What lessons can be learned from the launch of generic clopidogrel?

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Abstract

Introduction and study objectives: Resource pressures will continue to grow. Consequently, health authorities and health insurance agencies need to take full advantage of generics availability in order to continue funding comprehensive healthcare particularly in Europe. Generic clopidogrel provides such an opportunity in view of appreciable worldwide sales of the originator. However, early formulations contained different salts and only limited indications. Consequently, there is a need to assess responses by the authorities to the early availability of generic clopidogrel including potential reasons preventing them from taking full advantage of the situation. In addition, it is necessary to determine the extent of price reductions obtained in practice to guide future activities.

Method: Feedback from health authorities and health insurance personnel involved with the reforms surrounding generic clopidogrel was principally used to assess authority responses as there is limited information in the public domain. Abu Dhabi has been included as a representative of the Middle East since it has introduced compulsory international non-proprietary name (INN) prescribing except for limited situations. Generic clopidogrel is not one of these – providing direct to other health authorities alongside, e.g. Lithuania and Sweden.

Results: Authorities from across Australia, Europe and the Middle East typically adopted a pragmatic approach to the availability of generic clopidogrel to enhance its prescribing and dispensing once approved by regulatory agencies such as EMA. This included guidance to enhance its utilisation such as academic publications, co-payment incentives and compulsory INN prescribing. However, this was not always possible with challenges to the availability of generics in some countries. Again, there was appreciable variation in the price reductions for generic clopidogrel versus the originator.

Conclusion: Authorities can take full advantage of the early availability of generics despite different formulations and indications. Pharmaceutical companies need to accept this in order to help fund new premium price products as resource pressures grow.

Keywords: clopidogrel, demand measures, generics, pricing

Introduction

There is increasing focus on pharmaceutical expenditure globally [1], driven by factors including changing demographics and the continued launch of new premium priced medicines [1-7]. This has stimulated a number of initiatives surrounding generics, with European countries learning from each other as they continually search for additional measures to further enhance prescribing efficiency [1, 3, 4, 6, 7]. Initiatives include measures to enhance the utilisation of generics versus originators and patent protected products in the class or related class, as well as measures to obtain low prices for generics [1, 3, 4, 6-8]. This includes generic clopidogrel, with global sales of the originator at US$9.8 billion in 2009 and US$9.7 billion in 2010 [9, 10]. However, there have been concerns with different salts and indications between the originator and early generic clopidogrel formulations, which could reduce potential health authority and health insurance agency savings from the availability of generic clopidogrel. In addition in the US, the originator manufacturer also instigated a range of activities to delay the entry of generic clopidogrel. These included a recent successful and prolonged legal battle against a Canadian generics manufacturer [11, 12].

These issues regarding generic clopidogrel have arisen because manufacturers have been able to address the technicalities of PLAVIX’s European patent protection early by producing clopidogrel in a different salt, such as the besylate salt, and initially, only launching for secondary prevention of atherosclerotic events post myocardial infarction or post ischaemic stroke, i.e. without the acute coronary syndrome (ACS) indication [11, 13, 14].

The Swiss generics company Acino has been able to market its generic clopidogrel in Germany since August 2008. By the end of the 2008, Acino’s generic clopidogrel accounted for approximately one quarter of total clopidogrel utilisation [13, 14]. Other generics versions were also launched in Austria in 2008. However, it was not until mid 2009 that EMA was able to approve

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various generic clopidogrel preparations through its centralised procedure [11, 13, 14]. This included more than 20 generic clopidogrel products, which contained the besilate and hydrogen sulphate salts, of which eight were approved for both indications, i.e. both secondary prevention and ACS indications [15]. However, in the UK for instance, initial generics typically only included the secondary prevention indication in their submissions [15, 16].

Health authorities may face similar issues to drug licensing authorities when considering reimbursement and/or recommending the prescribing of generic clopidogrel versus the originator potentially impacting on outcomes. These included whether changing the salt would alter the rate of absorption, toxicity and stability of the active drug. In addition, efficacy questions were raised by the fact that bioequivalence studies measured only the parent compound or inactive metabolite rather than the low and transient concentrations of the active metabolite, present only briefly after dosing, as well as possible concerns with inter-patient variability [17-22]. There have also been concerns among some authorities that any putative interaction between clopidogrel and proton pump inhibitors will be less well known initially for the generic salts. These concerns were in addition to patent issues in each European country, the latter leading to widely different dates when generics become available for prescribing [3, 4]. Additionally, there have been issues regarding the functional integrity of CYP2C19 in patients as this could potentially affect the availability of the clopidogrel and hence outcomes in practice [23, 24]. As such, personalised medicine using tailored individualised antiplatelet treatment based on pharmacogenetic testing could be helpful in identifying which patients should be treated with clopidogrel and which with newer drugs such as prasugrel and ticagrelor. However, other studies have questioned this [25-29]. In any event, this should not impact on the debate of whether generic or originator clopidogrel should be prescribed. Of potential greater importance is the widely different timescales that currently exist among European countries when authorising reimbursement for generics [13, 30].

The situation for health authorities and health insurance agencies was further complicated by the EMA recall in March 2010 of clopidogrel besylate produced by Glochm Industry Ltd’s manufacturing facility in India [31-34]. The medicines concerned included Clopidogrel I A Pharma, Clopidogrel Acino, Clopidogrel Acino Pharma, Clopidogrel Acino Pharma GmbH, Clopidogrel Hexal, Clopidogrel Ratiopharm, Clopidogrel Ratiopharm GmbH and Clopidogrel Sandoz. The marketing authorisation holder of all these products was Acino Pharma GmbH [31-34], which held the market authorisation for the majority of early generics formulations. However, Acino and other companies have been able to source generic clopidogrel from other companies to overcome possible supply problems, with multiple companies and formulations now typically available across Europe. The originator manufacturer tried to take advantage of these recalls through pointing out the known quality of Plavix [35]. The impact of this approach though was reduced in reality by EMA approval of a number of generic clopidogrel formulations from different manufacturers. In addition, European health authorities and health insurance companies are continually seeking ways to fund new premium priced drugs and increased drug volumes from ageing populations within finite resources through encouraging greater generics utilisation, Table 1 below as well as references 1 and 36 contain examples of different authority approaches across Europe to enhance generics utilisation with similar approaches among managed care organisations in the US [1-4, 5-8, 36].

Consequently, the principal objective of this paper is to document health authority and health insurance agency responses to take advantage of the early availability of generic clopidogrel products. Secondly, to assess potential reasons preventing health

| Table 1: 4E methodology of demand-side initiatives across Europe [1, 3, 4, 6-8, 36-42, 45] |
|---------------------------------|----------------------------------|
| **4E methodology** | **Definition and examples** |
| **Education** | Programmes that influence prescribing through dissemination of material as well as monitoring and benchmark activities:  
- Distribution of printed guidelines and guidance including essential drug lists such as the ‘Wise List’ in Stockholm, Sweden  
- Academic detailing on a one-to-one basis or in groups  
- Monitoring of prescribing against agreed guidance coupled with educational feedback where pertinent  
- Encouraging international non-proprietary name (INN) prescribing through educational activities, monitoring, benchmarking and follow-up, e.g. UK  |
| **Engineering** | Organisational or managerial interventions:  
- Prescribing targets; quality targets  
- Disease management programmes  
- Agreed generics substitution rates in community pharmacies  
- Price: volume agreements  |
| **Economics** | Financial interventions (positive and negative):  
- Devolved budgets to physicians combined with financial incentives for staying within devolved budgets  
- Additional patient co-payments for a more expensive drug than the current drug for the molecule or class  
- Physician financial incentives for achieving agreed prescribing targets – generics versus originators and generics versus patent protected products in a class or related class  |
| **Enforcement** | Regulations including those enforced by law:  
- Prescribing restrictions, e.g. for atorvas-tatin in Austria and Norway as well as sartans in Austria, Croatia and Sweden  
- Mandatory generics substitution, e.g. Sweden – apart from a limited number of situations  
- Mandatory INN prescribing, e.g. Abu Dhabi and Lithuania – apart from agreed situations  |
authors and health insurance agencies from taking full advantage of the early availability of generic clopidogrel, and potential ways to address this in the future. Finally, to determine the extent of price reductions that have been obtained by a range of countries for generic clopidogrel versus pre-patent loss originator prices in the months following generic availability. This aims to provide knowledge of how the future availability of generics in high expenditure areas can be accelerated, combined with measures to enhance their rapid uptake versus originators, to rapidly release valuable resources.

Method
We first performed a literature review of English language papers in PubMed, MEDLINE and Embase between 2005 and April 2011 using the keywords 'generic clopidogrel'. But because this resulted in only a limited number of publications, e.g. only seven relevant English language papers were cited in PubMed, the literature search was supplemented by additional information, papers and web-based articles known to the many co-authors from health authorities, health insurance agencies and their advisers from across Australia, Europe and the Middle East regarding generic clopidogrel. This information was subsequently re-confirmed with each co-author by the lead co-author Dr Brian Godman to ensure the accuracy of the data provided, hence its robustness. This is an accepted technique where there is limited information publically available to achieve study aims [2-4, 6, 7, 37-42]. No attempt was made to review the quality of the published studies using the methodology of the Cochrane Collaboration [43] in view of the paucity of peer-reviewed published studies.

Reimbursed prices for generic clopidogrel were either provided directly from the co-authors from their own internal sources based on the 75 mg tablet [Personal communications from: Mr Iain Bishop, Mr Thomas Burkhardt, Dr Jurij Furst, Dr Kristina Garuoliene, Ms Hanna Koskinen, Mr Ott Latus, Dr Catherine Sermet, Mr Peter Sköld, Professor Ulrich Schwabe, Dr Agnes Vitry]; alternatively from administrative databases [Republic of Serbia’s Health Insurance Fund database, Ms Marija Kalaba]. The findings were again validated with pertinent co-authors to ensure accuracy. Data from administrative databases included reimbursed expenditure/defined daily dose (DDD)–with DDDs defined as ‘the average maintenance dose of the drug when used on its major indication in adults’ [44]–for both the originator and generics. This approach has been successfully used in previous publications when reviewing the impact of ongoing reforms to reduce generic prices versus originators to enhance future prescribing efficiency in Europe [2-4, 6, 7, 37-40]. The countries reviewed were selected based on their different demographics, financial base for the healthcare system (taxation or insurance based) and population size to enable comprehensive comparisons of payer activities as well as reimbursed prices to provide examples to others. In addition in some countries, generic clopidogrel has only recently been reimbursed, see Table 2.

The demand-side measures initiated in each selected country to enhance the utilisation of generic clopidogrel have been taken from published sources supplemented with additional information from the co-authors. The latter approach providing

<table>
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<th>Country</th>
<th>Health authority and health insurance responses to enhance the prescribing and dispensing of generic clopidogrel where possible</th>
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<tr>
<td>Abu Dhabi</td>
<td>Generic clopidogrel was reimbursed in January 2011. Demand-side measures to increase the utilisation of generic clopidogrel include compulsory INN prescribing (Enforcement). However, community pharmacists are currently fully reimbursed for any formulation dispensed (originator or generic) and patients do not have to cover the additional costs themselves for a more expensive product than the cheapest molecule, i.e. no reference pricing for the molecule unlike most European countries. These issues are now being addressed through the instigation of pharmacy benefit management and other activities.</td>
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| Austria    | Licensing authorities – activities  
- The first generic was Clopidogrel Winthrop (16 July 2008). On 28 July 2009, several other formulations were authorised including Clopidogrel 1A Pharma, Clopidogrel Acino, Clopidogrel Hexal, Clopidogrel Ratiopharm, Clopidogrel Teva and Grepid. Currently, there are over 30 branded generics available in Austria.  
- The authorities wrote a public letter in response to the Austrian Society of Cardiology, who had suggested to physicians that they should not prescribe generic clopidogrel as it may not work in all indications, especially the stent-indication, due to different salts. The letter from the authorities stated that there is no difference in efficacy or safety between the various salts, and even if there are some patent issues preventing all indications being listed, this is not due to safety and efficacy issues. This was followed by a pharmacological publication in 2010 elaborating why there is no reason for concern, which was subsequently published through joint activities with health insurance agencies in several medical and pharmaceutical papers as well as in all nine federal -regional health insurance newspapers. The Austrian Society of Cardiology subsequently indicated they better understood the salt-issue, and the article helped to allay their fears. |
|            | Health Insurance activities  
Activities to enhance generics prescribing include:  
- Education - Quarterly publications to health insurance physicians highlighting the current cheapest branded generic for the molecule. In addition, new IT systems available also highlighting cheapest generic.  
- Engineering - Listing generic clopidogrel in the ‘green box’, i.e. no restrictions versus ‘yellow’ box for Plavix. |

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<th>Country</th>
<th>Health authority and health insurance responses to enhance the prescribing and dispensing of generic clopidogrel where possible</th>
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| Croatia | Generic clopidogrel is reimbursed and prescribed for secondary prevention (post bypass surgery) and for patients with Acute Coronary Syndrome (ACS), with access to patients’ history to check prescribing if needed. The first generic clopidogrel was reimbursed in November 2006. There are currently five generics manufacturers (branded generics) with Plavix now on the reimbursement list following price cuts by Sanofi-Aventis. Demand-side measures include:  
  - Economics - Reference pricing for the molecule, with the Croatian Institute for Health Insurance only covering cost of the lowest priced generic, with patients covering the additional costs for a more expensive product. |
| Denmark | There is currently substitution of originator clopidogrel in Denmark to enhance the prescribing and dispensing of generic clopidogrel, with a number of generic versions now available (first one reimbursed in August 2009). There are currently no reported issues to adversely affect the dispensing of generic clopidogrel. |
| England | Primary Care Trusts in England typically took a pragmatic approach to the availability of generic clopidogrel in view of current sales and envisaged savings. This was typically endorsed by both specialists and General Practitioners despite initial concerns by the National Prescribing Centre. Demand-side measures include:  
  - Education - Benchmarking, formularies, IT support systems and academic detailing (where necessary) to continue high INN prescribing rates including clopidogrel.  
  - Engineering - Prescribing targets where necessary to enhance the prescribing of generic clopidogrel.  
  - Economics - Financial incentives (where necessary) to enhance the prescribing of generic clopidogrel. |
| Estonia | Generic clopidogrel was reimbursed on 1 January 2010, although generic versions were available before this helping to drive down the price of the originator. Demand-side measures to enhance generics prescribing include:  
  - Education - Health Insurance Fund provides information to physicians to enhance their prescribing efficiency where concerns.  
  - Economics - Patients have to cover the costs themselves for a more expensive product than the reference priced molecule.  
  - Enforcement - Compulsory INN prescribing in Estonia. Physicians can prescribe the originator product if they believe it is medically relevant; however, they have to provide an explanation in the medical records (difficult for generic clopidogrel). |
| France | Generic clopidogrel was first reimbursed in September 2009. This was clopidogrel hydrogenosulfate alongside Plavix and clopidogrel Winthrop. Currently, there are over 25 different manufacturers supplying generic clopidogrel. Activities to enhance prescribing of generic clopidogrel to address concerns particularly from cardiologists arguing in *La lettre du Cardiologue*, a newsletter for them, that only Plavix should be prescribed because of the lack of studies on the bioavailability of different clopidogrel include:  
  - Engineering - The national agreement for pharmacists in 2010 included a substitution target of 75% to be reached on 31 December 2010 (coming into force on 23 April 2010). This may have been aided by an article in Prescrire (Drug Information Journal in France) highly critical of the official position from the French Agency for the Safety of Health Products (Agence française de sécurité sanitaire des produits de santé), that the ‘generics of Plavix may not be prescribed for all principal indications ’ and indicating that it sees no reason why generic clopidogrel should be treated differently from other generics, i.e. the pharmacists should have the right to substitute for all indications. In addition, Teva complaining of unfair practices by the authorities.  
  - Economics - Financial incentives for patients to accept substitution as well as regular reminders.  
  - Other measures (CAPD) involving clopidogrel to enhance overall prescribing efficiency include a target prescribing indicator that 85% of patients treated with platelet aggregation inhibitors (all drugs included in class ATC B01 AC + pravadual) should be treated with low dose aspirin (Engineering). |

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### Table 2: (Continued)

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<th>Country</th>
<th>Health authority and health insurance responses to enhance the prescribing and dispensing of generic clopidogrel where possible</th>
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| Finland | The first generic clopidogrel received reimbursement status on 1st December 2009. There were no supply issues when a number of generic versions were withdrawn from the market as additional generic versions became available to cover the shortfall. Consequently, no additional activities from the Social Health Insurance to re-assure physicians and patients regarding generic clopidogrel. Demand-side measures:  
  - Economics and Enforcement - There appeared to be no concerns with substitution with the cheapest product mandatory unless forbidden by the physician or patients prepared to pay the additional costs for a more expensive product themselves (Economics) - not generally seen in practice. |
| Germany | Germany was one of the first Western European countries where generic clopidogrel was launched and reimbursed. The differences in the salt and indications between the generics and the originator were typically dismissed by physicians due to financial incentives/penalties in the system despite the originator manufacturer trying to make a big issue of both issues. Demand-side measures to enhance the prescribing and dispensing of generic clopidogrel:  
  - Education - Letter to physicians, articles in magazines, encouraging the prescribing of generic clopidogrel.  
  - Engineering - Rebate negotiations between manufacturers and sickness funds.  
  - Economic - Budgets linked with financial incentives and penalties related to prescribing and budget targets. |
| Lithuania | Generic clopidogrel was reimbursed in the last quarter of 2009. Demand-side measures include:  
  - Economics - Community pharmacists are obliged to stock the cheapest generics with financial penalties if they do not comply.  
  - Enforcement - INN prescribing mandatory unless physicians receive prior approval from the Hospital or Polyclinic Therapeutic Committee (does not apply to generic clopidogrel). The originator has reduced its prices to compete. |
| Norway | Generic clopidogrel (Clopidogrel Mylan) was first accepted for reimbursement 1 December 2009, with sales from January 2010 as the Norwegian Medicines Agency (Statens legemiddelverk, NoMA) considered the different salts and indications substitutable. However, following activities by the originator company challenging the patent and indications, generic clopidogrel was removed from the reimbursement list from 1 October 2010. Since then, generic clopidogrel (Clopidogrel Actavis) has received market authorisation with the reimbursed indication approved, and accepted for reimbursement from 1 March 2011. |
| Poland | The first generic clopidogrel was launched in 2008, with no issues since then. Currently six generics manufacturers make their formulations available (June 2011). Prescribing of generic clopidogrel is enhanced by reference pricing for the molecule, with patients covering the additional costs for a more expensive product (Economics) in addition to a 50% co-payment. |
| Portugal | The first generic clopidogrel was approved by Infarmed in April 2009 and reimbursed in December 2009 (69% reimbursement rate). Clopidogrel was subsequently introduced into the Portuguese reference price system (internal reference price) in January 2010. Certain formulations of generic Clopidogrel were withdrawn in 2010 due to concerns with manufacturing (March 2010). There are also cases where the originator manufacturer filed lawsuits against some generics companies leading to their quick withdrawal following the court decision. In March 2010, Infarmed published a document stating that by a decision of the Administrative Court there is temporary suspension of 11 formulations of generic clopidogrel: Clopidogrel Apilif, Clopidogrel Atlabinco, Clopidogrel Farmoz, Clopidogrel Hemopass, Clopidogrel Jaba, Clopidogrel Ketapi, Clopidogrel Mepha, Clopidogrel Placir, Clopidogrel ToLife, Clopidogrel Vasagrin and Clopidogrel Vastec. Other formulations were still reimbursed. On 26th March 2010, Infarmed informed key stakeholders that by decision of the Administrative Court of Lisbon, there is temporary suspension the marketing authorisation of Clopidogrel Tetrafarma, 75 mg. Again, this decision did not apply to other marketed medicines containing clopidogrel. |
| Scotland | In Scotland, there was a pragmatic approach with Area Drugs and Therapeutics Committees recommending prescribing of generic clopidogrel rather than Plavix. Again, the prescribing of generic clopidogrel is enhanced by high INN prescribing rates in Scotland (Education) coupled with regular monitoring of prescribing/academic detailing (Education) and financial incentives for General Practitioners (Economics). |

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most data in view of, as stated, limited available information in the public domain. Demand-side activities were again checked with pertinent co-authors to ensure the accuracy of the information provided. The various demand-side measures were subsequently collated using the 4E methodology, i.e. education, engineering, economics and enforcement, to simplify comparisons between countries, see Table 1. This approach has been successfully used in other settings to compare and contrast the influence of different demand-side interventions in practice [3, 4, 6, 38-40].
Results
Most health authorities and insurers have adopted a pragmatic approach towards differences in the salt and indications between the generic and the originator to enhance the prescribing of generic clopidogrel, see Table 2; with examples of pragmatic approaches documented in Table 3. However, this has not always been possible. For example, activities in Norway, Portugal and Slovenia have resulted in all or some versions of generic clopidogrel being removed from the marketplace for a period of time, see Table 2.

Table 3: Examples of pragmatic approaches towards the availability of generic clopidogrel [2, 7, 8, 16, 37, 38, 41, 42, 47-50]

<table>
<thead>
<tr>
<th>Country</th>
<th>Example of pragmatic approaches</th>
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<tbody>
<tr>
<td>Abu Dhabi</td>
<td>Compulsory INN prescribing with no exception for generic clopidogrel.</td>
</tr>
<tr>
<td>France</td>
<td>Seventy-five per cent substitution target for generic clopidogrel.</td>
</tr>
<tr>
<td>Lithuania</td>
<td>Based on the data provided by EMA and others, no problem if clopidogrel is prescribed by compulsory INN, i.e. does not warrant exemption from compulsory INN prescribing unlike a minority of other situations.</td>
</tr>
<tr>
<td>Netherlands</td>
<td>The Royal Dutch Society for the promotion of pharmacy, <em>De Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie</em>, stated that the prescribing of generic clopidogrel for the licensed indications for Plavix can be justified despite different salts and different indications from the originator.</td>
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| Northern Ireland | • Stated that ‘As all clopidogrel preparations are deemed to be bioequivalent, the Northern Ireland Medicines Management Forum recommends that prescribers should continue to prescribe generically for all indications in both primary and secondary care’.

• This arose because the authorities believed that since EU and UK licensing authorities were satisfied that available generic clopidogrel products are bioequivalent to the reference product, generic clopidogrel products should not differ significantly in terms of efficacy and safety from the originator. As a result, originator and generic clopidogrel preparations should be considered therapeutically equivalent.

• Alongside this, following instigation of recent supply side reforms in the UK leading to lower prices for generics, i.e. generic clopidogrel was already over 90% below originator prices in December 2010, the authorities believed National Health Service healthcare professionals have ‘a duty to make the best use of public resources; cost as well as clinical suitability and product quality must be considered when choosing appropriate preparations’.

Scotland | The advice from one of the leading health boards in Scotland, the Greater Glasgow Area Drugs and Therapeutics Committee, was that since bioequivalence had been proven, the risks from prescribing as yet unlicensed indications were ‘negligible’, and physicians should go ahead and prescribe generic clopidogrel.

Sweden | The Medicines Product Agency, Läkemedelsverket, decided ahead of generics availability that the originator could be substituted with the different generic salts, with compulsory generics substitution already in place in Sweden apart from a minority of situations.

Table 4: Reimbursed prices for generic clopidogrel among countries in April to July 2011

<table>
<thead>
<tr>
<th>Country</th>
<th>75 mg pack of clopidogrel (DDD = 75 mg)</th>
<th>Reimbursed/dispensed prices for 75 mg April to July 2011</th>
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<tr>
<td>Australia</td>
<td>28 × 75 mg</td>
<td>AUS$ 70.30 (Euros 52.99 – Euros 1.89/DDD) –12.5% below pre-patent loss prices. Co-payment (AUS$ 34.20) for general patients, AUS$ 5.60 for concessional patients</td>
</tr>
<tr>
<td>Austria</td>
<td>30 × 75 mg</td>
<td>Reimbursed price (KVP) Euros 17.95 (Euros 0.59/DDD) – 73% below pre-patent loss price</td>
</tr>
<tr>
<td>England</td>
<td>30 × 75 mg</td>
<td>GBP 2.50 (Euros 2.88) (Euros 0.096/DDD) – 93% below pre-patent loss prices</td>
</tr>
<tr>
<td>Estonia</td>
<td>28 × 75 mg</td>
<td>Cheapest generics – Euros 10.64 (Euros 0.38/DDD) – 77% below the 2009 originator price. Copays vary between 10 to 50%</td>
</tr>
<tr>
<td>Finland</td>
<td>28 × 75 mg</td>
<td>Euros 11.04 (Euros 0.39/DDD) – 86% below pre-patent loss prices</td>
</tr>
<tr>
<td>France</td>
<td>30 × 75 mg</td>
<td>Euros 30.75 (Euros 1.02/DDD) – 45% below pre-patent loss prices (NB only 65% reimbursed)</td>
</tr>
<tr>
<td>Germany</td>
<td>100 × 75 mg</td>
<td>April AVP price (cheapest generics) – Euros 44.18 (Euros 0.44/DDD) – 84% below 2009 originator price</td>
</tr>
<tr>
<td>Lithuania</td>
<td>28 × 75 mg</td>
<td>Euros 4.11 (Euros 0.15/DDD) – 52% below 2009 originator prices</td>
</tr>
<tr>
<td>Serbia</td>
<td></td>
<td>Euros 0.41/DDD – 33% below 2008 originator prices</td>
</tr>
<tr>
<td>Slovenia</td>
<td>28 × 75 mg</td>
<td>Euros 17.41 (Euros 0.62/DDD) – 33% below January 2010 originator prices</td>
</tr>
<tr>
<td>Sweden</td>
<td>30 × 75 mg</td>
<td>SEK64 (AUP) (Euros 9.20 – Euros 0.31/DDD) – 88% below pre-patent loss prices</td>
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NB: current reimbursed price in New Zealand (September 2011) for 90 x 75 mg is NZD$16.25 (Euros 9.4 – Euros 0.10/DDD). Currency conversion rates taken from publically available rates at the time.
There has also been extensive education of physicians in some European countries to allay their fears about prescribing generic clopidogrel with different salts and indications, see Table 2. As a result, utilisation of generic clopidogrel has been enhanced thereby helping health authorities and health insurance agencies gain savings from the early availability of generic clopidogrel given the global expenditure on Plavix pre-patent loss [9, 10].

The various measures instigated among countries to obtain low price of generics [2-4, 6, 7, 37-40] has already resulted in appreciable price reductions in some countries, see Table 4. However, this was not universal with a 20-fold difference in reimbursed prices existing between countries in April to July 2011, see Table 4.

Conclusion
Health authorities and health insurance agencies have typically adopted a pragmatic approach to enhance the prescribing and dispensing of generic clopidogrel once available. As a result, valuable resources have been released from the early availability of generic clopidogrel. This is despite different salts and more limited indications initially versus the originator, coupled with the withdrawal of some formulations of generic clopidogrel from the market place due to manufacturing concerns.

Activities undertaken by health authorities and health insurance agencies to enhance the prescribing of generic clopidogrel, see Table 2, mirror those undertaken for other generics [2-4, 6, 7, 37-40]. They also included extensive education among key stakeholder groups in some countries to enable health authorities and health insurance agencies to fully realise the financial benefits from the early availability of generic clopidogrel. However, activities in some countries have not always been possible following successful challenges to the availability of generic clopidogrel, which led to the removal of all or some formulations for a period of time, see Table 2.

It may well be in the long term that compliance is a greater issue to maximise outcomes from clopidogrel than any perceived differences in bioavailability between formulations, mirroring the situation with other cardiovascular drugs [51]. Consequently, some of the resources released from the availability of generic clopidogrel could be used to address this issue to maximise the health gain from clopidogrel alone or in combination with aspirin among pertinent patients.

There is considerable variation in reimbursed prices for generic clopidogrel, and versus the originator, see Table 4, mirroring the findings in other studies [2, 3, 4, 6]. Again the size of the country’s population does not appear to be responsible for these differences, confirming previous publications [37]. Price reductions appear to be determined largely by ongoing policies to enhance generics utilisation [1-4, 52]. It is likely though that in time reimbursed prices for clopidogrel will converge, driven largely by countries striving to release further resources from the increasing availability of generics [53]. This will be researched in future studies alongside the impact of the various policies in each country to enhance the prescribing of generic clopidogrel versus the originator, see Table 2.

In conclusion, payers across Europe are learning from each other how best to take full advantage of the early availability of generics, even when there are different salts and indications, to maximise the use of available resources. This will continue. However, as we have seen this is not always possible. We believe pharmaceutical companies should accept generics availability to enable continued funding of new premium priced products, and not try to delay their introduction through challenging reimbursement decisions. The alternative, as resource pressures continue growing, is limited or no funding for new drugs, which is not in the future interests of all key stakeholder groups [1-4, 8, 54].

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