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REVIEW ARTICLE

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

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Introduction and study objectives: Resource pressures will continue to grow. Consequently, health authorities and health insurance agencies need to take full advantage of the availability of generics in order to continue funding comprehensive health care 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 initial price reductions obtained in practice to guide future activities.
Methods: 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 direction to other health authorities alongside, e.g. Lithuania. Australia has also been included in view of the high court ruling in favour of generic clopidogrel.
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 initial 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 and study objectives

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 billon 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 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 various generic clopidogrel preparations through its centralised procedure [11, 13, 14]. This included more than 20 generic clopidogrel

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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 authority or health insurance agencies faced 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 exists 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 Glochem Industry Ltd's manufacturing facility in India [31-34]. The medicines concerned included Clopidogrel 1A 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 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 authorities 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

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 referenced priced 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 atorvastatin in Austria, Finland and Norway as well as sartans in Austria, Croatia, Lithuania 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

price reductions that have been obtained by a range of countries for generic clopidogrel versus pre-patent loss originator prices in the initial months following generics 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.

Methods

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, Dr Hanna Koskinen, Mr Ott Laius, Dr Catherine Sermet, Dr Peter Skiöld, Professor Ulrich Schwabe, Dr Agnes Vitry); alternatively from administrative databases (Republic of Serbia's Health Insurance Fund database, Dr 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 generics 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 geographies, 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 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].

Table 2: Individual countries' health authorities and health insurance companies' responses to enhance the prescribing and dispensing of generic clopidogrel [1-4, 7, 8, 15, 16, 22, 36-41, 45-47, 50, 55, 60]

Abu Dhabi	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 generics) 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.
Australia	The first generic versions of clopidogrel were reimbursed in April 2010 after the High Court of Australia dismissed Sanofi's bid to appeal to the Full Court's September 2009 judgment in favour of Apotex. A 12.5% statutory price reduction was applied in line with the current regulations for the first branded generics listed in the Prescribing Benefits Scheme (PBS). Further price reductions are envisaged with the recent introduction of a progressive system of price disclosure for all drugs where multiple sources are available. Activities to enhance generics prescribing included: • Education – Generic medicines awareness campaign and distribution of brochures on generic medicines in community pharmacies • Engineering – Price-volume agreements • Economics – Brand premium policy for consumers and financial incentives for pharmacists to dispense a substitutable product
Austria	**Licensing authorities – activities** • The first generic drug 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.

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	• 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 generics for the molecule. In addition, new IT systems available also highlighting cheapest generics. • Engineering – Listing generic clopidogrel in the 'green box', i.e. no restrictions versus 'yellow' box for Plavix. • Economics – Financial incentives (limited) for prescribing generics; reprimands for continued excessive prescribing costs versus colleagues. There have been no real issues from a health insurance perspective arising from the withdrawal of some formulations of generic clopidogrel from the market place.
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. At the time of submission, there were 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 generics, 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).
Finland	The first generic clopidogrel received reimbursement status on 1 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.

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	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.
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 to reach 75% on 31 December 2010 (came into force on 23 April 2010). This may have been aided by an article in *Prescrire* a 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 (CAPI – *Le programme d'evolution des pratiques*, a pay-for-performance programme introduced to enhance quality and efficiency of prescribing) 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 (anatomical, therapeutic, chemical) B01AC + pravadual) should be treated with low dose aspirin (Engineering).
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.
The Netherlands	• Clopidogrel is only reimbursed for patients after a myocardial infarction, ischaemic stroke or established peripheral arterial disease who cannot be treated with aspirin because of hypersensitivity to aspirin or other absolute contraindications to aspirin. In addition, potentially in combination with acetylsalicylic acid in patients with (a) acute coronary syndromes without ST-segment elevation, (b) acute coronary syndrome based on acute myocardial infarction with ST-segment elevation, or (c) stent placement in the context of a non-acute coronary syndrome. • The health insurers in The Netherlands typically took a pragmatic approach to generic clopidogrel versus Plavix endorsing its utilisation, which mirrors the recommendations from the Royal Dutch Hospital Pharmacists Association, see Table 3. • This has resulted in several health insurers including clopidogrel in their preference policy schemes to drive down the cost of generic clopidogrel. As a result, generic clopidogrel already accounts for 70% of clopidogrel prescriptions in The Netherlands and is rising (first half of 2011). Consequently, no further actions are planned by the health insurers to enhance the prescribing of generic clopidogrel versus Plavix. Currently, most health insurers only reimburse Grepid/Glenmark instead of Plavix and Iscover.

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Table 2: Individual countries' health authorities and health insurance companies' responses to enhance the prescribing and dispensing of generic clopidogrel [1-4, 7, 8, 15, 16, 22, 36-41, 45-47, 50, 55, 60] (*Continued*)

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 the National Authority of Medicines and Health Products (*Autoridade Nacional do Medicamento e Produtos de Saúde*, 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 Atlabiclo, 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 26 March 2010, Infarmed informed key stakeholders that by decision of the Administrative Court of Lisbon, there is temporary suspension of the marketing authorisation of Clopidogrel Tetrafarma, 75 mg. Again, this decision did not apply to other marketed medicines containing clopidogrel.
Serbia	The first clopidogrel was reimbursed in August 2006, with no real issues regarding different salts and indications, with clopidogrel only reimbursed for patients for 12 months after a stent or coronary artery bypass graft (CABG), or for secondary prevention in patients resistant to aspirin. Recent measures to lower the price of generics in Serbia include the originator and generic drugs must now have the same price to be reimbursed. There are currently five generic clopidogrel versions in Serbia (August 2011), all manufactured by the domestic generics industry except for one product.
Slovenia	There has been mixed availability of generic clopidogrel in Slovenia. Generic clopidogrel was available between June 2006 and June 2008. Subsequently, it was removed from the market because of patent problems following a challenge by the originator manufacturer. However, since May 2010 generic clopidogrel has again been available and reimbursed. Activities to enhance generics prescribing include additional co-payments for more expensive compounds than the reference product (Economics). Physician can write 'Do not substitute', but this is not frequently used.
Spain (Catalonia)	Generic clopidogrel was first approved in Spain in September 2009 and first reimbursed in April 2010. Measures to lower the price of generics include the reference price system, which establishes a maximum reimbursement price with no possibility for the patient to cover the additional costs themselves for a more expensive product. For products dispensed by INN name, the pharmacy should dispense the cheapest product (preferably generics). However, originator manufacturers of new molecules included in the reference price system have a period of two years to decrease their prices to the reference price, decreasing each year by 50% of the difference between the originator and the reference price. Consequently, these products can maintain a higher price for a period of time, with the resultant price difference sometimes substantial as seen with clopidogrel. More recently following reforms in November 2011, nearly all originator drugs where there is a generic drug available, have decreased their price to that of the generic drug. This includes Plavix. Health authority activities to enhance the prescribing of generic clopidogrel where there was a price differential were affected by hospital specialists. This was due to ongoing concerns regarding the effectiveness and safety of the generics, enhanced by the withdrawal of some generic compounds and the lack of all indications among the generics – especially the ACS indications.

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	Activities to address this until the recent reforms included: • Education - Information and other activities by the Catalan Drugs Information Center (*Centre d'Informació de Medicaments de Catalunya*) to address any misinformation regarding generic clopidogrel as well as highlighting the cost differential between the originator and generics. • Engineering - Asking the Health Minister to address the anomaly with substitution where there are different indications between approved generics and the originator. In addition, encouraging systematic substitution in ambulatory care with physician agreement coupled with patient information if needed to address any concerns regarding the effectiveness and/or safety of the generic versus the originator drug.
Sweden	The Swedish Medical Products Agency (*Läkemedelsverket*) decided that the originator could be substituted ahead of its availability despite different salts and indications from the originator. Alongside this, there appeared to be no real issues with the withdrawal of certain formulations of generic clopidogrel, e.g. Stockholm County Council's expert group discussed the withdrawal of certain formulations; however, no action was taken as none of the formulations withdrawn were recommended in the 'Wise List'. Grepid (Orifarm Generics) was the first generic clopidogrel to be reimbursed in Sweden (November 2009), with the generics from four companies becoming available the following month. Demand-side activities: • Education - Making sure recommended generics formulations are included within current County Council (Regional) formularies. • Enforcement - Mandatory substitution in the pharmacy unless concerns or the patient is prepared to pay the difference for a more expensive product (rare in practice).
UK (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). The only current recommendations regarding generic clopidogrel are concerning specific salts to dispense in nursing homes, when packs are broken down for unit dispensing, as there can be stability concerns.

Results

Most health authorities and insurers have adopted a pragmatic approach towards differences in the salt and indications between the generic and the originator drug 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 market place for a period of time, see Table 2.

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] has already resulted in appreciable price reductions in some countries. 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

Table 3: Individual countries' examples of pragmatic approaches towards the availability of generic clopidogrel	
Abu Dhabi [42]	Compulsory INN prescribing with no exception for generic clopidogrel.
Croatia [7, 36, 47]	• Reference pricing for the molecule irrespective of whether this is the originator or a generic drug in view of limited perceived differences between the different formulations of clopidogrel. • This mirrors the situation with other generics in Croatia.
France [2, 4]	Seventy-five per cent substitution target for generic clopidogrel.
Lithuania [3, 7, 8, 22]	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.
The Netherlands [48]	Royal Dutch Hospital Pharmacists Association (*De Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie*) 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.
Sweden [2, 4, 41, 50]	The Swedish Medical Products 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.
UK (Northern Ireland) [49]	• 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'.
UK (Scotland) [16, 22, 38]	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 generic clopidogrel for as yet unlicensed indications were 'negligible'.

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

Country	Clopidogrel pack (DDD = 75 mg)	Reimbursed/dispensed prices for 75 mg pack of clopidogrel in April to July 2011
Australia	28 × 75 mg	AUD 70.30 (Euros 52.99 – Euros 1.89/DDD) – 12.5% below pre-patent loss prices. Co-payment (AUD 34.20) for general patients, AUD 5.60 for concessional patients
Austria	30 × 75 mg	Reimbursed price (KVP) Euros 17.95 (Euros 0.59/DDD) – 73% below pre-patent loss price
England/ Scotland	30 × 75 mg	GBP 2.50 (Euros 2.88) (Euros 0.096/DDD) – 93% below pre-patent loss prices
Estonia	28 × 75 mg	Cheapest generics – Euros 10.64 (Euros 0.38/DDD) – 77% below the 2009 originator price, Co-pays vary between 10 to 50%
Finland	28 × 75 mg	Euros 11.04 (Euros 0.39/DDD) – 86% below pre-patent loss prices
France	30 × 75 mg	Euros 30.75 (Euros 1.02/DDD) – 45% below pre-patent loss prices (NB only 65% reimbursed)
Germany	100 × 75 mg	April AVP price (cheapest generics) – Euros 44.18 (Euros 0.44/DDD) – 84% below 2009 originator prices
Lithuania	28 × 75 mg	Euros 4.11 (Euros 0.15/DDD) – 52% below 2009 originator prices
Serbia		Euros 0.41/DDD – 33% below 2008 originator prices (NB only 65% reimbursed)
Slovenia	28 × 75 mg	Euros 17.41 (Euros 0.62/DDD) – 33% below January 2010 originator prices
Sweden	30 × 75 mg	SEK 64 (AUP) (Euros 9.20 – Euros 0.31/DDD) – 88% below pre-patent loss prices

DDD: defined daily dose; 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.

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.

Alongside this, recent studies [61, 62] have further questioned the clinical utility of measuring *CYP2C19* endorsing our earlier comments that this measurement should not impact on the debate of whether to prescribe generic or originator clopidogrel.

There was already considerable variation in reimbursed prices for generic clopidogrel 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].

For patients

Pharmaceutical expenditure is typically the largest or equalling the largest component of expenditure in ambulatory, i.e. non-hospital, care. Consequently, the increasing availability of multiple sourced products (generics) once a product loses its patent is welcomed by health authorities and health insurance agencies as these can be provided at considerably lower costs than the originator. This is the case with generic clopidogrel with its price already only 12% of the cost of the originator within a few months in some European countries, with prices expected to fall further.

However, there can be concerns among physicians and patients with the effectiveness of a generic drug if this is provided as a different salt to the originator. The availability, and hence effectiveness of a generic drug, is tested though by the European authorities before such medications can become available to help address such fears. In this case, the European authorities found no bioavailability problems with different salts of generic clopidogrel compared to the originator substance. The European authorities go on testing generics to ensure trust in the system, and will remove generics if there are justified concerns. This happened with some of the manufacturers of generic clopidogrel giving further confidence in the system.

Health authorities and health insurance companies across Europe also typically found no issue with early formulations of generic clopidogrel despite different salts indications than the originator drug. Consequently, they typically took a pragmatic approach to encourage physicians to prescribe generic clopidogrel versus the originator to release considerable monies. Patients can also play their part by accepting generics that have been approved by the European authorities rather than the originators, with the monies released used to help maintain the European ideals of comprehensive and equitable health care in these difficult economic times especially in Europe.

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The majority of the authors are employed directly by health authorities or health insurance agencies or are advisers to these organisations. No author has any other relevant affiliation or financial involvement with any organisation or entity with a financial interest in, or financial conflict with, the subject matter or materials discussed in the manuscript.

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