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Original Research Article

Pharmaceutical pricing in Croatia: a comparison of ordinances in 2013 versus 2009 and their potential savings to provide future guidance on potential new ordinances in Croatia

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Abstract

Introduction: Croatia has introduced a number of reforms to contain pharmaceutical expenditure whilst increasing access to new medicines. These include new regulations and new ordinances in 2013 including the pricing of new medicines and lowering the price of generics. **Aims:** Describe changes in the 2013 ordinance for new and established medicines in Croatia and the potential savings to provide future guidance. **Methods:** Descriptive review of the new ordinances for pricing and reimbursement of pharmaceuticals and calculations of potential savings from the various initiatives. **Results:** There were changes in the ordinance for the pricing of new medicines in Croatia including the order of reference priced countries. There were also changes in the pricing of biosimilars as well as comparator levels with other countries. Projections show that with the new ordinance, ambulatory care expenditure for the 54 product groups (internal reference price system) will be reduced by 9.64% (318.4 million kunas) and prices of new medicines lowered by 8 to 10% following changes in the order of referenced price countries. **Conclusion:** This paper demonstrates that changes in the reference pricing system can lead to considerable differences in overall reimbursed expenditure. In addition, European countries with smaller populations can be active with introducing a variety of measures to keep pharmaceutical expenditure under control whilst increasing access to new medicines. Further reforms will be needed to improve the quality of prescribing. It is also likely further ordinances will be needed to keep pharmaceutical expenditure under control.

Introduction

Rising pharmaceutical expenditure is causing concern among countries, with expenditure rising by more than 50% in real terms during the past decade among OECD countries (1, 2). These concerns have resulted in multiple reforms and initiatives across Europe, which includes regulations regarding prices, reimbursement and utilisation of medicines (2, 3). Initiatives for established medicines include measures to obtain low prices for generics as well as encourage their prescribing (3-9). This includes both internal reference pricing systems (IRP) and external reference pricing (ERP) (9-13), with internal reference pricing currently utilised among 20 or more EU Member States and ERP among 24 EU Member States (9, 12). Croatia is no different and has introduced a number of reforms in recent years to reduce debt levels, add new medicines to the reimbursement list and improve the quality of care (14-17). Measures include restricting medicines to second line, with follow-up by physicians

working for the Croatian Health Insurance Fund (CHIF) if abuse is suspected (18), as well as strict control of pharmaceutical company activities, with adherence enhanced through financial penalties (14, 15). In addition, regulations for lowering the prices of successive generics for a given molecule (14, 18).

However, there is a continual need to conserve resources, as well as a continuing need to encourage the reimbursement of new valued medicines, given the level of unmet need, ageing populations and continued high unemployment affecting CHIF revenues (23,24). This led to the development of a new ordinance for the pricing of both new and established medicines including biosimilars. The old ordinance was published in the Official Gazette 155/2009, and its amendment published in the Official Gazette 22/2010, while the new ordinance was published in the Official Gazette 83/2013 and its amendment in the Official Gazette 12/2014 and Official Gazette 69/2014 (19-24). There is a recognised need to evaluate the influence of the new ordinance on potential savings, and use the findings to plan further pertinent measures.

The Ordinance establishing the criteria for the inclusion of medicinal products onto the basic and supplementary Reimbursement Lists of the Croatian Health Insurance Fund (CHIF) has been enacted since 2013 (Official Gazette 83/2013) (20). The decision on accepting or rejecting new medicines for reimbursement is undertaken by the Committee for Drugs and Medicinal Products within the Administrative Council of the CHIF following a recommendation by the Commission for Drugs, which consists of 13 members who are all experts in their specific disease area.

Key criteria for assessing the value of new medicines in Croatia, and their potential prices, include improved outcomes versus current standards including improved quality-of-life and/ or reduced adverse effects, more 'user-friendly' formulations improving compliance as well as improved overall efficiency (14, 15). In addition, whether this is a new medicine where no treatment has previously existed; alternatively, a replacement treatment. There is also the potential for price reductions or price: volume agreements, including pay-backs or cross-product agreements, for new active substances with budget impact analyses requested for new medicines based on best practice and defined by the ordinance (14, 15, 17, 20).

The prices of established as well as new medicines are regulated by Ordinances including biosimilars, vaccines and small molecules (19, 20). The ordinances also describe the procedure of calculating annual drug pricing (external reference pricing - ERP) as well as the method for setting reference prices of medicines and reference price systems (internal reference pricing – IRP). ERP is a process in which the prices of medicines are compared with prices of medicines in comparable countries (Example contained in Table 3). IRP is based on the Anatomical Therapeutic Chemical (ATC) classification. This can be at ATC Level III (pharmacologic group, e.g. lipid modifying agents), Level IV (pharmacologic class e.g. HMG CoA reductase inhibitors) or Level V (individual molecule) (14, 17, 25). IRP is a process in which CHIF established the reference prices of medicines, which are the reimbursed prices (Example in Table 4). CHIF covers the reference price, with patients covering any additional costs themselves for a more expensive product out-of-pocket.

The reimbursed price on the two lists (basic and supplementary) is the ex-factory price combined with wholesale margins and other taxes up to 8.5%, which is wholesale price (WP) and tax (VAT) at 5%, as well as a pharmacy mark-up (fee) which is constant per package of medicines. Prices for non-reimbursed medicines including OTC medicines are typically determined by market demand. Prices include WP, taxes (5% and 25%) and pharmaceutical margins (up to 35%).

The Ordinances conform to the Directives of the European Commission regarding the pricing of medicines. According to these directives, each country determines the price of their medicines on the basis of a self-selected model, which must be clear and transparent, and must be implemented within set deadlines and in compliance with the directives (26). The basic list of drugs, which are fully reimbursed, and the supplementary list of drugs, with CHIF covering the reimbursed part with the patient covering the remainder, are the final results of the current procedures in 2013 (27, 28). The basic list also includes expensive medicines that are funded out of different budgets. Drug lists are constantly changing as new drugs are included, indications are revised and established medicines removed (27-29).

In Croatia, the share of public expenditures for health care is currently 6.6% of GDP (30, 31), with 14.6% spent on pharmaceuticals in 2012 (31). This is down from 17% in 2007 (31). The various reforms in recent years have resulted in similar financial expenditure on prescription medicines in 2012 compared with 2008, i.e. 3.303 billion kunas in 2012 (Euro 433million) versus 3.392 billion kunas (Euro 445million) in 2008. In addition between 2009 and 2011, 85 new medicines were added to the reimbursement list (30). Overall, 3044 packages of medicines were included in the basic drug list in 2012 and 390 drugs on supplementary list. This compares with 2047 packages of medicines in the basic list and 262 in the supplementary list in 2008.

Consequently, the principal objectives of this paper are firstly to report on the new ordinances including changes in the reference price systems and compare these with the previous the previous ordinances. Secondly, compare potential savings from the changes in the reference price system (internal reference pricing – IRP) at ATC Level III to V (current system) to just ATC Level V for comparative purposes among the 54 current reference price groups as a result of the recent reforms. Finally, suggest additional measures for consideration by CHIF in the future as CHIF strives to continue to provide comprehensive and equitable healthcare.

We are not aware of many publications that have assessed the impact of changes to their external and internal reference pricing systems, although authors have calculated potential savings through converging prices to the average (12). Consequently, we hope the findings and their implications will be of interest to the authorities in Croatia as well as other European countries that use reference pricing systems since we are aware there are some concerns with reference pricing initiatives (10, 17). We will discuss these in the context of the findings in Croatia to stimulate further debate in this growing area of interest.

Methods

This includes a narrative review of the reforms comparing the old ordinances (2009) with the new ordinances (2013) among the co-authors (principally LSB), including the regulations surrounding:

- a) Placing new medicines on the list either as replacements for existing established medicines or entirely new treatments where none have existed before. This will be compared and contrasted with the old ordinance.
- b) Placing new generic medicines onto the drug lists, as well as comparing the old and new ordinances.
- c) The model for calculating the external reference pricing (ERP) for medicines and the implications (Example in Table 3)
- d) Internal pricing using a reference price system. We will describe the model of the internal reference price system (IRP) as well as the projected potential savings based on expenditure of medicines in the various reference price groups in 2012 (Example in Table 4)

For external reference pricing, this included comparing potential savings with old and new ordinances.

The calculation of potential savings from the changes in the internal reference pricing system (IRP) for the 54 product groups are included in Box 1.

Box 1 – Calculations for potential savings from IRP among the 54 product groups as a result of the new ordinance

- a) Documenting the price of the drug unit (ATC Level V) by International non-proprietary name (INN), producer, trade name, formulation (including the number of capsules, tablets and other formulations as well as their strength) in 2012
- b) Documenting the reference prices in 2012 for each drug unit and each package in each of the reference classes based on the revised rules from the new ordinance (for unit price and price of package). This is based on the medicine with the lowest price within the referenced price group the previous year with a market share of at least 5%
- c) Deducting (a) from (b) to define potential savings per package
- d) Documenting total expenditure for each of the products in the 54 reference groups (ATC Level III to V) in 2011
- e) Multiplying the savings per package in 2012 by the 2011 consumption data to derive the overall projected expenditure for each package (c x d)
- f) Deriving the potential savings for each product group among the 54 reference groups (based on the presumption of similar expenditure in 2012 to 2011)
- f) Adding together all projected savings from (f) to derive potential savings from all 54 reference price product groups

The potential savings arising from all the changes in the ordinances will also be calculated to provide a basis for any pertinent additional future reforms. The analytic methods applied in the various situations are descriptive epidemiological methods, primarily involving a comparative analysis of pricing models of medicines under the old and new ordinances.

The quality of the data is assured by regular auditing of the CHIF database.

Suggestions for potential additional measures that CHIF could consider will be based on the considerable experiences of the co-authors.

Results

This will be divided into four sections starting with placing new medicines placed onto the reimbursed list including new generics.

A) Pricing of new medicines or new treatments including new generics

The principal difference between the old and new ordinances is the pricing of biosimilars as well as new hospital medicines (Table 1). Hospital medicines are now included where there is an added health benefit compared with existing standards as there have been problems with their pricing in the past in the implementation and finalization proceedings. The list price in the new ordinance for new active substances demonstrating additional health benefit versus existing standards is now increased to 100% of their calculated prices, up from 90% of the comparable medicine. There is a 10% patient co-payment for ambulatory care medicines but not hospital medicines (Table 1).

Table 1 - Model for placing new medicines on the drug list according to the old and new ordinances (16)

| Prices of new drugs on the lists | Old ordinance | New ordinance |
|---|---------------|---------------------|
| New active substance (% of ACP)* | 100 | 100 |
| New active substance (% of price of comparable drug) | 90 | 100 (90 reimbursed) |
| New active substance, hospital drug (% of price of comparable drug) | | 100 |
| Generic drug (% of price of previous drug) | 70 | 70 |
| Biosimilar (% of price of previous drug) | | 85 |
| Generic drug (% of price of previous drug) | 90 | 90 |
| Generic drug (% of price of previous drug) | 90 | 90 |

*ACP - average comparable price

For new medicines or new active treatments where no treatment has existed before for the particular disease, the price is calculated based on external reference pricing (Table 2) as well as a % of the Average Comparable Price (ACP) (Table 1), based on prices of similar treatments in comparable countries (Table 2).

It is envisaged the order of the countries used for external reference pricing (Table 2), alongside changes from the factors relating to retail versus wholesale prices, will affect subsequent reimbursed prices for new medicines in Croatia. This is because the average price of the package of medicines in comparable countries (without tax and margins) is translated into the unit price (in kunas) for that country and then into the price of the package of the drug that will be available in Croatia. After the translation, the ACP of the drug is calculated. The ACP is calculated as the average price of the same drug (same generic name, and the same or similar form and packaging) in the three chosen countries starting with Italy, Slovenia, and the Czech Republic, according to the new order established by the ordinance (Table 2). In cases where there is no comparative price for the new medicine in one country, then the average price of the medicine from the next country in the list of chosen countries is included and so on (Table 2)

As seen in Table 1, the price calculations for the first and subsequent generics for small molecules are similar between the old and new ordinances. The main difference is that biosimilars are now included to address this anomaly, with the price of the first biosimilar at 85% of the originator price. The inclusion of biosimilars should accelerate savings as more biosimilars are launched for existing molecules and more biologicals lose their patents given the current high prices for biological medicines (32-38).

B) Pricing of medicines under external reference pricing

The principal differences in the ordinance for the external reference pricing (ERP) of existing medicines and new medicines where no medicine has existed before is the order of the reference price countries for calculating external reference prices (Table 2).

ERP of established medicines is carried out once a year to make sure that the prices of established medicines in Croatia are not higher than the chosen European countries. ERP for established medicines used to take place the first Monday in February each year (20), but will now take place on the first Monday in March (21). If the price of the medicine in Croatia is found to be higher than the ACP price, its price is subsequently reduced to the level of the ACP.

- The sources for external pricing data are similar, i.e. official data from the countries included in the ordinance; however, there is now greater reliance on web-sources than publications (Table 2). Data sources include: Old ordinance: Italy - *Informatore Farmaceutico*; France – *Vidal*; Slovenia – *Register*; Spain - *Catalogo de Medicamentos*; Czech Republic - www.vzp.cz
- New: ordinance: Italy – www.Codifa.it; Slovenia – <http://www.jazmp.si>; Czech Republic - <http://www.sukl.cz/>; Spain – '*Catalogo de Medicamentos*' - latest electronic version, France – '*Vidal Expert*' latest electronic version. Other changes include greater interaction with the legal persons and their representatives in each country who are involved in the registration and/ or pricing of medicines during the reference pricing process

There have also been changes to some of the factors for the re-calculation from retail to wholesale prices to remove taxes and margins from the included countries and to enable comparisons based on WPs. The presented factors for the recalculation of the reference prices for the comparable countries, published table as a part of the ordinances, are included in Table 2.

Table 2 – External price regulations (17, 20)

| Description: | Old ordinance | New ordinance |
|---|---|---|
| Participants | legal persons | legal persons / their representatives |
| Prices of products (drugs) | wholesale prices | wholesale prices |
| Wholesale margins | up to the 8,5% | up to the 8,5% |
| Countries (for comparison of prices) | Italy / France / Slovenia / Spain / Czech | Italy / Slovenia / Czech / Spain / France |
| Factors of recalculation of RP* to WP** | ITA 0.685 / FR - list / SLO - WP / ES 0.693 / CZ 0,84 | ITA 0.685 / SLO - WP / CZ 0.86 / ES 0.721 / FR - list |
| Sources of prices | web-sources or publications | web-sources or publications |
| Level of comparison (% of ACP)*** | | |
| Original products (with patent protection) | 90 | 100 |
| Original products (without patent protection) | 65 | 100 |
| Generic drugs | 65 | 100 |

*RP - retail price

**WP - wholesale price

***ACP - average comparable price

Under the new ordinance, prices remain at 100% of the average comparative price (ACP) of the medicine under the various regulations for new and established medicines including generics and biosimilars (Tables 1 and 2). Consequently, the calculation of the prices of both new and established medicines under the new ordinance appears applicable and acceptable to all key stakeholder groups. This was not the case with the old ordinance, especially if Croatia was a reference price country, as under the old ordinance prices were reduced by 10% and 35% of the average comparative price (ACP), i.e. prices were at 90% if patent protected and 65% if no patent protection of the ACP (Table 2). Having said this, the order of countries for external reference pricing has changed potentially impacting on prices in Croatia along with changes in the factors involved (Table 2). In addition, the wording of the ordinances has changed (Table 2). 100% under the new ordinance for both originator and generic products enables fair market competition based on ACPs.

Table 3 provides an example of the impact of the change in the ERP policy for omeprazole, with the change in the factors for calculating ACPs based on the change in factors from retail to wholesale prices as well as changes in the order of the countries (Table 2).

Table 3 – Example of external reference pricing for established medicines (omeprazole) based on the new ordinance for calculating ACPs (2013)

| DRUG | | | | PRICES OF DRUGS (EUR / CZK) | | | PRICES OF DRUGS (KUNA) | | | EXTERNAL PRICING | | |
|----------|----------|-----------------------|------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------|---------------|-----------------------------|----------------------------|-------------------------------------|--------|
| Country | ATC code | INN | Trade name | Package of drug | Price in comparable country | | Wholesale price | | | Package of drug in Croatia | Price of package of drug in Croatia | |
| | | | | | Retail price for package | Wholesale price for package | for package | for drug unit | Average price for drug unit | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Italy | | No comparable package | | | | | 0,00 | 0,00 | 0,00 | | | |
| | | | | | | | 0,00 | 0,00 | 0,00 | | | |
| | | | | | | | 0,00 | 0,00 | 0,00 | | | |
| | | | | | | | 0,00 | 0,00 | 0,00 | | | |
| | | | | | | | 0,00 | 0,00 | 0,00 | 0,00 | | 0,00 |
| Slovenia | A02BC01 | omeprazole | ULTOP | caps. 28x40 mg | | 14,14 | 107,21 | 3,83 | | | | |
| | A02BC01 | omeprazole | ULTOP | caps. 28x40 mg | | 47,91 | 363,25 | 12,97 | | | | |
| | A02BC01 | omeprazole | ORTANOL | caps. 28x40 mg | | 14,14 | 107,21 | 3,83 | | | | |
| | A02BC01 | omeprazole | ULZOL | caps. 28x40 mg | | 10,71 | 81,20 | 2,90 | | | | |
| | | | | | | | 0,00 | 0,00 | | 5,88 caps. 28x40 | | 164,64 |
| Czech | A02BC01 | omeprazole | LOSEPRAZOL | caps. 28x40 mg | 580,97 | 499,63 | 147,86 | 5,28 | | | | |
| | A02BC01 | omeprazole | ORTANOL | caps. 28x40 mg | 563,96 | 485,01 | 143,53 | 5,13 | | | | |
| | | | | | | | 0,00 | 0,00 | 0,00 | | | |
| | | | | | | | 0,00 | 0,00 | 0,00 | 5,20 caps. 28x40 | | 145,60 |
| Spain | A02BC01 | omeprazole | BELMAZOL | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | EMEPROTON | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL A BDRUG | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL EDIGEN | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL ACTAVIS | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL NUPRAL | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL STADA | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL BEXAL | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL CINFA | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL CUV EF | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL DAVUR | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL KERN PHARMA | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL KORHISPANA | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL LAREQ | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL MABO | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL PENSA | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL RATIOPHARM | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL RIMAFAR | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL SANDOZ | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL SUMOL | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL PLACASOD | caps. 28x40 mg | 5,90 | 4,25 | 32,25 | 1,15 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL RIMAZOL | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL STADA | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL TARBIS FARMA | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL TEVAGEN | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL VIR | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | PEPTICUM | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | ULCERAL | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | A02BC01 | omeprazole | OMEPRAZOL ULCOMETION | caps. 28x40 mg | 4,64 | 3,35 | 25,36 | 0,91 | | | | |
| | | | | | | | 0,00 | 0,00 | | 0,91 caps. 28x40 | | 25,48 |
| France | | No comparable package | | | | | 0,00 | 0,00 | | | | |
| | | | | | | | 0,00 | 0,00 | | | | |
| | | | | | | | 0,00 | 0,00 | | | | |
| | | | | | | | 0,00 | 0,00 | | | | |
| | | | | | | | 0,00 | 0,00 | 0,00 | | | 0,00 |
| | | | | | | | AVERAGE COMPARABLE PRICE | | | | 111,91 | |

1 EUR = 7,581946 kn

1 CZK = 0,295927 kn

C) Internal reference pricing system

The internal reference pricing system (IRP) has been introduced since it can happen on the reimbursed list that there are the same medicines with different prices. This is because new medicines can be placed on the list which contain the same INN, same dosage and packaging but with different prices due for instance to successive generics necessarily being priced 10% lower than the previous one for reimbursement (Table 1). Similarly, new single-sourced products (ATC Level III to V) can be placed on the reimbursement list at potentially lower prices. Similar to ERP, internal reference pricing takes place once a year once ERP has been performed. If the prices of the same medicine differ, their prices are subsequently reduced to the level of the reference price or lower.

Prices of the originators are subsequently subject to internal reference pricing based on the lowest priced molecule in the class (ATC Level III to V) with a market share of 5% or more of the total market by volume. Should the authorization holder not accept the proposed price, i.e. want to keep the old price, the medicine is placed of the supplementary list with CHIF paying the reference price with patients covering any additional price themselves out-of-pocket.

To illustrate this, a comparison has been performed (Table 4) building on the methodology described in Box 1. Reference prices are determined in relation to the unit price of the drug, or at the price of the

package for the drug, or the amount of active compound in a unit form of the medicine based on similar defined daily doses (DDDs) (25). We are aware the WHO does not recommend the use of DDDs to compare prices of medicines. However, we are not aware of another appropriate comparator for determining (comparison) of prices especially if dosage forms and pack sizes vary. Determining reference prices of medicines by ATC Level III to V helps ensure similar prices are paid for the same molecule as well as for medicines that have the same or similar therapeutic effect. The reference price of a medicine requiring a prescription is determined by searching for the medicine with the lowest price within the pertinent reference group which in the previous year had a market share of at least 5% (14). We are also aware the reimbursement list may contain medicines that have not achieved a market share of 5%; however, their price cannot be used as reference price.

The reference groups (currently 54 groups) for internal reference pricing (IRP) are determined by the Committee for Medicinal Products of the Ministry of Health. If the marketing authorization holder for the medicine, or its authorized representative, accepts the proposed reference price, their medicines will be placed on the basic list of drugs. As mentioned, if the authorization holder (originator or branded generic) rejects the proposed reference price, or keeps the old price, the medicine is placed on the supplementary list of medicines and the CHIF just pays the reference price for the particular medicine. Any difference in the price is subsequently paid by the patient out-of-pocket. The authorization holder (legal persons and their representatives) may also propose a price of their medicine which is lower than the current reference price to enhance its market share.

Table 4 provides an example of the model for the internal reference price system (ATC level III to V) for the proton pump inhibitors (PPIs) in 2012.

Table 4 – Internal reference price system for the proton pump inhibitors (PPIs) -ATC levels III to V (2012)

| ATC code | INN | Trade name | Package | Price on list for drug unit (kuna) | Price on list for package (kuna) | Reference price for drug unit (kuna) | Reference price for package (kuna) |
|-------------|--------------|---------------------|----------------|------------------------------------|----------------------------------|--------------------------------------|------------------------------------|
| A02BC01 103 | omeprazole | Ulzol | caps. 28x10 mg | 1,75 | 48,96 | 1,47 | 41,15 |
| A02BC01 115 | omeprazole | Ortalox | caps. 14x10 mg | 2,24 | 31,36 | 1,47 | 20,57 |
| A02BC01 116 | omeprazole | Ortalox | caps. 28x10 mg | 2,24 | 62,72 | 1,47 | 41,15 |
| A02BC01 124 | omeprazole | Ortanol S | caps. 28x10 mg | 1,75 | 48,96 | 1,47 | 41,15 |
| A02BC01 132 | omeprazole | Ultop S | caps. 28x10 mg | 2,24 | 62,72 | 1,47 | 41,15 |
| A02BC02 101 | pantoprazole | Zipantola* | tbl. 28x20 mg | 1,47 | 41,15 | 1,47 | 41,15 |
| A02BC02 111 | pantoprazole | Zoltex | tbl. 28x20 mg | 2,24 | 62,72 | 1,47 | 41,15 |
| A02BC02 115 | pantoprazole | Apazol | tbl. 28x20 mg | 2,24 | 62,72 | 1,47 | 41,15 |
| A02BC02 121 | pantoprazole | Acipan | tbl. 28x20 mg | 1,63 | 45,60 | 1,47 | 41,15 |
| A02BC02 131 | pantoprazole | Nolpaza 20mg | tbl. 28x20 mg | 1,63 | 45,60 | 1,47 | 41,15 |
| A02BC02 133 | pantoprazole | Nolpaza 20mg | tbl. 30x20 mg | 1,63 | 48,86 | 1,47 | 44,09 |
| A02BC02 164 | pantoprazole | Controloc | tbl. 28x20 mg | 2,24 | 62,72 | 1,47 | 41,15 |
| A02BC03 101 | lanzoprazole | Lansoprazol Pliva | caps. 28x15mg | 2,12 | 59,24 | 1,47 | 41,15 |
| A02BC03 111 | lanzoprazole | Larona | caps. 28x15 mg | 2,24 | 62,72 | 1,47 | 41,15 |
| A02BC03 121 | lanzoprazole | Lazol | caps. 28x15 mg | 2,24 | 62,72 | 1,47 | 41,15 |
| A02BC03 132 | lanzoprazole | Lanzul S | caps. 28x15 mg | 2,24 | 62,72 | 1,47 | 41,15 |
| A02BC02 126 | pantoprazole | Zoprax 20 mg | tbl. 28x20 mg | 1,81 | 50,81 | 1,47 | 41,15 |
| A02BC02 141 | pantoprazole | Pantoprazol PharmaS | tbl. 28x20 mg | 1,63 | 45,72 | 1,47 | 41,15 |
| A02BC02 146 | pantoprazole | Pantoprazol Genera | tbl. 28x20 mg | 1,47 | 41,15 | 1,47 | 41,15 |

*1 EUR = 7,6 kunas

D) Potential savings with the new ordinances

Calculations undertaken before the new ordinances were implemented regarding ERP believed the new ordinances, with changes in the order of the reference price countries (Table 2), would lower prices by an average of 8 to 10%. This is less than the potential savings of 10% to 35% under the old ordinance with prices lowered by 65% to 90% of the ACP (Table 2). However, the documented price reductions under the old ordinance were seen as large and potentially restrictive to new medicines. The changes in the new ordinance to 100% of comparative prices (Table 1) are seen as more acceptable to key stakeholder groups especially if Croatia is a reference priced country.

The overall projections for potential savings are based on changes in the ERP system with the new ordinances, incorporating all medicines in the basic and supplementary list including generics and biosimilars, factors concerned with wholesale and retail prices as well as changes in the order of the reference countries (Tables 1 and 2) described in the Methodology section. This does not apply to new medicines where none has existed before to treat a given disease as these costs will be in addition. There are separate projections based on changes in the IRP system, including medicines placed in the 54 reference groups. As mentioned, IRP in Croatia is determined at ATC level III to V. Consequently, this was the principal model used to calculate potential savings for the new ordinance in the current reference groups. Potential savings were compared to just concentrating at ATC Level V when determining potential internal reference prices for comparative purposes.

Based on 2011 consumption and projected expenditure in 2012 outlined in the Methodology section, projections showed possible savings of 318.4 million kunas for CHIF for the 54 reference groups (Table 5). This represents savings of 9.64% for reimbursed drugs based on projected 2012 consumption figures. Setting the reference price of medicines (IRP) at the ATC level V rather than III to V yielded potential savings of 254.45 million kunas, i.e. 7.7% of total CHIF expenditure on ambulatory care medicines in 2012 (34). Table 5 shows projected savings for each of the 54 reference groups (ATC III to V). 2,028 packages of different medicines were included in the 54 reference price groups in 2012, forming the basis of the calculated savings.

Projected savings from the new ordinances for CHIF for medicines on the current lists will grow as more generic medicines are launched as well as more biosimilars for the same medicine and for new biological medicines losing their patents.

Table 5 – Projected savings for the 54 reference groups

| Referencing groups | | | ATC level III-V |
|--------------------|-----------|---|-----------------------|
| 1 | A02BA | H2 - receptor agoinsnts | 6,030,470.16 |
| 2 | A02BC | proton pump inhibitors | 43,641,912.50 |
| 3 | A06 | drugs for constipation | 164,915.66 |
| 4 | A07 | aminosalicylic acid and similar agents | 17,753.94 |
| 5 | A10A | inuslins | 2,561,124.80 |
| 6 | A10B | other drugs used in diabetes | 2,155,857.16 |
| 7 | B01 | antithrombotic agents | 8,503,059.07 |
| 8 | B03 | antianemic preparations | 0.00 |
| 9 | C01B | antiarrithmics | 204,514.74 |
| 10 | C01D | vasodilatators | 1,965,105.12 |
| 11 | C02 | antihypertensives | 1,584,140.45 |
| 12 | C03 | diuretics | 1,371,952.28 |
| 13 | C07 | beta blocking agents | 3,092,925.10 |
| 14 | C08 | calcium channel blockers | 3,602,841.53 |
| 15 | C09A | ACE - inhibitors | 26,686,891.22 |
| 16 | C09B | ACE - inhibitors, combinations | 29,414,074.57 |
| 17 | C09C | angiotensin II antagonists | 3,019,977.35 |
| 18 | C09D | angiotensin II antagonists, combinations | 2,183,246.03 |
| 19 | C10 | lipid modifyng agents | 69,885,918.43 |
| 20 | D01 (A01) | stomatological preparations, antimycotics | 1,071,092.01 |
| 21 | D06 | antibiotics and chemoterapeutics - dermatological use | 52,965.15 |
| 22 | D07 | corticosteroids, dermatological preprations | 1,819,225.95 |
| 23 | G01 | gynecological antiinfectives and antiseptics | 243,679.98 |
| 24 | G03 | sexhormones and other | 0.00 |
| 25 | G04B | urologicals | 199,072.36 |
| 26 | G04C | drugs used in benign prostatic hypertrophy | 6,640,684.37 |
| 27 | H02 | corticosteroids for systemic use | 0.00 |
| 28 | H03 | thyroid therapy | 214,972.65 |
| 29 | J01C | beta-lactam antibacterials, penicillins | 12,289,463.46 |
| 30 | J01D | other beta-lactam antibacterials | 4,030,062.84 |
| 31 | J01E | sulfonamides and trimethoprim | 0.00 |
| 32 | J01F | macrolides | 12,324,857.29 |
| 33 | J01M | quinolone antibacterials | 564,253.59 |
| 34 | J02 | antimycotics for system use | 240,049.71 |
| 35 | L02B | hormone antagonists | 14,554,448.15 |
| 36 | L04A | immunosupressants | 950,995.74 |
| 37 | M01 | antirheumatics | 1,179.48 |
| 38 | M05 | drugs for treatment of bone diseases | 646,884.70 |
| 39 | N02A | analgesics | 8,171,763.49 |
| 40 | N02C | antimigraine preparations | 17,267.31 |
| 41 | N03 | antiepileptics | 1,661,959.86 |
| 42 | N04 | anti-parkinsonian drugs | 0.00 |
| 43 | N05A | antipsyhotics | 22,874,399.11 |
| 44 | N05B | anxiolytics | 1,039,620.12 |
| 45 | N05C | hypnotics and sedatives | 1,064,121.74 |
| 46 | N06 | antidepressives | 14,413,394.91 |
| 47 | N07 | other nervous system drugs | 1,952,430.72 |
| 48 | R01 | nasal preparations | 0.00 |
| 49 | R03A | adrenergics, inhalants | 8,549.64 |
| 50 | R05 | cough preparations | 963,762.10 |
| 51 | R06 | antihistamines for systemic use | 1,253,949.20 |
| 52 | S01B | antiinflammatory agents | 113,711.25 |
| 53 | S01E | antiglaucoma preparations and other | 334,310.95 |
| 54 | V06 | nutrients | 2,598,341.64 |
| Total: | | | 318,398,149.58 |

*1 EUR = 7,6 kunas

Discussion

Different European countries have used different models and approaches for determining the price of new and established medicines including generics. This includes both internal and external reference pricing, with differences in external reference pricing in terms of the number of countries chosen, their sequence, methods for establishing reference prices as well as time frames for their review (10, 17, 39-42).

This paper demonstrates that changes in the reference pricing system can lead to considerable differences in overall reimbursed expenditure. In addition, European countries with smaller populations, i.e. 4.27 million inhabitants in 2012 year, can be active with introducing a variety of measures to help control pharmaceutical expenditure whilst increasing access to new medicines. This includes changes in reference price systems and the pricing of medicines losing their patent.

The calculated savings from the changes in the ERP system, including the order of chosen countries (Table 2), were estimated at an average of 8 to 10%. The calculated savings from the changes in the IRP systems were estimated at 318.4 million kunas among the 54 reference groups (Table 5), i.e. 9.64% of reimbursed drug expenditure in 2012, reduced to 254.45 million kunas, i.e. 7.7% of total CHIF expenditure, if the IRP is just based on ATC Level V (34). As a result, endorsing CHIF's decision to use ATC Level III to V for internal reference pricing and the development of the new ordinance. This provides guidance to other countries using reference pricing particularly once generics become available in a class to help control pharmaceutical expenditure. This difference is also a potential way to address concerns regarding the lack of transparency in the prices of reference priced countries.

We are aware of a number of controversies surrounding external reference pricing. This includes the fact that prices of medicines in countries may not reflect actual prices (10, 12, 43, 44). In addition, pharmaceutical companies may preferentially launch their new medicines initially in traditionally higher price countries thereby potentially increasing the prices in the remaining countries that directly or indirectly reference them (12). Thirdly, price reductions in one reference country may not automatically apply to other reference countries unless there are mechanisms to rapidly assess this. As a result, reduce potential savings (12). Finally, pharmaceutical companies could potentially withhold launching their new medicines in lower priced countries as this may adversely affect overall profitability. However, the initial reforms in Croatia resulted in 85 new medicines being added to the reimbursement list between 2009 and 2011 coupled with a deficit reduction (14, 30). This was up from 47 new medicines between July 2009 and 2010, with 13 new medicines added to the list of expensive hospital products (15). In addition, we believe the changes in the new ordinance (Tables 1 and 2) should be beneficial to all key stakeholder groups with prices of both patented and multiple sourced medicines remaining at 100% as opposed to 65% to 90% of ACP. Whilst potentially resulting in lower savings for CHIF, this should enhance the attractiveness of this ordinance to key stakeholder groups, addressing some of the concerns that companies will not launch their new medicines in lower priced countries. The new ordinances with no automatic price reductions for new medicines (Tables 1 and 2) should also be beneficial to pharmaceutical companies enhancing their desire to launch new medicines in Croatia. As mentioned, lower prices for established medicines including generics and biosimilars should be beneficial to patients, reducing their co-payment levels as well as creating headroom for new medicines.

We are also aware that there are controversies surrounding the selection of countries for external reference pricing, although most countries appear to reference those of similar income levels (10). In this respect, we believe the change in the order of countries brings Croatia in line with other European countries, i.e. higher income countries tend to include higher income countries in their basket whereas lower income countries tend to reference lower income countries (10). The use of 5 countries is also similar to other European countries, who tend to have less than 10 countries in their reference baskets (10). Wholesale prices should also be more uniform than pharmacy prices as there can be considerable differences in pharmacy remuneration and taxes between countries (10). As a result, endorsing the new approach (Tables 1 and 2).

We are aware that some European countries review their prices more regularly than Croatia to improve transparency (9, 11). Applying this approach in Croatia could potentially lead to greater

savings than those achieved by the recent changes in the ordinances (Tables 1, 2, and 5). However, instigating a greater number of internal and external pricing reviews would need new procedures and workflows, a consensus in how this can be achieved. In addition, an assessment of the implications for all key stakeholder groups including wholesalers, pharmacies, marketing authorisation holders and others. Alongside this, the necessity to have transparent information systems that will continually monitor prices of medicines in the external reference price countries as well as possible changes to legal entities. The increased costs would impact on the extent of any potential savings. Having said this, this possibility should not be discarded if further savings are needed in Croatia in the future.

Finally, we are aware that the new ordinance has not discussed potential initiatives to improve the quality of prescribing apart from prescribing restrictions for certain medicines, e.g. angiotensin receptor blockers and curbing pharmaceutical company marketing activities (14, 18). In addition, the instigation of ePrescribing from January 2011 making medicines more accessible without patients visiting their physician. Possible measures could include initiatives to reduce adverse drug reactions (ADRs) and drug interactions including decision support systems in conjunction with eprescribing (45, 46). Treating ADRs can be costly to health authorities as well as adversely affecting the health of patients. Published studies have shown that ADRs add to the costs of healthcare through increasing hospital admissions and other costs (47-49). For example, the average treatment costs in Germany were estimated at approximately €2250/ ADR, equating to €434million per year (50), with the cost of drug-related morbidity and mortality exceeding US\$177.4bn in the US in 2000 (51). This is despite the proclaimed goal of the authorities in Croatia to introduce and implement for instance external evaluation of the quality of health care institutions (31).

The strength of these findings are based on the fact that the ordinances and findings are based on CHIF data, which is regularly audited. The weakness is the fact that these are projections. We will continue to monitor the situation and provide feedback to CHIF if further ordinances are needed.

Potential ways forward in addition to potential price cuts to help Croatia stay within agreed pharmaceutical expenditure (52) could include greater education of patients concerning the medicines they receive. As a result, reduce unnecessary requests for medicines as well as improve compliance, which is a concern in patients with chronic asymptomatic diseases (53, 54). Other potential initiatives could include the instigation of active regional drugs and therapeutic committees deciding which medicines to use to treat common diseases in ambulatory care, building on the current reimbursement list. This is because there are concerns with the evidence base of the medicines included in the current reimbursement list (55), as well as typically physicians only knowing a relatively limited number of medicines well. This was the philosophy of the Stockholm Metropolitan Healthcare Region in Sweden where there has been a tradition of advocating "each recommended medicine should be of high value to the patient" (56, 57). Since 2000, approximately 200 medicines have been selected for common diseases in ambulatory care (56). Respected specialists, working jointly with clinical pharmacologists, pharmacists and general practitioners in over 20 expert groups, suggest which medicines should be selected and included in the 'Wise list' (56, 58), which is then widely communicated and disseminated throughout Stockholm (56, 57). Physician adherence to the voluntary 'Wise List' has increased during the past 10 years, now reaching 87% of all prescriptions, enhanced by physician trust in the 'Wise List' with its robust methodologies (56, 58). The 'Wise List' is now being translated into other languages to provide a stimulus to introducing such initiatives (59).

Concurrent with this, there is also likely to be increasing scrutiny over the value of new medicines where there is currently no existing treatment in Croatia for comparative purposes. This recognises the appreciable number of new medicines in development, especially new biological medicines which are currently often priced at between US\$100,000 - US\$400,000 (Euro74,000 – 296,000) per patient per course or per year (2, 35, 36, 38, 60-62).

Conclusion

In conclusion, we have described the similarities and changes to the ordinance in Croatia for both new and established medicines including generics and biosimilars and the implications. In addition, the implications for savings through re-ordering the list of reference priced countries (ERP) as well as the subsequent implications for savings with IRP at ATC Level III to V versus ATC Level V alone. We hope the findings will be of interest to other European countries. In addition, demonstrate that

European countries with smaller populations can be active with introducing a variety of measures when needed. This is in the best interests of all key stakeholder groups.

Conflicts and acknowledgements

There are no conflicts of interest from any author. However, one author (LSB) is employed by CHIF and one author by the Ministry of Health in Croatia (MB).

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Author contributions

All authors approved the final version of the paper

- LSB was the principal instigator of the paper, provided input regarding ongoing reforms in Croatia, was involved in the calculations of potential savings, wrote the first draft and critiqued subsequent drafts
- BBG critiqued the first draft based on his experience across countries, principally wrote the second and subsequent drafts and submitted the final approved paper
- MB was heavily involved in the study design, provided input into ongoing reforms in Croatia, help produce the first draft and critiqued subsequent drafts
- MS was principally involved with undertaking the calculations to ascertain potential savings from the different ordinances
- H-YK and WB helped critique subsequent drafts based on their experiences
- TT was involved with the study design as well as critiqued the first and subsequent drafts

Glossary

ACP – average comparable price

ADR - adverse drug reactions

ATC - The Anatomical Therapeutic Chemical classification system

CHIF – Croatian Health Insurance Fund

DDD - defined daily dose

ERP – external reference pricing

IRP – internal reference pricing

PPI – proton pump inhibitors

RP – retail price

WP – wholesale price

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