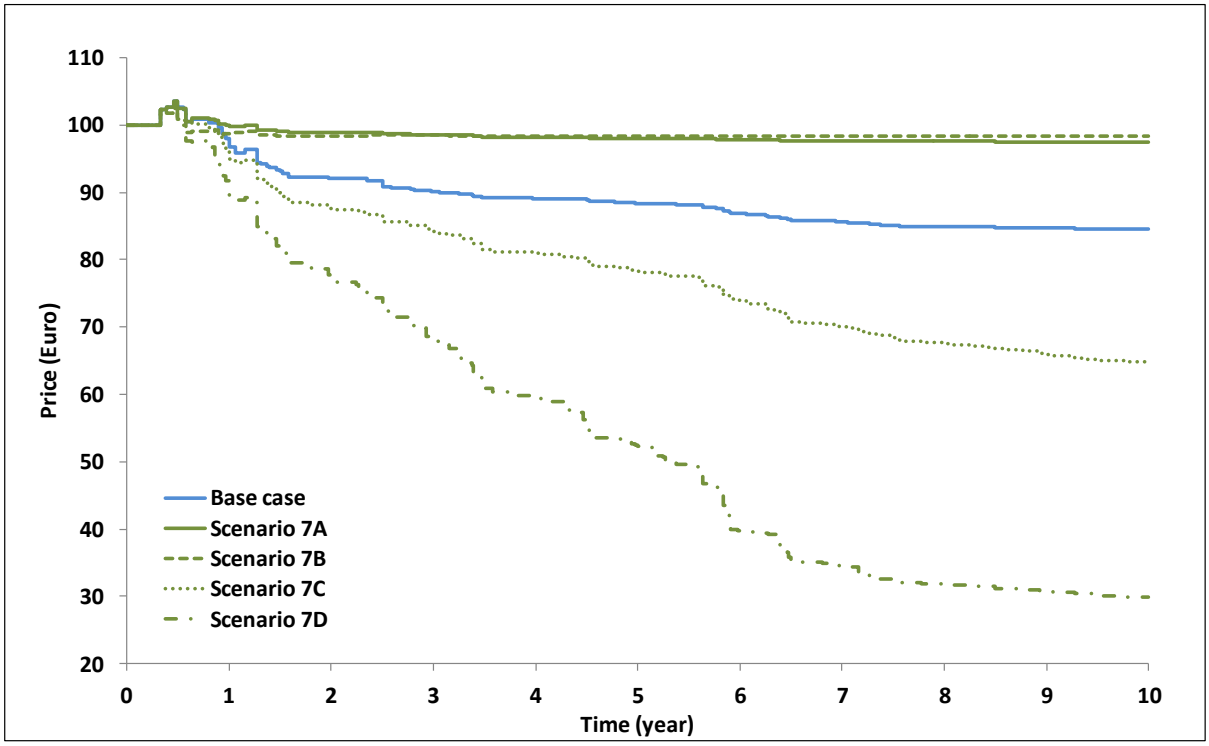
Assumptions

- Base case scenario, except for the calculation methods to set the ERP price

In this scenario, one single calculation method was adopted by the countries to set the ERP prices: all countries calculate ERP prices based on average price of the reference countries (**Scenario 7A**), median price of the reference countries (**Scenario 7B**), average of the 3 lowest prices of reference countries (**Scenario 7C**), and lowest price of reference countries (**Scenario 7D**).

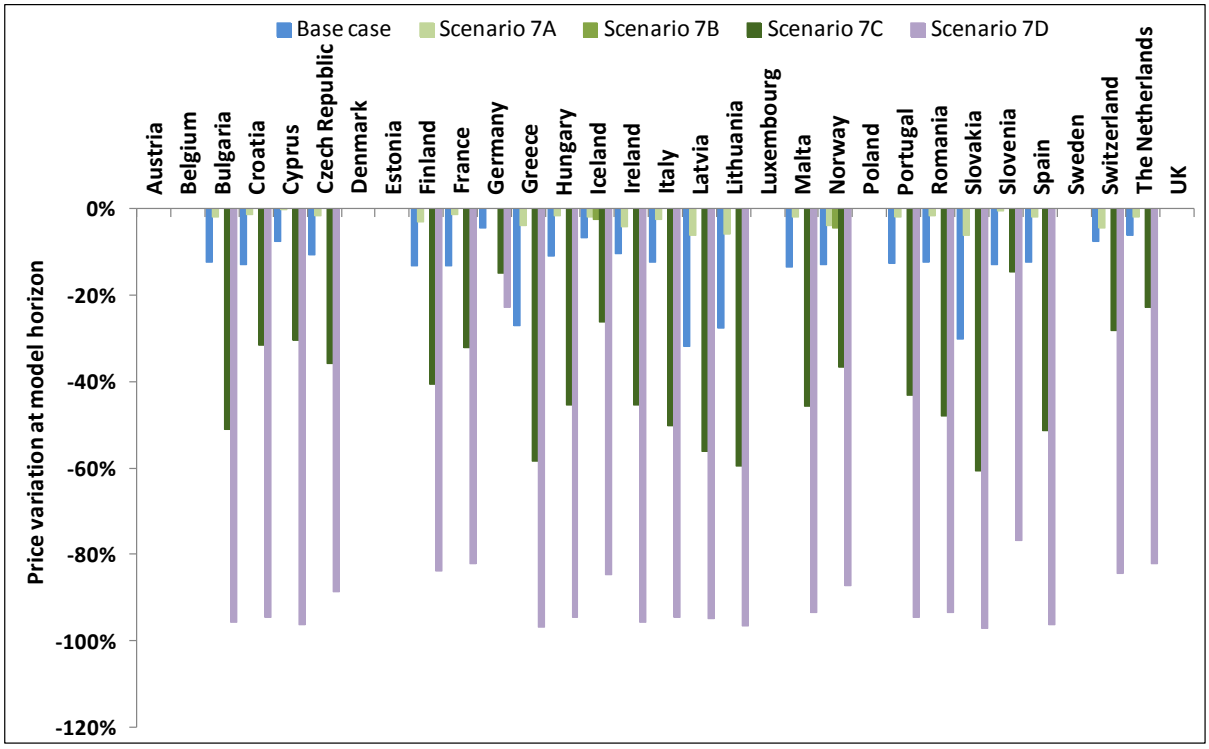
Figure 32 presents the evolution of the average drug price over time for all countries and Figure 33 presents the evolution of the drug price in percentage per country at 10 years.

Calculation method based on average price led to higher average drug price evolution than the base case (+15.32% at 10 years), with equilibrium reached faster. As expected, the calculation method based on the lowest price of reference countries drove much more the prices down compared to the base case, with a price erosion of -64.66% versus the base case at 10 years. This scenario illustrated how the price decreased dramatically when applying systematically the ERP calculation method based on the lowest price of reference countries.



Scenario 7A (calculation method based on average price of the country basket), Scenario 7B (calculation method based on median price of reference countries), Scenario 7C (calculation method based on average of the 3 lowest prices of reference countries), and Scenario 7D (calculation method based on average of the lowest prices of reference countries)

Figure 32. Scenario 7-Simulation of calculation methods to set the ERP price-Evolution of average drug price over time



Scenario 7A (calculation method based on average price of the country basket), Scenario 7B (calculation method based on median price of reference countries), Scenario 7C (calculation method based on average of the 3 lowest prices of reference countries), and Scenario 7D (calculation method based on average of the lowest prices of reference countries)

Figure 33. Scenario 7-Simulation of calculation methods to set the ERP price-Evolution of drug price per country at 10 years (in percentage)

6.1.9 Scenario 8. Simulation of annual price deflation in non ERP countries along with price revisions in ERP countries

Assumptions

- Base case scenario, except for price deflation

In this scenario, a price deflation in non ERP countries (UK and Sweden) of 5% per year was applied.

Figure 34 presents the evolution of the average drug price over time for all countries and Figure 35 presents the evolution of the drug price in percentage per country at 10 years.

As expected, price deflation in non ERP countries impacted the average drug price evolution with faster and higher price decrease over time pertaining at 10 years (-12.33% versus the base case at 10 years). Indeed, as an annual price deflation was applied, the impact on the price of countries using ERP became continuous and prevented any equilibrium to be reached.

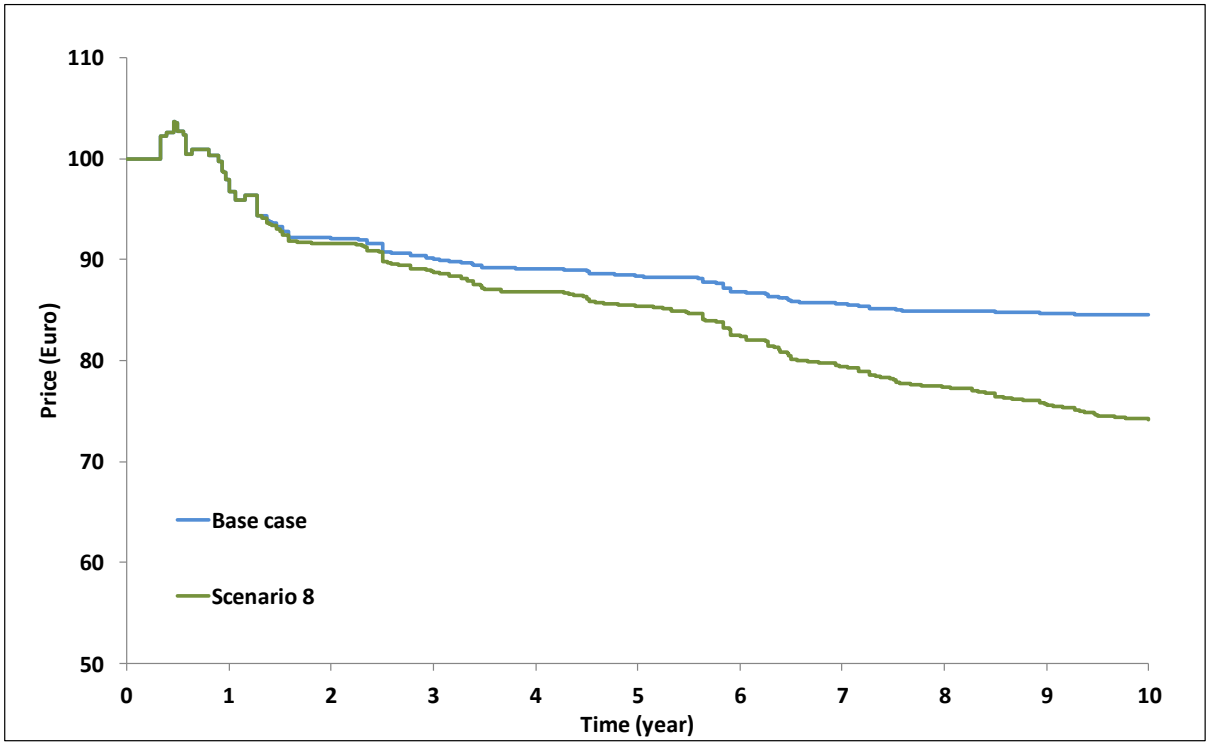


Figure 34. Scenario 8-Simulation of price deflation in non ERP countries (UK and Sweden) of 5% per year-Evolution of average drug price over time

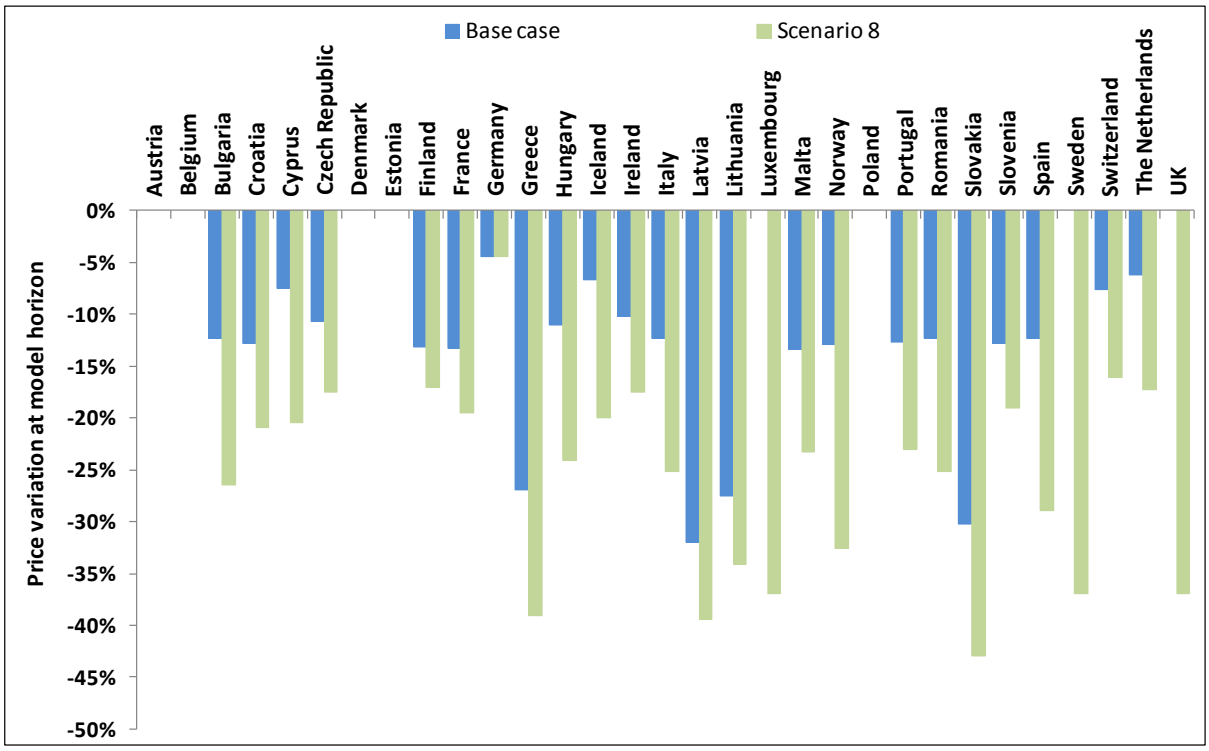


Figure 35. Scenario 8-Simulation of price deflation in non ERP countries (UK and Sweden) of 5% per year-Evolution of drug price per country at 10 years (in percentage)

6.1.10 Scenario 9. Simulation of price negotiations for country using ERP as supportive criterion and weighted according to GDP/capita

Assumptions

- Base case scenario, except for country using ERP as supportive criterion

In this scenario, an additional price discount on ERP price reflecting negotiation with stakeholders for countries using ERP as supportive criterion set to 5%, 10%, and 20% for countries with high, medium or low GDP/capita respectively was applied. The rationale for this scenario is that ERP used as supportive criterion is likely going to be used to inform payers' decision. This additional discount on ERP price reflects the fact that payers are likely to take a lower price than a higher price supported by ERP. Payers of the poorest countries were assumed to use a far lower price than the price that can be obtained with ERP compared to the payers of the richest countries.

Figure 36 presents the evolution of the average drug price over time for all countries and Figure 37 presents the evolution of the drug price in percentage per country at 10 years.

Applying a discount reflecting negotiation with stakeholders for countries using ERP as supportive criterion impacted the average drug price significantly (-11.38% versus the base case at 10 years). This was expected, as all model assumptions supported that ERP price would always be discounted. The poorest countries were exposed to the largest price decreases.

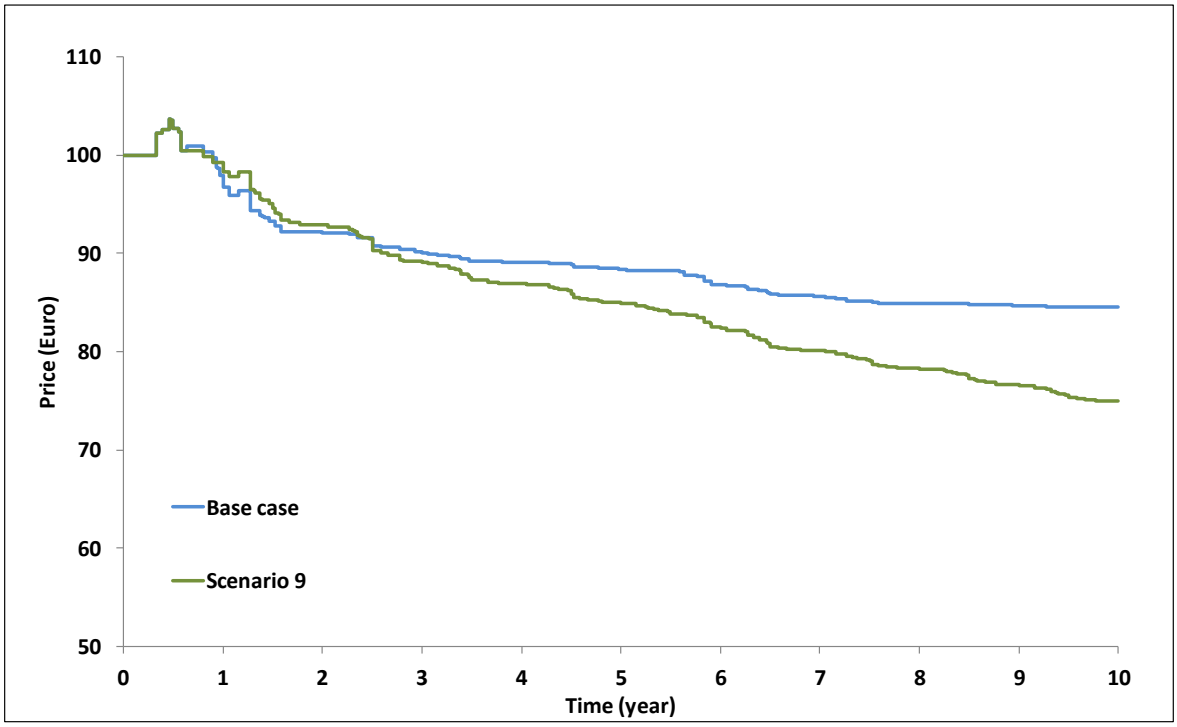


Figure 36. Scenario 9-Simulation of discount reflecting negotiation with stakeholders for countries using ERP as supportive criterion set to 5%, 10%, 20% for countries with high, medium or low GDP/capita respectively)-Evolution of average drug price over time

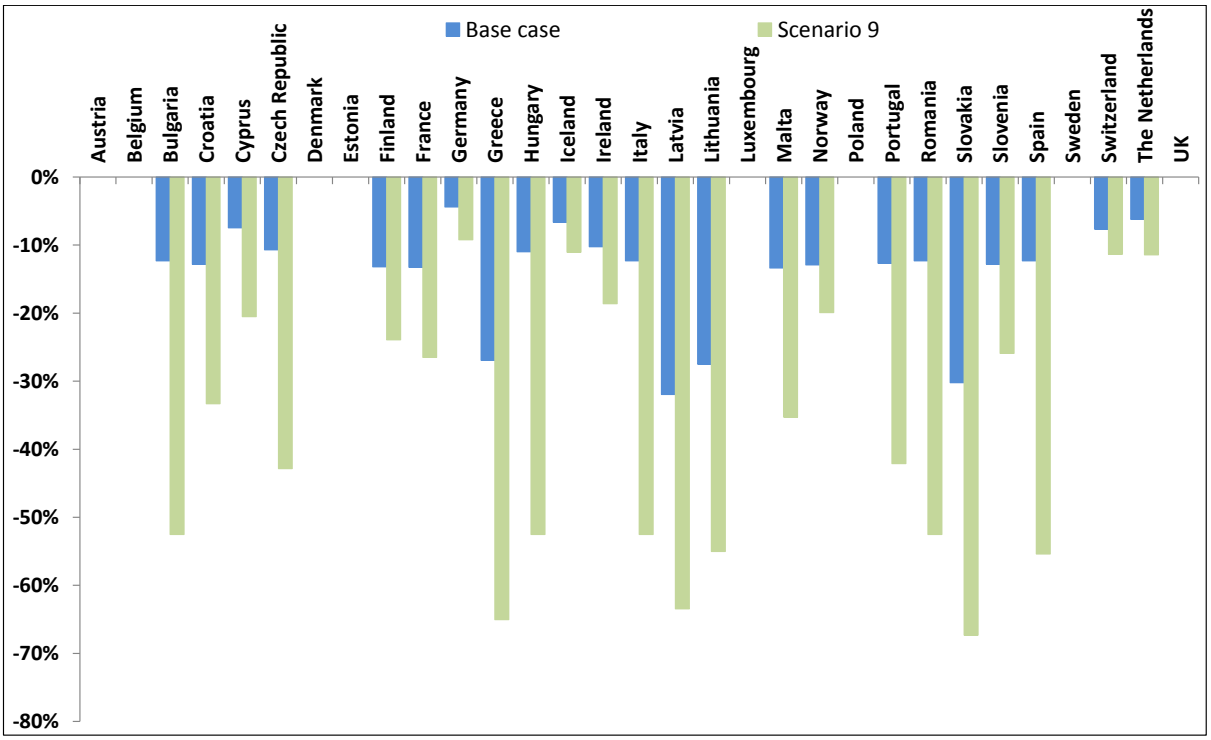


Figure 37. Scenario 9-Simulation of discount reflecting negotiation with stakeholders for countries using ERP as supportive criterion set to 5%, 10%, 20% for countries with high, medium or low GDP/capita respectively)-Evolution of drug price per country at 10 years (in percentage)

6.1.11 Scenario 10. Simulation of the impact of genericisation impact

Assumptions

- Base case scenario, except for price of the reference product in a sample of countries

6.1.11.1 Scenario 10A. Simulation of the impact of genericisation in "Southern" EU Member States

This scenario simulated the impact of genericisation introduced after the first 5 years of simulation in France, Italy, Portugal and Greece, if the brand drug was used as reference product **(Scenario 10A1)**, and if generic drug was used as reference product **(Scenario 10A2).**

The price reductions applied to the brand or to the generic versus the original product assumed for this scenario (derived from the literature review and internal proprietary database) are summarized in Table 5.

Table 5. Price reduction applied to the brand drug of to the generic drug versus the original product following genericisation

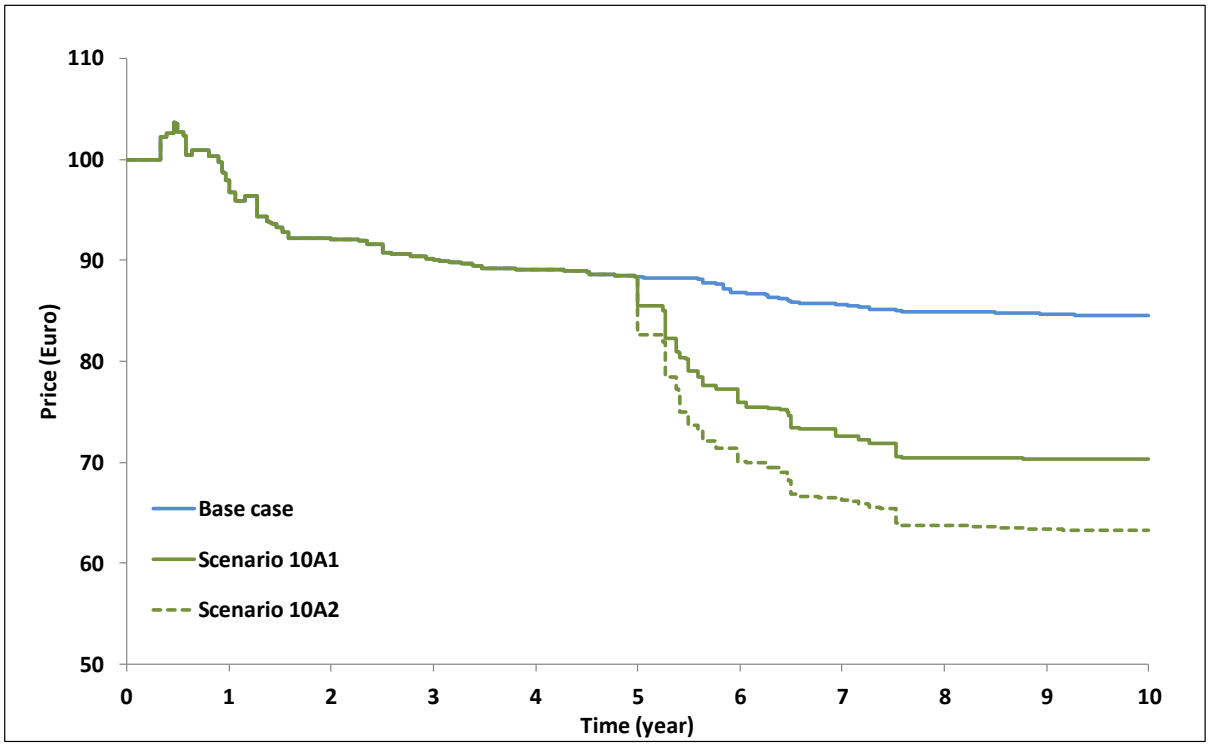
Price reduction following genericisation	France	Greece	Italy	Portugal
Brand	20%	50%	20%	20%
Generic	60%	50%	50%	50%

Figure 38 presents the evolution of the average drug price over time for all countries and Figure 39 presents the evolution of the drug price in percentage per country at 10 years.

The impact of genericisation decreased more importantly the average price of the drug when the generic drug was used as reference product versus the brand product (price erosion of -25.18% and -16.81% versus the base case at 10 years, respectively), with equilibrium reached in both scenarios at about 1.5 years.

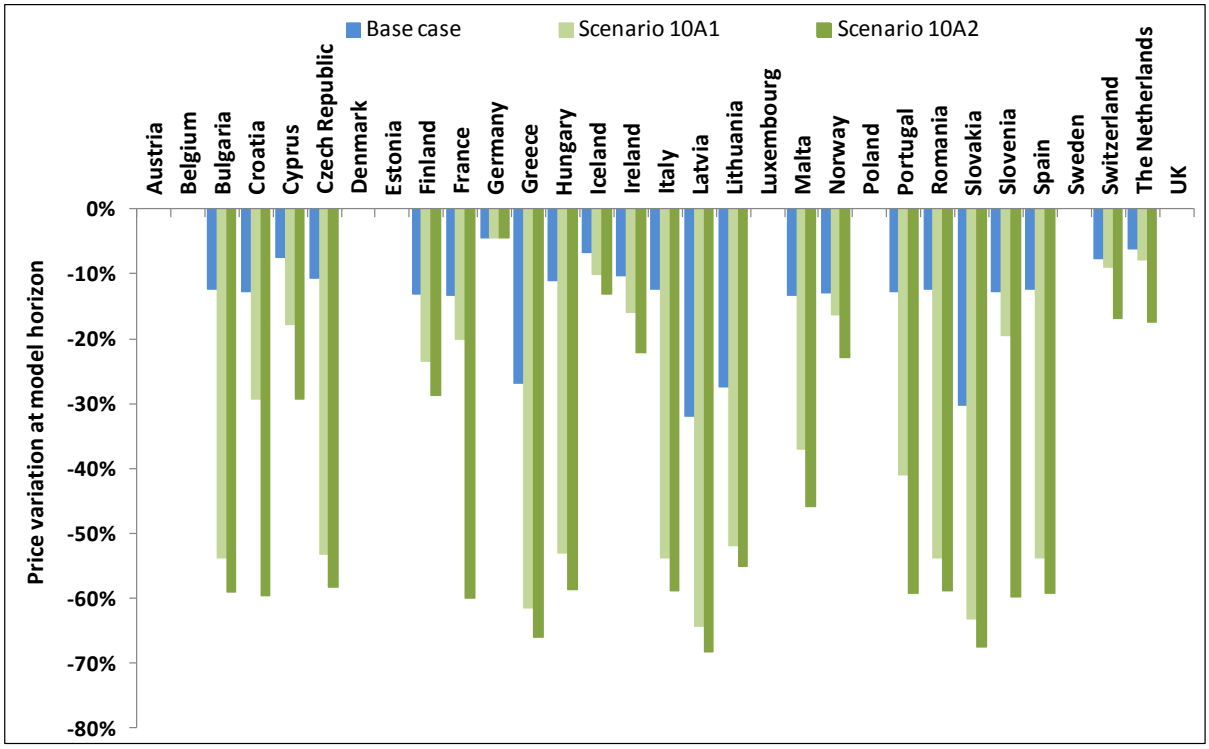
This scenario showed the critical impact of exclusivity loss, when not harmonized across countries (differential of patent/data protection across country (in decentralised procedure for example). Indeed, as patent/data protection expiry differ across countries, the generic entry in one country can negatively impact the price of a drug still in-patent in another country through ERP spill-over effects.

The decrease of the drug price might be dramatic, especially when generic prices are used for ERP, as it is reported for some countries.



Scenario 10A1 (Impact of genericisation in France, Italy, Portugal and Greece, if the brand drug was used as reference product) and Scenario 10A2 (Impact of genericisation in France, Italy, Portugal and Greece, if generic drug was used as reference product)

Figure 38. Scenario 10A-Simulation of the impact of genericisation in "Southern" EU MS-Evolution of average drug price over time



Scenario 10A1 (Impact of genericisation in France, Italy, Portugal and Greece, if the brand drug was used as reference product) and Scenario 10A2 (Impact of genericisation in France, Italy, Portugal and Greece, if generic drug was used as reference product)

Figure 39. Scenario 10A-Simulation of the impact of genericisation in "Southern" EU MS-Evolution of drug price per country at 10 years (in percentage)

6.1.11.2 Scenario 10B. Simulation of the impact of genericisation in "Northern" EU Member States

In this scenario, it was simulated the impact of genericisation introduced after the first 5 years of simulation in the UK, Germany, Austria and Denmark, if the brand drug was used as reference product **(Scenario 10B1)**, and if generic drug was used as reference product **(Scenario 10B2)**.

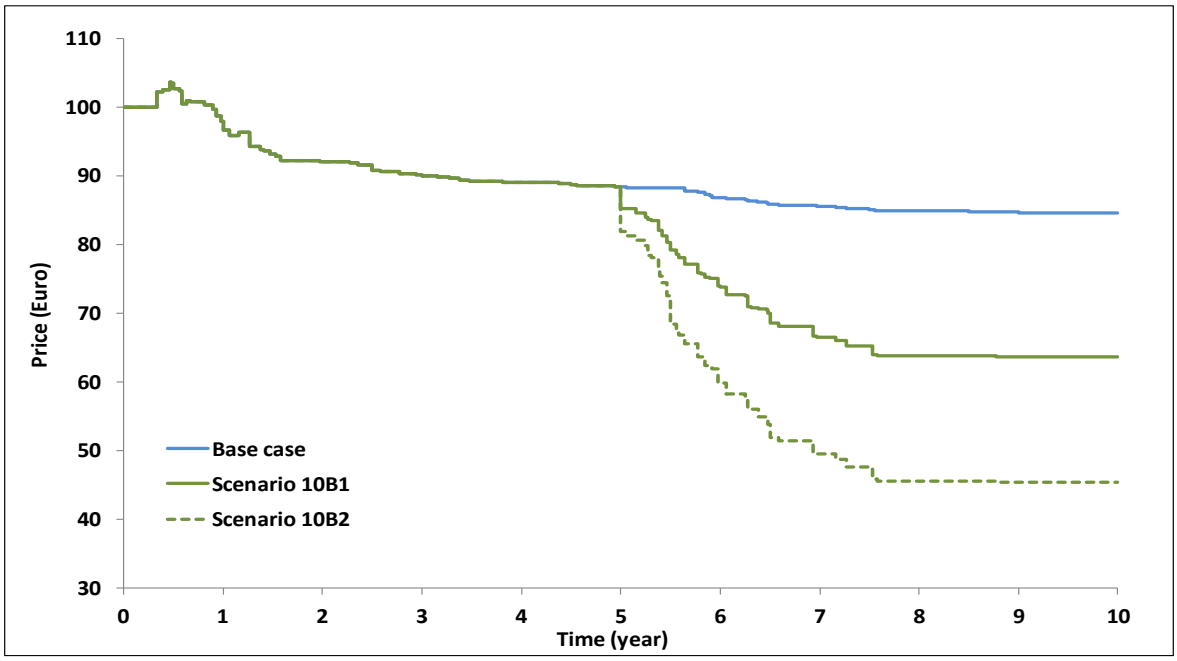
The price reductions applied to the brand or to the generic versus the original product assumed for this scenario (derived from the literature review and internal proprietary database) are summarized in Table 6.

Table 6. Price reduction applied to the brand drug of to the generic drug versus the original product following genericisation

Price reduction following genericisation	Austria	Germany	Sweden	UK
Brand	30%	0%	65%	0%
Generic	15%	30%	75%	80%

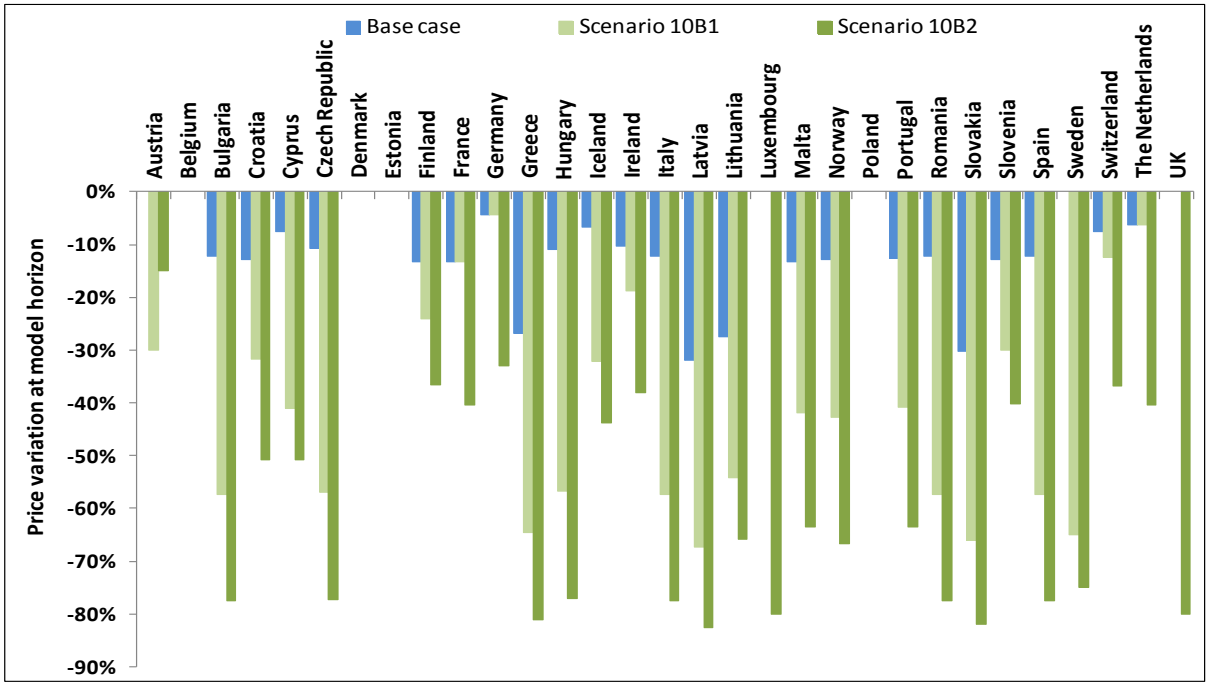
Figure 40 presents the evolution of the average drug price over time for all countries and Figure 41 presents the evolution of the drug price in percentage per country at 10 years.

This scenario showed the same trend as scenario 10A with a higher decrease of the average price of the drug related to a higher reduction of the price following genericisation in the selected countries, and the fact that the selected countries in this scenario were the most frequently referenced (16 to 17 countries referring these countries).



Scenario 10B1 (genericisation impact in UK, Germany, Austria and Denmark, if the brand was used as reference product) and Scenario 10B2 (genericisation impact in UK, Germany, Austria and Denmark, if the generic drug was used as reference product)

Figure 40. Scenario 10B-Simulation of the impact of genericisation in "Northern" EU MS-Evolution of average drug price over time



Scenario 10B1 (genericisation impact in UK, Germany, Austria and Denmark, if the brand was used as reference product) and Scenario 10B2 (genericisation impact in UK, Germany, Austria and Denmark, if the generic drug was used as reference product)

Figure 41. Scenario 10B-Simulation of the impact of genericisation in "Northern" EU MS-Evolution of drug price per country at 10 years (in percentage)

6.1.12 Scenario 11. Simulation of price cuts proportional to government deficit and to pharmaceutical expenditures

Assumptions

- Base case scenario with specific price cuts

6.1.12.1 Scenario 11A. Simulation of price cuts proportional to government deficit

In this scenario, fictitious price cuts, proportional to government deficit, were introduced after the first 3 years of simulation, as reported in Table 7.

- When the government deficit was inferior or equal to 3% of GDP, no price cut was applied. The threshold of 3% of GDP was defined in the Stability and Growth Pact clarifying the Maastricht Treaty on European Union, requiring each MS, to implement budgetary policies to stay within these limits on government deficit (3% of GDP)[65.]
- When the government deficit superior to 3% of GDP, a linear price cut proportional to the deficit relative to the public budget (about 50% of GDP for EU 28 countries[66]) was applied, with a maximum cut set at 20%.

Table 7. Price cuts proportional to government deficit applied for scenario 11 A

Country	General Government Deficit/Surplus (% GDP and million Euros)[67]	Price cut (%, proportional to government deficit)
Austria	-2.5	0%
Belgium	-4.0	8%
Bulgaria	-0.8	0%
Croatia	-5.0	9%
Cyprus	-6.4	12%
Czech Republic	-4.4	8%
Denmark	-4.1	8%
Estonia	-0.2	0%
Finland	-1.8	0%
France	-4.8	9%
Germany	0.1	0%
Greece	-9.0	17%
Hungary	-2.0	0%
Iceland	-3.8	7%
Ireland	-8.2	15%
Italy	-3	0%
Latvia	-1.3	0%
Lithuania	-3.2	6%
Luxembourg	-0.6	0%
Malta	-3.3	6%
Norway	13.6	0%
Poland	-3.9	7%
Portugal	-6.4	12%
Romania	-3.0	0%
Slovakia	-4.5	8%
Slovenia	-3.8	7%
Spain	-10.6	20%
Sweden	-0.2	0%
Switzerland	0.7[68]	0%
The Netherlands	-4.1	8%
UK	-6.1	12%

Figure 42 presents the evolution of the average drug price over time for all countries and Figure 43 presents the evolution of the drug price in percentage per country at 10 years.

An abrupt decrease of the average drug price evolution was observed when fictitious price cuts proportional to government deficit were applied, leading to a price decrease at 10 years, of -8.96% versus the base case.

As per assumption, the countries with the highest government deficit had the higher price decrease, and influenced the other countries through ERP. Obviously, this scenario drove average prices down since most countries in Europe operate under substantial budget deficit.

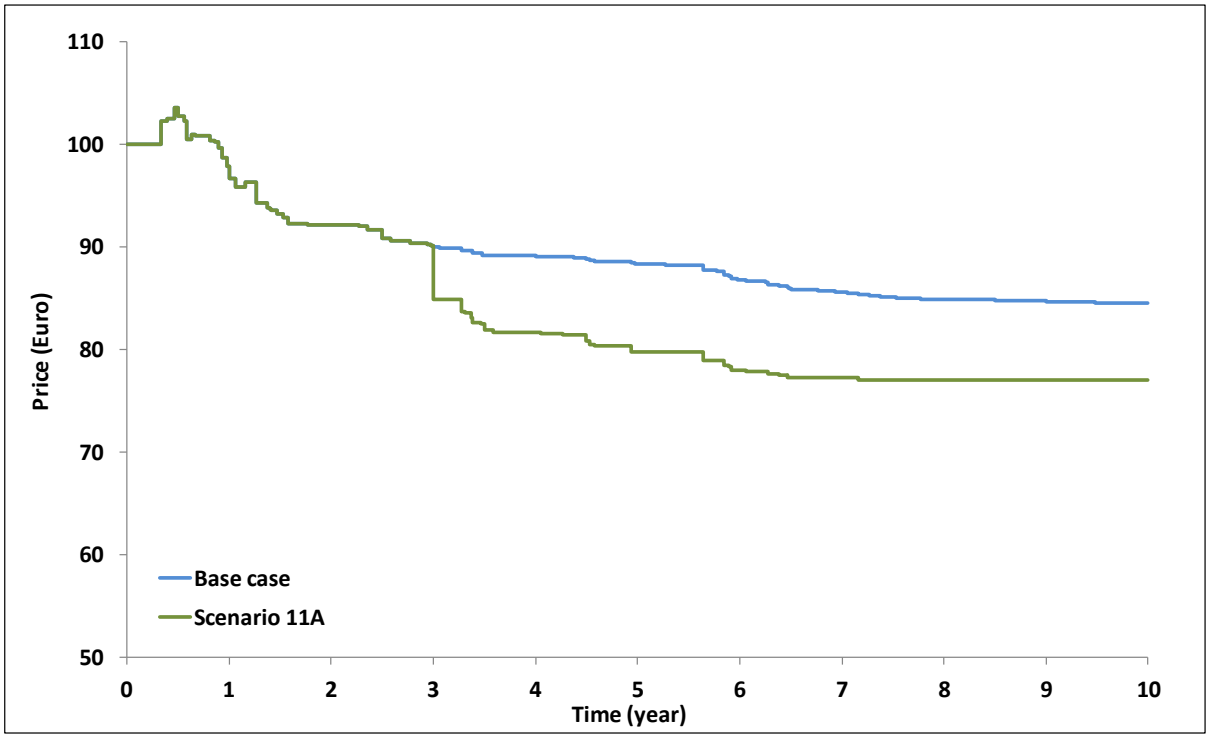


Figure 42. Scenario 11A-Simulation of fictitious price cuts proportional to government deficit-Evolution of average drug price over time

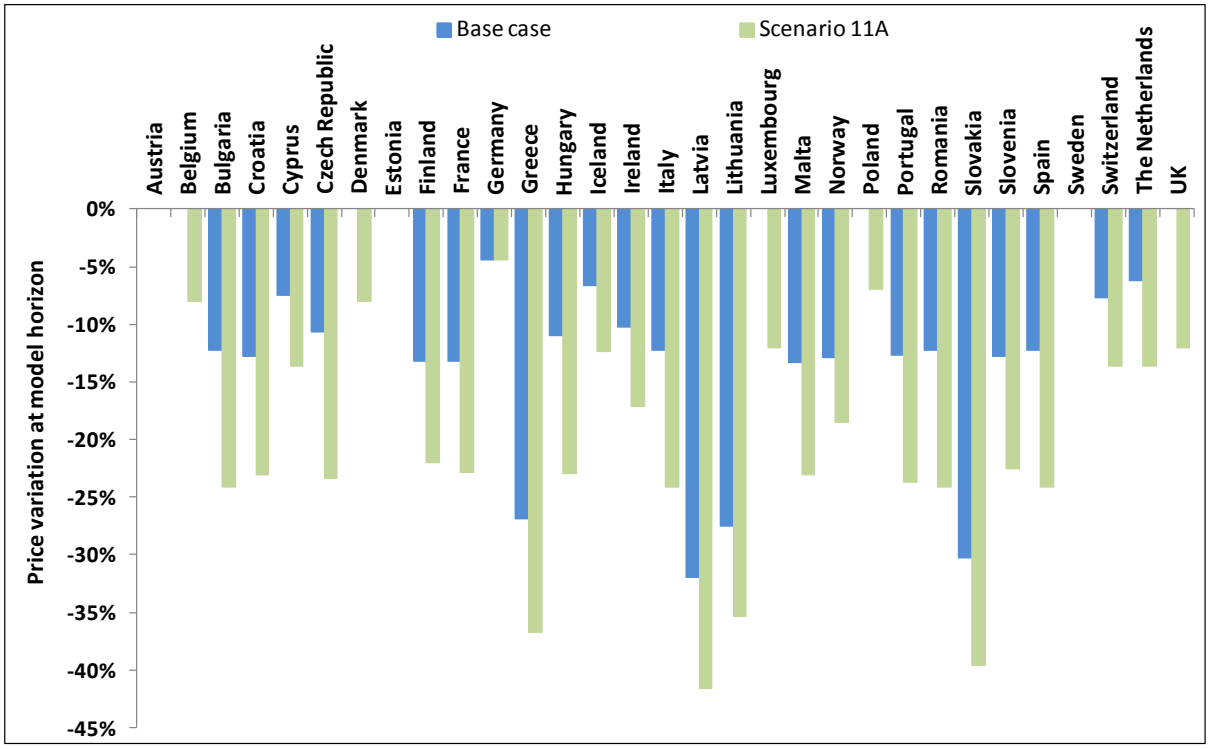


Figure 43. Scenario 11A-Simulation of fictitious price cuts proportional to government deficit-Evolution of drug price per country at 10 years (in percentage)

6.1.12.2 Scenario 11B. Simulation of price cuts proportional to pharmaceutical expenditure

In this scenario, fictitious price cuts, proportional to pharmaceutical expenditure as share of GDP, were introduced after the first 3 years of simulation, as reported in Table 8. Two scenarios were performed:

- A price cut equal to pharmaceutical expenditure as share of GDP **(Scenario 11B1)**
- A price cut equal to twice pharmaceutical expenditure as share of GDP **(Scenario 11B2)**

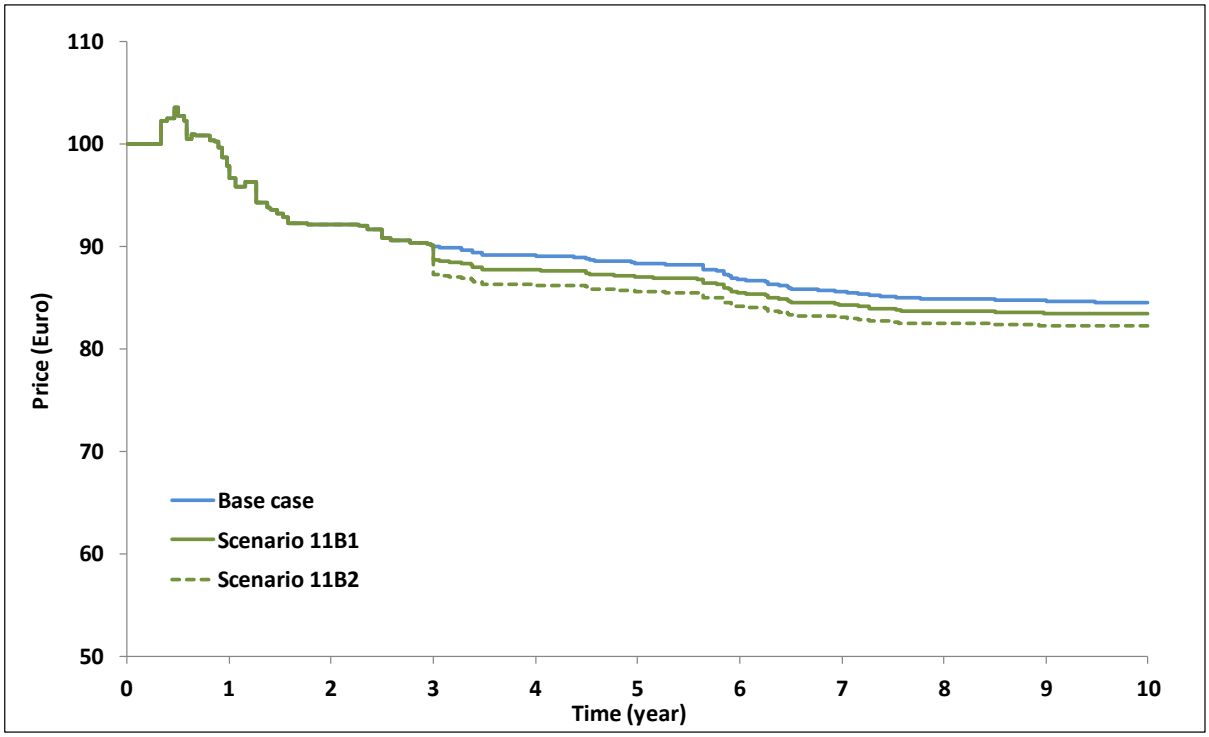
Table 8. Price cuts proportional to pharmaceutical expenditure applied for scenario 11 B

Country	Price cut equal to pharmaceutical expenditure as share of GDP [27]	Price cut equal to pharmaceutical expenditure as share of GDP [27] × 2
Austria	1.3%	2.6%
Belgium	1.7%	3.4%
Bulgaria	2.8%	5.6%
Croatia*	2.6%	5.2%
Cyprus	1.3%	2.6%
Czech Republic	1.5%	3.0%
Denmark	0.8%	1.6%
Estonia	1.4%	2.8%
Finland	1.2%	2.4%
France	1.9%	3.8%
Germany	1.7%	3.4%
Greece*	1.3%	2.6%
Hungary	2.6%	5.2%
Iceland	1.5%	3.0%
Ireland	1.7%	3.4%
Italy	1.6%	3.2%
Latvia	1.5%	3.0%
Lithuania	1.9%	3.8%
Luxembourg	0.6%	1.2%
Malta*	2.0%	4.0%
Norway	0.7%	1.4%
Poland	1.6%	3.2%
Portugal	2.0%	4.0%
Romania	1.4%	2.8%
Slovakia	2.4%	4.8%
Slovenia	1.8%	3.6%
Spain	1.8%	3.6%
Sweden	1.2%	2.4%
Switzerland	1.1%	2.2%
The Netherlands	1.1%	2.2%
UK	1.0%	2.0%

*The same pharmaceutical expenditure as Hungary was assumed for Poland, as Cyprus for Greece and as Portugal for Malta

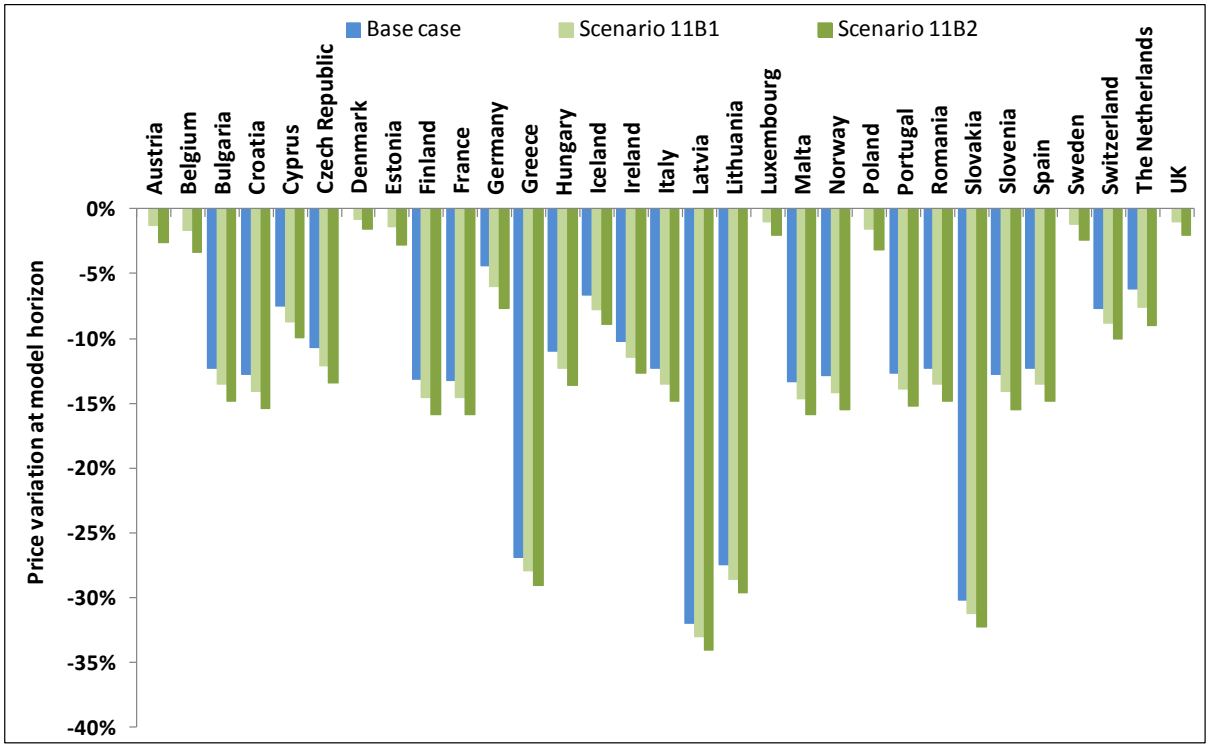
Figure 44 presents the evolution of the average drug price over time for all countries and Figure 45 presents the evolution of the drug price in percentage per country at 10 years.

This scenario showed a small price decrease when applying price cuts equal to or twice the pharmaceutical expenditure (-1.40% and -2.80% versus the base case, respectively).



Scenario 11B1 (fictitious price cuts proportional to pharmaceutical expenditure as share of GDP) and Scenario 11B2 (fictitious price cuts proportional to twice pharmaceutical expenditure as share of GDP)

Figure 44. Scenario 11B-Simulation of fictitious price cuts proportional to pharmaceutical expenditure as share of GDP-Evolution of average drug price over time



Scenario 11B1 (fictitious price cuts proportional to pharmaceutical expenditure as share of GDP) and Scenario 11B2 (fictitious price cuts proportional to twice pharmaceutical expenditure as share of GDP)

Figure 45. Scenario 11B-Simulation of fictitious price cuts proportional to pharmaceutical expenditure as share of GDP-Evolution of drug price per country at 10 years (in percentage)

6.1.13 Scenario 12. Simulation of historical price cuts/discounts

Assumptions

- Base case scenario with specific price cuts/discounts

In this scenario, historical price cuts/discounts reported in the literature in a selection of countries at fixed point time were applied as described in Table 9.

Table 9. Historical price cuts/discounts applied in a selection of countries

Period of time	Years 3-Q1/Q2			Year 3-Q3/Q4			Year 4-Q1/Q2	Year 4-Q3/Q4	Year 5-Q1/Q2
Country	Czech Republic	Spain	Greece	Lithuania	Portugal	Germany	Czech Republic	Greece	Greece
Price cut/discounts	-7%[3]	-7.5%[3]	-21,5%[69]	-10%[3]	-6%[3]	-11%[3]	-7%[3]	-10% [48]	-9%[70]

Figure 46 presents the evolution of the average drug price over time for all countries and Figure 47 presents the evolution of the drug price in percentage per country at 10 years.

A steady but important decrease of the average drug price evolution was observed when historical price cuts were applied, leading to a price decrease at 10 years of -12.76% versus the base case.

This scenario showed how price cuts contributed to induce significant price decreases in all countries, and might be considered as one of the limitation of ERP. These price cuts appeared reasonable enough to reflect affordability of the considered countries. However, the domino effect of these price cuts on wealthy countries can become a vicious effect of ERP.

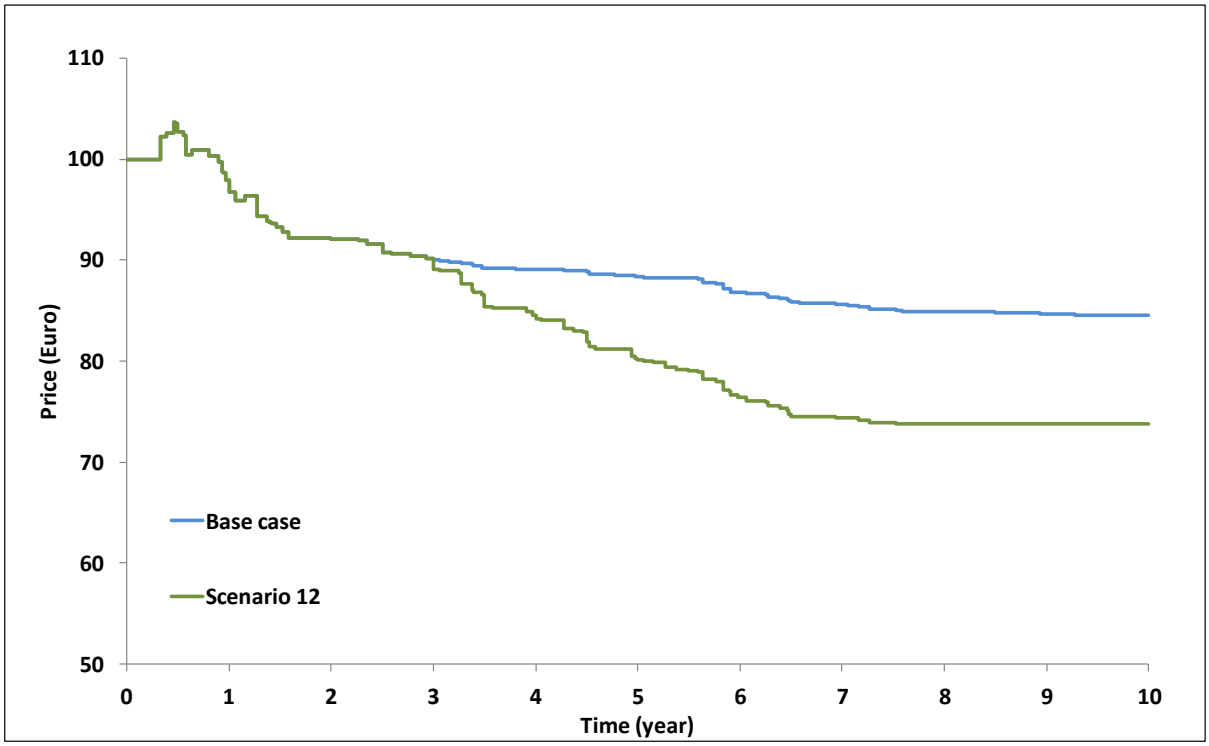


Figure 46. Scenario 12-Simulation of historical price cuts/discounts in a selection of countries-Evolution of average drug price over time

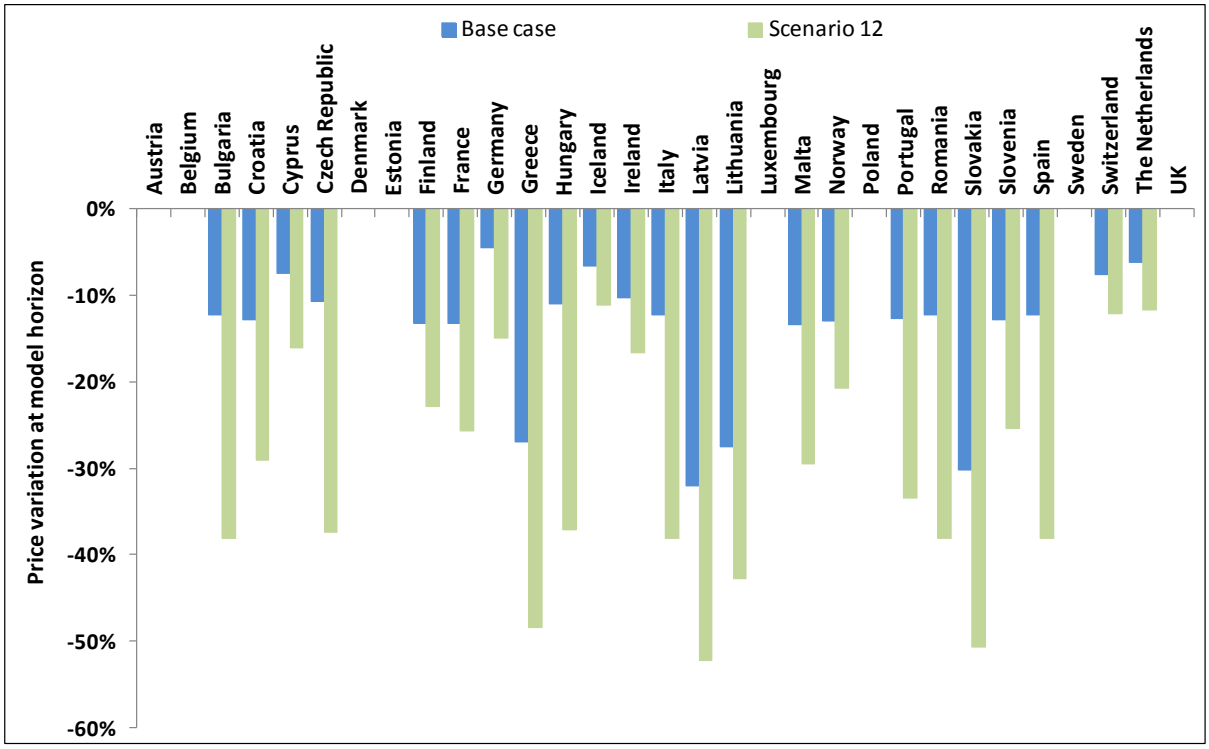


Figure 47. Scenario 12-Simulation of historical price cuts/discounts in a selection of countries-Evolution of drug price per country at 10 years (in percentage)

6.1.14 Scenario 13. Simulation of several price cuts on a same year in Greece

Assumptions

- Base case scenario with specific price cuts

In this scenario, a price decrease of 3% was applied in Greece every 3 months.

Figure 48 presents the evolution of the average drug price over time for all countries and Figure 49 presents the evolution of the drug price in percentage per country at 10 years.

Greece is referenced by 13 countries. Thus, applying regular price decrease over time led to an important decrease in the average drug price over years (-21.98% versus the base case at 10 years).

This scenario highlighted how a country facing major budget constraint issues and taking repeated drastic price cuts have a very important impact on all countries.

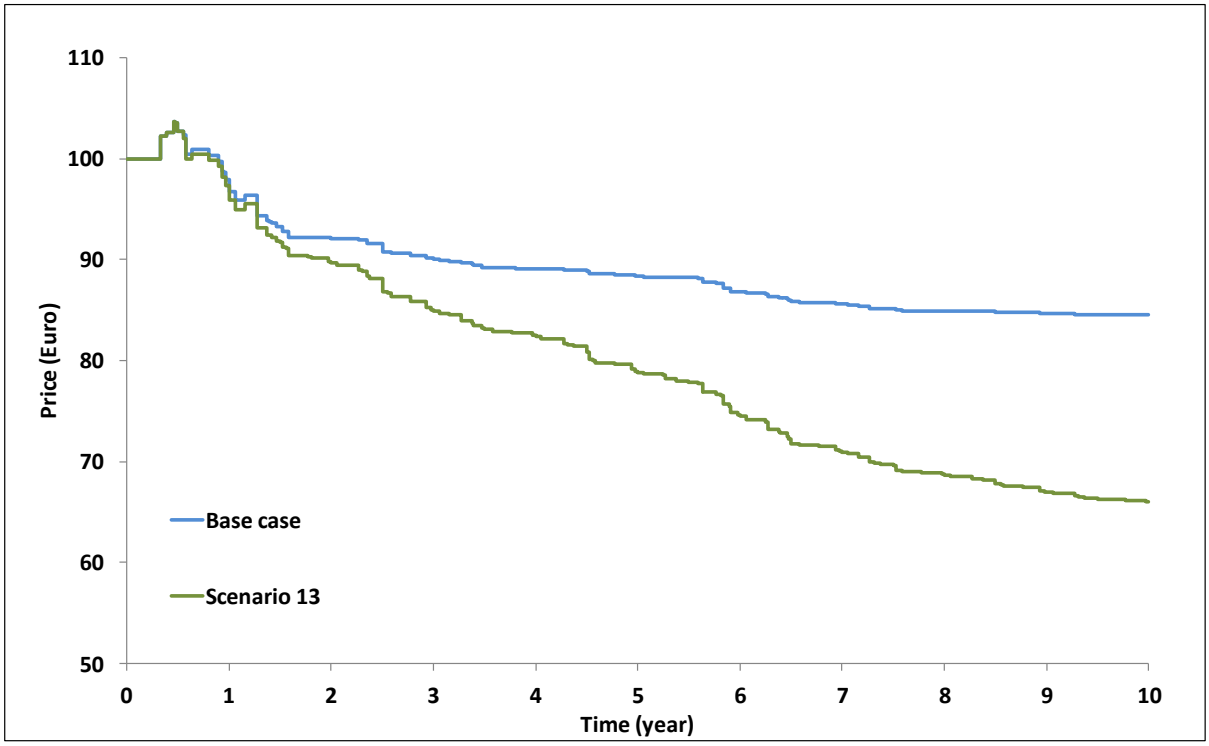


Figure 48. Scenario 13-Simulation of price decrease of 3% in Greece every 3 months-Evolution of average drug price over time

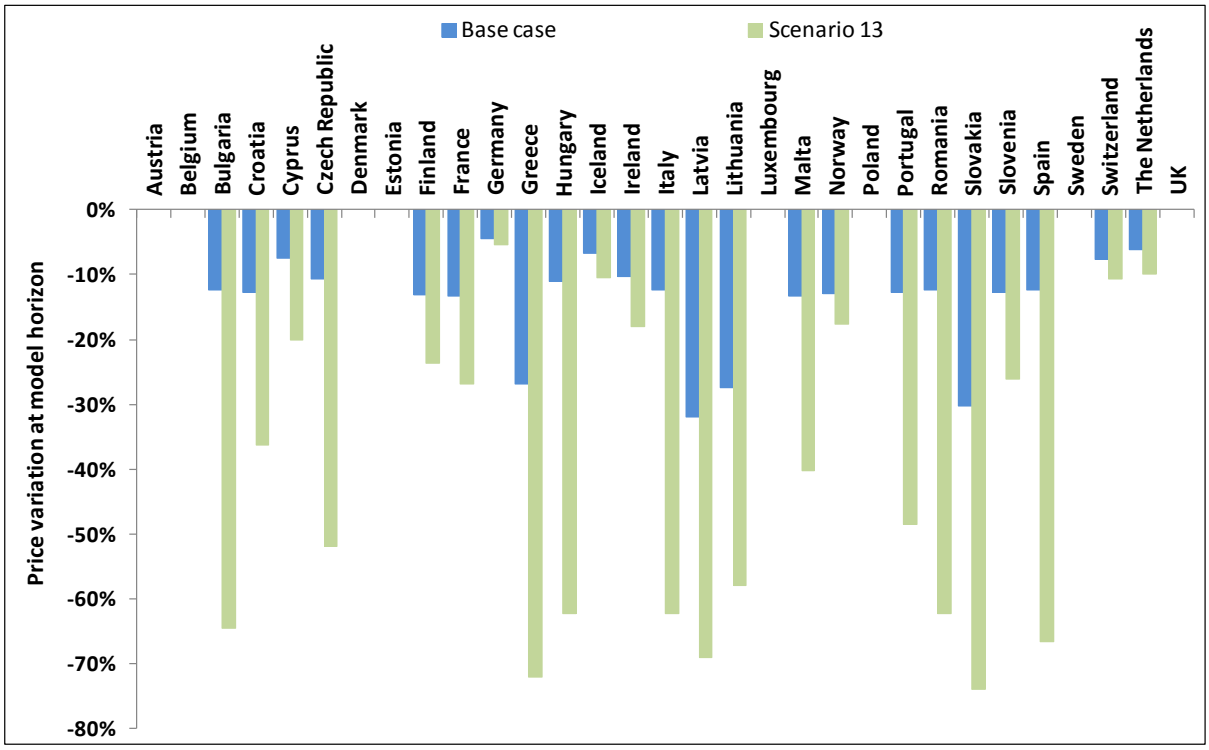


Figure 49. Scenario 13-Simulation of price decrease of 3% in Greece every 3 months-Evolution of drug price per country at 10 years (in percentage)

6.1.15 Scenario 14. Simulation of setting fixed price in Germany and decreasing fixed price set in UK

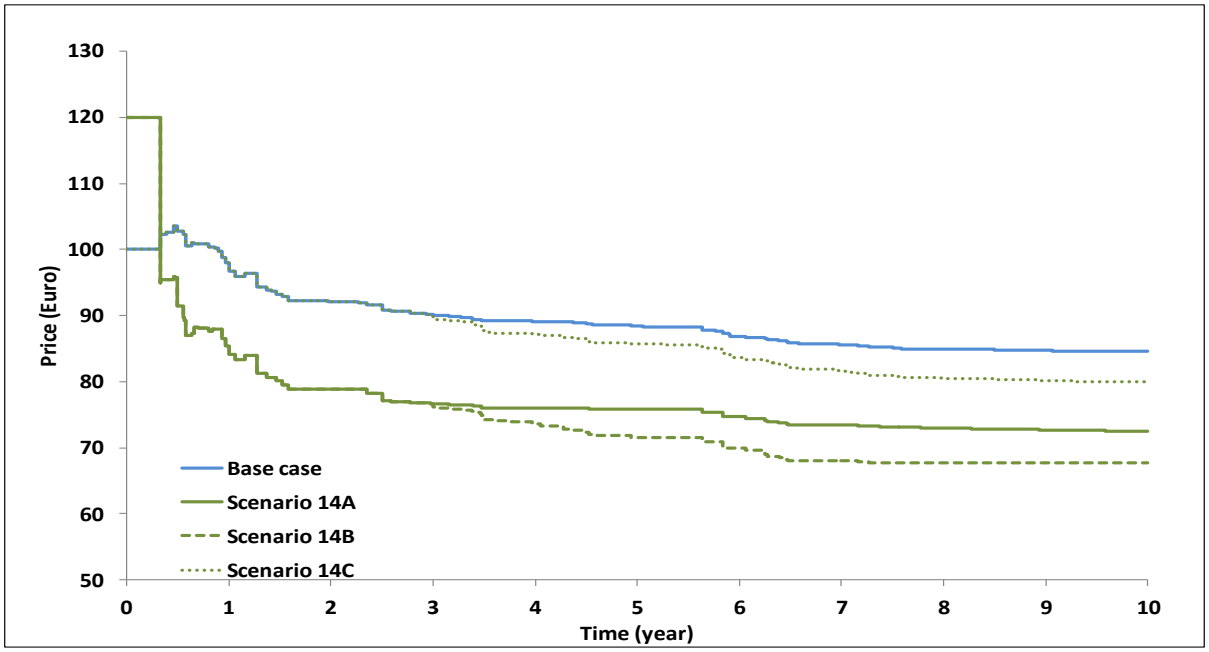
Assumptions

- Base case scenario, except for the fixed price initially set in non ERP countries

In this scenario, the ex-factory drug price was set at €100 in Sweden and at €70 in the UK (non ERP countries) and at €120 in Germany (**Scenario 14A**). This scenario was compared to a similar scenario for which a decrease of 20% in exchange rate from British Pound to Euro was introduced after the first 3 years of simulation (**Scenario 14B**), as well as to the scenario 3A for which a decrease of 20% in exchange rate from British Pound to Euro was introduced after the first 3 years of simulation (**Scenario 14C**).

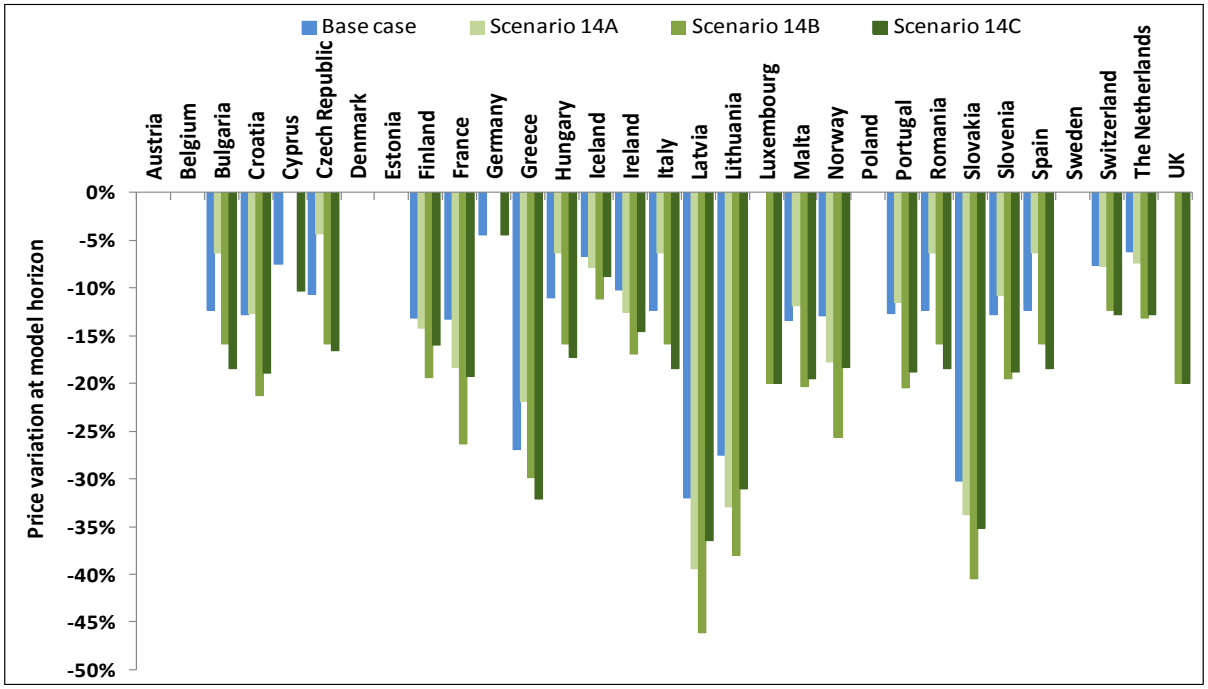
Figure 50 presents the evolution of the average drug price over time for all countries and Figure 51 presents the evolution of the drug price in percentage per country at 10 years.

An important decrease in the average drug price was observed for scenario 14A (-14.20% versus the base case at 10 years). Applying a decrease of 20% in exchange rate from British Pound to Euro had a similar impact, of about -5.5%, versus the base case and versus scenario 14A. Therefore, setting the UK price at €100 or €70 did not change significantly the impact of the British Pound decrease of 20%.



Scenario 14 A (ex-factory drug price was set for non ERP countries at €100 in Sweden and at €70 in UK, and was also set in Germany at €120), Scenario 14 B (Scenario 14A with decrease of 20% in exchange rate from British Pound to Euro introduced after the first 3 years of simulation), and Scenario 14 C (as Scenario 3A, decrease of 20% in exchange rate from British Pound to Euro introduced after the first 3 years of simulation)

Figure 50. Scenario 14-Simulation of setting fixed price in Germany and decreasing fixed price set in UK-Evolution of average drug price over time



Scenario 14 A (ex-factory drug price was set for non ERP countries at €100 in Sweden and at €70 in UK, and was also set in Germany at €120), Scenario 14 B (Scenario 14A with decrease of 20% in exchange rate from British Pound to Euro introduced after the first 3 years of simulation), and Scenario 14 C (as Scenario 3A, decrease of 20% in exchange rate from British Pound to Euro introduced after the first 3 years of simulation)

Figure 51. Scenario 14-Simulation of setting fixed price in Germany and decreasing fixed price set in UK- Evolution drug price per country at 10 years (in percentage)

6.1.16 Scenario 15. Simulation of various packaging or dosage or formulation of a drug launched in the countries

Assumptions

- Base case scenario, except for the fictitious drug with a same pack size/dosage/formulation available in all countries

In this scenario, a basket of countries, which could not set the price of a drug based on ERP rules because different pack sizes and/or dosage and/or formulation were approved in the reference countries, was considered. These countries were selected based on the literature review and stakeholder consultation (Refer to Appendix 9-Overview of ERP Processes in Europe): Croatia, Cyprus, Czech Republic, Hungary, Italy, Latvia, Lithuania, Malta, Poland, Portugal, Slovakia, and the Netherlands.

A same drug was considered to be available with same pack size/dosage/formulation in Germany, the UK and Sweden but at different pack size/dosage/formulation in the selected countries.

Figure 52 presents the evolution of the average drug price over time for all countries and Figure 53 presents the evolution of the drug price in percentage per country at 10 years.

A small increase in the average drug price evolution over time was observed when considering various packaging, dosage or formulation of a drug launched in the countries (+2.83% versus the base case at 10 years). This scenario does not support the need to create specific rules to reference similar packaging, dosage or formulation, as it leads to complications in the ERP management with no significant impact on the prices. Moreover, ERP rules based on similar pack sizes and/or dosage and/or formulation could lead to the development of specific pack size and/or dosage and/or formulation in each country with different levels of affordability.

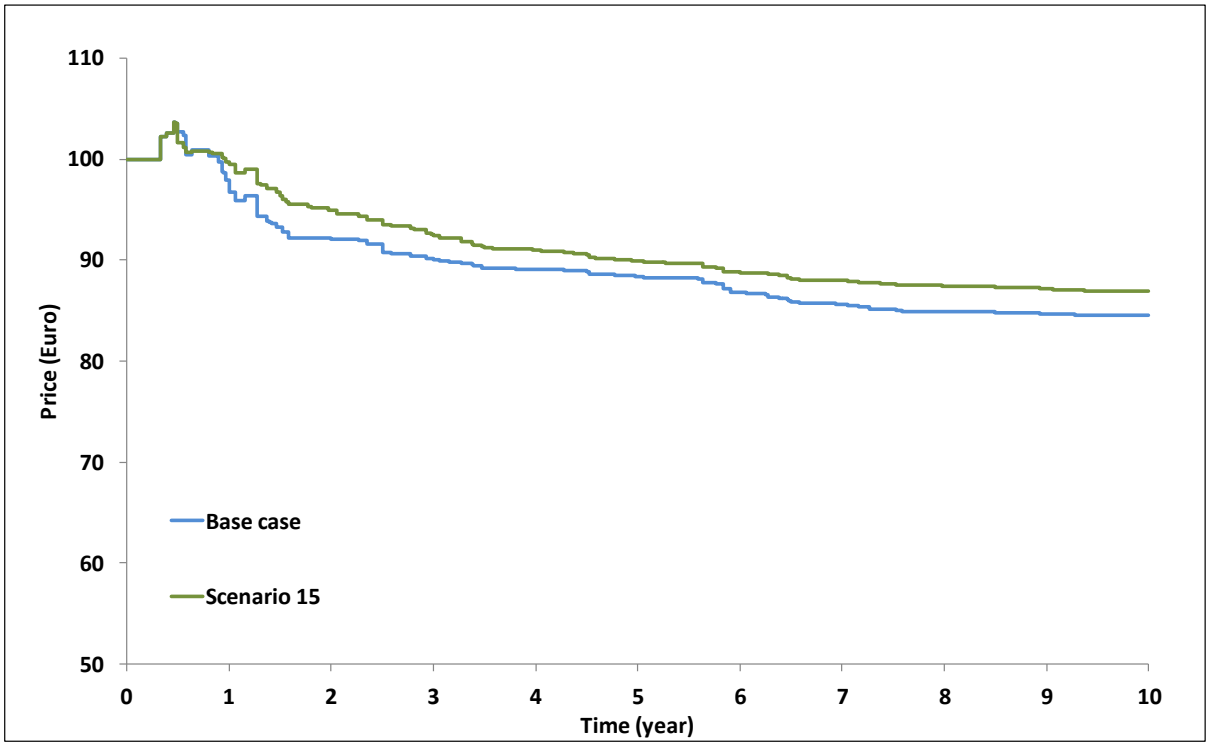


Figure 52. Scenario 15-Simulation of various packaging or dosage or formulation of a drug launched in the countries-Evolution of average drug price over time

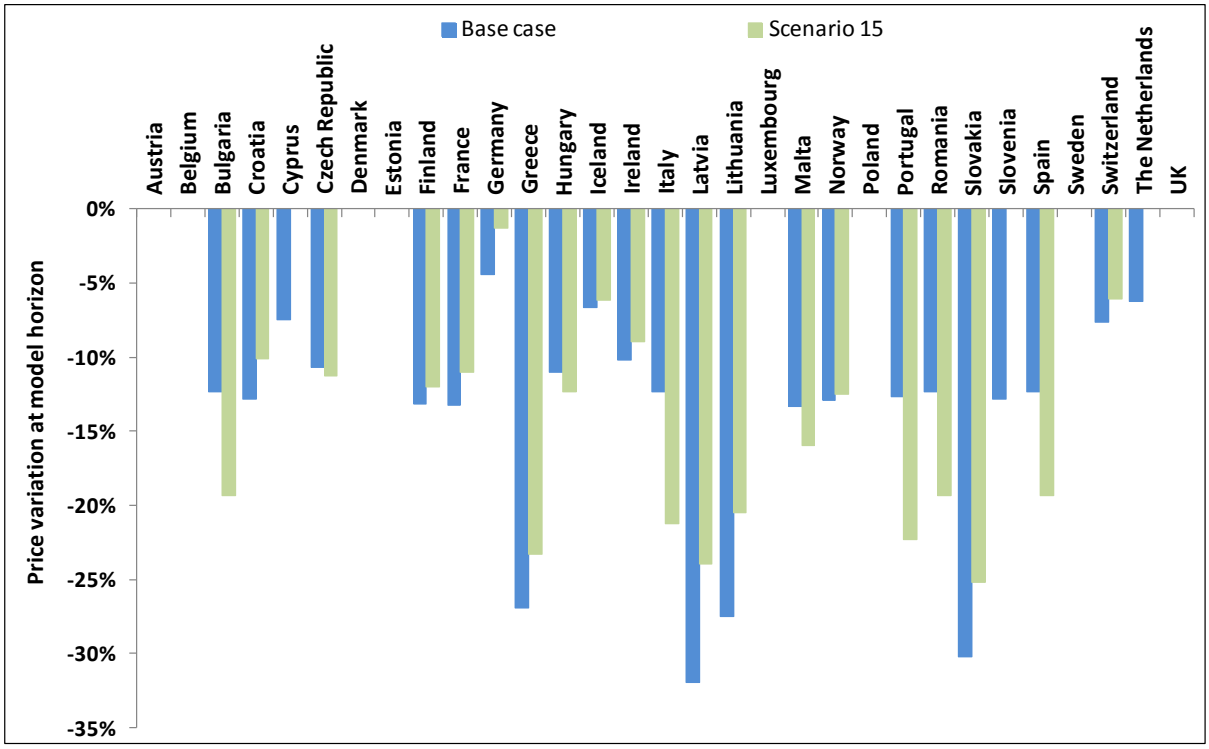


Figure 53. Scenario 15-Simulation of various packaging or dosage or formulation of a drug launched in the countries-Evolution of drug price per country at 10 years (in percentage)

6.1.17 Scenario 16. Simulation of the use of net drug prices instead of facial prices for reference purposes

Assumptions

- Base case scenario, except for the use of facial prices

Two countries for which mandatory price discounts are publicly known but not directly included on the listed price were selected for this scenario: Italy and Germany.

In this scenario, a price cut of 25% on the facial prices was applied in Germany and of 10% in Italy, to simulate the use of the rebates price in these countries.

In Germany, the AMNOG law introduced in 2011 the early benefit assessment of innovative drugs to inform pricing negotiations between the pharmaceutical companies and the health insurance (GKV-Spitzenverband). The size of the discount is in the public domain and range from about 15 to 40% (77% in one case).[71] An approximate rebate of about 25% on the listed price taken into account by the countries referencing German prices was considered for this scenario.

In Italy, Italian Medicines Agency (AIFA) implemented two mandatory price discounts of 5% on the Pharmacy Retail Price of all reimbursable drugs in 2006 and 2007.[72] An approximate rebate of 10% on the listed price taken into account by the countries referencing Italian prices was considered in this scenario.

Figure 54 presents the evolution of the average drug price over time for all countries and Figure 55 presents the evolution of the drug price in percentage per country at 10 years.

As expected, an important decrease of the average drug price was observed over time (-17.01% versus the base case at 10 years). This decrease was related to the very high discount in Germany.

This scenario pointed out the potential huge impact of disclosing confidential discounts in the public domain which could be taken into account when the countries using ERP set their prices. There is a trend among EU MS to hide net prices through various types of confidential agreements with pharmaceutical companies. Countries applying ERP as supportive criterion tend to estimate the actual net price when negotiating prices with pharmaceutical companies. Facial prices are becoming more and more distant from net price in order to cope with ERP rules. As a consequence, largest countries with better affordability will end up with lower actual prices while small countries with low affordability will not have volume leverage and will end up with higher average net prices.

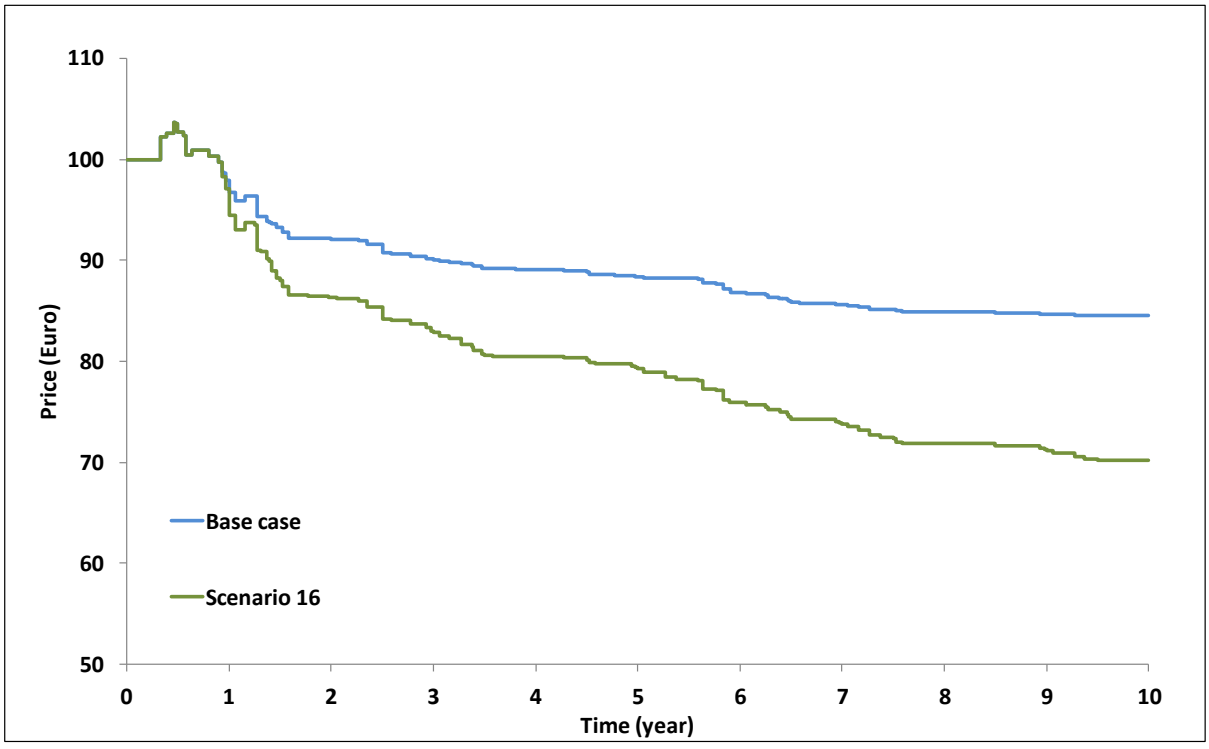


Figure 54. Scenario 16-Simulation of applying a price cut of 25% in Germany and of 10% in Italy on the facial prices to simulate the use of the rebates price-Evolution of average drug price over time

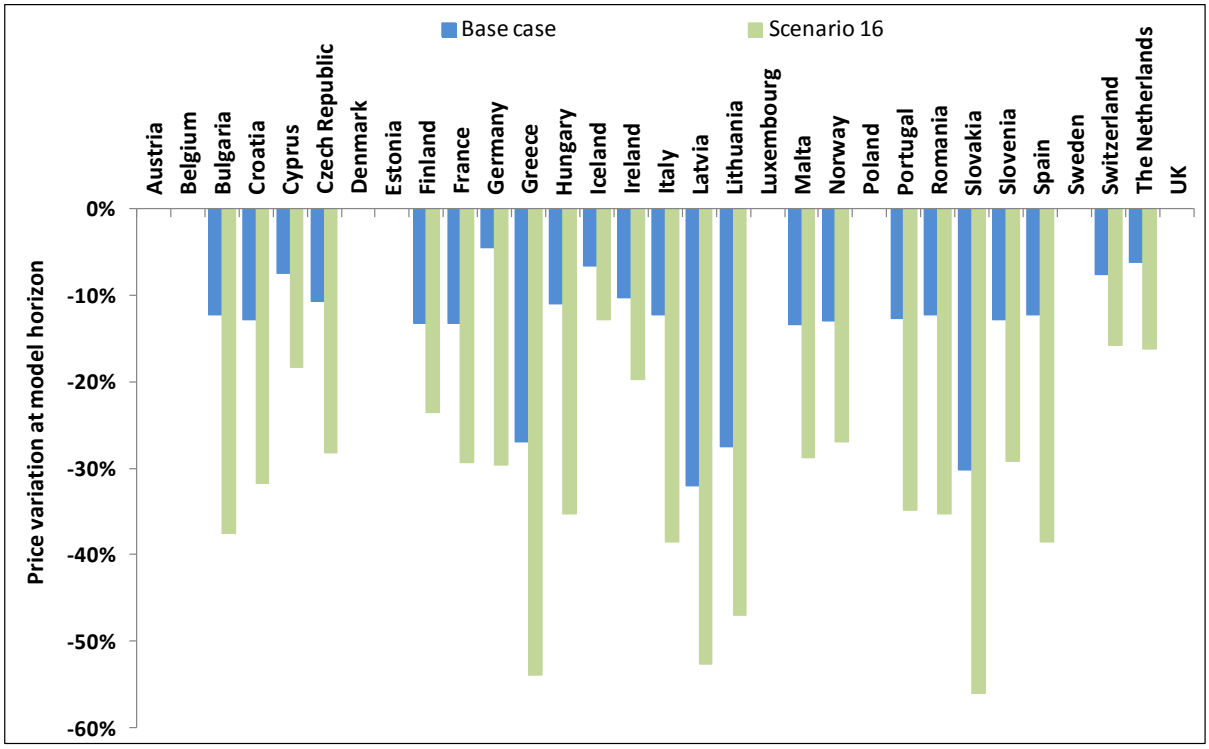


Figure 55. Scenario 16-Simulation of applying a price cut of 25% in Germany and of 10% in Italy on the facial prices to simulate the use of the rebates price-Evolution of drug price per country at 10 years (in percentage)

6.1.18 Scenario 17. Simulation of price dynamics if all countries leading to important price decreases were removed from the baskets

Assumptions

- Base case scenario, except for the number of countries in the basket

In this scenario, the drug was launched in all countries, but all countries leading to important price decreases were removed from the country baskets (countries using the lowest price as calculation method or the average price with additional price reduction, i.e, Bulgaria, Romania, Hungary, Estonia, Slovenia, Spain, Italy, Croatia, and Lithuania).

Figure 56 presents the evolution of the average drug price over time for all countries and Figure 57 presents the evolution of the drug price in percentage per country at 10 years.

A small decrease of the average drug price evolution was observed when all countries leading to important price decreases were removed from the basket (+9.53% versus the base case at 10 years). Prices of each country were multiplied by the country's population's size and computed to assess the impact of excluding some countries on drug sales. For this scenario we assumed that the prevalence of diseases and the proportion of treated patients were similar for all countries. Figure 58 showed that the sales (in Euro) were higher when countries with ERP policies driving prices down removed from the country basket (+6.58% versus the base case at 10 years). This highlighted the risk of dramatically delaying or not launching in some low price countries.

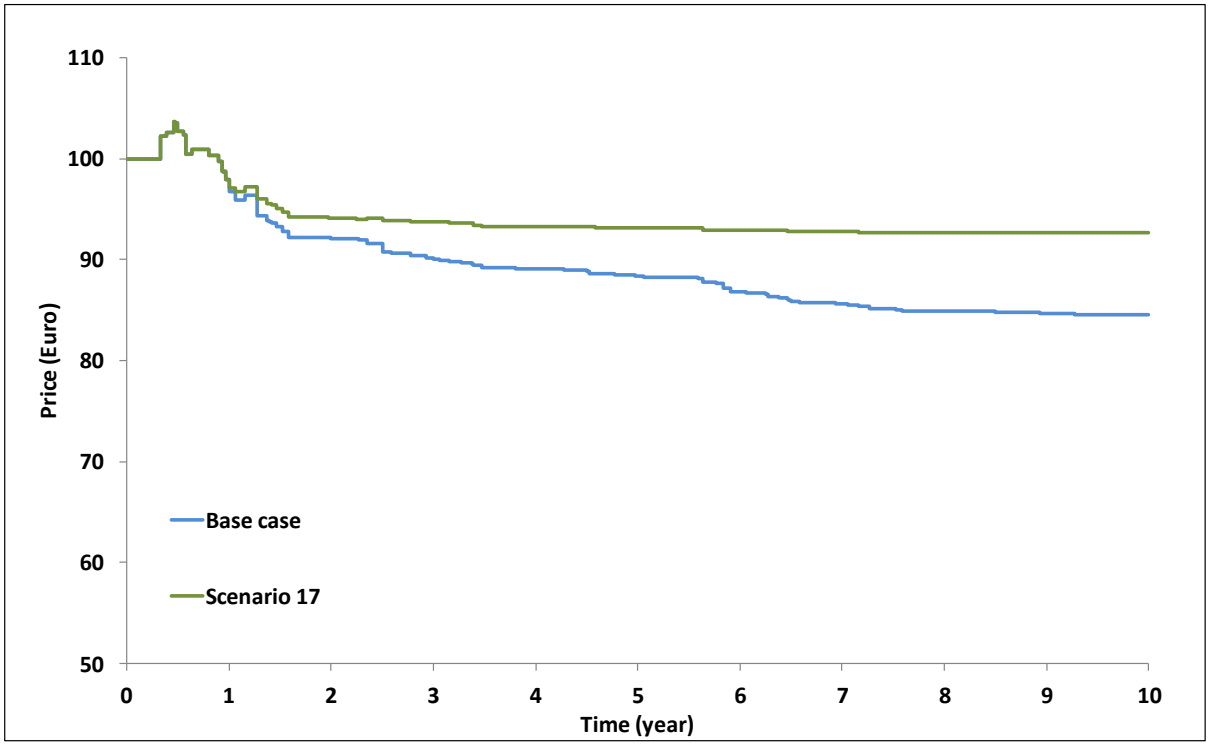


Figure 56. Scenario 17 -Simulation of price dynamics if all countries leading to important price decreases were removed from the country baskets-Evolution of average drug price over time

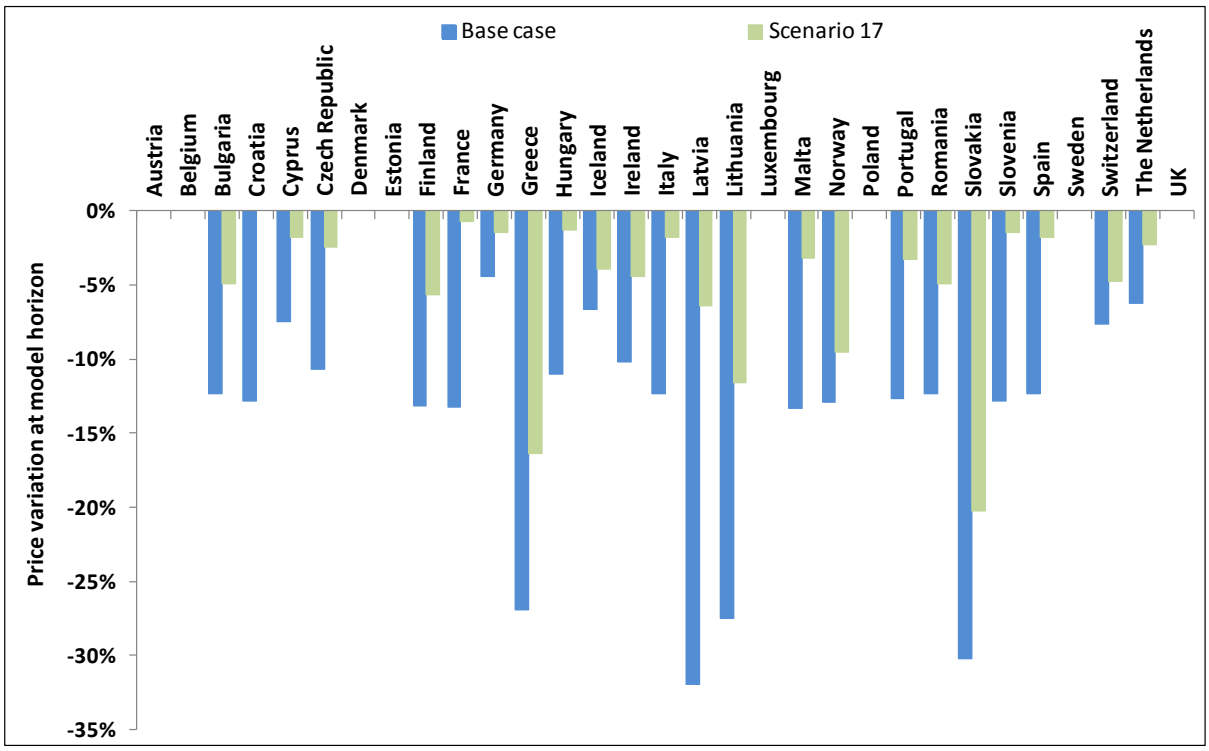


Figure 57. Scenario 17-Simulation of price dynamics if all countries leading to important price decreases were removed from the country baskets-Evolution of drug price per country at 10 years (in percentage)

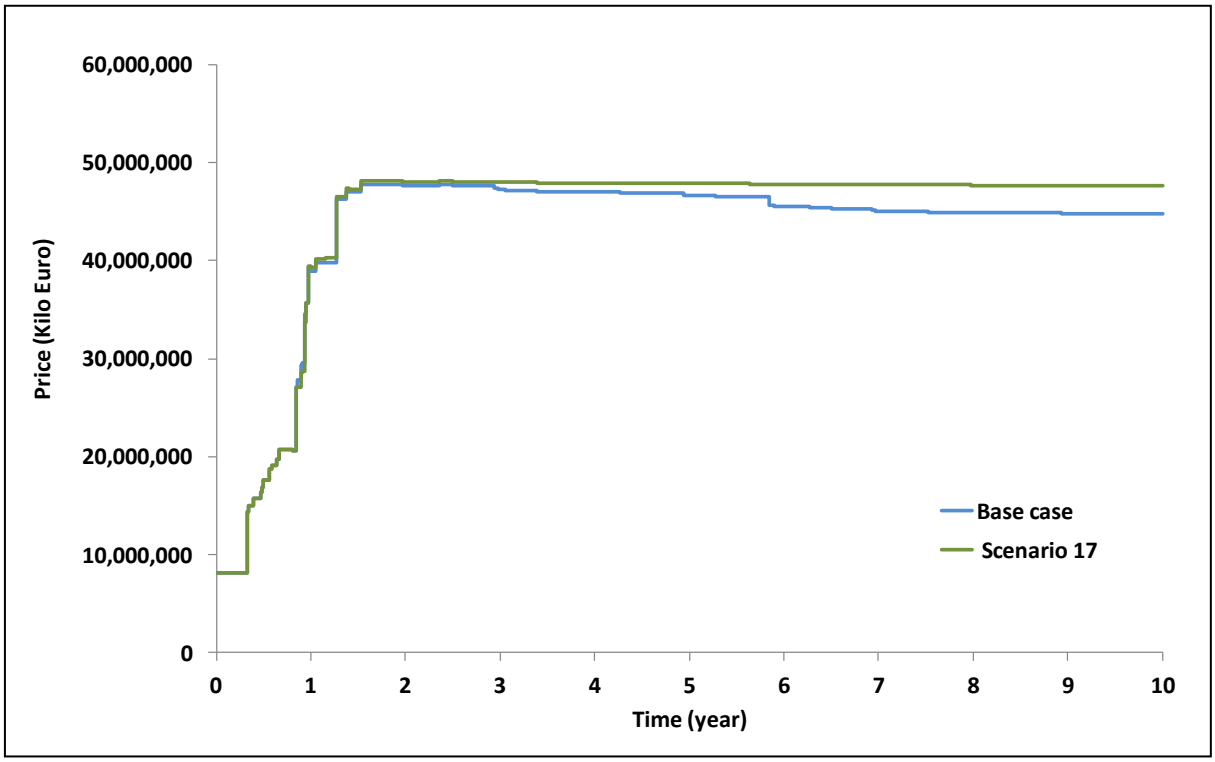


Figure 58.Scenario 17-Simulation of price dynamics if all countries leading to important price decreases were removed from the country baskets)-Proxy of sales over time (drug price per country X country population)

6.1.19 Scenario 18. Simulation of the increase in the number of countries in the basket

Assumptions

- Base case scenario, except for the number of countries in the basket

In this scenario, all countries are referencing the big EU 5 -France, Germany, Spain, Italy, UK - (or big EU 4 for the big EU5 themselves) and 3 basket sizes were defined as:

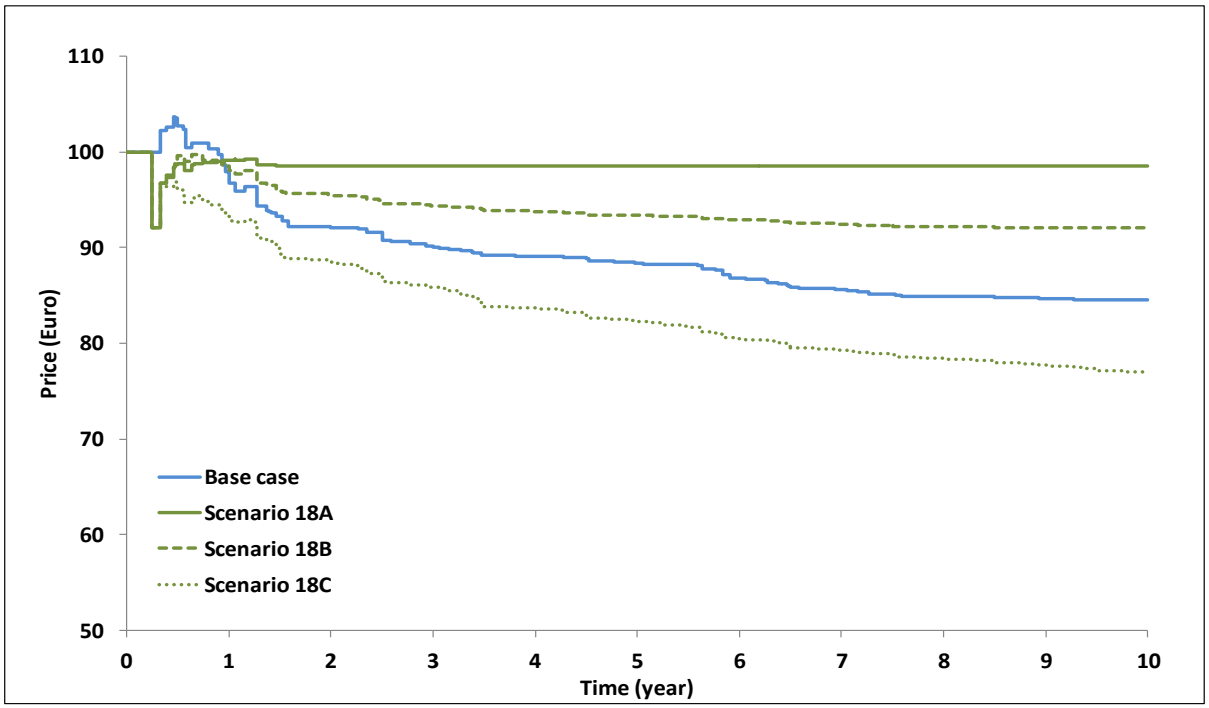
- One basket with the big EU 5 **(Scenario 18A)**
- One basket with the big EU 5 and countries with GDP per capita superior to €25,000 (Iceland, Belgium, Finland, Ireland, the Netherlands, Austria, Sweden, Denmark, Switzerland, Norway and Luxembourg) **(Scenario 18B)**
- One basket with all selected countries **(Scenario 18C)**

Figure 59 presents the evolution of the average drug price over time for all countries and Figure 60 presents the evolution of the drug price in percentage per country at 10 years.

An increase of the average drug price at 10 years of +16.44% and +8.82% versus the base case was observed when the basket included the big EU 5 and the big EU 5 plus countries with the highest GDP respectively.

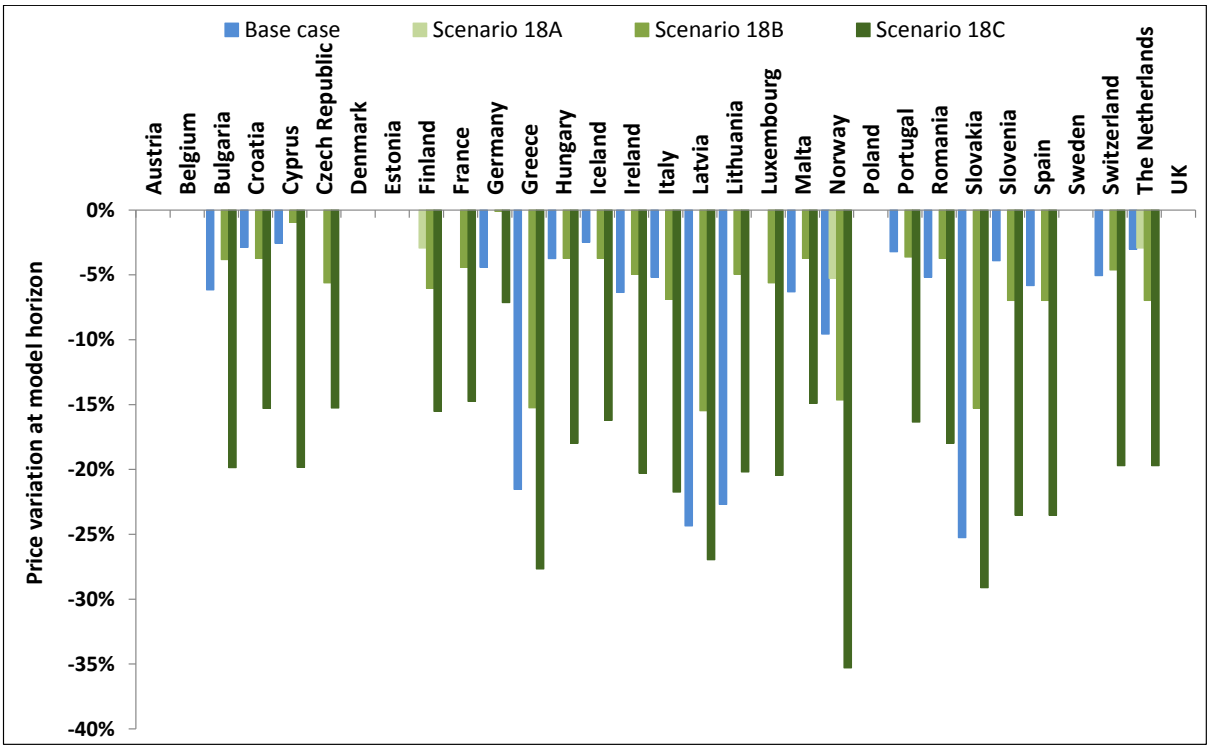
When all selected countries were included from the basket, the average drug price decreased of -9.02% versus the base case at 10 years.

Countries with the highest GDP are generally using ERP calculation method based on the average price of the country basket and thus, drive the average drug price up. Countries with lower GDP often use ERP calculation methods such as the lowest price or the average of the 3 lowest prices of the country basket and drive the average drug price down when included in the basket.



Scenario 18A (countries in the basket: France, Germany, Italy, Spain, UK) and Scenario 18B (countries in the basket: France, Germany, Italy, Spain, UK+ Iceland ,Belgium , Finland ,Ireland , the Netherlands, Austria , Sweden , Denmark , Switzerland, Norway , Luxembourg), Scenario 18C (all selected countries in the basket)

Figure 59. Scenario 18-Simulation of the increase in the number of countries in the basket-Evolution of average drug price over time



Scenario 18A (countries in the basket: France, Germany, Italy, Spain, UK) and Scenario 18B (countries in the basket: France, Germany, Italy, Spain, UK+ Iceland ,Belgium , Finland ,Ireland , the Netherlands, Austria , Sweden , Denmark , Switzerland, Norway , Luxembourg), Scenario 18C (all selected countries in the basket)

Figure 60. Scenario 18-Simulation of the increase in the number of countries in the basket-Evolution of drug price per country at 10 years (in percentage)

6.1.20 Scenario 19. Simulation of price of one drug available only in the hospital or in the out-patient sector

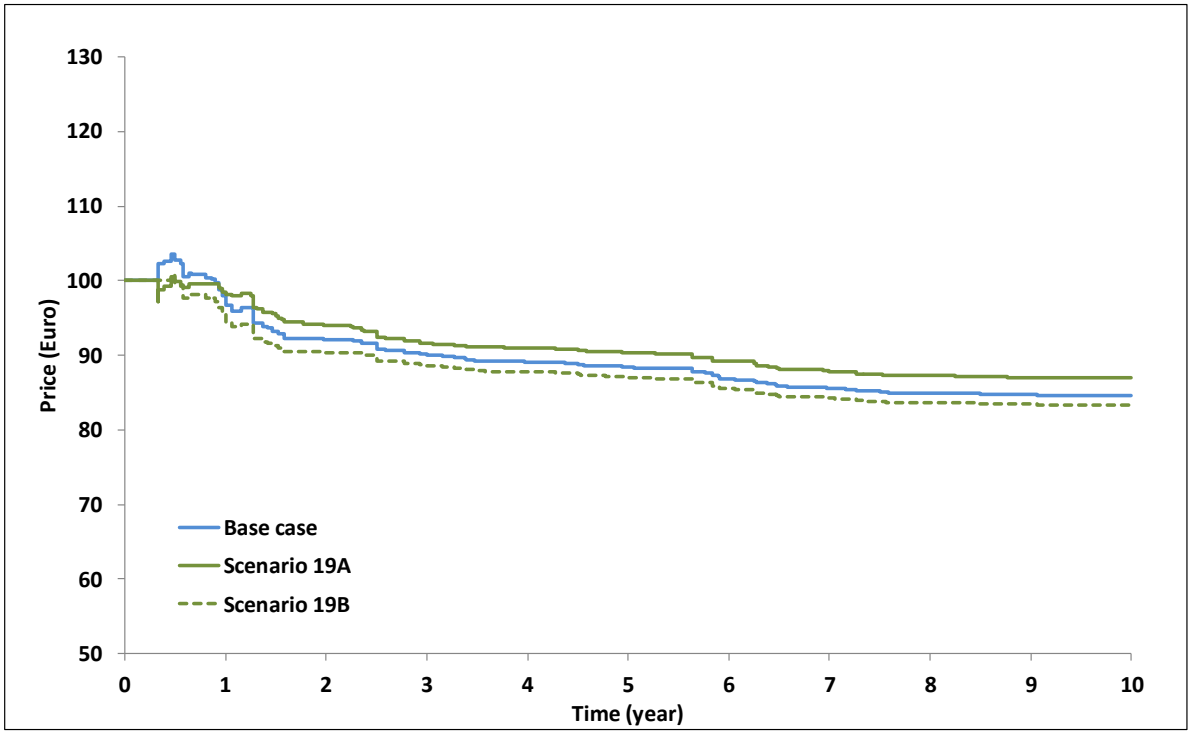
Assumptions

- Base case scenario, except for the fictitious drug available in hospital/out-patient sector

In this scenario, the ERP impact was simulated using a fictitious drug available only in the hospital sector (**Scenario 19A**) or only in the out-patient sector (**Scenario 19B**).

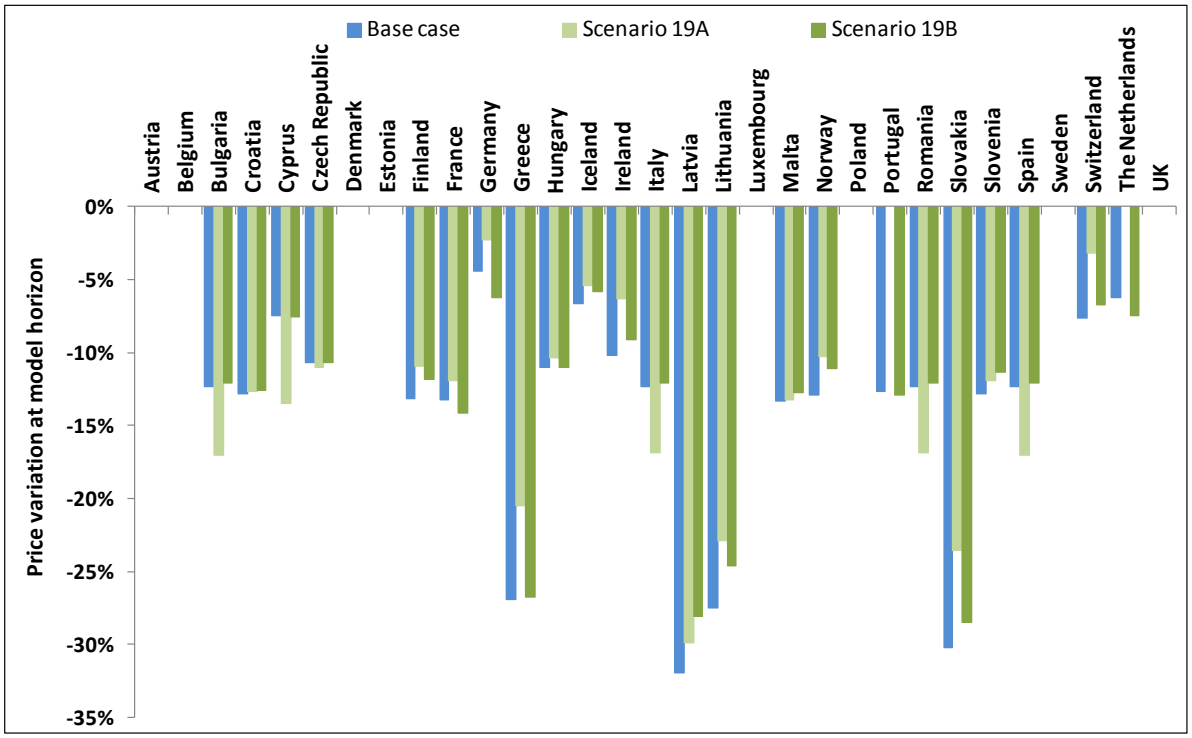
Figure 61 presents the evolution of the average drug price over time for all countries and Figure 62 presents the evolution of the drug price in percentage per country at 10 years.

In this scenario, few changes in the average drug price evolution were observed over time (+2.86% versus base for a drug only available at hospital and -1.48% versus the base case for a drug only available in out-patient sector at 10 years). This evolution was explained by the fact that few countries reported accurate rules regarding out-patient versus hospital medicines regulated by ERP. Only Denmark has been reported to use ERP for hospital-only product and Austria, Portugal and the Netherlands for out-patient drugs. In general, ERP is assumed to be mainly used for out-patient drugs, while tenders and price negotiations are the key pricing policies used for hospital-only medicines.



Scenario 19 A (drug only available in the hospital sector) and Scenario 19B (drug only available in the in-patient sector)

Figure 61. Scenario 19-Simulation of price of one drug available only in the hospital or in the out-patient sector-Evolution of average drug price over time



Scenario 19 A (drug only available in the hospital sector) and Scenario 19B (drug only available in the in-patient sector)

Figure 62. Scenario 19-Simulation of price of one drug available only in the hospital or in the out-patient sector-Evolution of drug price per country at 10 years (in percentage)

6.1.21 Scenario 20. Simulation of several scenarios together

Assumptions

- Base case scenario, except for reference price calculation, price revisions, country basket and for average time to market entry for new drugs

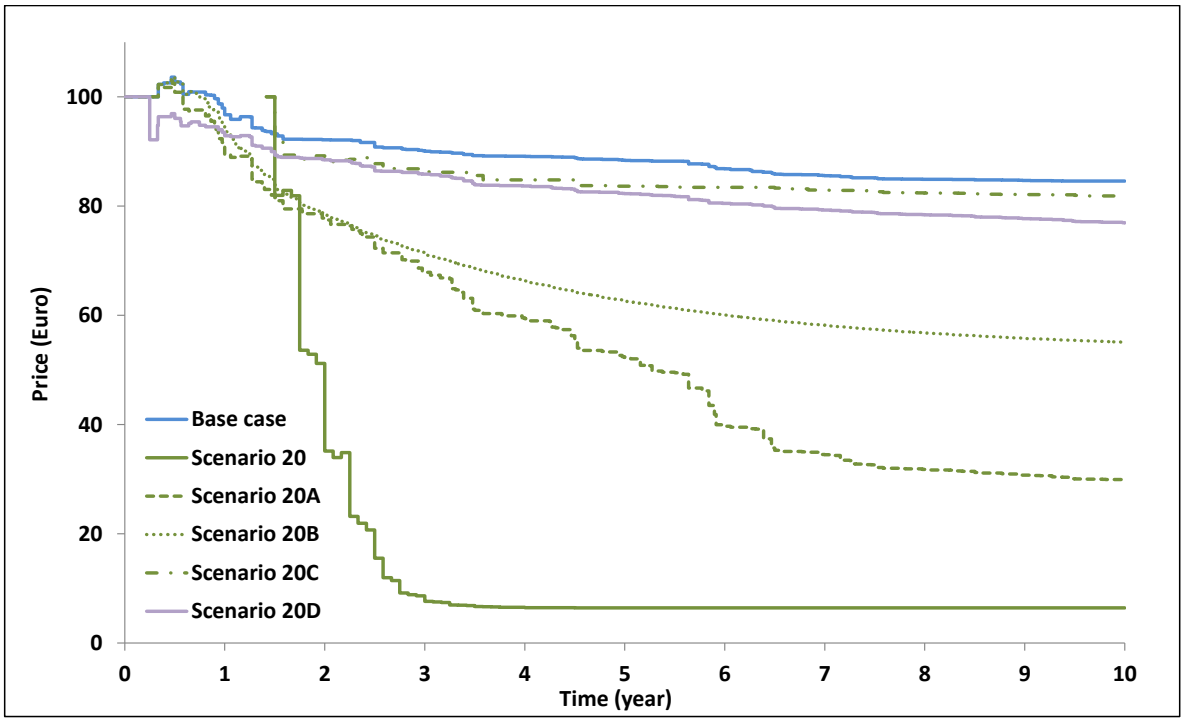
In this scenario several scenarios together were combined:

- Reference price calculation based on the lowest price **(Scenario 20A)**
- Price revision set every 3 months **(Scenario 20B)**
- Drug launch sequences were performed in the countries by ascending order of GDP/capita **(Scenario 20C)**
- Country basket: all selected countries **(Scenario 20D)**

Figure 63 presents the evolution of the average drug price over time for all countries and Figure 64 presents the evolution of the drug price in percentage per country at 10 years.

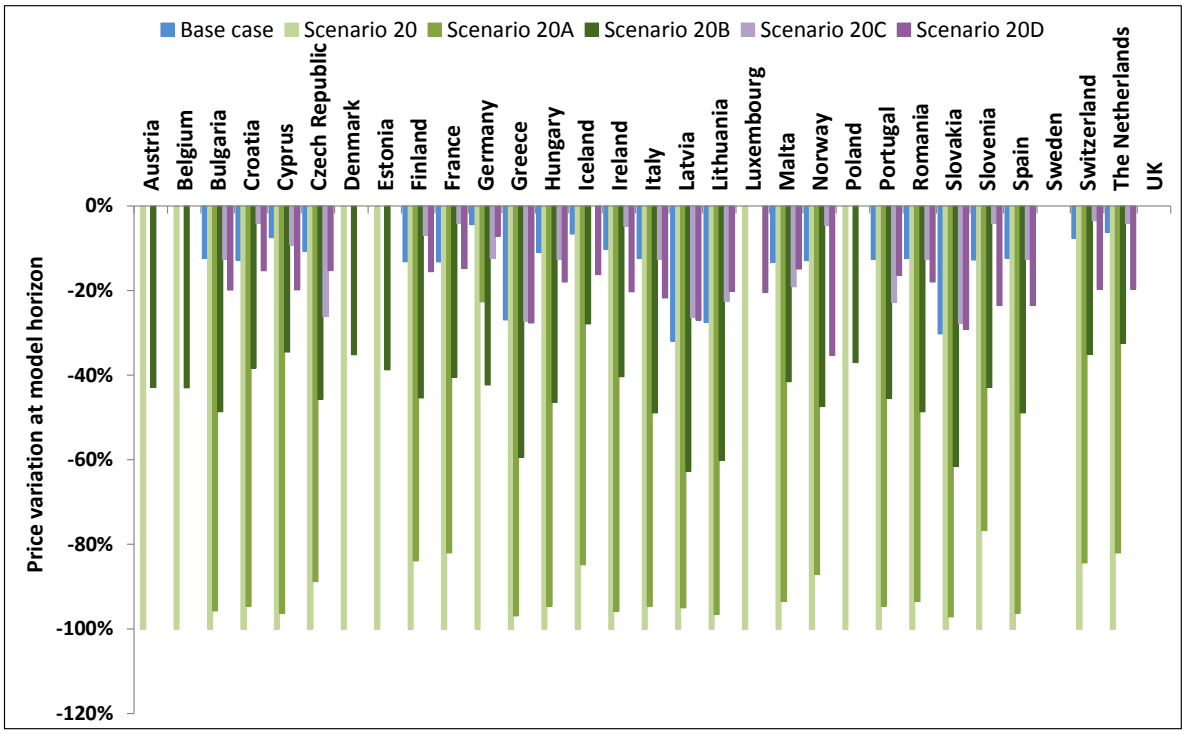
This scenario impacted importantly the evolution of the average drug price over time with an average drug price decrease of -92.37% versus the base case at 10 years.

This scenario clearly showed that the combination of policies and situations that drive prices down had a dramatic effect on price development overtime, with each scenario impacting more or less drug prices. The scenario with the most important impact was the reference price calculation based on the lowest price scenario (price decrease of -64.66% versus the base case at 10 years) followed by price revision set every 3 months (-34.87% versus the base case at 10 years), then all countries selected in country baskets (-9.02% versus the base case at 10 years) and the drug launch sequences performed in the countries by ascending order of GDP/capita (-3.20% versus the base case at 10 years).



Scenario 20A (Reference price calculation based on the lowest price), Scenario 20B (Price revision set every 3 months), Scenario 20C (Drug launch sequences were performed in the countries by ascending order of GDP/capita) and Scenario 20D (Country basket: all selected countries)

Figure 63. Scenario 20 -Simulation of combined scenarios-Evolution of average drug price over time



Scenario 20A (Reference price calculation based on the lowest price), Scenario 20B (Price revision set every 3 months), Scenario 20C (Drug launch sequences were performed in the countries by ascending order of GDP/capita) and Scenario 20D (Country basket: all selected countries)

Figure 64. Scenario 20-Simulation of combined scenarios-Evolution of drug price per country at 10 years (in percentage)

6.2 Real-life scenarios

Fifty three medicines were selected for the analysis of real-cases, based on the drugs available in IMS price database and the number of countries where the drug was launched using the same strength and formulation. Selected drugs, including selected form and strength, are presented in Appendix 16.

As these figures contain confidential information through the computing and analysis of the cases, the results for each drug are presented in Appendix 17 which is not published.

Four figures were presented per drug in this appendix:

- One figure representing the actual drug launch sequence using as proxy the drug's uptake time
- One figure representing the actual and the model average drug price evolution since launch
- One figure representing the actual and the model drug price at launch
- One figure representing the actual and the model drug price at present time

The ERP model seemed to well predict actual prices and the following trends were observed:

- When a product was initially recognized as an innovative product, the actual price of this product appeared to consistently achieve a higher price than the ERP model price. This trend acknowledges the fact that ERP is not the unique driver of price decision in most of the countries, for innovative drugs. In that case the value appreciation led to a positive reward from payers.
- The actual price of the product tended to become lower than the ERP model price over time when a product had extension of indications over time (expanding target population size) and generated high revenue. This trend acknowledged that prices are pushed down by payers, overtime, when volume of sales increased due to extension of indication or important commercial success.
- Low GDP countries tended to be the last to achieve drug entry, suggesting the use of launch sequence strategy from the marketing authorization holder. High GDP countries, such as Germany, Austria, Ireland, the UK and Norway, were generally among the first countries to achieve drug entry and low GDP countries, such as Romania, Bulgaria, Latvia, Estonia and Lithuania, among the last ones. However the same low GDP country was not always among the last countries reaching the market.

A more specific and systematic research on these trends might be useful to achieve a clear understanding of the role of launch sequence for price optimization.

7. Discussion

7.1 Potential impacts of external reference pricing

The DES model was used to simulate the price evolution of a fictitious drug over time through the ERP process in the 31 selected countries. The aim of this theoretical exercise was to identify the impacts of the main criteria of ERP policies to gain a better understanding of the influence of each criterion on the evolution of the drug price.

The flexibility of the DES model enabled to display multiple scenarios. Twenty fictitious scenarios were chosen based on the potential rapid and important price erosion attributed to ERP as reported from the literature and stakeholder consultation. The different impacts of these scenarios on prices were classified as low, moderate or important depending on changes in average drug price versus the base case (<5%, 5-10%, >10%, respectively) (Table 10).

The main findings of the modelling exercise are presented below.

ERP drives prices down

Applying solely ERP as a pricing rule led to a low average drug price decrease (about 15% at 10 years), with an apparent equilibrium reached in approximately 7-8 years. Price differentials between countries remained substantial over 10 years (about 30%) when applying a proxy of a real launch sequence, suggesting a limited impact of ERP in price convergence. However, based on the authors' knowledge and as supported by the launch sequences of real cases, pharmaceutical companies apply specific launch sequence strategy to maximize facial price convergence, whereas net price differences might increase with the multiplication of managed entry agreements.

Even if the impact differed depending on scenarios, all tested scenarios induced price decreases and demonstrated the circular and spill-over effects of ERP. ERP lowered prices, in particular when there were frequent price revisions, iterative price cuts, when country baskets were very large, and when a country used the lowest price or average of the three lowest prices in the country basket rather than the average price.

ERP is a complex system with important synergies between several factors. Although some policies happened to be less impacting than anticipated (e.g. fluctuations in currency exchange rates or strategies related to pack size, dosage, formulation of a drug), the repetition and the combination of various policies generated an important cumulative price discount (as illustrated in scenario 20 where several scenarios were simulated simultaneously). This complexity made the interpretation of the results sometimes difficult and even counter intuitive.

Price revisions, an important driver of price changes over time

The periodicity of price revision is an important driver of price changes overtime when applying ERP. Going for a systematic price revision for all country every year almost doubled the price decrease compared to price revision every 3 years. It should be noted that time to equilibrium was delayed when price revisions were done more frequently. Thus, revising the periodicity for all countries will have impacts on countries with long periodicity because increasing the revision frequency will contribute to decrease prices. This price decrease will have an impact on the prices in countries with high frequency of revision because of the reference system.

Genericisation impact might induce important brand drug price decrease

Genericisation was one of the scenarios which led to the most important repercussion on prices (scenario 10). Few countries are reported to reference generic prices; however this could have a major impact on brand prices if it was applied. Moreover, the mandatory price reductions of the brand drug following patent expiry in some countries might also have an important impact in countries using this price cut for ERP and where the brand is not yet generic, since gaps in intellectual propriety duration still exist in Europe.

Different distribution margins might impact ERP prices

The use of heterogeneous price levels for reference (such as ex-factory and pharmacy purchasing prices) impacted the prices due to differential in distribution margins across countries.

Applying specific launch sequences starting in high GDP countries might minimize price decreases

Applying launch sequences by ascending order of GDP per capita induced average drug price decreases versus the base case. Removing all countries leading to important price decreases from the country baskets led to average drug price increase versus the base case. These scenarios clearly suggests that delaying launch of a new drug in countries using more ERP policies driving down the drug prices (generally low GDP countries) minimize the impact on other country prices and could therefore explain the drug launch sequences applied by companies to counteract ERP effects, as described in the literature.

Important price heterogeneity versus the base case were observed for scenarios 1 (price revisions), 4 (using ex-factory of pharmacy purchasing price), 5 and 18 (change in the country basket number). Price heterogeneities between countries could represent an incentive for pharmaceutical companies to set specific drug launch sequences.

Type of price used as reference and source of pricing are critical for ERP-based systems

France, Germany, and the UK are the most referenced countries among the selected countries.

France, being historically a low price country, is the most referenced country. This became a strong incentive for companies and French Drug authorities to create complex and sophisticated hidden price payback rules; the authorities get the opportunity to buy the drug at an affordable price, while the companies get access to one of the largest and most attractive- despite applied discounts- drug market. This situation induced a gap between the net price actually paid to pharmaceutical companies and the facial price, with discounts exceeding 20% in many cases. The actual net price is not public in France. It could neither be used by competitors for benchmarking, nor by foreign countries to establish ERP related drug price leading to one of the common ERP counter effect on pricing.

Germany and the UK are the second most referenced countries. They were both known to be high prices countries due to their free pricing systems. However, the UK has become a low price country and a source country for parallel trade, following British Pound devaluation from 2008 to 2013. Net prices are no longer available in the UK, as in France, and patient access schemes became confidential. From the authors' knowledge, ERP was a driver for the introduction of confidential patient access

schemes. In Germany, the AMNOG law replaced free pricing by the early benefit assessment in Germany since 2011. As of now in Germany, prices are set for free for one year for drugs without reference price group (6 months if reference price group), and then negotiated between manufacturers and insurers following early benefit assessment. This price is consistently cheaper than the one set by the manufacturers. Price discounts agreed between manufacturers and insurers are publicly available. Even if most of the countries reported using facial prices to set ERP prices, these rebates could be used by the authorities of the countries referencing Germany.

The aim of ERP instauration in countries was to ensure that prices are partly set using larger countries expertise in assessing and valuing benefit. Major evolutions in how prices are set and the level of information in the public domain such as seen for the three most referenced countries ended up creating a dual price with a high facial price and a lower net price, distorting dramatically the initial objective of ERP. High facial price could mislead countries using ERP as illustrated with the scenario 16; this scenario showed an important price erosion when using net price for two countries where discount are totally (Germany) or partly (Italy) in the public domain.

Implementing fair ERP policy is challenging

According to Bouvy J. and Vogler S. (2012)[11], differential pricing is limited within EU market, mainly due to parallel trade and ERP, and might negatively impact the low-income countries in terms of affordability and access to medicines. The authors reported that shifting from ERP towards VBP would not resolve the issue of parallel trade. The authors proposed, instead EU MS revised their country basket to have only countries with comparable GDP per capita, or for lower income country, to have a high list price for drugs, while negotiating confidential discounts and rebates.

ERP countries should preferably only reference countries not using ERP in order to avoid the spill-over and circular effect on prices as illustrated by the fictitious scenarios. However, this appears to be nearly impossible as ERP is used in almost all EU countries.

It is questionable whether countries should use VBP and ERP in parallel since this does not make sense conceptually, as explained in section 4.6. However, ERP could contribute to inform price negotiation when uncertainties remain at new drug launch. Those uncertainties can be appropriately addressed using coverage with evidence development.

One of the issues encountered when applying ERP is the choice of the country basket. It is logical to assume that comparable countries would be selected for price comparison based on criteria such as affordability, health status, health care resources, health care organization, population size and age structure.

Implementing fair ERP policy is challenging in the current pharmaceutical environment. It is anticipated that ERP will continue to be a suboptimal tool because it is not used to set prices but to contain pharmaceutical expenditure in a context of fast growing cost of innovative medicines.

7.2 Study limitations

A number of limitations should be considered when interpreting the results of the fictitious scenarios:

- The ex-factory drug price was set at €100 for non-ERP countries (the UK and Sweden) and starting with a different price for the UK decreased the average drug

price at base case. Scenario 14 showed that a 20% depreciation of the British Pound had almost the same effect irrespective of the initial UK price. This is consistent for other scenario data not presented in this report. Thus, the initial UK price set at €100 did not affect the outcomes of the various tested scenarios.

- It was assumed the UK and Sweden initially launched the product at the same price which is unlikely in the real life. However, this helped to understand the dynamic of each scenario by limiting the factors that could affect the variability of the price.
- The fictitious drug used in the model was assumed to be referenced by all countries of the study. In reality, some countries apply ERP only for some specific products. For example, France applies ERP only to products rated innovative by the Transparency Committee, thus France becomes a non-ERP country for non-innovative products (about 95% of the medicines in France). In France, non-innovative products have lower prices compare to prices of the other comparable European countries. In this study, the drug was considered as an innovative product in France, overlooking the fact that France would have probably driven prices down if the product was a non-innovative drug.

The IMS price database was selected for the real-life scenarios, as it covered most of the selected products in a large number of countries (26 countries) and included 12 years history data. However, a number of limitations should be considered when interpreting the results since:

- No price data were available for Croatia, Cyprus, Denmark, Iceland and Malta.
- No price data were available for the Netherlands before Q3 2007 and for Sweden before Q1 2004.
- Hospital-only medicines were not included in the real-life scenarios as explained in methodology section 5.2.3.
- Countries that did not use the selected form -strength of the drug were excluded from the analysis (1 or 2 countries for 14 drugs and more than 2 countries for 7 drugs).
- The model started after the actual launch for products being authorized before 2001 (5 products and this altered the launch sequence).
- Actual ERP rules were applied over time. This assumption was conservative since the most likely trends over time were the extension of the country basket and ERP calculation methods going for minimum rather than average price.

Each of these limitations was not considered as critical and the ability for the ERP model to predict prices, and more importantly, trends overtime, argues for the validation of the developed model.

Parallel trade was not modelled in this project because it was not planned in the initial scope of this project. As such, the price below which parallel trade was triggered and the potential economic impact of parallel trade was not assessed through this model. This could very well complement the current work and might be considered as an additional project in the future.

Table 10. Impact of fictitious scenarios on average drug price evolution versus the base case

(<5%: low impact, 5-10%: moderate impact, >10%: important impact) [Positive impact Price increase versus the base case; Negative impact: Price decrease versus the base case]

Number of Scenario	Title of Scenario	Positive Impact			Negative Impact		
		Low Impact	Moderate impact	Important Impact	Low Impact	Moderate impact	Important Impact
Scenario 1	Simulation of price revisions each year (1A) and every 3 years (1B)				B		A
Scenario 2	Simulation of drug launch sequence in countries by ascending (2A) or descending (2B) order of GDP/capita	B			A		
Scenario 3	Simulation of changes in exchange rates 3A1: Increase of 20% from British Pound to Euro 3A2: Decrease of 20% from British Pound to Euro 3A3: Historical fluctuations from British pound to Euro 3B1: Decrease of 10% from Polish Zloty and Hungarian Forint to Euro 3B2: Historical fluctuations from Polish Zloty and Hungarian Forint to Euro 3C1: Decrease of 10% from all non Euro-currencies to Euro 3C2: Historical fluctuations from all non Euro-currencies to Euro	A1			A2, A3, B1, B2, C1		C2
Scenario 4	Simulation of using ex-factory price (4A) or pharmacy purchasing price (4B) as price basis taken for reference purpose	A	B				
Scenario 5	Simulation of the country basket composed of all countries under study						
Scenario 6	Simulation of rules on minimum number of countries in basket having approved prices to set the ERP price 6A: one country 6B: half of countries	A		B			
Scenario 7	Simulation of calculation methods to set the ERP price 7A: average price			A, B			C, D

Number of Scenario	Title of Scenario	Positive Impact			Negative Impact		
		Low Impact	Moderate impact	Important Impact	Low Impact	Moderate impact	Important Impact
	7B: median price 7C:3 lowest prices 7D: lowest price						
Scenario 8	Simulation of annual price deflation in non ERP countries along with price revisions in ERP countries						
Scenario 9	Simulation of price negotiations for country using ERP as supportive criterion and weighted according to GDP/capita						
Scenario 10	Simulation of the impact of genericisation 10A1: "Southern" EU MS-brand used as reference product 10A2: "Southern" EU MS-generic drug used as reference product 10B1: "Northern" EU MS-brand used as reference product 10B2: "Northern" EU MS-generic drug used as reference product						
Scenario 11	11A: Simulation of price cuts proportional to government deficit 11B: Simulation of price cuts proportional to pharmaceutical expenditure as share of GDP				B	A	
Scenario 12	Simulation of historical price cuts						
Scenario 13	Simulation of several price cuts on a same year in Greece						
Scenario 14	Simulation of adding fixed price in Germany and decreasing fixed price set in UK						
Scenario 15	Simulation of various packaging, dosage or formulation of a drug launched in the countries						
Scenario 16	Simulation of the use of net drug prices instead of facial prices for reference purposes						
Scenario 17	Simulation of price dynamics if all countries leading to important price decreases were removed from the baskets						
Scenario 18	Simulation of the increase in the number of countries in the basket		B	A		C	

Number of Scenario	Title of Scenario	Positive Impact			Negative Impact		
		Low Impact	Moderate impact	Important Impact	Low Impact	Moderate impact	Important Impact
	18A: one basket with big EU5 18B: one basket with the big EU5 and countries with GDP per capita>€25,000 18C: one basket with all selected countries						
Scenario 19	Simulation of price of one drug available only in the hospital (19A) or in the out-patient sector (19B)	**A**			**B**		
Scenario 20	Simulation of several scenarios together -Reference price calculation based on the lowest price -Price revision set every 3 months -Drug launch sequences by ascending order of GDP/capita -Country basket: all selected countries						

8. Conclusion

This project aimed to build a theoretical ERP model including the main ERP characteristics, based on 28 EU Member States, as well as Iceland, Norway, and Switzerland. This model was used to assess the price dynamics through ERP-based systems and the impact of changes in ERP policies using several scenarios.

A DES model was thus built to simulate the evolution of the price of any given drug over time through the ERP process and to identify the main drivers of price evolution. The flexibility and adaptability of this model allowed several ERP scenarios testing.

This model showed that ERP -considered as an isolate pricing rule- led to lower drug price erosions than what could be observed in the real-life, suggesting that other pricing policies, potentially amplified by ERP, are involved in driving prices down.

The different scenarios illustrated spill-over and circular effects of ERP. Frequent price revisions, iterative price cuts, large country baskets, price calculation methods, genericisation impact and prices' sources were among the most influent parameters on the evolution of the drug price over time through ERP-based systems.

The simulations support previous studies on industry's incentives to engage into launch sequence strategy. However, the simulation model did not show any substantial price convergence over time and it remains unclear whether price divergence would be larger without ERP.

The use of ERP as a tool to set price seems an appropriate way forward for some countries as discussed in this report. Using ERP to contain pharmaceuticals expenditure is not conceptually appropriate but this study showed that it could be a very effective tool especially when a number of "high price decrease scenarios" are combined.

To the authors' knowledge, this DES model is the first comprehensive ERP published model across drug life cycle and that allows testing various policy scenarios. It represents a flexible and efficient tool for decision makers. It will help ensure a trade-off between the sustainability of the public health insurance and the pharmaceutical industry. Further researches to include parallel trade into the model could make this tool even more powerful.

Challenges to set appropriate ERP policies happen to be high and difficult to overcome in the current environment. It is likely that payers will be tempted to continue to use it as a cost containment tool as it is very effective for that purpose.

9. Appendices *(attached separately)*

9.1 Appendix 1-Country-specific Document-Pricing and Reimbursement Systems (Not published, Confidential)

9.2 Appendix 2-Literature Review Methodology

9.3 Appendix 3-Literature Review Protocol

9.4 Appendix 4-Stakeholder Consultation

9.5 Appendix 5-List of Stakeholders

9.6 Appendix 6-Stakeholders' Consultation- Template of Country Questionnaire

9.7 Appendix 7-Stakeholders' Consultation- Template of International Organization Questionnaire

9.8 Appendix 8-ERP Processes in Europe: Results from the Literature Review and Stakeholder Consultation (Not Published, Confidential)

9.9 Appendix 9-Overview of ERP Processes in Europe

9.10 Appendix 10-Presentation of Main Models Related to ERP

9.11 Appendix 11-Simulation model inputs used to assess the current price dynamics of ERP-based systems

9.12 Appendix 12-Country characteristics taken into account in the simulation model

9.13 Appendix 13-Summary of main model inputs

9.14 Appendix 14-Average drug price evolution over time for all countries weighted by country population for Scenarios 1 to 20

9.15 Appendix 15-Exchange rates variation since 2003 in all non-euro currency countries against the Euro

9.16 Appendix 16-Drugs selected for real-life scenarios

9.17 Appendix 17-Results for Real-life Scenarios (Not published, Confidential)

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