Bilaga II

Kartläggning av pågående initiativ och erfarenheter kring ordnat införande av nya läkemedel i Europa

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Kartläggning av pågående initiativ och erfarenheter kring ordnat införande av nya läkemedel i Europa

(Review of ongoing initiatives and experiences of the managed introduction of new medicines across Europe)
Content

1. Executive summary 1 - 3
2. Background 6 - 17
   2.1 General 6 - 7
   2.2 Reforms and initiatives around existing drugs 7 - 8
   2.3 New medicines 9 - 17
3. Aims, Objectives and Methodology 17 - 18
4. Findings 18 - 43
   4.1 Literature review 18
   4.2 Risk sharing arrangements 18 - 23
   4.3 Follow-up of prescribing restrictions 23 - 27
   4.4 Patient registries post launch 27 - 29
   4.5 Dabigatran 29 - 37
   4.6 Personalised medicine 37 - 40
   4.7 Improved interface management 40-43
5. Areas where Sweden already provides direction to other countries 43
6. Suggested activities for Sweden 43 - 50
   6.1 Pre-launch activities 44 – 46
   6.2 Peri-launch activities 46 - 48
   6.3 Post-launch activities 48 - 50
7. Research areas for the future 50 - 51
   7.1 Models to enhance the managed entry of new drugs 50
   7.2 Specific drug classes 50 – 51
8. References 51 - 59
9. Appendix (Tables and Figures) 60 - 73
1 Executive summary

Pharmaceutical expenditure has risen rapidly in recent years, averaging more than 50% in real terms between 2000 and 2009 among OECD countries. As a result, pharmaceutical expenditure is now the largest or equalling the largest cost component in ambulatory care. Pharmaceutical expenditure is set to continue rising unless addressed driven by well known factors including changing demographics, rising patient expectations and the continued launch of new premium priced drugs. The continued launch of new premium priced drugs is seen as the greatest challenge to the continued provision of equitable and comprehensive healthcare in Europe, especially with over 500 biological drugs in clinical development.

There are ongoing reforms to increase the prescribing efficiency of existing drugs, aimed at enhancing the prescribing of generics versus patented products in a class or related class where feasible at low prices for generics, However, whilst the reforms have been successful in releasing considerable resources in Sweden, they will be insufficient to keep pharmaceutical expenditure under control in the future given the large number of premium priced biological drugs in development. The growth in personalised medicine holds the promise to improve the use of resources through reducing NNTs and increasing NNHs. Alongside this, reduce the appreciable burden associated with adverse drug reactions. However, this is counterbalanced by concerns that companies will seek orphan status for new targeted drugs with associated high prices. This is already happening with companies typically seeking orphan status for their new targeted cancer drugs, and new drugs being priced at over US$300,000/ patient/ year purely on the basis of being seen as orphan drugs.

These concerns led the Piperska group to develop new models to optimise the managed entry of new drugs in the absence of any comprehensive model encompassing all 3 pillars – namely pre-launch, peri-launch and post-launch activities. Various groups including Stockholm County Council have researched elements of these 3 pillars, but no one has published a comprehensive model together with examples.

Typically, criteria for reimbursement of new drugs centre on their clinical and economic value versus current standards. The Scottish Medicines Consortium (SMC) is seen as particularly aggressive giving cost/ QALY guidance as well as only recommending 1/3 of new drugs/ new indications for reimbursement, 1/3 having a restricted license and 1/3 not recommended. The latter include situations where the company has not submitted any information to SMC. The TLV though has increased the number of new products not recommended in recent years. Concerns with the funding of new premium priced drugs has resulted in an explosion of risk sharing arrangements across Europe. Key issues for national and regional health authorities to consider before implementing any risk sharing scheme include:

- Is the new drug a novel treatment with envisaged health gain, are there currently few effective treatments available with/ without long term safety concerns
- Translational science suggests good effectiveness and delaying treatment may not be in key stakeholders’ interest
- Can the likely health gain be determined within a relatively short time frame with proven biomarkers
- Can any patient access scheme proposed appreciably lower health service costs having factored in all administrative costs

Post-launch activities include patient registries to monitor the use of new drugs against agreed criteria as well as assess the effectiveness and safety of new drugs in practice. Typically registries have been instigated either to conserve resources, e.g. the many risk sharing schemes in Italy, or monitor safety in practice, e.g. registries for the TNF alpha drugs as well as natalizumab in France. This is likely to remain. Post-launch activities also include ways to improve the interface management between hospital and primary care in
recognition of the influence of hospital prescribing on ambulatory care costs. They also include prescribing restrictions to help conserve costs.

Case histories were used to provide guidance to national and regional authorities in Sweden in the absence of peer-reviewed publications discussing new models apart from the publications (published and being submitted) by the Piperska group. The case histories and their rationale included:

- Risk sharing schemes/activities from groups involved in evaluating and monitoring their introduction to provide future direction, e.g. Scotland
- Examples of how prescribing restrictions are monitored in practice
- Examples of registries for new drugs across Europe and their rationale
- Dabigatran – to provide guidance on future models based on health authority and health insurance company activities across Europe and suggested ways forward
- Health authority/health insurance company personnel views and guidance on personalised medicine given the appreciable number of new targeted drugs in pipelines
- Examples of approaches to improve Interface Management given concerns

The various case histories, particularly those regarding dabigatran and new targeted treatments/personalised medicine, led to suggested models to better manage the entry of new drugs and suggested activities for all key stakeholder groups (Figure 1).

Figure 1 – Proposed model for optimising the managed entry of new drugs across Europe incorporating national and regional stakeholder groups where pertinent

It is recognised that there are areas where Sweden provides direction to other countries. These include developing forecasting models to improve budgeting, undertaking critical drug evaluations pre-launch using independent experts and developing essential drug lists to improve the quality and efficiency of ambulatory care prescribing. Alongside this, the extensive use of drug and patient registries to monitor care against agreed guidance (both
economic and safety driven) as well as assessing the effectiveness and safety of drugs in practice, e.g. registries for TNF alpha inhibitors.

Suggested activities for national/ regional groups in Sweden build on the 3 pillars of pre- to post-launch. They are seen as critical - especially given the plethora of new expensive biological drugs, including new targeted drugs, likely to be launched in Sweden over the coming years (Figure 12). They build on existing activities that are already undertaken well in Sweden to help improve the managed entry of new drugs as well as ongoing initiatives to enhance prescribing efficiency of both new and existing drugs. In more detail:

- Pre-launch – greater integration between national and regional bodies to avoid duplication of horizon scanning/ budget impact analyses, building on current national/ regional projects to improve the knowledge base; critically challenging pharmaceutical companies with the data they provide to support premium prices; developing joint guidance on the prescribing of new drugs that cross sectors. In addition, start developing quality indicators as well as start planning patient registries where pertinent

- Peri-launch – consider cost/QALY guidance for national reimbursement along with budget impact considerations; extend national reimbursement considerations to include hospital only products; learning from other countries regarding risk sharing arrangements as well as refining key considerations for any patient registries/ quality indicators instigated post launch

- Post-launch – routinely monitor whether prescribing restrictions are being followed; instigate pertinent quality indicators to improve patient care post launch with new drugs; re-assess the value of new drugs in practice using patient registries -- especially where concerns with their effectiveness and/ or safety in practice; improve interface management between primary and secondary care where there are continuing concerns

One major theme for the future is that national and regional groups and authorities in Sweden should seek to publish their activities in peer reviewed English speaking journals to guide future activities in Sweden as well as across Europe. This includes for instance the impact of the recent prescribing restrictions on subsequent usage patterns of duloxetine using patient registries. The data has been collected but not submitted for publication.

All studies instigated to monitor the influence of prescribing restrictions, as well as the effectiveness and safety of pertinent new drugs in practice, must involve academic units. This is in view of the serious concerns with protocols submitted by pharmaceutical companies for monitoring prescribing restrictions coupled with concerns with bias if pharmaceutical companies instigate such activities.

Programmes should also be implemented to enhance INN prescribing to help avoid patient confusion/ potential duplication of prescriptions that currently arise when patients are dispensed different branded generics on each occasion - enhanced with current monthly auctions for generics in Sweden and community pharmacists spending little time with patients allaying any fears/ concerns.

Funds for suggested activities could include an extension to ongoing national/ regional projects, levies to companies for their submissions to national reimbursement agencies (mirroring the situation in Poland) and/ or a tax on pharmaceutical company promotional activities. The latter is already in existence in Italy to fund independent R & D studies.

Finally, suggested projects for the future centre on reviewing the uptake of NOACs along with ongoing reforms to optimise their use. Similarly for new drugs for Type 2 diabetes as well as new premium priced drugs for patients with hepatitis C. The findings will help further refine ongoing models in Sweden.
2 Background

2.1 General

Pharmaceutical expenditure has risen appreciably during the past decade among Western Countries, with growth rates typically greater than other components of healthcare\textsuperscript{[1-13]. As a result, pharmaceutical expenditure in ambulatory care is now the largest or equalling the largest cost component in this sector\textsuperscript{[1-16]. Overall, pharmaceutical expenditure has risen by more than 50% in real terms between 2000 and 2009 among OECD countries\textsuperscript{[12]. This growth is set to continue unless addressed, driven by well-known factors including stricter clinical management targets, changing demographics with ageing populations, the continued launch of new premium priced drugs and rising patient expectations\textsuperscript{[1-5,7,8,14-18]. Among these, the continued launch of new premium priced drugs is seen as the greatest threat to maintaining the European ideals of comprehensive and equitable healthcare\textsuperscript{[19].}

As a consequence, health authorities and health insurance companies across Europe have instigated multiple supply- and demand-side measures and initiatives to slow down pharmaceutical growth rates, or even reverse these when required, to maintain the European ideals\textsuperscript{[20-42]. These include measures to enhance the quality and efficiency of prescribing of both new and existing drugs, including improved interface management. This latter is in recognition that hospital recommendations and treatments (in-patient and out-patient care) can appreciably influence the cost of subsequent patient care among primary care physicians\textsuperscript{[34,44,46}, especially if they are not fully aware of all the drugs being prescribed to patients across sectors. However, to date, this has been an under-recognised area. Potential ways forward include\textsuperscript{[37,45-49].}

- Contracts in hospitals increasingly taken account of drug prices across all care sectors, e.g. Isosorbide Mononitrate MR tablets was heavily discounted in hospitals in Scotland although costs in the community were approximately £10/month/patient higher than the lowest cost product in hospital (factor of 30). This led some Health Boards in Scotland to work outside the contracting system to maximise whole system efficiency
- Authorities endorsing the continued prescribing of patients’ medications in hospitals provided patients with chronic conditions have been on the medication for at least a month (to avoid possible switching of therapies in hospitals to more expensive medications typically donated by companies - Lithuania)
- Development of prescribing guidance on suggested common drugs in out-patients, building on the guidance for primary care physicians (Stockholm, Sweden)
- Switching patients in hospital who have been prescribed other angiotensin receptor blockers (ARBs) apart from generic losartan for management of hypertension or congestive heart failure to generic losartan (UK) to conserve costs in the community post discharge given the substantial price difference between generic losartan and patented ARBs

There would be reduced funding for new drugs without ongoing multiple initiatives to improve prescribing efficiency as we are already seeing countries no longer able to fund new premium priced drugs due to increasing resource pressure\textsuperscript{[24,25,50]. This situation will worsen given the considerable number of biological drugs in clinical development\textsuperscript{[51] unless pro-actively addressed. Alongside this, there can be concerns with safety issues for certain new drugs once they are used in a wider population than those studied during clinical development, which has resulted in product withdrawals\textsuperscript{[52-56]. Consequently, again a need in some circumstances to improve the managed entry of new drugs.

The growth in personalised medicine and pharmacogenomics should help address some of these issues through reducing the number of patients needed to treat (NNTs) and increasing the number of patients needed to harm (NNHs). As a result, improve the use of resources through reduced waste\textsuperscript{[57] as well as reduce the costs associated with adverse drug reactions (ADRs). In addition, reduce the number of product withdrawals post launch.
Product withdrawals are not surprising in view of the considerable variability that exists in how individual patients respond to pharmacological treatments, which may not be fully captured within the confines of Phase II and III clinical trials.

Currently, ADRs account for between 5 to 10% of all acute internal medicine related hospital admissions across continents[58-64], with the costs of adverse events due to drugs estimated at US$177bn per year in the US alone[65]. More specifically, over 2 million people are hospitalised annually in the US due to serious adverse events[66,67], with the cost of drug-related morbidity and mortality exceeding US$177.4bn in 2000 alone[66,68].

Examples where pharmacogenomics testing has saved resources are KRAS testing prior to cetuximab. It is estimated that KRAS testing saves the US health care system over US$600mn annually in cetuximab costs[69]. Other examples include atypical antipsychotic drugs. US$14.6bn was spent in the US alone on atypical antipsychotic drugs in 2009[70]. However, it is recognised that whilst there appears to be limited differences in effectiveness between the different atypical antipsychotic drugs apart from clozapine, the variation in effectiveness between patients can be substantial[71-75]. Consequently, the ability to target these drugs depending on patients’ characteristics should be welcomed not only to reduce drug acquisition costs as more atypical antipsychotics lose their patents[76,77] but also relapses, with their considerable resource consequences. This could happen with accumulating data suggesting that DNA information may be an important predictor of treatment response to atypical antipsychotic drugs in schizophrenia[78].

Pharmacogenetic models are also being developed to better predict the effectiveness of methotrexate in patients with rheumatoid arthritis before more expensive TNF-alpha drugs[78].

However, there are concerns among health authorities and health insurance agencies that pharmaceutical companies will seek ‘orphan status’ for their new targeted treatments. As a result, considerably enhance requested prices and increase rather than reduce overall costs[80-82]. This is already happening. In the US, abiraterone was the only cancer drug approved by the FDA in 2011 without an orphan designation[83,84]. As a result, potentially leading to high acquisition drug costs and increase the overall cost burden[81,82,85,86]. This is seen with crizotinib and vermurafenib, both of which have been launched at over US$10,000 month excluding the cost of diagnostic tests and administration costs[87-90] versus lower costs for HERCEPTIN[91]. This is at a time when the number of new cancer cases is expected to increase by over 60% in the next 20 years[91-96]. Other examples of high acquisition costs being requested include new targeted drugs for patients with cystic fibrosis. These have been launched at over US$25,000 per month, based on the concept of a targeted therapy in a select population[97].

There are also concerns regarding the high cost of some genetic tests combined with their utility. This is because the advice regarding some tests has now been reversed. These include CYP2D6 genotyping testing prior to initiation of tamoxifen[98-103] and pharmacogenomic testing prior to initiation with either clopidogrel or warfarin[104,105].

2.2 Reforms and initiatives around existing drugs

Alongside these challenges and concerns, health authorities and health insurance agencies across Europe have made considerable efforts to release appreciable resources through increasing the use of generics at low prices[11-15,16,43]. This has been fuelled by an estimation that the global sales of pharmaceutical products likely to lose their patents between 2008 and 2013 are approximately US$50 to 100bn (€35 – 70), growing to approximately US$255bn between 2011 and 2016[6-9,10,17,106,107].
The various initiatives undertaken by authorities across Europe can be divided into supply-side reforms and demand-side reforms. Supply-side reforms include measures to lower the price of generics, accelerate their marketing authorisation, reference pricing for the molecule (Anatomical Therapeutic Classification – ATC – Level 5), the class (ATC Level 4) or the therapeutic area (ATC Level 3), as well as compulsory price cuts when target budgets are being exceeded\cite{17,20-24,27,29,30,32,40,43,108}.

Demand-side measures include those to enhance the prescribing and dispensing of generics versus originators, as well as enhance the prescribing of generics in a class or related class versus patented products where all drugs are seen as essentially similar for all or nearly all patients\cite{1-11,17,20-27,29-43}. Patient care should not be compromised with increased use of generics versus originators apart from a small number of well-known examples\cite{3,4,6-8,10,17,26,27,29,30,109-112}. Demand-side measures can be grouped under the 4 Es (Education, engineering, economics and enforcement)\cite{38}, with Table 1 containing definitions and examples to enhance the prescribing and dispensing of generics versus originators.

**Table 1 – Definition and examples of the 4Es to enhance the prescribing and dispensing of generics across Europe and the Middle East\cite{2,4,6-8,10,26,27,29,38,43}**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Explanation and initiative</th>
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| Education | • Activities range from simple distribution of printed material to encourage the prescribing of generics versus originators to more intensive strategies including academic detailing and monitoring of prescribing habits  
  • Examples include:  
    o Education of trainee doctors in medical schools to prescribe by INN, e.g. UK  
    o Information and other campaigns including TV adverts among patients to address fears about the effectiveness and/ or safety of generics including speaking with patients to address any fears, e.g. France and Portugal  
    o Physicians and pharmacists developing a list of potentially non-substitutable products where there are concerns with bioequivalence as well as the therapeutic equivalence of generics, e.g. Abu Dhabi, Sweden and UK |
| Engineering| • This refers to organisational or managerial interventions  
  • Examples include substitution targets for certain drugs in community pharmacies if physicians are still prescribing the originator, e.g. France |
| Economics | This includes financial incentives for physicians, patients and pharmacists, e.g.:  
  • Higher co-payments for patients if they wish to receive a more expensive product than the current referenced price molecule, e.g. Finland, France and Sweden  
  • Devolution of drug budgets to physicians with sanctions for over budget situations, e.g. Germany, Sweden and the UK |
| Enforcement| This includes regulations by law such as mandatory INN prescribing or mandatory generic substitution at pharmacies apart from a limited number of agreed situations, e.g. Abu Dhabi, Estonia, Finland, Lithuania and Sweden |

Table 1A contains details of the demand-side measures introduced within two Counties in Sweden (Östergötland and Stockholm) and nationally up to 2009 to enhance the prescribing of generic drugs including generics versus patented products in a class or related class\cite{4}.

Table 2A contains successful case histories of countries that have implemented multiple supply- and demand-side initiatives to enhance the use of generic PPIs, statins and renin-angiotensin inhibitor drugs vs. originators and patented products in the class/ related class.
2.3 New medicines

New medicines are only of real value when they improve care either because they are more effective, have less side-effects than current standards, or both. European health authorities also wish new drugs to be cost-effective especially as only approximately 10% of new drugs are truly innovative\(^{[2,113]}\). In addition, an increasing number of standard drugs are now available as low cost alternatives\(^{[106,107]}\).

This concerns led to the development of a model to optimise the managed entry of new drugs by the Piperska group\(^{[188]}\). This is based on three pillars; namely, pre-launch, peri-launch and post-launch activities (Figure 1). The Piperska group consists of health authority and health insurance personnel from across Europe together with their advisers to research ways to enhance the quality and efficiency of prescribing, with countries learning from each other\(^{[19]}\). There is a particular emphasis on new drugs given the ongoing concerns with the ability to maintain the European ideals.

**Figure 1 – Proposed model for the introduction of new drugs in Europe for the German Health Insurance Funds\(^{[113]}\)**

Pre-launch activities include detecting emerging new health technologies early before they are launched, especially those that are likely to have a significant budget impact and/or safety concerns in routine clinical care\(^{[113-115]}\). This is undertaken using horizon scanning or early warning systems, and may also include forecasting the potential budget impact of new drugs ahead of their launch\(^{[115,116]}\). Such activities start up to three years before launch\(^{[113,115]}\). Prioritisation of drugs for review, and the timing of reviews by horizon scanning units, is typically based on factors such as their potential budget impact, likely health benefit and when the information is needed for decision making\(^{[113,115,116]}\).

Peri-launch activities include critical drug evaluation before to immediately after marketing authorisation of a new drug (second pillar). This may well include developing agreed prescribing guidance (for post launch) as well as an assessment of potential risk sharing arrangements\(^{[113]}\).

Post-launch activities (third pillar) include patient registries assessing the outcome and side-effects of new drugs in routine clinical practice. Alongside this, assessing physician prescribing against agreed guidance\(^{[118]}\).
Various groups within Stockholm County Council have also been active pre- to post-launch to improve the managed entry of new drugs\[113,116\]. Activities include horizon scanning and forecasting activities up to 2 years before launch including forecasting the potential budget impact of new drugs in patient populations where their value is greatest (Figure 2), critical drug evaluation 3-6 months before launch as well as post launch registry activities\[113,116\]. However to date, there has been no publication encompassing all 3 pillars for any new drug/group of drugs.

**Figure 2 - Current forecast Stockholm County (red) 2012-2013 (mSEK)\[114\]**

Criteria for reimbursement of new drugs across Europe is generally based on their level of their health gain versus current standards alongside economic considerations\[113\]. Typically the level of health gain versus current standards is considered first before economic considerations\[1,2,113,117\]. Medical considerations are often based on the perceived innovation level of the new drug within a pre-defined scale.

For example in France, new drugs are divided into five different categories (I-V), where category I equates to major improvement and category V no improvement\[2,113\], whereas in Austria, new drugs are divided into three levels of innovation\[1\]. Cost per quality adjusted life year (QALY) considerations are also used to make reimbursement or funding decisions for new drugs in for instance Norway, Sweden and the UK. There are no formal cost/ QALY (Quality Adjusted Life Years) cut-off levels in Norway or Sweden with variable levels depending on the disease area\[3,4,113,118\]. This was endorsed in a recent analysis involving TLV decisions in Sweden between October 2002 and October 2007\[119\]. A correlation was found between the disease severity and the willingness to pay for a QALY. Typically the cost/ QALY for positive decisions averaged €35,000. However, for more severe conditions this increased in the region of €100,000. As a result, no formal cost/ QALY thresholds currently appear to exist for new drugs in Sweden\[119\], although others may disagree\[120\].

There are more formal considerations in the UK, although again cut-off levels are not rigid\[20\]. An analysis by the Scottish Medicines Consortium (SMC) showed the following\[113,121\]:

- **Cost per QALY < £10K – 79% ‘yes’**
- Cost per QALY £10-20K – 74% ‘yes’
- Cost per QALY £20-30K – 55% ‘yes’
- Cost per QALY > £30K – 29% ‘yes’

Overall among SMC decisions, cost per QALY was not the only consideration; however, it did play a large role when considering funding for new drugs\(^{113,114,121}\). In addition, the inclusion of Health Board personnel looking also at issues of funding post launch led to approximately one third of new drugs/new indications not being recommended for funding, one third with restrictions and one third recommended for use without restrictions (Figure 3)\(^{122}\).

**Figure 3 – Outcome of assessments by the Scottish Medicines Consortium 2002 to 2011\(^ {122}\)**

This compares to TLV which denied reimbursement for 13 out of 107 drug applications between October 2002 and March 2005\(^{3,4}\). Similarly in 2006, 10% of new chemical entities (4 out of 40 products) were not approved for reimbursement\(^{3,4}\), and in 2007 five new applications (10%) were denied reimbursement\(^{3,4}\). During this period, between 11% to 20% of NCEs had restrictions associated with their reimbursement\(^{3,4}\). Between 2009 and 2011, the number of new drugs denied reimbursement increased to an average of 17% of new drug applications\(^{123}\). However, these figures for denying reimbursement do not include products withdrawn by pharmaceutical companies before TLV reached a decision. This compares to the situation in Scotland where ‘not recommended’ includes drugs where companies did not provide any economic evidence to support the requested price. These differences are particularly important since the higher the percentage of new premium priced products granted reimbursement by the TLV the greater the pressure on county council budgets\(^{3,123}\).

Alongside this, SMC (and also NICE) are different to TLV in that they consider all products and not just community care products. A similar situation is seen for example in Italy and Spain. This difference does increase concerns among the counties in Sweden regarding requests to fund new premium price drugs especially with the continuing launch of complex premium priced drugs, which are likely to be targeted at the hospital sector. This is because the counties are responsible for the funding of drugs in both the hospital and ambulatory care sectors\(^{3,4}\).

The number and range of risk sharing schemes have also grown across Europe in recent years, no doubt enhanced by patient and physician pressures on governments to accelerate access to new and more costly medicines. This is despite often significant uncertainty
surrounding the likely health gain of new drugs which may be even more limited in routine clinical practice \cite{113,124-129}. These pressures may well be exacerbated by pharmaceutical companies keen to address lost revenues from patent expires, which have been accelerating in recent years\cite{108,107}.

Against this, there is still considerable confusion surrounding the terminology of risk sharing arrangements, which is being addressed. There are also concerns among health authority personnel with the level of administrative intensity associated with some of the current schemes, and health authorities could end up contributing substantially to the development costs of new products\cite{130-132}. Certainly in the past, a great deal of the risk associated with outcomes of coverage decisions have been borne by health authorities and insurance companies\cite{133}. This is starting to change given the number of new expensive technologies being launched coupled with their budget impact\cite{87-91,113,133}. These challenges are magnified by the lack of scientific studies to date evaluating the implementation and outcome of many existing schemes for pharmaceuticals in terms of their overall costs and benefits\cite{133,134}.

However, the benefits of risk sharing schemes include\cite{125,128,135}:

- Enhances the opportunities for reimbursement and for payers to work within defined budgets
- Price: volume agreements shift the cost and usage considerations to pharmaceutical companies. This is seen as essential where there are concerns with potential excessive utilisation in practice and there are currently limited demand-side measures in place to control physician prescribing habits
- Limits ‘off label’ usage/ indication creep in practice. This is seen as especially important for expensive biological drugs and new orphan drugs
- Payers only fund treatments that produce desired health gain
- Treatments can be targeted to those patients where health gain is greatest (encourages development of biomarkers)
- Payers can monitor the safety and effectiveness of new treatments in practice especially given the selective nature of Phase III clinical trials and possible safety concerns with some new drugs

These benefits though have to be balanced against concerns for patient care if new drugs are launched too early with considerable uncertainty regarding their safety as well as potentially paying for cost-ineffective technologies (type I error)\cite{136}.

Overall, ‘risk sharing’ schemes for pharmaceuticals should be considered as agreements concluded by payers and pharmaceutical companies to diminish the impact on the payer’s budget of new and existing medicines brought about by either the uncertainty of the value of the medicine and/ or the need to work within finite budgets\cite{129}. These include both financial based and performance based/ outcome based schemes\cite{125}:

- Financial based schemes (Table 3A, 4A):
  - Price-volume agreements (PVAs)/ budget impact schemes. These focus on controlling financial expenditure with pharmaceutical companies refunding over budget situations
  - Patient access schemes. These typically involve either free drug or discounts for an agreed period to enhance the value of the new medicine and improve the potential opportunity for their funding/ reimbursement. Patient access schemes also include price-capping schemes, which focus on controlling the financial impact but from an individual patient perspective. Typically drugs are provided free once patients have exceeded an agreed utilisation limit to again enhance reimbursement/ funding within finite resources
- Performance based/ outcome-based models (Table 5A). These can include schemes whereby companies refund agreed monies or provide free drug if the desired outcomes are not reached. Alternatively, a price reduction if the new drug fails to deliver the
desired health gain in practice. In reality, the latter is likely to lead to price shifting from payers to manufacturers as new drugs may well not be able to fully reproduce the desired benefits once prescribed in a wider population than those in the clinical trials, i.e. the net monetary benefit is lower in reality.

The number of schemes in operation, as well as confusion over the terminology, has led to a number of concerns with current risk sharing schemes. These include (Table 2):

Table 2 – Current concerns among health authority and health insurance company personnel with risk sharing schemes [125]

<table>
<thead>
<tr>
<th>Risk-sharing scheme</th>
<th>Concerns</th>
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| Financial based schemes | • The ‘first’ patients in PVA schemes may not always be the most appropriate  
• The schemes may not always factor in issues such as compliance  
• Pharmaceutical companies may benefit from early access of ‘unproven’ technologies  
• Can be complex to administer reducing savings in reality  
• Potentially issues of patient confidentiality and follow up, e.g. dose capping schemes |
| Performance based/outcome based schemes | • Whether the objective of the schemes are fully explicit and transparent, and the level of evidence sufficient to make robust decisions  
• Who will end up funding registries/databases in reality, and whether these can be introduced in practice with current regulations/staff  
• Length of follow-up – impacting especially on issues such capacity and compliance in practice  
• General administration burden in practice and whether sufficient staff to monitor all stages (capacity issues) ensuring any rebates come back to the units  
• Whether the system can cope with time scales for refunds, e.g. time between monitoring disease progression and the next physician visit to stop therapy  
• Potentially accelerating the uptake of new and potentially unproven medicines in practice  
• Whether refunds/rebates are passed back to the payers in reality – especially within DRG systems |

The administrative burden, lack of communication, and concerns with passing on savings have all been highlighted as key issues with current schemes as seen for cancer drugs in the UK including bortezomib and sunitinib. Published research has highlighted the following in the UK [125,132]:

- 73% of hospitals reported they did not have the capacity to manage current schemes as these typically required additional staff to manage, co-ordinate and track them. This is especially the case if hospital personnel have to spend time manually tracking patients, retrospectively adjusting stock control systems and ensuring the necessary financial systems are in place to fully realise any savings.
- A need for greater flexibility around the time limits for processing claims.
- A need for good communication between key stakeholder groups, e.g. in the case of bortezomib every missed claim results in a loss of GB£12,000.
- The need to ensure savings are passed back to the payers – this is not happening in 47% of hospitals.

Overall, it is suggested that a number of issues need to be considered by all key stakeholder groups when appraising risk sharing schemes. These include (Table 3) [125,135]:

Table 3 – Key issues for health authorities to consider before implementing risk sharing schemes[125,135]:

<table>
<thead>
<tr>
<th>Key issues for health authorities to consider</th>
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<tr>
<td>• Appropriateness for the situation/ circumstances, e.g. containing utilisation in practice where there are currently limited demand side measures to influence prescribing; as a result enhance reimbursement at premium prices</td>
</tr>
<tr>
<td>• Whether the objective(s) of the scheme and scope are explicit and transparent</td>
</tr>
<tr>
<td>• Openness where appropriate, i.e. similar to the contracting process for hospital drugs</td>
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<tr>
<td>• Whether the new drug is novel in a high priority disease area backed up by good transitional science</td>
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<tr>
<td>• The economics and outcomes, e.g. whether the new drug could have a substantial beneficial impact on service delivery and/ or safety but difficult to prove this in Phase III trials</td>
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<tr>
<td>• Time scales – overall and for specific situations (outcome schemes)</td>
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<tr>
<td>• The likely administration costs/ burden</td>
</tr>
<tr>
<td>• Whether health services can monitor outcomes in practice via patient registries, who funds these and who owns the data</td>
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As a result, health authority and health insurance companies should be highly critical of proposed risk-sharing schemes from Pharmaceutical Companies when[125,135]:

• Effective and low cost treatment standards already exist
• Health authorities will end up funding a substantial proportion of a new drug’s development costs without payment
• Patient compliance is important but has not been fully addressed in the proposed scheme – especially for asymptomatic chronic conditions
• There will be a high administrative burden – but this has not been considered/ factored into the proposed scheme
• Ethical considerations have not been fully addressed in the proposed scheme
• Insufficient competent staff available to monitor the scheme as well as IT support
• Provisional reimbursement schemes whereby the health authorities fully reimburse the cost of new drugs until any concerns with effectiveness and/ or safety are seen following patient registries

In view of this, health authorities and health insurance agencies should only typically consider risk sharing schemes proposed by commercial organisations when the meet a number of agreed criteria. These are (Table 4)[125,135]:

Table 4 – Key criteria for health authorities and health insurance agencies considering future risk sharing schemes[125,135]

<table>
<thead>
<tr>
<th>Key Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• When the objectives and scope are explicit and transparent</td>
</tr>
<tr>
<td>• When the new drug is:</td>
</tr>
<tr>
<td>o A novel treatment with envisaged health gain</td>
</tr>
<tr>
<td>o Few effective treatments currently available</td>
</tr>
<tr>
<td>o With/ without long term safety concerns</td>
</tr>
<tr>
<td>• Translational science suggests good effectiveness and delaying treatment may not be in key stakeholders’ interest</td>
</tr>
<tr>
<td>• When the likely health gain can be determined within a relatively short time frame with proven biomarkers</td>
</tr>
<tr>
<td>• Patient access schemes can appreciably lower health service costs having factored in all administrative costs especially processes to claim refunds/ rebates</td>
</tr>
<tr>
<td>• Price: volume schemes enable access to new cost-effective treatments whilst at the same time controlling usage in practice</td>
</tr>
</tbody>
</table>
Post-launch activities are also being increasingly undertaken by health authorities and health insurance agencies across Europe in recognition that there is a lack of information about the risks and benefits of drug therapy in patient groups outside of those contained within Phase II and III clinical trials, which could constitute an appreciable patient population.

Post-marketing surveillance studies, which have traditionally been organized by pharmaceutical companies to investigate primarily the safety of new drugs in wider patient populations than those contained in Phase II/III clinical trials, are now increasingly conducted independently by authorities, health providers and professional and scientific associations to address issues such as potential bias. Some of studies are performed using large scale health data registries linking drug exposure to outcomes in different settings (effectiveness and safety considerations). These population registries have been available for many years in the Nordic countries; however, now increasingly established in other countries. Examples of registries include the Swedish Association of Local Authorities and Regions (SALAR) and the National Board of Health and Welfare (SoS) supporting the development of over sixty national healthcare quality registers. Examples of post-marketing surveillance registries include the Italian population-based registry organised by Psocare, an Italian group of dermatologists, psoriasis patients, epidemiologists and drug safety experts. There are also ongoing registries in Italy to monitor the dose and indication(s) for high costs drugs, especially new biological drugs, as part of ongoing risk sharing arrangements (Section 4.2.2). The natalizumab registry in France is an example of a patient registry to assess the safety of new drugs in practice once re-launched.

Natalizumab became available again in 2006/2007 under strict regulations, i.e. second line treatment after for instance beta-interferon, in view of its effectiveness with reducing relapse rates as well as reducing the progression of disability. Programmes are also ongoing to investigate whether seropositivity for JCV antibodies will help accurately predict the development of PML to aid benefit-risk discussions between patients and physicians. This is in addition to the pharmacovigilance programme in France. The objective of these programmes is to improve the understanding of the potential benefits of natalizumab as second line treatment in more severe patients as well as ascertain the likelihood of patients developing PML if they remain seronegative to JCV; alternatively the possible risks of developing PML if they convert from seronegativity to seropositivity.

Under the terms of the registry in France, the objectives are to:

- Determine the benefit-risk ratio of natalizumab in routine clinical care
- Minimise morbidity and mortality of natalizumab through developing PML through early detection due to intensive clinical vigilance activities
- Minimize the risk of PML by treating only patients that are not immunocompromised
- Warn physicians against concurrent use of antineoplastics, immunosuppressants or immunomodulators
- Determine the incidence and risk factors for PML and other serious opportunistic infections, particularly after >= 2 years of treatment

The scheme involved the following (Figure 4):
By June 2011 there were more than 2,800 patients enrolled and monitored, with most investigators enthusiastic to participate. Serious adverse events have been observed in 86 cases (65 patients), of which 36 cases led to treatment cessation. There have been 8 cases of PML, with one death, and one 'pre-clinical diagnosis' (MRI), and was associated with the duration of therapy (>2yrs), prior use of immunosuppressive agents, and anti-JCV antibodies\cite{140}. The efficacy of natalizumab measured in RCTs has also been confirmed in real-life setting on more severe patients.

There are also administrative databases in France to help with pharmacovigilance post launch. These include SNIRAM (Système National d'Information Inter-Régimes de l'Assurance Maladie) with linkage to PMSI (Programme de médicalisation des systèmes d'information) - the national hospital discharge database. SNIRAM contains data on the whole French population from 2006 including physicians/professionals involved in care, reimbursed medicines, procedures, biological tests, and medical devices. There is also a prospective database of 1/100 random sample of individuals with follow-up from January 2003, allowing multiple cross-analyses with linkage to ambulatory-hospital data\cite{141} primarily for safety reasons.

These databases were used to review benfluorex and the risk of valvular cardiopathy and the risk of bladder cancer with pioglitazone\cite{141}. Several cases of valvular cardiopathy reported in benfluorex-treated patients suggested an increase in risk with this drug marketed since 1976, mainly for hypertriglyceridemia, but more recently in patients with diabetes. Analysis of the risk of hospitalization in 2007 and 2008 for a diagnosis of cardiac valvular insufficiency in diabetic patients exposed or not to benfluorex indicated an increased risk - leading to its removal from the market place\cite{141} (confirming the use of such databases primarily for safety considerations).

Pharmaceutical manufacturers in Sweden are required in some cases to provide the TLV with information that agreed restrictions are being applied in practice (principally economic considerations). This includes prospective and retrospective observational studies and market prescribing data. However, two internal audits conducted in 2006 showed there were concerns with the quality of some of the study protocols as well as how specific questions were posed by TLV\cite{4}. As a result, a number of counties have instigated their own studies to monitor prescribing in practice. This includes Stockholm County Council\cite{4} with their registry
for rimonabant (effectiveness and safety considerations). Physician prescribing was regularly monitored against agreed guidelines along with the drug’s impact on BMI, side-effects and persistence\[4,142,143\]. This monitoring helped reduce its usage in practice, with persistence rates similar to other studies\[4\]. Despite monitoring, some patients though were still co-prescribed antidepressants alongside rimonabant. As a result, registries have become more widespread in Sweden where there are concerns with the safety of new drugs in routine clinical practice such as those for dabigatran (Section 7.2).

Patient registries can also help determine whether prescribing restrictions are being followed in practice such as the prescribing restrictions for angiotensin receptor blockers (ARBs) in Sweden\[36\], i.e. principally for economic considerations. Under the restrictions, ARBs should be reserved for patients experiencing unacceptable side-effects or intolerance to ACEIs. Subsequent analysis using patient registries showed that the proportion of the patients initiated on ARBs decreased by 24%, whilst increasing for ACEIs and calcium channel blockers, by 14% and 12%, respectively\[36\]. The proportion of patients initiated on ARBs prescribed an ACEI within 24 months prior to an ARB also increased from 51% to 67%, although there was a substantial regional variation\[36\].

The use of patient registries is likely to grow in view of the development of risk sharing arrangements\[125-129\], the need to monitor usage of premium priced drugs against agreed guidance as well as the need to monitor the safety and effectiveness of new premium priced drugs in practice where concerns to make sure their perceived value is being realised. If not, seek to limit utilisation, alter prices or both.

3 Aims, Objectives and Methodology

The continued introduction of new premium priced drugs will increase the pressure on healthcare systems seeking to cope with the demands of an increasing elderly population, stricter clinical management targets as well as rising patient expectations.

This is particularly the case with new drugs for cancer in view of rising incidence rates, cancer increasingly being seen as a chronic disease, drug acquisition costs typically higher than average drug costs - now at over US$10,000/ month, and new cancer drugs a significant proportion of new drugs in development - currently estimated at over 350\[88-91,94,95,126,144-149\]. Consequently, new models are needed to optimise the managed entry of new drugs to maintain the ideals of equitable and comprehensive healthcare.

The objectives of this project are to undertake a literature review of potential models across Europe to provide future guidance to key stakeholder groups in Sweden. This will be supplemented by additional references, including in-house documents and web-based references, known to the Karolinska Institutet team as well as interaction with health authority and health insurance company colleagues throughout Europe involved with activities to optimise the managed entry of new drugs. This includes new targeted drugs.

Secondary objectives include suggested ways forward to optimise the effectiveness and safety of new drugs in practice including patient registries as well as methods to enhance the prescribing of new drugs in accordance with agreed guidance/ reimbursement criteria.

It is envisaged that there will only be a limited number of references in the literature regarding suggested models. Consequently, activities will be supplemented by using case histories and incorporating the expertise of leading health authority and health insurance company personnel across Europe to give guidance.

Case histories and subjects chosen, and their rationale, include:
- Risk sharing schemes/ activities from groups involved in evaluating and monitoring their introduction to provide future direction, e.g. Scotland
• Examples of how prescribing restrictions are monitored in practice among European countries - Austria, Finland and the Republic of Srpska - to provide guidance to Swedish authorities
• Examples of registries for new drugs across Europe and the potential implications for Sweden for the future
• Dabigatran – to provide guidance on future models based on health authority and health insurance company activities across Europe and suggested ways forward given the extensive number of new drugs in development
• Health authority/health insurance company personnel views and guidance on personalised medicine given the appreciable number of new targeted drugs in company pipelines and targeted drugs being projected as orphan drugs
• Examples of approaches to improve Interface Management including the prescribing of new premium priced drugs, e.g. Scotland and Spain (Catalonia), and the implications for Sweden

The methodology involved discussions and interactions with key health authority and health insurance company personnel from across Europe.

It is envisaged that the information arising from the project will be submitted to peer review journals for publication as well as presented and discussed at International Scientific meetings to enhance the credibility of suggested activities.

4. Findings

4.1 Literature review

There were no peer-reviewed publications in Pub Med dealing with the complete manage entry programme for new drugs starting with pre-launch activities and ending with post-launch activities. This was apart from the publication generated by the Piperska group following its workshop on this subject earlier this year[114]. The Piperska group publication for the German Sickness Funds on managing the entry of new drugs was published in German[113]; consequently not listed in Pub Med.

As a result, a case history approach was principally used to suggest activities for the various authorities in Sweden.

4.2 Risk sharing arrangements/ patient access schemes, e.g. Scotland, Sweden and Italy

4.2.1 Scotland and Sweden

The Patient Access Group of the Scottish Medicines Consortium has evaluated 42 Patient Access Schemes (PAS)/ risk sharing schemes up to April 2012. Not surprisingly, most of these have been in oncology given the high requested prices of new oncology drugs with limited health gain among most (Figure 5).
Most schemes have been simple finance schemes involving discounts or rebates as opposed to more complex finance schemes involving for instance price capping or performance/outcomes based schemes (Figure 6). Not surprisingly perhaps, a number of the more complex financial schemes have been rejected as unworkable within NHS (Figure 6).
The good points of PAS/Risk sharing schemes in Scotland include\textsuperscript{[150]}:

- Reduce uncertainty in the outcomes obtained as well as providing ‘real world’ effectiveness data (outcome based schemes)
- Treatments become more cost-effective; as a result, enhancing the potential for reimbursement/funding. As a consequence, patients gain access to high cost medicines
- National/local operating procedures can provide some consistency and clarity on operations within the health service
- IT systems can be developed to record patient specific data, which can subsequently be used in other settings

The recommendations for future PAS/risk sharing schemes from NHS Scotland based on their experiences include\textsuperscript{[150]}:

- Risk sharing/PAS schemes should be the exception rather than the rule
- Any scheme proposed/evaluated must be clinically robust, plausible, practical and able to be monitored.
- In addition, any PAS scheme must be operationally manageable for the health service in question
- Any rebate options proposed must include both credit notes and the potential for direct bank transfer if needed/pertinent
- No patient-identifiable data should be shared between the national health service and the pharmaceutical company proposing the PAS
- The duration of any scheme must be explicit and there must be clear exit strategies if required. This must be alongside a formal agreement between the relevant health service and the pharmaceutical company
- Ideally, there should be agreed terms of reference/operating procedure for any Risk Sharing/Patient Access Schemes being evaluated by the health service. This includes areas such as maintenance of verification records, hospital stock management, and rebate/discount management
Overall, the simpler the better for any PAS/ risk sharing scheme as there can be problems with complex financial arrangements as well as with outcome schemes.

These schemes are different to provisional reimbursement schemes. Under these schemes, key assumptions regarding the effectiveness and/ or safety of new products are assessed in practice during which the new drugs are reimbursed at agreed prices\(^{124-126}\). Such schemes exist in Sweden and are called ‘conditional reimbursement based on further evidence development (CED) schemes’\(^{151}\), and have been included in a limited share of the reimbursement decisions made by the TLV since 2003\(^{151}\). Such schemes typically run for 3 to 4 years before a re-assessment to confirm or challenge key assumptions made in the cost-effectiveness model provided by the Company.

TLVs’ evaluations of the reports for Risperdal Consta (risperidone i.m.), Lucentis (ranibizumab) and Champix (varenicline) resulted in no further actions by the agency since the assumptions made in the original applications for reimbursement, and were the subject of the study, appeared to be valid\(^{151}\). However, it is likely these studies were performed by the pertinent pharmaceutical company and not by independent academic units to enhance the credibility of the findings. TLVs’ evaluations of the reports for Firazyr (icatibant) and Berinert (human C1 esterase inhibitor) resulted in a recommendation to re-evaluate the pricing of products used for the treatment of hereditary angioedema\(^{151}\).

Having said this, a number of other European health authorities are against such schemes as they believe they encourage the use of newer premium priced with still uncertainty regarding their value. In addition, health authorities may end up paying for an appreciable proportion of a company’s clinical trial costs.

4.2.2 Italy

Managed entry/ risk sharing programmes have been a key element of the pricing and reimbursement process for new expensive drugs in Italy since 2006, especially new biological drugs\(^{124,125,128,129,152,153}\). This is in view of the fact that by law in Italy retail and hospital drugs must not exceed 13.3% and a 2.4% of the total healthcare budget\(^{129,153}\). If pharmaceutical expenditure exceeds this limit, pharmaceutical companies, Regions and the distributors (pharmacists and wholesalers) must cover the deficit respectively. In addition, pharmaceutical companies will now be asked to cover 30% of the deficit in hospitals and be subject to price cuts for ambulatory care drugs\(^{128,129,153}\). This led to the development of performance based/ managed entry schemes. Examples of these are included in Table 5.

These registries have been primarily developed for economic reasons (see below).
Table 5 – Examples of performance linked schemes in Italy\textsuperscript{[129,153]}

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Brand</th>
<th>Indication</th>
<th>Date</th>
<th>Payback</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>Afinitor</td>
<td>mRCC</td>
<td>Jun. 2010</td>
<td>100%</td>
<td>Non responders after 3 treatment months</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>mRCC (EGFR+, KRAS wild-type)</td>
<td>Jun. 2009</td>
<td>50%</td>
<td>Non responders after 2 treatment months</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>Advanced squamous HNC</td>
<td>Jun. 2010</td>
<td>100%</td>
<td>Non responders after 2 treatment months</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>EGJ AC</td>
<td>Dec. 2010</td>
<td>50%</td>
<td>Non responders after 2 cycles</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Iressa</td>
<td>NSCLC EGFR mut</td>
<td>May 2010</td>
<td>100%</td>
<td>Non responders after 3 treatment months</td>
</tr>
<tr>
<td>Vinflunine</td>
<td>Javor</td>
<td>UCC</td>
<td>Dec. 2010</td>
<td>100%</td>
<td>Non responders after 2 cycles</td>
</tr>
<tr>
<td>Mozobil</td>
<td>Plenixafor</td>
<td>Stem cell mobilization</td>
<td>Dec. 2011</td>
<td>100%</td>
<td>Refund Treatment (if CD34+ &gt; 2 x10^6/Kg)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Nexavar</td>
<td>HCC</td>
<td>Jun. 2008</td>
<td>100%</td>
<td>Non responders after 2 treatment months</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Sprycel</td>
<td>CML / ALL</td>
<td>May 2007</td>
<td>100%</td>
<td>Non responders after 1 treatment month</td>
</tr>
<tr>
<td>Nitotinib</td>
<td>Tasigna</td>
<td>CML Philadelphia chromosome+</td>
<td>Aug. 2008</td>
<td>100%</td>
<td>Non responders after 1 treatment month</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Torisel</td>
<td>mRCC</td>
<td>Oct. 2008</td>
<td>100%</td>
<td>Non responders after 2 treatment months</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Tyverb</td>
<td>mBC</td>
<td>May 2009</td>
<td>100%</td>
<td>Non responders after 3 cycles (6 months)</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Vectibix</td>
<td>mRCC (EGFR+, KRAS wild-type)</td>
<td>Jan. 2009</td>
<td>50%</td>
<td>Non responders after 2 treatment months</td>
</tr>
<tr>
<td>Votrient</td>
<td>Pazopanib</td>
<td>RCC</td>
<td>May 2011</td>
<td>100%</td>
<td>Non responders after 24 treatment weeks</td>
</tr>
<tr>
<td>Trabectedina</td>
<td>Yondelis</td>
<td>ASTS</td>
<td>Jan. 2009</td>
<td>100%</td>
<td>Non responders after 2 cycles</td>
</tr>
</tbody>
</table>

**Acronyms**

- **ALL**: Acute Lymphoblastic Leukemia
- **ASTS**: Advanced Soft Tissue Sarcoma
- **CML**: Chronic Mieloid Leukemia
- **EGFR mut**: Epidermal Growth Factor Receptor - activating mutations
- **EGJ AC**: Early esophago-Gastric Junction AdenoCarcinoma
- **HCC**: HepatoCellular Carcinoma
- **HNC**: Head and Neck Carcinoma
- **mBC**: metastatic Breast Cancer
- **mRCC**: metastatic Renal Cell Carcinoma
- **NSCLC**: Non-Small-Cell Lung Cancer
- **UCC**: Urothelial Carcinoma \textit{(transitional cell carcinoma)}
To date there are 78 schemes for new medicines/therapeutic indications via AIFA (Italian Reimbursement Agency) monitoring registries. 44 are in oncology, 15 for rare diseases, 7 for diabetes and the remaining 12 for other disease areas\textsuperscript{[152]}.

Among the 28 ‘AIFA Monitoring Registry’ risk sharing schemes, the majority are either payment by results schemes (Table 5) or discount/rebate schemes (referred to as cost sharing schemes)\textsuperscript{[152]}. Registries are in place for the remaining 50 medicines/indications. These schemes are in place to make sure the drugs are prescribed according to their reimbursed indication as well as post marketing surveillance of safety and efficacy (although this can be difficult in practice).

Under the systems put in place, each prescription is validated by the physician and a request automatically sent to the hospital pharmacy by e-mail to release the drug\textsuperscript{[128]}. If a patient is a non-responder (Table 5), the hospital pharmacist must apply for a rebate from the manufacturer. However, this requires non-responders to be documented by the hospital and relevant health authority. Otherwise, any undocumented non-responder will be treated as a success and no rebate given. There are also concerns regarding the criteria used for non-responders especially as this has not been made public and sometimes the time frames appear too short to allow a reliable assessment\textsuperscript{[126]}. In addition, there are concerns whether the Regions are able to fully claw back pertinent refunds from manufacturers for non-responders, with the suspicion that these may be delayed/not received as no data has yet been released by AIFA\textsuperscript{[128]}.

Having said this, one benefit of these schemes in Italy is that they do limit the off label use of expensive biological drugs, which is a recognised problem in the cancer field. In addition, help with obtaining rebates from Companies (Table 5). Consequently as previously mentioned, the main reason for initiating such registries in Italy appears to be for economic rather than for safety/effectiveness reasons.

4.3 Follow-up of prescribing restrictions among selected European countries

Typically prescribing restrictions have been initiated among European countries to help conserve resources. Different mechanisms are in place though to enhance their implementation. However, increasingly such schemes are administered electronically. Consequently, the authorities are increasingly able to follow-up adherence in practice.

4.3.1 Republic of Srpska

In the Republic of Srpska, only permitted diagnoses are recognized by the Information system of the Health Insurance Fund (HIF). As a result, all prescriptions with different diagnose than permitted for the drug will be automatically rejected and returned back to the pharmacy\textsuperscript{[15]}. Prescriptions with missing specialist’s recommendation on the back will also be returned to the pharmacy. In both cases, the invoice from the pharmacist will be reduced by the drug costs. Consequently, it is in the interest of the pharmacist to check prescriptions against the diagnosis/ requested data and alert the patient if needed, else they could lose income. Alternatively, patients pay the full cost of their medicines in the pharmacy themselves if the indication for the prescribed medicine is different from those permitted by HIF, or there is a missing opinion or other missing details on the prescription (if identified); otherwise they must return to the doctor for a revised prescription to limit their co-payment\textsuperscript{[16]}.

The impact of this enforcement is seen with the prescribing of ACEIs vs. ARBs in the Republic of Srpska\textsuperscript{[15]}. ARBs (losartan) were restricted to second line in patients having side-effects or intolerance to ACEIs and only upon specialist recommendation; they were also subject to a 50% co-payment\textsuperscript{[15]}. This was because of higher requested than similarly
effective ACEIs. This appreciably limited their utilisation in practice enhanced by only limited (10%) or no co-payment for established ACEIs (Figure 7)[15].

Figure 7 – Utilisation of ACEIs and ARBs in the Republic of Srpska 2003 to 2010[15]

NB. DD/ TID = DDDs per 1000 inhabitants per day

4.3.2 Austria, Croatia, Finland and Norway

In Austria there is an automated system for approving the prescribing of new drugs in where there are prescribing restrictions requiring prior authorisation (Figure 8). This is initiated via the Chief Medical Officer of the patient’s Social Health Insurance Fund[1,31,34,57].

Figure 8 – Automated approval system among the Social Health Insurances in Austria[57]
NB ABS = Arzneimittel Bewilligungs Service (Automatic Prior Approval Process); GINA = Gesundheits Informations Netzwerk-Box (Hardware for communication between GPs and the Social Health Insurance Fund)

From 2005, approval was granted via electronic communication systems between the prescribing physician and Chief Medical Officer (CMO) of the patient's social health insurance fund. Under this system, answers to the prescribing request must be received within 30 minutes for the first prescription. This can include a request for additional information if the supplied information is deemed insufficient to make a decision.

Having said this, the number of rejections/requests for further information has reduced appreciably in recent years as physicians and the various CMOs have developed a common understanding of what information is needed and sufficient for a successful approval request, i.e., reducing from 40% of requests in 2005 to only 2% to 3% of all requests currently.

If there is no response from the CMO of the patient’s social health insurance fund within 30 minutes, which is typically from the lead Sickness Fund at the time, the physician may prescribe the drug after completing the documentation. This includes the history of the patient in accordance with the prescribing restrictions. The documentation for the prescribing restrictions is subsequently integrated into the doctor's office software (Figure 8) leading to an integrated prescribing process.

This compares with Finland where enforcement of any prescribing restrictions such as those for dabigatran (Table 6A) takes place in the pharmacy. It typically takes an average of 16 days for the national health insurance agency (central review) to appraise the request from the physician together with the accompanying documentation, make a decision and inform the physician. This approval is needed for the prescription to be reimbursed; otherwise 100% co-pay without authorisation.

In Austria, there can also be situations where no prior authorisation is needed for certain drugs subject to prescribing restrictions. This is taken on trust. However, there is a payback mechanism if the physicians are found on random checking to be abusing the system. This was the situation with ARBs in Austria versus ACEIs, with the ARBs restricted from launch to patients having unacceptable side-effects from ACEIs or intolerant to ACEIs.

ARBs were also restricted to second line in Croatia. However, there was greater follow-up from physicians from the Health Insurance as well as the potential for fines and other measures if abuse was suspected. This had a greater influence in practice (Figure 9).
There was a more limited influence of prescribing restrictions when these were introduced in Norway for patented statins (atorvastatin and rosuvastatin) versus generic statins (Table 6)[34]. This was because the restrictions were based on trust with no aggressive follow-up by the authorities.

Table 6 – Influence of different prescribing restrictions on the utilisation of atorvastatin (A) and rosuvastatin (R) versus all statins (DDD basis)[34]

<table>
<thead>
<tr>
<th>Country and statins</th>
<th>Nature of the restriction</th>
<th>Overall change in utilization of patent-protected products</th>
<th>Change over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria – atorvastatin only (prescribing of rosuvastatin restricted from outset)</td>
<td>Physicians in Austria need the permission of the Chief Medical Officer of the patient’s Social Insurance Fund for atorvastatin to be reimbursed, otherwise 100% copayment</td>
<td>31.6% of statin utilization in 2003 (year before restrictions) to 10.9% in 2007</td>
<td>66% reduction</td>
</tr>
<tr>
<td>Finland – atorvastatin and rosuvastatin</td>
<td>Physicians in Finland have to specify on the prescription that second-line treatment is required before atorvastatin or rosuvastatin reimbursed, i.e., write ‘treatment-resistant disorder of lipid metabolism’ on the prescription</td>
<td>44.2% of statin utilization before restrictions to 18.3% 1.2 years after restrictions</td>
<td>59% reduction</td>
</tr>
<tr>
<td>Norway – only atorvastatin as rosuvastatin not reimbursed during the study period</td>
<td>Specific permission only needed in Norway if physicians wish to prescribe lower strength atorvastatin (10 and 20 mg), otherwise physicians trusted just to write the rationale for atorvastatin in the patient’s notes – although this could be followed up by NIS</td>
<td>46.2% in 2004 (full year before restrictions) to 26.2% in 2008</td>
<td>44% reduction</td>
</tr>
</tbody>
</table>

NIS: Norwegian National Insurance System.
4.3.3 Sweden

There was limited impact on the utilisation of patented statins following recent prescribing restrictions instigated by the TLV in Sweden\[154\]. This was no doubt affected by the timing of the introduction of prescribing restrictions, with the prescribing restrictions for atorvastatin and rosuvastatin introduced 6 or more years after intensive county council activities to try and enhance the prescribing of generic statins first line\[4,6-8\]. This compares with the more successful introduction of prescribing restrictions for ARBs introduced much earlier by the TLV\[36\].

The recent prescribing restrictions for duloxetine in Sweden, restricting its use to second line after for instance mirtazapine and venlafaxine, also appeared to have limited impact on the utilisation of duloxetine (Figure 10)\[155\]. This may be because of heterogeneity in the licensed indications for duloxetine. However, there was a significant increase in the utilisation of venlafaxine (Figure 10).

Figure 10 – Utilisation of newer anti-depressants before and after the introduction of generic venlafaxine as well as the prescribing restrictions for duloxetine\[155\]

4.4 Patient registries post launch

Patient registries in France have already been discussed (Section 2.3). As mentioned, these appear to be mainly for safety reasons. However, they do allow prescriptions to be monitored where there are concerns with usage patterns in practice. In addition, the potential to enhance prescribing efficiency with more appropriate sequencing of prescribing patterns such as generic PPIs and generic statins first line versus patented PPIs and statins respectively.

4.4.1 Scotland

There have been developments with databases within the national health service in Scotland, assisted by over 90% of the population having unique identifiers, to track patients
in both primary and ambulatory care\textsuperscript{156}. These registries are increasingly being used to potentially evaluate patient care including sequencing, as well as assess the effectiveness of different treatment approaches in practice (economic, safety and effectiveness issues). These registries are funded by NHS Scotland.

As a result, there is now the ability to link changes in prescribing patterns with health policy and other initiatives, including quality initiatives, from those implementing and analysing the changes. This linkage enhances the robustness of any policy measures analysed as well as help plan for the future\textsuperscript{156}.

Overall, NHS Scotland is now able to\textsuperscript{156}:
- Estimate the incidence and prevalence of diseases (drug specific to a given condition) and link with other registers
- Review the prescribing history of patients broken down by age, sex and deprivation
- Review the extent of co-prescribing, e.g. statins in patients over 40 with diabetes
- Review the actual sequencing of drug use, e.g. extent of therapeutic switching
- Assess the extent of persistence rate/ switch rate in practice
- Link with other datasets such as Hospital admissions, A & E, and out-patients to help assess outcomes in practice as we; as event linking for pharmacovigilance studies
- Determine the actual usage of drugs in children for potential paediatric licences

This is similar to a number of registries in Sweden, enhanced again by a unique number for each patient.

4.4.2 Key considerations when considering patient registries

Major issues for any patient registries based on experiences across Europe include\textsuperscript{57}:
- Whether there is an explicit rationale for instigating the registry, e.g. effectiveness, safety or economic considerations, or a mixture
- Funding arrangements – these need to be explicit and transparent. Such arrangements will no doubt vary according to the objectives of the patient registry. There can though be co-arrangements between health authorities and commercial organisations for funding as seen with the registry for natalizumab in France and the registries in Italy through AIFA (Italian Reimbursement Agency). However, these need to be agreed in advance and be transparent
- Ensuring any registries developed comply with the current regulations in each country including current legal requirements. However, recognising that there is a lack of any regulations in many countries
- Any issues regarding ownership need to be addressed and agreed in advance along with e.g. funding arrangements
- Ensuring sufficient time to develop ‘user friendly’ registries that will fully capture all the patient variables of interest and which satisfy the interests of all key stakeholder groups (compromise will be inevitable). This includes:
  - Ensuring as far as possible ease of use and acceptability of effort of all those involved
  - Ensuring the competence of those entering the data at every data entry point, especially with key issues such as adverse events; enhanced if patients are already experiencing difficulties with their condition such as depression, sleep disorders, fatigue and mobility, as seen in patients with multiple sclerosis. This is helped if the disease area is the speciality of those entering the data
- Ideally any registries developed need to be endorsed by leading research groups/ scientific societies, authorities and patient groups

Consequently, any patient registries need to be considered early, and time given to recruiting personnel competent in computer science and knowledgeable in the major
medical issues for the disease area\[57\]. The objective being to ensure user friendly screens are developed for data entry to enhance the completeness and accuracy of data entry\[52\]. Alongside this, incorporate systems that help detect errors quickly regarding data entry, e.g. contrasting replies to given queries, to quickly rectify these.

4.5 Dabigatran as well as new biological drugs generally

4.5.1 Health authority and health insurance company activities regarding dabigatran

Dabigatran received EU marketing authorisation in August 2011\[157,158\] for the prevention of stroke and systemic embolism/clot formation in adult patients with non valvular atrial fibrillation (AF) with one or more of the following risk factors:

- Previous stroke, transient ischemic attack or systemic embolism/clot formation
- Left ventricular ejection fraction < 40%
- Symptomatic heart failure > New York Heart Association (NYHA) class 2
- Age > 75
- Age > 65 in combination with one of the following disease(s): diabetes mellitus, coronary artery disease or arterial hypertension

Dabigatran has the potential to be an important new treatment for the prevention of stroke in patients with AF\[114,157,159\] especially where regular monitoring when patients are on warfarin is problematic. In addition, offering an alternative to warfarin where the initial or continued prescribing of warfarin is a concern due to adverse events or other issues.

However health authorities and health insurance companies have been active across Europe (Table 6A) to limit the use of dabigatran and/ or obtain discounts due to concerns with excessive bleeding, no known antidote, considerable variation in plasma drug concentrations in practice and the complete dependence on renal elimination of the active metabolite\[114,157,159-161\]. Table 7 summarises these activities to help reduce subsequent bleeding in practice especially among patients with poor renal function and potentially help preserve its availability.
Table 7 – Examples of activities across Europe to improve the quality and efficiency of prescribing of dabigatran

<table>
<thead>
<tr>
<th>Timing</th>
<th>Examples of activities</th>
</tr>
</thead>
</table>
| Pre-launch      | A) Sweden  
  • Extensive pre-launch activities among the counties in Sweden including critical drug evaluation written pre-launch before each approved indication  
  • Key messages from these have been broadcasted both to the public and to prescribers through websites of the Drug and Therapeutics Committee as well as the Swedish Medical Journal. In addition:  
  i) Appreciable number of pre-launch meetings and training sessions with all major physician groups around the key issues and concerns with dabigatran as well as its likely place in care  
  ii) Production of educational folders regarding dabigatran, slide kits, published articles, and data on the Janus website as well as published information for patients  
  • Forecasting the potential budget impact in 2011 and 2012 ahead of launch and monitoring this in practice  
  • Development of a laboratory method to monitor dabigatran in plasma with LC-MS/MS technology, and currently recommended sampling in the introductory phase of dabigatran to build a knowledge database. This to be followed by more situation-based sampling to improve patient safety in the future |
| Peri-launch     | A) England - Region  
  • Development of guidance stating that warfarin remains the first-line option for anticoagulation in patients with AF at high risk of a stroke, and PCTs should ensure optimal existing warfarin therapy services - including access to INR clinics, use of computerised decision-support software, and access to drugs for patients who are allergic to warfarin (the latter rare in practice)  
  • In addition, in view of the considerable financial implications, dabigatran treatment should only be prescribed for those patients:  
  o with co-morbidities who are adherent to warfarin monitoring and lifestyle requirements but need frequent co-prescribed medications that interact with warfarin and affect the patients’ time in therapeutic range (TTR)  
  o who are adherent to monitoring and lifestyle requirements but whose TTR remains unacceptable despite attempts to optimise treatment with warfarin (TTR rates should be set locally)  
  B) Germany  
  • Physician Associations stressing when launched that the current knowledge regarding safety with dabigatran was insufficient to answer all questions and physicians should be careful with prescribing particularly in the elderly  
  • The reporting of deaths from excessive bleeding further endorsed these concerns. As a result, limited prescribing in practice in ambulatory care  
  C) Slovenia  
  Reimbursed in line with the licensed indication in conjunction with a complex price: volume agreement |
| Post-launch     | A) Austria  
  • Ex ex-ante approval by the head physician of the patient’s social health insurance fund before reimbursement of dabigatran; otherwise 100% co-payment (mirroring other situations)  
  • Renal function has to be assessed and recorded prior to initiation of therapy with dabigatran through determining Creatinine-Clearance (CrCl) levels to exclude patients with severe renal dysfunction (= CrCl < 30ml/min). In addition during treatment, renal function has to be monitored where a decline is envisaged, e.g. patients with hypovolaemia, dehydration and the use of specific additional medication, and renal function has to be assessed at least once a year in patients aged 75 or older, and/or in patients with compromised renal function  
  B) England (Region)  
  Instigation of potential rebate schemes with the company to reduce the cost of dabigatran  
  C) Finland  
  • Reimbursement restrictions (Enforcement) - limiting the reimbursement of
dabigatran to patients with risk factors where satisfactory control has not been reached with warfarin; alternatively, warfarin cannot be prescribed due to side-effects or contra-indications.

- Enforcement at the pharmacy with on average 16 days needed for requests to be centrally reviewed and authorised. 100% co-pay without authorisation

D) Scotland (Region)

- Dabigatran should only be prescribed in line with advice from Healthcare Improvement Scotland, i.e. on balance of risks and benefits of dabigatran, warfarin remains the anticoagulant of clinical choice for moderate or high risk atrial fibrillation patients (CHA2DS2-VASc ≥ 2) with good INR control, and clinicians should only consider prescribing dabigatran in patients with:
  - poor INR control despite evidence that they are complying, or
  - allergy to or intolerable side effects from coumarin anticoagulants

E) Slovenia

- Education of all involved specialists and primary physicians on key safety aspects/ adverse events with dabigatran
- Prescribing restrictions (Enforcement)
  - Only reimbursed if initiated by an internist or neurologist in line with the approved indications and only for patients who are unstable on warfarin with the TTR < 65
  - Patients have to be followed in a tertiary or secondary anticoagulation centre; in primary care - only if authorized by tertiary or secondary centre.
  - Every patient has to be registered in a database and followed by the computer anticoagulation programme
  - Anticoagulation centres have to report once yearly to the tertiary centre regarding the number of patients experiencing minor and major bleeding, thromboembolic events, as well as deaths from bleeding or thromboembolism

4.5.2 FDA and EMA response to dabigatran

There is low mean oral bioavailability of dabigatran at only 6%, and complete dependence on renal elimination of the active metabolite\(^{[57]}\). As a result, careful considerations on dosage adjustments is needed in the elderly\(^{[162-164]}\), especially as published studies have already demonstrated a considerable variation in plasma drug concentrations as a result of this low bioavailability\(^{[169]}\), and even if the majority of patients achieve adequate drug levels, an appreciable proportion will either be sub-therapeutic or attain supra-therapeutic levels with fixed doses.

To help address these issues, the FDA in 2010 published data on the relationship between dabigatran concentrations in plasma and the risks of suffering a stroke or major bleeding. These data show a substantial variability in plasma drug levels between patients, demonstrating it is important to avoid too low or too high levels of dabigatran\(^{[166]}\). Consequently similar to warfarin, there appears to be a need to monitor patients on dabigatran and other NOACs in practice, reducing their value compared with early hopes of no monitoring\(^{[157,167,168]}\). The EMA in their Risk Minimization Plan for dabigatran also defined a cut-off for the risk of bleeding with the 150mg bid regimen of 200 ng/mL dabigatran in plasma at C\(_{\text{trough}}\)\(^{[169]}\). These developments emphasise that major stakeholder groups, including regulators, now favour the monitoring of patients to minimize the risks with dabigatran and/or to evaluate compliance in practice\(^{[167-172]}\).

4.5.3 Proposed model for managing the entry of new drugs

In view of the activities regarding dabigatran, a new model is proposed by health authorities and health insurance company personnel from across Europe to better manage the entry of new premium priced drugs (Figure 11). This builds on Figure 1 - again incorporating the three pillars of pre-, peri- and post launch activities\(^{[57]}\).
In the case of dabigatran, earlier efforts by regulators may have prevented cases of excessive bleeding and deaths, with the European Medicines Agency (EMA) reporting on 6 November 2011 that there had already been 256 spontaneous case reports of serious bleeding resulting in death recorded in the EudraVigilance database associated with dabigatran[161]. This resulted in warning letters to physicians (Table 6A). In addition, one health authority in Europe (Poland) is not reimbursing dabigatran in view of concerns with excessive bleeding in practice.

Consequently, one way forward for the authorities in Sweden to prevent such occurrences in the future could be closer co-operation between academic clinical pharmacology units in performing critical evaluations for drugs well before launch and the authorities prior to new drugs being submitted to the EMA. This builds on existing critical evaluation activities already being undertaken by groups such as the Clinical Pharmacology Units at the Karolinska Institutet as part of regional/ County horizon scanning/ budget forecast activities.

The situation regarding dabigatran, coupled with concerns regarding the number of new products in development with potential high costs (Figure 12), has resulted in suggested activities for all key stakeholder groups regarding new products where there are concerns with their safety and/ or budget impact in reality (Table 8).
Figure 12 – Number of new products in development among 117 companies that trade on the NASDAQ Stock Exchange – 42% of which are biological products (fourfold increase versus current marketed products dominated by drugs for cancer and immunological diseases)\[51\]

Table 8 – Key considerations among stakeholder groups to optimise the managed entry of new drugs\[57\]

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health Authorities/Health Insurance Companies/Physician Associations</strong></td>
<td><strong>Pre-launch</strong></td>
</tr>
<tr>
<td></td>
<td>- Plan early for the launch of new drugs especially those that could have an appreciable budget impact and/or safety considerations. This can be through working with countries/regions already engaged in such activities</td>
</tr>
<tr>
<td></td>
<td>- Work alongside key physician groups such as university clinical pharmacology groups to help critically appraise the potential role and value of new treatments ahead of launch, and use the data to develop robust budget impact models for future budget impact forecasts. Where possible, also give Drug and Therapeutic Committees and expert groups a major role to ensure consistent priorities for recommendations across divergent pharmaco-therapeutic groups</td>
</tr>
<tr>
<td></td>
<td>- Alongside this, work with Regulators to review potential areas of concern with new treatments especially around safety issues and potential ways to address this. In addition, check that any information provided by commercial organizations is comprehensive addressing any potential publication bias</td>
</tr>
<tr>
<td></td>
<td>- Plan early for the:</td>
</tr>
<tr>
<td></td>
<td>i) Incorporation of any pharmacogenetic tests that should to be available when a new ‘valued’ drug is launched to enhance its appropriate use</td>
</tr>
<tr>
<td></td>
<td>ii) Development of any patient registries to assess the effectiveness/safety of new drugs in practice (pharmacovigilance) as well as monitor prescribing against agreed guidance (Table 9)</td>
</tr>
<tr>
<td></td>
<td>- Regularly assess which products are likely to lose their patent in the next one to two years to help fund new premium priced drugs in the disease area/related disease area – especially with growing resource pressures. This can also assist with financial planning generally</td>
</tr>
<tr>
<td></td>
<td>- Work with pertinent patient groups especially regarding new treatments that could have serious patient issues to help develop appropriate educational campaigns for physicians and patients pre- to post-launch. Similarly also with key physicians, including those within Drug and Therapeutic Committees, to develop educational and communication strategies for GPs where pertinent</td>
</tr>
<tr>
<td></td>
<td><strong>Peri-launch</strong></td>
</tr>
<tr>
<td></td>
<td>- Consider the development of any potential new quality or prescribing indicators together with key stakeholder groups within and across European countries.</td>
</tr>
</tbody>
</table>
This includes their assessment in practice acknowledging that any indicators developed must have content validity, face validity, concurrent validity, construct validity and predictive validity

- Any indicators developed should subsequently be included in new guidance/guidelines as well as be part of any ongoing financial incentive schemes for physicians to optimise the use of priced drugs at launch
- Be critical of any proposed risk sharing arrangements using the criteria in Table 10 - mindful that such arrangements post launch could facilitate reimbursement and funding of new premium priced drugs (Table 6A)
- Continually check likely launch dates for new treatments with pertinent pharmaceutical companies to improve financial planning

**Post launch**

- Use administrative and/or medical databases to compare ‘real world’ patients with those included in Phase III RCTs in terms of their clinical features, treatments and potential outcomes to further refine future guidance
- Build in regular reviews of any reimbursement/funding/guidance especially as more data becomes available, e.g. more recent data challenges the key claim of ’no patient monitoring’ with dabigatran with ‘no patient monitoring’ typically built into submitted economic analyses
- Monitor physician adherence to any agreed guidance/reimbursement restrictions and seek to instigate academic detailing and other activities where continued concerns with prescribing

<table>
<thead>
<tr>
<th>Physicians</th>
<th>Peri-launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Work with health authority and health insurance companies pre-launch to critically review new treatments, especially where there are concerns with patient safety, to help enhance their appropriate use at launch. As a result, help keep them on the market</td>
<td></td>
</tr>
<tr>
<td>- As part of this, provide guidance to health authorities and health insurance agencies regarding optimal patient populations that maximize the value of new drugs, as well as potential quality/prescribing indicators</td>
<td></td>
</tr>
<tr>
<td>- Provide input into any discussions on the potential value of pertinent pharmacogenetic tests that may help optimise the use of new drugs post-launch</td>
<td></td>
</tr>
<tr>
<td>- Help with the development of educational materials for physicians and patients peri- and post-launch based on agreed guidance</td>
<td></td>
</tr>
<tr>
<td>- Assist with the design of any patient registries prior to launch, and follow this up after launch (Table 9). This can also include programmes that measure drug sequencing against any agreed guidance</td>
<td></td>
</tr>
<tr>
<td>- Help authorities critically assess proposed risk sharing arrangements, especially regarding the administrative burden and other key issues (Table 9)</td>
<td></td>
</tr>
<tr>
<td>- Assist hospital and ambulatory care DTCs with critically evaluating new treatments, as well as with planning of any interface arrangements to improve the co-ordination of care between primary and secondary care physicians</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient organisations</th>
<th>Pre-launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Provide input to health authority and health insurance companies pre-launch regarding any safety and effectiveness issues for new drugs from a patient’s perspective</td>
<td></td>
</tr>
<tr>
<td>- This includes any pertinent pharmacogenetic tests that may help optimise the use of new drugs to patient populations where the benefit: risk ratio (and hence ‘value’) is maximised</td>
<td></td>
</tr>
</tbody>
</table>

**Pre- and peri-launch**

- Help with the design and distribution of any patient information regarding new drugs, especially where potential safety issues, pre- and peri-launch |
- Help with the design of any quality/prescribing indicators for new drugs especially where there are issues of safety and sequencing as well as where
Major issues for health authorities and health insurance companies to consider before implementing patient registries, building on experiences discussed in Section 4.4, are included in Table 9.
Table 9 – Key considerations for patient registries[^57]

<table>
<thead>
<tr>
<th>Events/timing</th>
<th>Key considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Funding and other considerations</strong></td>
<td><strong>Funding</strong></td>
</tr>
<tr>
<td></td>
<td>• Funding arrangements need to be agreed, be explicit and transparent before initiation</td>
</tr>
<tr>
<td></td>
<td>• It is feasible and potentially pertinent (depending on the nature of the registry) for joint arrangements between authorities and commercial organisations, as seen with the registry for natalizumab in France and the registries in Italy through AIFA (Italian Reimbursement Agency)</td>
</tr>
<tr>
<td></td>
<td>• Any funding arrangements need to be transparent</td>
</tr>
<tr>
<td><strong>Legal considerations</strong></td>
<td>• Any patient registry considered must comply with current regulations in each country including current legal requirements. However, recognising that there is a lack of any regulations in many countries</td>
</tr>
<tr>
<td><strong>Ownership</strong></td>
<td>• Any issues regarding ownership need to be addressed and agreed in advance</td>
</tr>
<tr>
<td><strong>Endorsement</strong></td>
<td>• Ideally any registries developed need to be endorsed by leading research groups/scientific societies, authorities and patient groups</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>• Ensure sufficient time is made available to develop ‘user friendly’ registries that will fully capture all the patient variables of interest and which satisfy the interests of all key stakeholder groups (compromise will be inevitable). This includes:</td>
</tr>
<tr>
<td></td>
<td>• Ensuring as far as possible ease of use and acceptability of effort of all those involved</td>
</tr>
<tr>
<td></td>
<td>• Ensuring the competence of those entering the data at every data entry point, especially with key issues such as adverse events; enhanced if patients are already experiencing difficulties with their condition such as depression, sleep disorders, fatigue and mobility, as seen in patients with multiple sclerosis. This is helped if the disease area is the speciality of those entering the data</td>
</tr>
<tr>
<td></td>
<td>• As a result, any patient registries need to be considered early pre-launch (Figure 6), and time given to recruiting personnel competent in computer science and knowledgeable in the major medical issues for the disease area. The objective being to ensure user friendly screens are developed for data entry to enhance the completeness and accuracy of data entry. Alongside this, incorporate systems that help detect errors quickly regarding data entry, e.g. contrasting replies to given queries, to quickly rectify these</td>
</tr>
</tbody>
</table>

[^57]: Key issues that national and regional health authorities and health insurance companies should consider when appraising any risk sharing arrangements suggested by commercial organisations to enhance the chance of reimbursement, outside of price: volume agreements, straight discounts or rebates, are included in Table 10. These build on the experiences in for instance Scotland and Italy (Section 4.2).
Table 10 – Key issues for health authorities and health insurance companies when considering risk sharing arrangements for new drugs

<table>
<thead>
<tr>
<th>Key issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Appropriateness of the arrangement for the situation/ circumstances including current or proposed service delivery arrangements</td>
</tr>
<tr>
<td>• Whether the objectives and scope of the proposals are explicit and transparent</td>
</tr>
<tr>
<td>• Whether the new drug is a novel treatment with envisaged health gain and few effective treatments in a high priority disease area backed up by good translational science</td>
</tr>
<tr>
<td>• Whether health authorities will end up funding a substantial proportion of a new drug’s development costs through exposure registries post launch, and who will own the data. Ideally, all key stakeholders should be involved in their development and in principal funded by the manufacturer</td>
</tr>
<tr>
<td>• Whether the new drug could have a substantial beneficial impact on service delivery and/ or safety but this is difficult to prove in Phase III trials</td>
</tr>
<tr>
<td>• Whether there will be a high administrative burden reducing overall savings</td>
</tr>
<tr>
<td>• Whether patient compliance is important but has not been fully addressed</td>
</tr>
</tbody>
</table>

As previously mentioned, regulatory agencies and academic and other units involved with critical drug evaluation pre-EMA approval, such as those in Stockholm and Italy, need to work closely together especially where there are concerns with the safety of new drugs in a wider patient population.

4.6 Personalised medicine

4.6.1 Research activities including future suggestions for licensing authorities

It is crucial that researchers and commercial organisations obtain data from trials demonstrating an association between any suggested biomarker and disease outcomes to enhance future endorsement and funding, similarly for new targeted treatments. However, it is recognised that such trials may be extremely complex and costly, and may pose serious ethical dilemmas, especially if it becomes increasingly impractical to have multiple subgroups in a study with different treatment approaches.

One potential way forward is to have clinical trial evidence convoluted with systems biology modelling such that multiple trials validate the mathematical models produced, which can subsequently be used to predict treatment effect for individual patients and their tumours. However, such studies will need specific objectives including the prospective definition of diagnostic, screening or prognostic biomarkers alone and/ or in combination before any studies are undertaken. The combination of prospective clinical trials and observational studies may also help accelerate the translation of clinical research results into routine medical practice.

In addition, it is increasingly important for the national and authorities across continents (e.g. EMA and FDA) collaborate on the development and establishment of guidelines for genotyping and biomarker testing, and their incorporation into future targeted treatments, to guide companies in the future. This could include standardising trial data documentation before endorsing genetic and biomarker testing. This is important with up to 50% of current clinical pipelines among leading companies including targeted or stratified medicines. In addition in oncology, it is increasingly a pre-requisite for pharmaceutical companies to design clinical trials including biomarkers.
4.6.2 Resource concerns with personalised medicines

There are concerns that pharmaceutical companies will seek orphan status for new targeted treatments. This will increase treatment costs and away from the desired goal of reduced or similar costs of care with the added benefit of reduced NNTs and/ or increased NNHs for drugs prescribed. Potential ways forward for key stakeholder groups to optimise the benefits of personalised medicine/ targeted approaches - building on Table 8 - include (Table 11):

Table 11 – Key issues surrounding the utilisation and funding of new targeted treatment approaches among key stakeholder groups

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Major issues and barriers to consider building on Table 6</th>
</tr>
</thead>
</table>
| Governments, Health Authorities and Health Insurance Agencies | **General**  
- To push for stricter definitions of orphan drug status to reduce the number of targeted drugs seeking this definition and their anticipated high acquisition costs, i.e. 5/100,000 rather than currently 5/10,000  
**Pre-launch**  
- Where pertinent and feasible, seek partnerships between health authorities, academic institutions, and commercial organisations to accelerate developments that can improve care at reduced costs - especially through greater use of generic therapies  
**Peri-launch**  
- Consider developing new quality indicators around new targeted therapies together with key stakeholder groups. This should include their assessment in practice acknowledging that any indicators developed must have content validity, face validity, concurrent validity, construct validity and predictive validity  
- Seek to include new indicators in any new guidance/ guidelines associated with new targeted treatments, as well as potentially consider their inclusion in any ongoing financial incentive schemes for physicians  
**Post launch**  
- Build in regular reviews of any reimbursement/ funding/ guidance especially as more data becomes available  
- Monitor physician adherence to any agreed guidance/ reimbursement restrictions instigated for new targeted treatments, and instigate additional activities if needed |
| HTA units | **General (in addition to providing critical input peri-launch)**  
- To develop and refine new methodological approaches that take into account potential changes in clinical trials and increasing use of models in systems biology-based personalised medicine approaches – especially around defining sub-populations  
- This could include progression of constructive technology assessments until more data becomes available. However, mindful of concerns with surrogate data  
- HTA units could also become involved with discussions to modify the legal framework as well as approval processes as more information regarding personalised medicines become available  
**Post launch**  
- Assist with post launch follow-up of drugs particularly to re-assess product safety in routine clinical care, as well as provide guidance where concerns |
| Physicians | **General**  
- To provide independent input into clinical trial design for new biomarkers that are disease based; alternatively aimed at differentiating patients/ populations based on either differences in drug metabolism, drug transporter capacity or receptor variants  
- This includes helping design trials that meet the designated sensitivity and specificity goals. Such studies could include cohort studies with samples and data collected prospectively. Nested case-control studies are also potentially useful so long as blinding is maintained  
- To assist with the design of technology platforms and mathematical models that help with future decision making for individual patients at the complexity of biological systems unfold. By doing so, improve the translation of research results into clinical practice  
- To push for ongoing independent re-interpretation of the implications of genetic tests |
and therapies in the light of new discoveries, through using trained clinical pharmacologists and physicians specialising in areas such as molecular oncology

**Pre-launch**
- To help translate the language of genomics into lay language to assist patients with their decision making, including the benefit-risk ratio of treatments
- To work with health authority and health insurance companies pre-launch to critically review new targeted treatments, especially where there are concerns with their potential value in practice
- As part of this, provide guidance to health authorities and health insurance agencies about potential new quality indicators
- In addition, to provide input into discussions on the potential value of new pharmacogenetic tests that optimise the use of new drugs post-launch

**Peri-/ post-launch**
- To assist with the design of any patient registries prior to launch, and follow this up after launch building on the experiences with e.g. natalizumab
- Help authorities critically assess proposed risk sharing arrangements, especially regarding the potential administrative burden
- To assist hospital and ambulatory care DTCs with critically evaluating new targeted treatments, as well as the planning of any interface arrangements to improve the co-ordination of care between primary and secondary care physicians
- To help with the development of educational materials for physicians and patients peri- and post-launch based on agreed guidance

### Patients/ patient groups

**General**
- To help incorporate personalised medicine into patient education schemes to enhance patient understanding of this complex field for better informed discussions with physicians

**Pre-launch**
- To provide input to health authority and health insurance companies pre-launch discussions regarding key issues for new targeted treatments from a patient’s perspective
- To support the development of patient registries or data collection activities around new targeted approaches; the results of which can also be used to inform future clinical trials

**Pre- and peri-launch**
- To help with the design and distribution of any patient information regarding new drugs, especially where potential safety issues, pre- and peri-launch
- To help with the design of any quality indicators for new targeted drugs from a patient’s perspective
- To provide input into the potential value of new technologies especially where the findings including potential biomarkers are inconclusive

**Post launch**
- Help further refine information for patients as more knowledge becomes available about new targeted drugs regarding any key side-effects and their implications

### Pharmaceutical and diagnostic companies

**Pre-launch**
- Instigate realism into Corporate discussions regarding potential requested prices acknowledging that the cost of providing tests includes both the acquisition costs as well as facility costs as resource pressures grow. This becomes even more important if multiple genetic tests are needed
- As part of this, avoid the temptation to seek ‘orphan status’ for new targeted therapies as resource pressures grow since this may avoid rejection/ delayed funding even with risk sharing/ patient access schemes to lower acquisition costs. This includes recognition that without targeting, new products would be unlikely to achieve premium prices as more standard drugs become available as generics and niche areas diminish
- To acknowledge that the definition of orphan drug status may need re-defining to smaller patient populations, especially with the increasing costs of orphan drugs and growing resource pressures
- To seek scientific advice from relevant registration, HTA and funding bodies pre-launch on the potential need and relevance to develop markers and tests concurrently with developing new drugs
- Similarly, scientific advice for new drugs that require associated genetic testing to
maximise their value
- To explore possible partnerships between diagnostic and pharmaceutical companies to provide a combined package

### 4.7 Improved interface management including Spain (Catalonia) and Scotland

Figure 13 illustrates the waste of resource that can occur with poor interface management. Prescribing restrictions were introduced in Norway to limit the prescribing of premium priced esomeprazole versus generic PPIs such as omeprazole\(^\text{[34]}\). However, the first prescription or first recommendation is via hospital specialists who were not subject to the same restrictions. As a result, limited pressure to change their prescribing habits coupled with GPs reluctant to change any prescriptions meant limited change on utilisation patterns in reality (Figure 13) compared to the situation with the statins (Table 6).

**Figure 13 – Influence of the prescribing restrictions for esomeprazole following the availability of generic omeprazole in Norway**\(^\text{[34]}\)

<table>
<thead>
<tr>
<th>Year</th>
<th>2001</th>
<th>2003</th>
<th>2005</th>
<th>2007</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Generic omeprazole launched</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic lansoprazole launched</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Prescribing restrictions for esomeprazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.7.1 **Catalonia**

A number of measures have been recently introduced in Catalonia to help contain expenditure for expensive out-patient drugs. These include\(^\text{[18]}\):

- Development of prescribing indicators for both new and existing drugs:
  - Indication: Antiretrovirals (new treatments, monotherapy), Onco-hematology (use of EPO and GSF related to chemotherapy), Nephrology (use of EPO pre-dialysis and dialysis, safe haemoglobin levels)
  - Selection: Antiretrovirals (type of HAART), Onco-hematology (cost/patient of cytostatics, use of pegfilgrastim), treatment of secondary hyperparathyroidism in nephrology, anti-TNF alpha selection, drugs for multiple sclerosis and pulmonary hypertension, use of biosimilars
  - Duration: cost/patient or length of treatment
- Development of information systems to capture the data and indicators for hospitals (direction and management teams, pharmacists and physicians) and community: benchmarking between hospitals to enhance the quality and efficiency of care
- Regular meetings between professionals of hospitals and health authorities

Within the Catalan Health Service - information processing, scorecard evaluation, benchmarking, data diffusion, technical discussions with physicians, pharmacists and hospital managers, follow-up and contracts around the selected indicators of drug use (indication, selection, duration), bilateral agreements, continuous monitoring and budget allocation\(^{180}\).

Alongside this, the instigation of incentive schemes (Table 12) in out-patients to improve the interface management between outpatient care and primary healthcare centres, especially given the incentive system in PHCs and current budget devolution. Incentive schemes in primary care include limiting the prescribing of expensive drugs with limited health gain compared to current standards such as dabigatran (Table 6A), aliskeran, dabigatran, ezetimibe and others\(^{181}\).

Table 12 – Current incentive scheme for out-patient care within the Catalan Health Region\(^{263}\)

<table>
<thead>
<tr>
<th>Indicators (DTC)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-recommended new medicines</td>
<td>2 -1</td>
</tr>
<tr>
<td>ARB / (ARB + ACEI)</td>
<td>1 - 0,5</td>
</tr>
<tr>
<td>Recommended Antiulcer drugs</td>
<td>0,5</td>
</tr>
<tr>
<td>Recommended NSAID</td>
<td>0,5</td>
</tr>
<tr>
<td>Recommended Lipid Lowering drugs</td>
<td>1 - 0,5</td>
</tr>
<tr>
<td>Recommended Non- insulin Antidiabetic drugs</td>
<td>1 - 0,5</td>
</tr>
<tr>
<td>Safe use of drugs</td>
<td>1,5</td>
</tr>
<tr>
<td>@prescribing for outpatient/discharged/emergency</td>
<td>1,5</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

Alongside this, the instigation of an electronic system whereby Primary HealthCare Physicians can request from the specialists the rationale behind a given prescription (e-cap) (Figure 14) especially if there are concerns with the recommendation against agreed guidance\(^{181}\).
Figure 14 – Example of the e-cap interface between GPs and hospital specialists in Catalonia[181]

Such systems are likely to evolve in other countries to improve the interface management between GPs and hospital specialists to improve care in the future.

4.7.2 Scotland

There have been integrated systems in Scotland for many years. This includes early introduction of joint working between primary and secondary care. This includes Drug & Therapeutics (D & T) in each of the Health Boards working across sectors with safe and quality prescribing seen as the initial driver with cost containment soon also a factor applying equally in primary and secondary care[122]. This was facilitated by a single budget for healthcare (primary and secondary care) within each Health Board in Scotland. As a result, joint working became the norm, and is now transferred to other areas of activity.

Individual D & T committees are seen as beneficial to enhance local acceptance and ownership. Key criteria of DTCs include[122]:

- Multidisciplinary in nature
- Contain people from both primary and secondary care
- May include patient/public input
- Decisions are evidence-based with full declarations of interest from members
- There is a limited role for ‘key opinion leaders’
- Decisions/recommendations apply equally in primary and secondary care with no ‘carte blanche’ for specialists. However, some medicines may be limited to use on specialist advice (or even requiring a specialist prescription)
- DTC minutes are published on the website of the pertinent Health Board
- Formularies must be regularly updated to keep them current, and regularly communicated to all stakeholders to enhance subsequent adherence
All prescribing is subsequently monitored together with Formulary adherence by pharmacists and others working in the Health Boards. There are also ‘Drug of choice’ initiatives to aid quality and efficiency in prescribing\(^{(122)}\).

Non-formulary drugs are permitted if they can be justified through individual patient treatment requests, etc. Their use would be questioned if high in primary care, with individual prescribers targeted for academic detailing and other activities where concerns. Such prescribing may also be questioned in ‘real time’ in hospital\(^{(122)}\).

Any guidelines written locally within Health Boards must follow national guidance (SIGN) and be jointly written. Again, full declarations of interest and evidence-based rather than opinion-based, with interface issues usually specifically addressed, e.g. guidance on referral to secondary care\(^{(122)}\).

There are also Managed Clinical Networks (MCNs) in Scotland, which are disease-specific networks. These cross specialty, e.g. physician/surgeon/pharmacist, and the interface between primary and secondary care. They aim to cover all aspects of the management of identified diseases including diagnosis, investigation, and monitoring, with medicines use also analysed. These are seen as facilitating the managed introduction of new drugs – especially if these cross sectors, with adherence to all aspects of MCN monitored to improve future quality and efficiency of care\(^{(122)}\).

5 Areas where Sweden already provides direction to other countries

Areas where national authorities in Sweden as well as the counties provide direction to other countries and regions include:

- Developing forecasting models to improve budgeting with good accuracy overall, e.g. Stockholm model, which is now being looked at with others as part of the 4 counties project with SKL
- Undertaking critical drug evaluations pre-launch using independent experts to guide future activities including physician and patient education pre-launch as well as development of guidelines for new drugs before their launch, e.g. Stockholm County Council
- Developing essential drug lists to improve the quality and efficiency of ambulatory care prescribing with high acceptance rates, e.g. ‘Wise List’ in Stockholm County Council
- Extensive use of drug and patient registries to monitor care against agreed guidance, e.g. DU09%, ARBs second line after ACEIs and the follow-up of rimonabant prescribing post launch, as well assessing the effectiveness and safety of drugs in practice, e.g. registries for TNF alpha inhibitors
- Instigation of compulsory generic substitution, apart from an agreed limited number of situations, alongside recent measures including monthly auction of generics to obtain still lower prices for generics as well as smooth prices out (reduce spikes that had occurred previously)
- Re-assessment of the value of drugs in classes at a national level leading to activities including price reductions, prescribing restrictions and delisting where concerns with the value and usage of existing drugs
- Instigating assessments by patients of the services provided by Primary Healthcare Centres following budget devolution to ensure quality of care and reduce criticism that physicians in PHCs will choose the cheapest products/approaches to care rather than consider all key aspects before treatment

6. Suggested activities for Sweden to improve the managed entry of new drugs

Suggestions build on those for health authorities and other key stakeholder groups contained in Tables 8 - 11, and are again broken down into the 3 pillars (Figure 11). These suggestions arise from the fact that, as stated, there appear to be no publications from
national/ regional authorities in Europe in peer reviewed journals discussing new models to optimize the managed entry of new premium priced drugs and their outcome. European regions and countries have though published or discussed elements of the 3 pillars including horizon scanning, forecasting, registry, risk sharing/ ‘coverage with evidence’ and interface management activities; however, these publications have not been consolidated apart from proposals from the Piperska group (Figures 1 and 11).

These suggestions are seen as critical especially given the plethora of new expensive biological drugs, including new targeted drugs, likely to be launched in Sweden over the coming years (Figure 12). They also build on existing activities that are already undertaken well in Sweden to help improve the managed entry of new drugs, as well as ongoing initiatives to enhance prescribing efficiency of both new and existing drugs (Section 5).

In more detail:

- **Pre-launch** – greater integration between national and regional bodies to avoid duplication of horizon scanning/ budget impact analyses building on current national/ regional projects to improve the knowledge base; critically challenging pharmaceutical companies with the data they provide to support premium prices; developing joint guidance on the prescribing of new drugs that crosses sectors. In addition, start developing quality indicators as well as start planning patient registries where pertinent pre-launch

- **Peri-launch** – consider cost/QALY guidance for national reimbursement along with budget impact considerations; extending national reimbursement considerations to include hospital only products; learning from other countries regarding risk sharing arrangements as well as refining key considerations for any patient registries/ quality indicators instigated post launch

- **Post-launch** – routinely monitoring whether prescribing restrictions are being followed; instigate any quality indicators developed to improve patient care – especially with the new drugs; seek to re-assess the value of new drugs in practice using patient registries – especially where concerns with their effectiveness and/ or safety; instigate measures to improve interface management between primary and secondary care especially where there are continuing concerns; help resurrect the eSPC project

One major theme for the future is that national and regional groups and authorities in Sweden should seek to publish their activities in peer reviewed English speaking journals to guide future activities in Sweden as well as across Europe. This includes for instance the impact of the recent prescribing restrictions on subsequent usage patterns using patient registries. The data has been collected but not submitted for publication.

Programmes should also be implemented to enhance INN prescribing to help avoid patient confusion/ potential duplication of prescriptions that currently arise when patients are dispensed different branded generics on each occasion (when new drugs eventually lose their patents) and limited contact between pharmacists and patients\(^{186}\). Confusion is enhanced with the current monthly auction situation for generics in Sweden\(^{43,183}\). Without INN prescribing, community pharmacists will need to spend time with patients allaying any fears/ concerns\(^{4,25,43}\), which is currently not happening\(^{186}\). To address this, pharmacists are now requesting additional payment for these activities\(^{183}\).

In more detail:

### 6.1 Pre-launch activities

There should be improved co-ordination of activities among the counties/ national bodies regarding Horizon Scanning and Budget Impact analysis if this is not already happening. This though needs to accelerate to avoid duplication as well as pool expertise given the number of complex premium priced biological drugs in pharmaceutical company pipelines.
All pertinent national agencies need to be part of this process. This includes providing information to the national/ regional bodies undertaking horizon scanning/ critical evaluations on all clinical trials undertaken with new products as there is still suspicion that Companies are withholding vital information from reimbursement/ funding bodies - especially negative information\(^{[184]}\). This can be addressed by relevant personnel knowing the full extent of any Phase II/ III and other trials instigated during product development and requesting such data from Companies if not already provided.

Acceleration and subsequent activities could be funded from the same source as the current regional/ SKL activities. If needed, additional funds taken from research programmes (see below).

Alongside this, national agencies should seek to improve their interactions with key academic units undertaking critical evaluations of new drugs on behalf of the counties before launch. Such interactions should enhance the critical nature of future interactions between national agencies and pharmaceutical companies during the submission and review process, e.g. the excessive bleeding and deaths with dabigatran were predicted before launch due to the characteristics of the drug particularly in the elderly population with poor renal function. These concerns with dabigatran led to extensive activities among the counties in Sweden (Table 6A) to inform physicians as well as help limit the prescribing of dabigatran post-launch to second line after warfarin. Potential activities that could have been pursued by national authorities ahead of launch could have been a requirement of the Company to develop a test pre-launch/ pre-approval to monitor dabigatran blood levels in practice as part of the registration/ reimbursement process. In addition, highlight the extra care/ extra caution needed in the elderly in the SPC along with monitoring - especially elderly patients with poor renal function.

During the pre-launch phase, key national and regional groups including academic groups and those from County Council can use their combined knowledge to develop guidance for the prescribing of new drugs post launch, especially where there are safety concerns. Any guidance developed can be further refined prior to launch if needed as more data becomes available. This can be part of pan-Sweden horizon scanning/ budget impact/ critical drug evaluation exercise as key academic groups and others already contribute to budget impact/ critical drug evaluation exercise for new drugs.

Any guidance on the prescribing of new drugs post launch can be used to develop pertinent quality indicators during the pre-launch phase for immediate introduction once new drugs are on the market. Any quality indicators developed must have content validity, face validity (relevance, credibility and acceptability), concurrent validity (compared with gold standard), construct validity (theoretical construct of quality), and predictive value to be of use\(^{[114]}\). Consequently, this will require resources to develop appropriate indicators, and can again be part of the current regional/ SKL activities.

For instance, quality indicators for dabigatran in the prevention of stroke in patients with AF could potentially have been based around adherence to the following (building on Table 6A):

- Warfarin remaining the drug of choice for new patients unless contra-indicated
- The renal function of patients to be assessed and recorded prior to initiation of therapy with dabigatran through determining Creatinine-Clearance (CrCl) levels to exclude patients with severe renal dysfunction (= CrCl < 30ml/min)
- During treatment, renal function to be regularly monitored where a decline is envisaged, e.g. patients with hypovolaemia, dehydration and the use of specific additional medication
- Renal function to be assessed at least once a year in patients aged 75 or older, and/or in patients with compromised renal function
• Patients who are well adjusted on Vitamin K antagonists should not be switched to dabigatran

It is likely that the development of appropriate quality indicators will require additional funds. These could be derived from two sources:

• Universal levy from Pharmaceutical Companies when they submit their new drugs for reimbursement considerations (this already happens in Poland when companies submit their dossiers for new drugs to the National HTA agency)
• Levy on pharmaceutical company marketing activities. A 5% levy is already in existence in Italy to fund independent R & D activities[^186]. This is in addition to any funding for current registries, etc., within Sweden

Key national and regional groups involved with horizon scanning/ budget impact/ critical drug evaluations could also start progressing patient registries for pertinent drugs pre-launch ready to refine their characteristics including data entry criteria peri- and post-launch as more data becomes available. These in accordance with the suggestions in Table 9 and Section 4. Medical societies, clinical pharmacology and County Council personnel need to be included in this development, with funding potentially coming from a levy on pharmaceutical company marketing activities.

Starting the development of registries pre-launch should help ensure robust and workable registries are in place at launch. To date, patient registries across countries have been initiated particularly regarding patient safety. This is certainly the case for registries involving the TNF alpha inhibitors for rheumatoid arthritis and psoriasis. As already mentioned, the registry in France for nataluzimab was developed both for patient safety reasons as well as gain vital information to improve patient management in the future given the effectiveness of this drug in clinical trials and now in practice. The major exception is Italy where patient registries for biological drugs and others appear to have been initiated mainly for economic reasons, e.g. to help reduce off label use as well as help lower the cost of these expensive drugs.

Funding of patient registries post launch also needs to be sorted out and agreed before launch. Funding sources can include commercial organisations where pertinent. However, any funding arrangements have to be transparent and the registries scientifically sound, including potential endorsement by the relevant scientific societies, for the long term benefit of all key stakeholder groups.

6.2 Peri-launch activities

6.2.1 General considerations

Key areas for the authorities in Sweden to consider in the future to enhance the quality and efficiency of prescribing for new drugs include:

• National reimbursement agencies to assess the role and value of all new drugs and not just ambulatory care drugs. This mirrors the situation in other European countries including Italy, Poland, Spain and the UK
• Giving cost/ QALY guidance for new products. This mirrors the situation in for instance Poland and the UK. This should reduce the number of new premium priced drugs automatically reimbursed (although the number rejected has increased from 10% of new drugs in recent years to 17%)[^214], as well as increase the number of new drugs with restricted reimbursement - mirroring the situation in for instance Scotland (Figure 3), especially as the number of standard drugs losing their patents will continue growing
• National and regional bodies to formally consider the inclusion of risk sharing/ patient schemes to enhance the value of new drugs for reimbursement if needed in all or selected populations. This mirrors ongoing activities across Europe (Section 4.2 and Table 10). Any risk sharing schemes proposed and evaluated though should take
cognisance of earlier suggestions and recommendations based on the experiences across Europe

The increasing workload of the TLV to evaluate all products, rather than just ambulatory care products, could potentially be funded from a levy on pharmaceutical companies when they present their application files for new hospital products. However, potential levies can be minimised by using the expertise of personnel involved with national/ regional groups undertaking critical drug evaluations pre- and peri-launch.

Alongside this, reimbursement decisions should be regularly reviewed by national authorities as more standard comparators lose their patents and/ or more information becomes available to question initial assessments. Dabigatran is a good example where initial cost-effectiveness analyses were based on the premise of no monitoring, which is now no longer the case.

6.2.2 Development of prescribing restrictions, registries and coverage with evidence schemes

There is an opportunity for Sweden to learn from other countries when considering how to enhance the impact of prescribing restrictions for new and existing drugs. This is in view of their variable impact to date for anti-depressants, anti-hypertensive drugs and statins.36,154,155

Suggested ways forward include mirroring the Austrian prior authorisation system (Figure 8) whereby IT upgrades are installed in each physician office, and the offices of each County Council, building on electronic prescribing software systems that already exist within each County. As a result, prior approval systems can be streamlined and become effective within a short time frame, mirroring the situation in Austria.

The county councils should combined such activities to make any new system efficient, building on the ongoing co-operation regarding horizon scanning/ budget impact analyses to avoid duplication. Such activities though will need to be monitored and reported back by independent academic units, with the lessons learnt helping to guide and refine future activities and practices.

Other suggestions include refining risk sharing arrangements such as ‘coverage with evidence’ schemes. Potentially, pharmaceutical companies should initially cover the additional acquisition cost of the new drug over and above the current standard drug themselves until data is available to either refute or approve the funding of the new technology at premium prices. This can be administered centrally given the good databases that currently exist in Sweden. It addition, avoid the situation whereby national and regional authorities appreciably contribute to the development costs of a new pharmaceutical product whilst its value is being assessed in practice. Ideally, it is up to pharmaceutical companies to provide data to support premium prices. Otherwise, such schemes should be rejected unless there are very good reasons.

It is particularly important for their scientific credibility that the assessment of any post launch ‘coverage with evidence’ studies are undertaken by independent academic units. This is because this will:

- Reduce/ negate any suspicion of bias when undertaken by companies in association with groups
- Improve the scientific content of the studies given previous concerns with the scientific credibility of the protocols submitted by the pharmaceutical companies to demonstrate that physicians were complying with prescribing restrictions for new drugs.34
• Enhance the chances of publishing the findings in peer-reviewed journals with increasing notice being paid to conflict of interests. In addition, universities are incentivised to seek publication
• Enhance the chances of the findings being viewed and considered by health authorities in other countries as they seek information about new technologies

An illustration of these points is seen with atypical antipsychotic drugs:

• Head-to-head studies post launch of the effectiveness or cost-effectiveness of different atypical antipsychotics favoured the sponsoring company[73]. However, meta analyses performed by the Cochrane Collaboration and others failed to demonstrate any meaningful difference between atypical antipsychotics apart from perhaps clozapine[71,74,75]
• There is increasing concern regarding increased the prescribing efficiency of Risperdal depot (long acting risperidone injections - RLAI) in practice given that most of the published studies with RLAI are open label and subject to sponsor bias coupled with a number of independent randomised and observational studies showing no benefit versus oral treatments[186-194]. However other academic units have demonstrated benefits

Such activities could be funded by pertinent pharmaceutical companies co-ordinated and funded by national agencies. The chosen academic units must be free to publish their findings to provide future guidance to health authorities in Sweden as well as across Europe. However before initiation, any coverage with evidence schemes should be very critically considered as the uptake of the new drug may be accelerated as companies seek to answer questions as soon as possible.

6.2.3 – Interface management

The instigation of one national agency evaluating both hospital and ambulatory care products should facilitate interface management.

Potential ways forward for regional authorities to improve interface management includes (building on existing activities within the counties):

• Making hospital physicians financially responsible for their prescribing actions, building on activities that are ongoing in ambulatory care
• DTCs integrated across sectors – this could include producing additional formularies for drugs that are mainly prescribed in hospital out-patient clinics rather than primary healthcare centres (PHCs). As a result, authorities indirectly endorsing the continued prescribing of patients' medications in hospitals especially those with chronic conditions
• Physicians in PHCs able to interrogate hospital specialists about their prescribing habits where deemed appropriate and impacting on PHC budgets (as seen currently in Catalonia in Spain)
• Endorsing switching of medications in hospital if these help reduce costs in ambulatory care without compromising care, e.g. patented ARBs to multiple sourced ARBs. In addition, potentially also regarding biosimilars if this helps reduce costs in the community without compromising care

6.2.3 eSPCs

Concurrent with these activities, national agencies in Sweden should push for continued development of eSPCs to accompany the launch of any new product. The objective being that the eSPCs eventually become an important information source for prescribing information for new drugs at launch as the use of electronic prescribing systems grow.
This project was started by the EMA with KI, Sweden, playing a key role\textsuperscript{[175]}. However, it has currently stalled.

### 6.3 Post-Launch activities

#### 6.3.1 Registries, prescribing restrictions and quality indicators

Implementation of any registries, prescribing restrictions and quality indicators should build on activities already taking place in the pre-launch (Section 6.2) and peri-launch (Section 6.3) phases.

The review of any information arising from registries should include academic units for the reasons stated above. This also applies to any ‘coverage with evidence’ activities as well as the assessment of prescribing restrictions in practice.

It is vital that national agencies seek to publish the findings from any registry studies as well as any coverage with evidence schemes/ prescribing restrictions in peer reviewed English speaking journals. This enhances the methodology undertaken, increases the learnings for all key stakeholder groups in Sweden as well as provides vital information for health authorities across Europe. National authorities in Sweden have not always published their findings, and this needs to be rectified as ever more expensive drugs are launched.

This also applies to the use of any quality indicators developed for new drugs especially if these need to be refined as more data becomes available.

#### 6.3.2 Risk sharing arrangements

Mechanisms should be put into place regarding risk sharing arrangements as these are new to Sweden. These could include involving personnel from other countries/ localities who have been involved with researching/ implementing risk sharing arrangements to provide guidance/ input into national/ regional groups when risk sharing arrangements are proposed by pharmaceutical companies to enhance the value of their new drugs. This could also include establishing a ‘second opinion’ committee – funded from existing/ planned national budgets to optimise the managed entry of new drugs.

In addition, national and regional authorities in Sweden should seek to research and publish their activities and findings where possible so they and others can learn from these new experiences in Sweden.

#### 6.3.3 Routine re-assessment of the value of new drugs

National agencies to routinely re-assess the value of drugs in a class when the first product in a class/ related class becomes available as a generic. Currently this only happens when complete classes have been re-assessed such as those for depression, hypertension and hypercholesterolaemia\textsuperscript{[35,154,155]}. This could include patented ARBs after generic losartan or aliskeren now that generic ACEIs and ARBs are available, patented and new atypical anti-psychotics after generic risperidone and olanzapine, and Risperdal Depot after generic risperidone. Such activities could result in prescribing restrictions, delisting or rebates once their ‘value’ is appreciably altered.

Prescribing restrictions are already in operation among some European countries for patented ARBs versus multiple sourced ARBs as well as for Risperdal depot.
6.3.3 Drug utilisation, signals and ADR reporting

It is recognised that the reporting of adverse events is generally under-reported across Europe including Sweden. One way forward could be for national authorities to consider rolling out across the Counties current schemes whereby primary health care centre physicians are incentivised to write an annual quality report about ways to improve their prescribing habits\[196\]. Typical areas for improvement include greater knowledge of pharmacotherapy as well as greater reporting of adverse events.

Other suggested ways forward with ever more complex drugs could include promoting drug utilisation research linked with adverse event reporting - especially where there are concerns with the safety of drugs. This builds on the ongoing ARITMO project regarding drugs that potentially increase cardiac arrhythmias including antibiotics, anti-histamines (H1) and anti-psychotics\[197,198\].

7 Research areas for the future (in addition to activities mention in Section 6)

7.1 Models to enhance the managed entry of new drugs

Ongoing models in existence among regional bodies in Sweden to optimise the managed entry of new drugs should be formally evaluated for at least 2 new drugs - building on the activities for 3 classes (NOACs, oral drugs for patients with Type 2 diabetes and those with chronic hepatitis C.

This is because, as already mentioned, there are currently no publications that track the managed entry of new drugs nationally or regionally around the 3 pillars, i.e. pre- to post-launch. As also discussed, countries and regions across Europe have published/ reported on the various parts of the 3 pillars including horizon scanning activities, forecasting activities, registries and risk sharing arrangements – but no one has published on combined models across all 3 pillars for specific premium priced drugs/ drugs where there are safety concerns.

This dearth of publications led to the development of suggested models by the Piperska group (Figure 1), further refined for new NOACs (Figure 11) and new targeted treatments including suggested future activities for all key stakeholder groups in the future (Tables 8 and 11).

Academic units along with national/ regional authorities should be involved with suggested research activities as well as potential publication in peer reviewed journals. These activities can be resourced from funds already committed nationally to better manage the entry of new drugs.

7.2 Specific drug classes

7.2.1 New oral anti-coagulant drugs (NOACs)

There have been ongoing activities by NEPI and others to document current usage patterns for dabigatran\[194\]. These show currently limited utilisation of dabigatran in practice compared with the number of patients with AF. However, there is considerable variation among the counties.

Alongside this, patients on dabigatran have been entered into specific patient registries with good uptake, e.g. over 90% of patients in Ostergotland and Kalmar.

Consequently, suggested activities include analysing the uptake of all recent anti-coagulants (dabigatran, rivaroxaban and apixaban) along with warfarin both within the counties in
Sweden and across Europe along with health policies to influence their use. This builds on existing activities within the counties, as well as the initial publication regarding dabigatran\(^{(57)}\). The findings can be used to refine further models (building on Figure 11) as well as help with the development of future measures and initiatives to improve the managed entry of new drugs where there are concerns with their budget impact and/or safety in a wider patient population.

7.2.2 New drugs for patients with Type 2 diabetes

There are currently a number of drugs classes available to treat patients with Type 2 diabetes. These include well established drugs such as metformin and the sulfonylureas as well as newer drugs including the dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin and saxagliptin, meglitinides, and glucagon-like peptide-1 (GLP-1) receptor agonists.

Meta analyses have demonstrated that all these oral drugs reduce HbA1c levels by a similar amount. However, metformin appeared to be more effective in reducing HbA1c than the DPP-4 inhibitors as monotherapy. Drug combinations with metformin (such as metformin plus sulfonylureas or metformin plus DPP-4 inhibitors) have generally been more effective in reducing HbA1c than metformin monotherapy, with most combinations including those with metformin, sulfonylureas, and thiazolidinediones similarly efficacious in lowering HbA1c levels.

Compared with metformin, thiazolidinediones and sulfonylureas have a greater effect on weight gain, with metformin decreasing LDL cholesterol relative to pioglitazone, sulfonylureas, and DPP-4 inhibitors. Sulfonylureas have a fourfold higher risk of mild/moderate hypoglycemia compared with metformin alone.

The newer agents are though appreciably more costly than older drugs such as metformin and sulfonylureas. Consequently, suggested activities include reviewing the utilisation of oral drugs to treat Type 2 diabetes within the counties in recent years alongside demand-side measures to increase the quality and efficiency of care. Subsequently, compare the utilisation patterns for these drugs combined with ongoing reforms in Sweden with other Western European countries. The findings can again be used to refine potential new models to improve the managed entry of new drugs, especially given the rising prevalence of patients with Type 2 diabetes.

7.2.3 New premium priced drugs for patients with Hepatitis C

New drugs are being launched to treat patients with chronic hepatitis C who have previously been treated with interferon alfa(pegylated or non-pegylated) alone or in combination with ribavirin. These include telaprevir and boceprevir at GBP22,000 – 31,000/ course. Consequently, these drugs should be reserved.

Again it is suggested that the utilisation patterns of these new drugs to treat patients with chronic hepatitis C be assessed in each county along with ongoing measures to enhance their use as second line drugs. The subsequent findings can be used to further refine new models for new drugs if needed. Utilisation patterns and ongoing reforms can also be assessed among Western European countries, with the findings compared with Sweden to again further refine new models if needed.

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9 Appendix

Table 1A – Demand-measures introduced especially in Östergötland and Stockholm to enhance prescribing efficiency[4]

<table>
<thead>
<tr>
<th>Measure</th>
<th>Stockholm</th>
<th>Östergötland</th>
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<tbody>
<tr>
<td>Education – Takes many forms including drug formularies and guidance, distribution of educational materials, academic detailing, feedback or a combination of these</td>
<td>Wise Drug List&lt;br&gt;Guidelines/ guidance, Implementation enhanced by a strict policy of all DTC members declaring any conflicts of interest&lt;br&gt;Support throughout the county by DTCs of specialty focused continuous medical education&lt;br&gt;Computerised tools and decisions to support rational prescribing including DU90% methodology&lt;br&gt;Feedback on performance including prescribing targets&lt;br&gt;Patient oriented educational activities</td>
<td>Guidelines and academic detailing&lt;br&gt;Computerised tools for analysis and bench-marking of drug prescribing&lt;br&gt;Support for local quality assurance programs&lt;br&gt;Feedback on performance of drug prescribing focusing particularly on equity&lt;br&gt;Patient information programmes on drugs</td>
</tr>
<tr>
<td>Engineering - concerned with introducing organisational changes including monitoring the quality of care</td>
<td>Structured programmes for the introduction of new medicines&lt;br&gt;Prescribing targets</td>
<td>Introduction of new drugs through ordinary processes for prioritisation and resource allocation</td>
</tr>
<tr>
<td>Economic interventions - including devolving drug budgets and co-payments</td>
<td>Financial incentives&lt;br&gt;Limited projects devolving budgets</td>
<td>Total budget devolution for drugs to PHCs and specialist clinics at hospitals and in out-patient settings&lt;br&gt;Monitoring the cost-effectiveness of drug prescribing</td>
</tr>
<tr>
<td>Enforcement - includes initiatives that physicians or companies are obliged to follow</td>
<td>Monitoring prescribing of restricted drugs against agreed guidance with additional interventions if required</td>
<td>Focusing on equity in access to drugs within different therapeutic classes as part of payment process</td>
</tr>
</tbody>
</table>

Table 2A – Case histories of combined measures amongst European countries and their outcome[17,183]

<table>
<thead>
<tr>
<th>Class/Country</th>
<th>Countries, measures and their influence with increasing prescribing efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPIs A)</td>
<td>Sweden versus Ireland&lt;br&gt;Multiple demand side measures, including education, economics, and engineering, appreciably increased the prescribing of omeprazole in Sweden once generics became available, with stable and low utilisation of esomeprazole&lt;br&gt;This compared with Ireland with more limited demand side measures to combat industry activities, where utilisation of omeprazole decreased and the utilisation of esomeprazole increased following generic omeprazole (Figure 1A)&lt;br&gt;This combined with the measures to lower the prices of generics in Sweden (Figure 2A) resulted in reimbursed expenditure for PPIs decreasing by 49% in 2007 vs. 2001 despite utilisation increasing by 53%. This compares with a 2.6 fold increase in expenditure in Ireland during the same period versus a 2.4 fold increase in utilisation&lt;br&gt;As a result, reimbursed expenditure (Euros/ 1000 inhabitants/ year in Ireland (GMS population – greater co-morbidity than the normal population) in 2007 was over 10 fold greater at over €60,000 versus €5832 for Sweden</td>
</tr>
<tr>
<td></td>
<td>B) Netherlands&lt;br&gt;Multiple demand-side measures, coupled with supply-side measures to lower generic prices, led to reimbursed expenditure for the PPIs falling by 58% in 2010 vs. 2000.</td>
</tr>
</tbody>
</table>
This was despite a 3 fold increase in utilisation

C) Scotland
- Multiple demand side measures, coupled with supply-side measures to lower generic prices, resulted in expenditure/1000 inhabitants/ year for the PPIs in 2010 at GBE5481 (€6301), 56% below 2001 levels despite a 3 fold increase in utilisation
- It is estimated that PPI expenditure in Scotland would have been GBE159mn per year greater in 2010 - assuming similar overall utilisation coupled with utilisation patterns and their costs kept the same as the pre-patent loss situation

Statins

A) Austria
Restrictions limiting the prescribing of patented statins (atorvastatin and rosuvastatin), combined with measures to lower the prices of generics and originators, resulted in a 3% decrease in total expenditure for the statins in 2007 versus 2001 despite approximately 2.4 fold increase in utilisation

B) Sweden versus Ireland
- There was a similar situation with the statins, with the utilisation of atorvastatin and rosuvastatin rising appreciably in Ireland following the availability of generic simvastatin, accounting for nearly 80% of all statin utilisation (DDD basis) in 2007 (Figure 3A)
- As a result, statin expenditure increased 4.9 fold in Ireland between 2001 and 2007 for the GMS population (utilisation increasing 7.3 fold) versus a 39% reduction in Sweden (compared with a 3.2 fold increase in utilisation)
- Again, reimbursed expenditure (Euros/1000 inhabitants/ year) in Ireland (GMS population) in 2007 was over 10 fold greater than Sweden at over €60,000 versus €5192 for Sweden

C) Netherlands
Multiple demand-side measures, coupled with supply-side measures to lower generic prices, led to reimbursed expenditure for the statins falling by 14% in 2010 vs. 2000 despite a 3.8 fold increase in utilisation

D) Scotland
- Multiple demand-side measures, coupled with supply-side measures to lower generic prices, resulted in expenditure/1000 inhabitants/ year for the statins in 2010 at GBE11420/1000 inhabitants (€13113) only 7% above 2001 levels despite a 6.2 fold increase in utilisation
- Expenditure for the statins would have been GBE290mn per year greater in 2010 assuming similar overall utilisation coupled with utilisation patterns and their costs kept the same as the pre-patent loss situation

ACEIs/ARBs

A) ACEIs and ARBs in Austria, Croatia and Scotland
- Expenditure (Euros)/1000 inhabitants/ year remained relatively stable for the renin-angiotensin inhibitor drugs in Austria, Croatia and Scotland between 2001 and 2007 despite volumes increasing by between 69% to 159% during this period through multiple supply- and demand-side measures
- Demand-side measures in Austria and Croatia centred on prescribing restrictions, limiting the prescribing of ARBs to patients having unacceptable side-effects from ACEIs or unable to tolerate them. Multiple initiatives were undertaken in Scotland to limit ARB prescribing including education, economics and engineering initiatives

B) ACEIs, ARBs and other antihypertensive drugs in Sweden
- The proportion of the Swedish population being dispensed antihypertensive drugs increased by 0.5%-units to 16.5% in September–December 2008 (after the review of anti-hypertensive drugs by the TLV and the introduction of prescribing restrictions for ARBs) compared to the same period in 2007
- Patients initiated on ARBs decreased by 24%, whilst increasing for ACE inhibitors (ACEI) and calcium channel blockers, by 14% and 12%, respectively
- The proportion of patients initiated on ARBs prescribed an ACEI within 24 months prior to an ARB increased from 51% to 67%
- As a result of these initiatives combined with initiatives to lower the prices of
generics in Sweden, total expenditure on anti-hypertensive drugs decreased by 4.7% to €73 million in September–December 2008 compared to the same period in 2007.

C) Generic losartan in Austria
- Prescribing restrictions have recently been lifted in Austria for losartan (following generic availability) but not the other patented ARBs
- As a result, its utilisation increased significantly compared to the patented ARBs helping to increase ARB prescribing efficiency in Austria

Table 3A – Examples of patient access schemes in Australia and Europe including free drug or discounts[125]

<table>
<thead>
<tr>
<th>Country</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>* Pricing arrangements for Section 100 drugs (restricted supply of specialist drugs to hospitals or other similar facilities) whereby companies typically provide free drugs to lower the cost per unit; alternatively provide an agreed percentage discount to Medicare Australia*</td>
</tr>
<tr>
<td></td>
<td>- Examples include:</td>
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<td>- Abacavir – the Pharmaceutical Benefit Scheme would only pay for 2 packs for every 3 supplied</td>
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<td>- Cirone progesterone gel – Listing was achieved with the help of a 49.5% discount</td>
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<td></td>
<td>- Deferasirox – a 20% discount was applied to achieve reimbursement</td>
</tr>
<tr>
<td>UK (England, Wales)</td>
<td>Sunitinib for patients with metastatic renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>- The first treatment cycle (6-weeks costing an average of GB£3139/ patient) is provided free via a patient access programme. Subsequent cycles are funded by the NHS until disease progression</td>
</tr>
<tr>
<td></td>
<td>- The Department of Health considered the scheme did not constitute an excessive administration burden on the NHS</td>
</tr>
<tr>
<td></td>
<td>Sorafenib for metastatic renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>- The first pack (200mg x 112 tablets) will be provided free by the manufacturer under the agreed patient access programme</td>
</tr>
<tr>
<td></td>
<td>- This equates to £2980.47p excluding VAT</td>
</tr>
</tbody>
</table>
Table 4A – Examples of patient access schemes involving price caps in operation in Europe[115]

<table>
<thead>
<tr>
<th>Country</th>
<th>Examples of Price Capping Schemes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>Bevacizumab for the management of approved cancers cannot exceed €25,941 per year.</td>
</tr>
</tbody>
</table>
| Sweden           | • Stockholm County Council initially signed an agreement in April 2008 lasting until end December 2009 whereby if patients with advanced cancer exceeded an accumulated dose of 10,000mg of bevacizumab, the additional costs would be fully covered by the Company.  
• The scheme has now been extended into 2010.  
• Other regions in Sweden have also been offered similar schemes. |
| UK – England, Wales | Ranibizumab  
• The first 14 injections in the eye for the management of wet age-related macular degeneration (AMD) are paid for by the national health service with patients demonstrating an 'adequate response' to therapy to continue with treatment.  
• The drug costs of any subsequent ranibizumab injections will be reimbursed by the company (Novartis) either as free drug or as a credit note.  
Ustekinumab for moderate to severe psoriasis  
• Two 45mg vials (90mg) are provided for people who weigh more than 100kg at the same cost as a single vial in the form of free drug. |
Table 5A – Examples of performance-based or outcome-based schemes in Europe[^125]

<table>
<thead>
<tr>
<th>Country</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Denmark        | • A population based ‘no cure, no pay’ strategy for valsartan to lower BP was initiated to enhance market share (similar to the US – below)  
• Money back initiative for nicotine chewing gum if patients do not like the taste of any of the four flavours on offer  
• ‘No play; no pay’ schemes for drugs for erectile dysfunction |
| Italy          | **CRONOS scheme for Alzheimer drugs**  
• Initially the acetyl cholinesterase inhibitors were ‘C’ classification in Italy, i.e. 100% co-payment  
• However, under the CRONOS scheme, companies initially provided acetyl cholinesterase inhibitors such as donepezil free of charge to specialist clinics for the first four months of treatment  
• The NHS subsequently covered the drug costs in responders, with patient outcomes recorded  
• This observational study, which demonstrated health gain in patients with mild to moderate AD, resulted in the NHS subsequently funding these drugs (‘A’ classification) provided patients were treated in specialist outpatients. However, there were no quality checks on the completed forms |
| UK – England and Wales | **Bortezomib for the treatment of first relapse of multiple myeloma**  
• This scheme is based on a 50% reduction in serum paraprotein levels (M-protein) by the fourth cycle. The NHS will continue funding treatment in responders, with the cost/ QALY reduced from £38,000/ QALY to a more acceptable £20,700/ QALY, with manufacturers refunding the cost of the drug if a 50% reduction was not achieved. This is usually in the form of free drug, which is seen as easier to implement  
• In addition, prices remain at the launch price despite up to a 60% discount in reality, which is important with the UK often used as a reference price country  
• However as there have been concerns whether M-protein is a good surrogate for life expectancy. Alongside this, 10 to 15% of patients do not have measurable serum M-protein levels  
**Atorvastatin for CHD prevention**  
• The pharmaceutical company agreed to fund the health authority for wasted resources if atorvastatin failed to reduce LDL-C levels to agreed targets when properly titrated  
• No refunds were given as all properly titrated patients reached target lipid levels helped by the recruitment of two nurses. The nurses worked with GPs and practice nurses aiding issues such as concordance, although a 20% adjustment was included in the outcome guarantee model  
• GP and patient participation was helped by CHD being a high priority disease area in the UK with national initiatives to improve care  
• However, there were problems with the scheme once generic simvastatin became available and lipid level targets lowered |
Table 6A – Examples of national and regional health authority and health insurance company activities across Europe regarding dabigatran for the prevention of stroke in adults with non-valvular AF from pre-launch to July 2012

<table>
<thead>
<tr>
<th>Country</th>
<th>Date dabigatran reimbursed for AF</th>
<th>Summary of activities till July 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>February 2012</td>
<td>Enforcement - Ex ante approval by the head physician of the patient’s social health insurance fund before reimbursement of dabigatran; otherwise 100% co-payment (mirroring other situations). This is now fully automated, with the first prescription typically taking approximately 30 minutes to approve (Figure 1)</td>
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<td>The renal function has to be assessed and recorded prior to initiation of therapy with dabigatran through determining Creatinine-Clearance (CrCl) levels to exclude patients with severe renal dysfunction (= CrCl &lt; 30ml/min). In addition during treatment, renal function has to be monitored where a decline is envisaged, e.g. patients with hypovolaemia, dehydration and the use of specific additional medication, and renal function has to be assessed at least once a year in patients aged 75 or older, and/or in patients with compromised renal function. Otherwise 100% co-payment</td>
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<td>Health Insurers (WGKK – Vienna) have also stated that patients who are well adjusted on Vitamin K antagonists should not be switched to dabigatran as there is no additional clinical benefit, enhanced by currently no known antidote.</td>
</tr>
<tr>
<td>Croatia</td>
<td>Not currently reimbursed</td>
<td>Only reimbursed for the prevention of venous thromboembolism in patients undergoing hip or knee surgery, and only in hospitals.</td>
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<td>Prescriptions can be traced in hospital if abuse is suspected.</td>
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<tr>
<td>England</td>
<td>August 2011</td>
<td>A) National – NICE: Dabigatran is recommended in line with the licenced indication, with the decision whether to start treatment made after an informed discussion between clinicians and patients about the risks and benefits of dabigatran versus warfarin.</td>
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<td>For patients already on warfarin, the potential risks and benefits of switching to dabigatran should be considered in light of current INR control.</td>
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<td>B) Regions (Midlands – MTRAC) - Education Guidance stating that warfarin remains the first-line option for anticoagulation in patients with AF at high risk of a stroke, and PCTs should ensure optimal existing warfarin therapy services - including access to INR clinics, use of computerised decision-support software, and access to drugs for patients who are allergic to warfarin (the latter rare in practice)</td>
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<td>In view of the considerable financial implications, dabigatran treatment should only be prescribed for those patients:</td>
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<td>• with co-morbidities who are adherent to warfarin monitoring and lifestyle requirements but need frequent co-prescribed medications that interact with warfarin and affect the patients’ time in therapeutic range (TTR)</td>
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<td>• who are adherent to monitoring and lifestyle requirements but whose TTR remains unacceptable despite attempts to optimise treatment with warfarin (TTR rates should be set locally)</td>
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<td>Alongside this, patient follow-up via agreed shared care protocols with ongoing monitoring of prescribing costs and feedback from Pharmaceutical Advisers.</td>
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<td></td>
<td>C) Localities</td>
</tr>
<tr>
<td></td>
<td>i) Coventry and Warwickshire Area Prescribing Committee (Education, engineering):</td>
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</tr>
<tr>
<td></td>
<td>• Dabigatran should only be initiated by a specialist</td>
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<td></td>
<td>• Follow on prescribers should receive a checklist from the initiating specialist indicating patients are suitable for dabigatran and have received appropriate guidance from the specialist</td>
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<tr>
<td></td>
<td>• No follow-on prescribing if checklist is unavailable from the specialist</td>
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ii) East Lancashire (Education):
Initially not approved (October 2011); but subsequently approved for usage in January 2012. As part of this:
- Patients currently stable on warfarin therapy should not be considered for dabigatran.
- Dabigatran should only be considered for prescribing by appropriate specialists (including GPs initiating therapy as part of specially commissioned anti-coagulation services).
- Dabigatran should only be considered as an alternative to warfarin for stroke prevention in AF patients in the following:
  1. Patients for whom warfarin is contra-indicated or not tolerated or not suitable (e.g. Mental/cognitive impairment) - NOTE: If warfarin is contra-indicated due to increased bleeding risk then dabigatran would also be contra-indicated.
  2. Patients who are poorly controlled on warfarin, i.e. a clinical judgement based on patient reviews relating to the extent of INR results outside of target therapeutic range (TTR). If dabigatran is considered as a suitable alternative, prescribers must fully document the rationale.

iii) NHS Lancashire (Education, economics):
- Currently developing a position statement/guideline for AF which endorses warfarin as the drug of choice and dabigatran should only be used in certain situations
- Alongside this, possibility of ongoing rebate schemes to reduce the cost of dabigatran to NHS Lancashire

iv) NHS Bury
- Greater Manchester Medicines Group [GMMMG] and the Greater Manchester and Cheshire Cardiac and Stroke Network [GMCCSN] agreed joint guidance for the use of dabigatran behind warfarin which resulted NHS Bury establishing a “Gateway” whereby GPs had to seek permission from NHS Bury to prescribe dabigatran.
- This resulted in very few requests, with even fewer requests granted due to ongoing clinical and economic concerns. However, this changed following NICE advice [TA249] in March 2012 arguing for use according to the licensed indication.
- Consequently, NHS Bury are looking to fill this information void including prescribing decision aids to help maintain current usage levels.

<table>
<thead>
<tr>
<th>Country</th>
<th>Status</th>
<th>Reason</th>
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</thead>
<tbody>
<tr>
<td>Estonia</td>
<td>Not reimbursed</td>
<td>Dabigatran rejected for this indication as not seen as sufficiently cost-effective versus warfarin in view of its high acquisition costs.</td>
</tr>
</tbody>
</table>
| Finland | April 2012 | Reimbursement restrictions (Enforcement) - limiting the reimbursement of dabigatran to patients with risk factors where satisfactory control has not been reached with warfarin; alternatively, warfarin cannot be prescribed due to side-effects or contra-indications.  
Enforcement at the pharmacy with an average 16 days needed for requests to be centrally reviewed and authorised. 100% co-pay without authorisation. |
| France | ASMR Rating February 2012 | Classified as ASMR V (no additional therapeutic value) compared with current therapies for the prevention of strokes in adults at risk who have 'non-valvular atrial fibrillation' and are considered to be at risk of stroke.  
a) April 2012 – Education:  
i) Publication of information about dabigatran from the authorities including a warning from the medicine agency ANSM (ex afssaps):  
  - risk of haemorrhagia and overdose  
  - absence of biological tests and an antidote  
ii) Publication of advice for 1) change of prescribing from or to other anticoagulants, 2) patients undergoing surgery  
b) May 2102  
Translation of the latest advice from the EMA  
Once reimbursed, patients will be followed up to assess the effectiveness and safety of dabigatran in practice (pharmacovigilance). |
| Germany | August 2011 | Activities (education and engineering) included the following:  
- Information from State and National Physician Associations to ambulatory care stressing concerns and potential sanctions with ‘off label’ use in AF prior to licensing approval  
- Physician Associations stressing when launched that the current knowledge regarding safety with dabigatran was insufficient to answer all questions and |
physicians should be careful with prescribing particularly in the elderly
• The reporting of deaths from excessive bleeding further endorsed these concerns. As a result, limited prescribing in practice in ambulatory care
• A warning letter from Boehringer Ingelheim following issues and deaths from excessive bleeding in Japan. In the letter, BI stated that patients should not be prescribed dabigatran if their creatinine clearance is <30ml/min and/or significant renal impairment. In addition, the need to monitor renal function when using dabigatran especially in patients prone to poor renal function or where renal function is deteriorating (measured using the Cockroft-Gault formula)
• Information to patients about anti-coagulation in general including dabigatran

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<tr>
<th>Country</th>
<th>Action/Status</th>
<th>Relevant Information</th>
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| Ireland     | July 2012                    | August 2011: The National Centre for Pharmacoeconomics (NCPE) stated that ‘dabigatran etexilate could be considered a cost effective treatment for the prevention of stroke and systemic embolism for adult patients with atrial fibrillation and one or more of the specified risk factors. However there are uncertainties associated with some of the clinical input data and the model assumptions in addition to the considerable opportunity cost, in the region of €13 million over 10 years’. In view of this a reduction in price is recommended to ensure value for money for the health service in Ireland (HSE).

November 2011: A HSE Statement advises that the drug will not be reimbursed if prescribed for any new patients for SPAF due to concerns with the relatively short median follow up period of 2 years in the RE-LY study, the rates of major GI bleeding and GI life-threatening bleeding with dabigatran 150 mg, the absence of a specific antidote to dabigatran and the increased frequency of myocardial infarction in the dabigatran arms of the RE-LY trial.

July 2012: A HSE Statement states that: Warfarin is the recommended first line agent for stroke prevention in atrial fibrillation (SPAF). Dabigatran should be reserved for:
• Existing patients on warfarin with poor INR control despite adhering to monitoring and lifestyle requirements. Documentation of attempts to optimise warfarin therapy is required.
• Existing patients who require regular periodic treatment with medicines that are known to interact with warfarin
• Patients with a documented allergy to warfarin

As part of the implementation, the physician responsible has to make a specific application for each patient to HSE. Otherwise, pharmacists will not be reimbursed for dispensing dabigatran to patients for SPAF without prior reimbursement approval (enforcement)

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<tr>
<th>Country</th>
<th>Action/Status</th>
<th>Relevant Information</th>
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| Italy       | Undergoing evaluation        | Prelaunch activities included:
• Educational meetings at regional and national level with different stakeholders to (i) identify possible prescriber(s) (cardiologists only or GPs as well) and the target population; (ii) define a sustainable price and the features of a follow-up programme for patients treated with dabigatran
• Forecasting the potential budget impact in the first and second year post launch with the help of key stakeholder groups
Post launch activities will include planning a national registry containing details of the clinical characteristics, current pharmacological treatments, and outcomes of patients with AF prescribed dabigatran (in line with new biological and other drugs)

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<tr>
<th>Country</th>
<th>Action/Status</th>
<th>Relevant Information</th>
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<tbody>
<tr>
<td>Lithuania</td>
<td>Undergoing evaluation</td>
<td>No reimbursement decision</td>
</tr>
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</table>

Netherlands Not yet reimbursed
• The National Health Council advised the Ministry of Health to reimburse dabigatran (and rivoraxaban) but additional research concerning the specific Dutch situation is needed. The research should be performed in the real population in practice
• The Ministry of Health subsequently asked prescriber organizations to establish a guideline for the safe and responsible introduction of dabigatran. This guideline should contain a protocol for calamities, prioritized patient groups (which groups are high priority) and instructions to contribute to a patient registry. Decisions for reimbursement will be postponed till after the publication of this guideline.
• As part of reimbursement, the Ministry of Health aims for a price-volume agreement with the manufacturers.
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<tr>
<th>Country</th>
<th>Status</th>
<th>Information</th>
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<tbody>
<tr>
<td>Norway</td>
<td>Not yet reimbursed</td>
<td>Dabigatran was recently assessed by the National Medicines Agency of Norway (NOMA) and considered cost-effective for the prevention of stroke in adults with non-valvular AF. However, due to the calculated budget impact (&gt; 5 million NOK five years after introduction of general reimbursement), the decision to reimburse resides with Ministry of Health and Care Services. No ongoing activities such as price; volume agreements or educational activities.</td>
</tr>
<tr>
<td>Poland</td>
<td>Not reimbursed</td>
<td>The Transparency Council of the Polish HTA Agency assessed dabigatran for its licensed indication for inclusion in the national reimbursement list. The Transparency Council subsequently rejected reimbursement due principally to safety concerns. The Council was concerned about information on the number of serious bleeds and death in the United States and New Zealand in the short term after its launch in these countries.</td>
</tr>
<tr>
<td>Portugal</td>
<td>August 2011 for 110mg (when PL granted)</td>
<td>Reimbursed for 110mg for the prevention of stroke in patients with atrial fibrillation once approved by EMA, as already reimbursed for prophylaxis in patients undergoing hip and knee surgery (current legislation in Portugal). As a result, appreciably increasing utilisation of 110mg strength. 150mg is currently not reimbursed for AF, and is currently under evaluation with an accompanying pharmacoeconomic study vs. warfarin submitted by the Company to demonstrate the cost-effectiveness of 150mg dabigatran vs. warfarin. Ongoing activities to seek lower acquisition costs (price) for AF patients for the 110mg strength.</td>
</tr>
<tr>
<td>Republic of Serbia</td>
<td>Not reimbursed</td>
<td>Dabigatran not reimbursed in Serbia due principally to concerns with its price/budget impact versus warfarin for the prevention of stroke in patients with AF and the perceived benefits in practice.</td>
</tr>
<tr>
<td>Republic of Srpska</td>
<td>Not reimbursed</td>
<td>Not currently reimbursed by Health Insurance Fund (HIF) and not listed on any of HIF’s lists (Positive drug list or Hospital drug list) as currently HIF has not received any reimbursement request from either the clinicians or the manufacturer.</td>
</tr>
<tr>
<td>Scotland</td>
<td>August 2011</td>
<td>A) National (SMC) Dabigatran is accepted for use in accordance with the approved indication as it was seen to be at least as effective as standard oral anticoagulation at preventing stroke or systemic embolism and was not associated with an increased risk of major bleeding. B) Health Boards (Regions) a) Fife (December 2011) Dabigatran should only be prescribed in line with advice from Healthcare Improvement Scotland, i.e. on balance of risks and benefits of dabigatran, warfarin remains the anticoagulant of clinical choice for moderate or high risk atrial fibrillation patients (CHA2DS2-VASc ≥ 2) with good INR control, and clinicians should only consider prescribing dabigatran in patients with: poor INR control despite evidence that they are complying, or allergy to or intolerable side effects from coumarin anticoagulants. b) Highlands (December 2011) Warfarin remains the anticoagulant of choice as a greater rate of GI bleeding and GI symptoms with dabigatran. In addition, much easier to manage major bleeding in patients with warfarin as no licensed product available to reverse bleeding with dabigatran (unlike warfarin). If needed, dabigatran should only be started when patient's INR has dropped below 2. c) Lothian (May 2012 Bulletin) Dabigatran classified as 'not preferred as suitable alternatives exist'. The main concerns were safety and the management of bleeding. d) Tayside (December 2011) Prescribing restricted to patients with poor INR control on warfarin, or with allergy to or intolerable side-effects from coumarin anticoagulants. Under the guidance, anticoagulant clinics in NHS Tayside will identify eligible patients.</td>
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and make contact with relevant GPs with the decision to transfer patients resting with GPs

- In addition, prescribers should note recent MHRA advice that renal function should be assessed in all patients before starting dabigatran. While on treatment, renal function should be assessed at least once a year in patients >75 years and when a decline in renal function is suspected.

Slovakia
April 2012

- Dabigatran was assessed by Categorisation Committee at the Slovak Ministry of Health and considered cost-effective for the prevention of stroke in adults with non-valvular AF. The incremental cost-effectiveness ratio (ICER) of dabigatran versus standard treatment was estimated at €17,437, which is below the Slovakian acceptable threshold (€18,000 per QALY gained). The sensitivity analysis consistently demonstrated the cost-effectiveness of dabigatran.
- Only reimbursed though if prescribed by cardiologists, neurologists or internists in line with the approved indications (enforcement). One of the following requirements are also needed for reimbursement in all indications apart from a previous stroke, TIA or systemic embolism:
  - Chronic warfarin treatment is not properly controlled in the therapeutic range INR 2-3, and 2 out of 6 INR values are out of this range, or
  - During the first 3 months of warfarin treatment, INR 2-3 is not reached, or
  - warfarin is contraindicated

Slovenia
Probably September 2012

Reimbursement in line with the licensed indication in conjunction with a complex price: volume agreement

Demand-side activities:
- Education of all involved specialists and primary physicians on key safety aspects/ adverse events with dabigatran
- Prescribing restrictions (Enforcement)
  - Only reimbursed if initiated by an internist or neurologist in line with the approved indications and only for patients who are unstable on warfarin with the TTR < 65
  - Patients have to be followed in a tertiary or secondary anticoagulation centre; in primary care - only if authorized by tertiary or secondary centre.
  - Every patient has to be registered in a database and followed by the computer anticoagulation programme
  - Anticoagulation centres have to report once yearly to the tertiary centre regarding the number of patients experiencing minor and major bleeding, thromboembolic events, as well as deaths from bleeding or thromboembolism

Spain – Catalonia
November 2011

Typically no pre-launch activities.

Post-launch activities in Catalonia included:
A) Education
  - General evaluation of dabigatran in the prevention of thromboembolism in patients with AF performed by the Catalan HTA.
  - A second evaluation undertaken by the Drugs and Therapeutics Committee (DTC) of the Catalan Institute of Health (CIH) resulted in a more restricted patient population, i.e. only in atrial fibrillation patients with (i) prior acenocumarol treatment and lack of control of INR values (2-3) in more than 60% of the last controls, in spite of good adherence to treatment, (ii) patients who have difficulties to follow INR control and (iii) those with allergy to acenocumarol
  - A third evaluation is currently being undertaken by the Catalan HTA to evaluate the different drugs available and their potential use for the prevention of thromboembolism
  - Distribution of a document describing the Drug and Therapeutics Committee decision to all Primary Health Care (PHC) physicians, as well as electronic notices and warnings regularly published on physician computers (100% of PHC physicians use computers). The same documents also distributed to hospital DTCs as well as Cardiology, Neurology, Internal Medicine and Haematology clinics.

B) Engineering
  - Catalan Health Service contracts with providers (primary and secondary care) to incorporate quality of care indicators including new drugs where there are concerns
with their value versus existing gold standards. This now includes dabigatran, with the list updated annually.

C) Economics
- There are financial incentives for Catalan Health Service providers aimed at limiting the prescribing of new premium priced drugs with limited health gain versus current standards, with pertinent indicators included in the current range of quality of care indicators.
- Physicians who do not attain agreed standards do not receive the financial incentive.

D) Post launch follow-up
- A centralized follow-up of all patients prescribed dabigatran has been established in the CIH. Patients' age, previous treatment with oral anticoagulants or antiplatelet agents, renal function and previous history of ischemic heart are monitored.
- Patients at risk of bleeding because of abnormal or unknown renal function, or with inadequate dabigatran prescriptions, are identified. Physicians in charge of these patients are contacted to confirm whether the indication for dabigatran conforms to CIH guidance and whether patients could be changed to acenocumarol.
- Data on patients using dabigatran for AF are regularly sent to PHC pharmacists and clinical pharmacologists, hospitals and CIH DTCs. This electronic tool allows primary health care physicians to self-audit, and the region to monitor dabigatran use.
- A qualitative prescription study is also currently being performed among PHCs in Barcelona. All patients prescribed dabigatran during the last semester of 2011 (n=331) will be followed for 12 months. The objective is to evaluate dabigatran’s effectiveness and adverse effects in practice.

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<th>Country</th>
<th>Region/Year</th>
<th>Activity Details</th>
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| Sweden   | November 2011 | A) National
- SBU alert advisory report containing a statement that dabigatran seems to be no better than warfarin when applied to Swedish health care system.
- TLV did not introduce any additional prescribing restrictions apart from those in the SPC when authorising reimbursement for dabigatran.
B) Regional/County activities – Stockholm County Council
D) Extensive pre-launch activities including critical drug evaluation written pre-launch before each approved indication.
E) Key messages from these have been broadcasted both to the public and to prescribers through the website of the Drug and Therapeutics Committee as well as the Swedish Medical Journal. In addition:
   iii) Appreciable number of pre-launch meetings and training sessions with all major physician groups around the key issues and concerns with dabigatran as well as its likely place in care. This included meetings of the "Wise List forum".
   iv) Production of educational folders regarding dabigatran, slide kits, published articles, and data on the Janus website as well as published information for patients.
   - Forecasting the potential budget impact in 2011 and 2012 ahead of launch and monitoring this in practice.
   - Development of a laboratory method to monitor dabigatran in plasma with LC-MS/MS technology, and currently recommended sampling in the introductory phase of dabigatran to build a knowledge database. This to be followed by more situation-based sampling to improve patient safety in the future.
   - Post launch guidance in the 'Wise List' with warfarin recommended as first line treatment (education). In addition, budget incentives to physicians in out-patient care with all drugs in the 'Wise List' not charged to their clinical budget in contrast with non-recommended drugs (economics).

| Turkey   | Not reimbursed | Currently only reimbursed (75mg) for prophylaxis in patients undergoing elective hip (maximum 35 days) or knee (maximum 10 days) replacement, and only reimbursed with special authorised reports from orthopaedic surgeons (initial); subsequent follow-up prescriptions only reimbursed via orthopaedic surgeons and subject to co-pay (enforcement).
- 110mg and 150mg currently not reimbursed (100% co-pay).
Figure 1A – Utilization patterns on a DDDs basis in 2007 for omeprazole and esomeprazole versus prepatent loss of omeprazole (unless stated) among Western European countries. 

NB: EU Abbreviations used. †Baseline = 2003; Catalonia = Spain; ‡2006 vs 2008; §Baseline = 2004; ¶Baseline = 2000. DDD: Defined daily dose; PL: Before patent loss.
Figure 2A – Expenditure/ DDD for high volume generics in Sweden following the introduction of compulsory substitution in 2002[^4]
Figure 3A - Utilization of simvastatin, atorvastatin and rosuvastatin prior to the availability of generic simvastatin and in 2007 on a DDD basis in Western European countries[7]

NB: EU Abbreviations used. †Baseline = 2003; Catalonia = Spain; ‡2006 vs 2008; §Baseline = 2004; ¶Baseline = 2000. DDD: Defined daily dose; PL: Before patent loss