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Management of hypertension: roles for the angiotensin II receptor blockers and the impact of patent losses

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Management of hypertension: roles for the angiotensin II receptor blockers and the impact of patent losses

In our final article on generic medicines we consider where the angiotensin II receptor blockers (ARBs) can play a useful role in managing hypertension and focus on the developments in the ARB market – notably the impending loss of patent protection for many ARBs. Dr Peter Budden, GP and prescribing advisor in Salford, helps explore the potential implications of the upcoming ARB patent expiries on prescribing and drugs savings.

Introduction

In our first article we considered some of the current issues relating to the recent Government consultation on generic substitution, which is aimed at addressing the need to increase productivity and reduce drugs spending.[1] With help from Gail Chan, medicines management team leader for practice-based commissioning groups across Liverpool and medicines management leader for diabetes, our second article looked at healthcare professionals' views about generic substitution and generic switch policies and considered the costs and potential savings of switching from branded to generic products.[2] In this article we note some of the concerns and issues raised about generic substitution in the literature, which tended to centre around four main areas. These were: worries about patient welfare; relationships between healthcare providers and patients; legal ramifications of policy, and about the practicalities of generic substitution (see Table 1). Undoubtedly, debates will continue in an effort to clarify best practice and allay the concerns of prescribers, dispensers, patients and policy-makers during this period of policy development. We begin this article with a brief consideration of the cost burden of hypertension and by outlining the role of the ARBs in hypertension management. We then explore the likely impact of

Table 1. Some concerns raised in the literature about generic substitution

Some of the main issues raised in the literature centre around the following areas:

a) Worries about patient welfare. This included concerns about:
- ☐ Whether patients will become confused with changing tablets and packaging – particularly the elderly.[3]
- ☐ Whether concordance or compliance will be adversely affected by generic substitutions.[3]
- ☐ Whether the predicted bioavailability for certain drugs will be sufficiently different in clinical patients compared with the bioequivalence study population to cause under- or over-treatment. This is a particular concern for drugs with narrow therapeutic indices.[4,5]
- ☐ Whether *generic* substitution (ie, switching branded to generic products with the same active ingredient) will lead to *therapeutic* substitution (ie switching a branded to generic product from the same therapeutic class or group) – and how this will impact on patient outcomes.[3,6]

b) Worries about relationships between healthcare providers and patients, including:[7]
- ☐ How patients will react to community pharmacists (CPs) over-ruling a GP's prescribing decision – will they perceive their GPs as having made an error and lose confidence in their competence?
- ☐ Whether friction will be created between GPs and CPs if they over-rule GP prescribing decisions.

c) Worries about legal ramifications of policy, for example:[7]
- ☐ Who will be legally responsible if harm befalls a patient as a result of Government policy, of PCT policy and of a CP substitution of a GP prescription item?
- ☐ Will pharmacists be penalised if they wish to opt out of making a generic substitution that they felt would not be in a patient's best interest?

d) Worries concerning putting generic substitution into practice, such as:
- ☐ Whether the time spent by CPs in reviewing prescriptions for generic substitutions would be more cost-efficiently spent addressing higher priority issues such as improving compliance.
- ☐ Whether making wholesale patient switches would yield the projected savings after deducting costs of patient reviews, clinical and other testing appointments and follow-ups – particularly in a climate of falling prices, as found recently for a therapeutic switch.[8,9]

Table 2. ARB licensed indications in addition to essential hypertension and patent expiry dates

ARB	Expected patent expiry	Adult licensed indications in addition to essential hypertension
Losartan (Cozaar)	Expired March 2010	Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria 0.5 g/day as part of an antihypertensive treatment. Treatment of chronic heart failure in patients >60 years old, when treatment with ACE inhibitors is not considered suitable. Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by electrocardiogram.[10]
Valsartan (Diovan)	May 2011[11]	Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours–10 days) myocardial infarction. Treatment of symptomatic heart failure when ACEI cannot be used, or as add-on therapy to ACE inhibitors when beta-blockers cannot be used.[12]
Candesartan (Amias)	April 2012[11]	Treatment of patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction 40%) as add-on therapy to ACEI or when ACEI are not tolerated.[13]
Irbesartan (Aprovel)	August 2012[14]	Treatment of renal disease in patients with hypertension and type 2 diabetes as part of an antihypertensive regimen.[15]
Telmisartan (Micardis)	January 2014[16]	Reduction of cardiovascular morbidity in patients with atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage.[17]

the impending ARB patent expiries (see Table 2) on prescribing – and in the light of an ever-thrifty spending climate for the NHS – on potential savings.

Hypertension – a significant and modifiable economic burden

Hypertension is a modifiable risk factor for several diseases including heart failure, myocardial infarction, stroke and worsening renal function.[18] Data from the Information Centre for Health and Social Care survey for England in 2007 showed that around 30% of adults aged 45–54 years in England who did not have diabetes, had a blood pressure (BP) that was at least 140/90mmHg, which is considered to represent mild hypertension.[18,19] The proportion of people with hypertension increased to around 70% in people who were 75 years or older[18,19] and the cost of pharmacological intervention for *essential* hypertension per annum was estimated in June 2006 at £409.8 million by NICE.[20]

Diabetes complications – an additional cost burden

Diabetes is one of the most common of all chronic medical conditions and represents a huge potential problem for our health services.[21] The prevalence of diabetes in the UK is increasing. It almost doubled between 1994 and 2003 and a further rise was seen during 2003 and 2006 to 5.6% in men and 4.2% in women[19] More than 90% of people with diabetes have type 2 diabetes.[21] They are at increased risk of developing microvascular and macrovascular complications, such as cerebrovascular and peripheral vascular disease, renal disease, neuropathy and retinopathy,[22] and their overall risk of cardiovascular disease (CVD) is more than doubled, and life expectancy reduced by an average 7 years[21] compared with the general population. These risks are even higher in people with diabetes and hypertension[23] and control of raised blood pressure is thought to be at least as important as control of blood glucose in diabetes – decreasing the risk of any diabetes-related end point by around 24%.[23]

Managing renal disease – a further expense

Both hypertension and diabetes are associated with,[24] and risk factors for,[25] kidney disease. Equally importantly, population studies have shown that people with diagnosed chronic kidney disease (CKD) have a far greater likelihood of cardiovascular death than of progression to established renal failure.[25] A large primary care study (practice population 162,113) suggested the age standardised prevalence of CKD at stage 3 to 5 is 8.5% (10.6% in females and 5.8% in males) in UK adults, and that prevalence increases dramatically with age.[24,25]

The economic consequences of hypertension – whether in isolation or in association with diabetes and/or renal disease – underline the importance of instigating rapid and appropriate management strategies.

Recommendations on prescribing in hypertension

In 2006, national clinical guidance on the drug treatment of hypertension was updated to incorporate new evidence from outcome trials and to collaborate with the

Estimated local prevalence and cost burden for 'an average primary care organisation' based on a total population of 394,000[26–32]

Hypertension	45,800 patients	£45.8 million
Type 2 diabetes	15,900 patients	£12.1 million
Chronic kidney disease	27,200 patients	£3.9 million

Assumptions on estimated disease prevalence and burden: these numbers assume an equal population density, an equal disease prevalence throughout the UK and an equal spread of service provisions.

British Hypertension Society (BHS) to produce new joint advice for primary care prescribers in the NHS.[33] The main aim of this rapid partial update was to make recommendations regarding the optimal sequencing of drug treatment for essential hypertension, incorporating a systematic review of head-to-head studies.[33]

Generally accepted thresholds above which people are classified as having hypertension that requires correcting are ≥140mmHg[33–36] systolic pressure and ≥85mmHg[35,36] or ≥90mmHg[33,34,36] diastolic pressure.

Current recommendations

NICE recommends that hypertension treatment should begin with a single antihypertensive agent and if BP remains uncontrolled further agents should be added in a sequential manner, as illustrated in Figure 1.[33] Briefly, diuretics (D) or calcium channel blockers (CCBs) are recommended as equal first-line choices for people who are black (ie of African or Caribbean descent, not mixed race, Asian or Chinese) or aged 55 years or older (step 1). For people younger than 55 years recommended starting treatment is angiotensin converting enzyme inhibitors (ACEIs; A in Figure 1).

Many people will need more than one drug to achieve BP control and where two drugs are needed (step 2) NICE recommends A with either C or D depending upon the starting agent, as shown in Figure 1. If BP is still inadequately controlled and a third drug is needed, the combination of A with C and D should be used (step 3). In the event of needing further measures to reduce BP (step 4) adding a selective alpha-blocker or beta-blocker, or a high dose thiazide or an additional diuretic can be considered. If this still proves insufficient, expert opinion should be sought.[33]

Renin-angiotensin system blockers offer reno-protection

Reviewing the evidence for benefits of ACEIs over other antihypertensive agents or placebo in type 2 diabetes NICE found no significant differences in terms of CV outcomes or evidence of superiority over other agents in BP-lowering power (unless combination therapy is compared with monotherapy). However, the evidence did suggest that ACEI treatment had greater benefits in terms of renal outcomes compared with other BP-lowering agents.[21] Similarly, NICE considered that ARB therapy was associated with greater benefits for type 2 diabetes patients in terms of renal outcomes (eg progression to end stage renal disease, doubling of serum creatinine, proteinuria) than treatment with placebo, CCB or sympatholytic agents.[21] In addition, treatment with ARBs was also associated with a better metabolic and BP profile than sympatholytic therapy.[21] Consequently, overall the guideline development group (GDG) felt that the best evidence for prevention of renal disease and limitation of metabolic worsening related to the renin angiotensin system-blockers (RAS-blockers) ACEIs and ARBs.[21]

Figure 1. Algorithm: treatment of newly-diagnosed hypertension

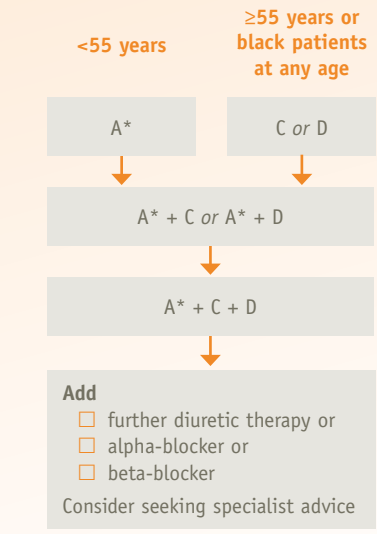

Figure 1 Algorithm. A = ACEI (* or ARB if ACEI-intolerant); C = calcium-channel blocker; D = thiazide-type diuretic. Beta-blockers are not a preferred initial therapy for hypertension but are an alternative to A in patients <55 years in whom A is not tolerated, or contraindicated (includes women of child-bearing potential). Black patients are only those of African or Caribbean descent. In the absence of evidence, all other patients should be treated according to the algorithm as non-black.[33]

The GDG noted that 25% of people with type 2 diabetes develop diabetic nephropathy within 20 years of diagnosis[21] and that this is an important outcome when considering choice of therapy for people with type 2 diabetes.[21] Treatment of hypertension in diabetes is acknowledged to be essential to minimise long-term microvascular and macrovascular complications, such as diabetic neuropathy, diabetic nephropathy, CVD and stroke.[37] Given the benefits in terms of reno-protection and retinopathy of RAS blockade, it was therefore felt appropriate to recommend RAS-blockers as first-line medication in the treatment of hypertension in type 2 diabetes.[21]

On the grounds of cost a generic 24-hour ACEI was the recommended first-line choice. This should be substituted with an ARB only in the event of significant ACEI intolerance usually chronic cough, (and not if hyperkalaemia or decreased renal function is the problem).[21] Scottish Intercollegiate Guidelines Network guidelines also recommend that patients with diabetes who have microalbuminuria or proteinuria start taking an ACEI or be considered for ARB therapy.[37]

Evidence for a reno-protective effect of ACEIs and ARBs

The NICE GDG identified a Cochrane review that considered antihypertensive agents for *preventing* diabetic kidney disease, which found that ACEIs versus placebo/no treatment reduced microalbuminuria development, and when compared with CCBs they reduced the risk of developing kidney disease. A further Cochrane review was identified that considered ACEIs and ARBs for preventing the *progression* of diabetic kidney disease. This review found that ACEIs compared with placebo reduced the progression from micro- to macroalbuminuria, increased the regression from micro- to normoalbuminuria, and reduced the risk of ESRD.[21] It also found that ARBs versus placebo/no treatment was associated with reduced risk of doubling serum creatinine concentration, (seen for both losartan[38] and irbesartan[39]) reduced risk of progression from micro- to macroalbuminuria and increase in regression from micro- to normoalbuminuria.[21]

The NICE GDG also identified a *post hoc* analysis of irbesartan in patients with type 2 diabetes and microalbuminuria (IRMA) study,[40] which reported that after 2 years of follow-up urinary albumin excretion ratio (UAER) decreased in the irbesartan 150mg (by 34%) and 300mg (by 60%) groups with no significant reductions in the placebo group.[21] One month after withdrawal of irbesartan therapy no significant increases were seen in UAER in patients receiving placebo or irbesartan 150mg compared with baseline values. However, UAER remained persistently reduced by 47% in the irbesartan 300mg group compared with baseline.[21]

Only two ARBs have an additional licensed indication for treatment of renal disease in patients with diabetes and hypertension: irbesartan[15] and losartan.[10] Trials with irbesartan demonstrated renal protection in both early and late stages of renal disease,[39,40] and losartan demonstrated protection in late-stage renal disease (protection in early-stage renal disease has not been investigated).[38]

Economic impact of generic ARB availability and prescribing considerations

The patent for losartan has now expired and by August 2012 it is expected that valsartan, candesartan and irbesartan will also have lost their patent protection (see Table 2). With focus being set on getting the best value for money and because generic products are often cheaper than their branded equivalents per prescription item, switching to generics might appear to make economic sense. However, it is very difficult to predict future drug prices because their cost-decay curves vary[11] and are subject to market fluctuations so that even where generic entry does occur, this does not *automatically* mean that effective price competition will result.[41] Also, experience in clinical practice has shown that various essential costs can erode initial savings. For example, administrative costs when searching patient records to identify for suitable patients, staff costs when conducting patient reviews and consultations to ensure compliance is not jeopardised, and essential tests (BP, drug serum concentrations, biochemistry

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values etc)[9] needed to determine patients' current clinical status and whether they are achieving target values. After conducting a switch of medication the costs of patient follow-up appointments and repeat tests after a switch may also eat into savings. But, perhaps the biggest impact could be felt from price competition after the introduction of generics, such that prices fall unpredictably and reduce the anticipated savings as was found in a UK primary care practice where a policy-driven switch from losartan to candesartan was made for the purposes of cost saving.[8]

The difficulty of estimating prescribing costs that can reflect the clinical situation is illustrated by a study that used Markov modelling to determine 5-year cost-consequences of switching ARBs in order to reveal the switch option that offered the best value for money in a context of changing price structures.[11] The author applied dose-specific BP lowering and cost to a typical population with mild-to-moderate hypertension, assuming equal BP lowering efficacy across the ARB class.[11] The model was based on the cost-decay curve of ramipril, which after 8 months had levelled off at around 22% of its pre-expiry price and was felt likely to be comparable with the potential situation of the ARBs.[11] At the time of the study candesartan was the lowest-priced ARB, followed by losartan and irbesartan, followed by valsartan and all prices were estimated to deflate to 22% of their baseline values over a 7-month period after their expiry. Based upon the expected dates of patent expiry (see Table 2) the model predicted that a losartan-based regimen represented the least costly option, but the author noted that switching hypertensive patients taking ARBs to the agent with the lowest current acquisition cost may yield only transient budgetary savings.[11]

Losartan has now lost its patent protection and the expected patent expiry dates for valsartan, candesartan and irbesartan are soon (see Table 2). Although generics are likely to become available for several ARBs with a range of indications by 2012, Peter Budden, GP and prescribing advisor in Salford, *"does not think this will change prescribing habits, which are based on clinical evidence and experience"*, he says. For example, *"in practice the ratio of ACEIs to ARBs used is set by the degree of tolerability of ACEIs"*, says Peter. This is estimated at around 20%, *"but is more like 10–15% in practice, and these intolerant patients are offered ARBs"*, he adds. *"Trials show the benefits of ACEI in type 1 diabetes, and ARB in type 2 diabetes, but there are no impressive head-to-head trials assessing this, and therefore, no evidence base"*.

> "It is very difficult to predict future drug prices because their cost-decay curves vary[11] and are subject to market fluctuations so that even where generic entry does occur, this does not *automatically* mean that effective price competition will result.[41]"

The availability of generic losartan would not prompt Peter to undertake 'wholesale' switching of his patients receiving a sartan to a cheaper generic losartan either. *"Most sartans come off patent within the next few years and there is not much cost differential in switching. The only reason to switch a patient might be if side-effects appear or if a patient is not well controlled"*, he says. *"It is much better to take a long-term pragmatic approach – cheaper products would be considered first in new cases, but in any event decisions must be made in discussion with patients. Although we might make short-term savings by switching patients to the cheapest available product this*

"Most ARBs come off patent within the next few years and there is not much cost differential in switching. The only reason to switch a patient might be if side-effects appear or if a patient is not well controlled."

generates a lot of work with costs associated, it is better to have a gradual period of transition to cheaper drugs", he adds. The cost-benefits of switching across a class from branded to generic products where the timeframe to patent loss for the branded products is short, as is the case for the ARBs, may be short-lived. A more cost-efficient and long-term strategy is likely to be to initiate new suitable patients on the generic ARB with the same licensed indication as the branded product at its patent expiry, and for established patients to only experience drug change if clinical reasons suggest it is appropriate. Before any patient is switched, however, it is important to consider the suitability of a potential switch as outlined below.

Assessing the suitability of switching patients' ARBs: how best is this achieved?

Any switching of antihypertensive therapies can only be implemented after careful consideration of the suitability of a specific drug for a particular individual, taking into account their medical history including comorbities, concurrent medications and previous therapies.[42]

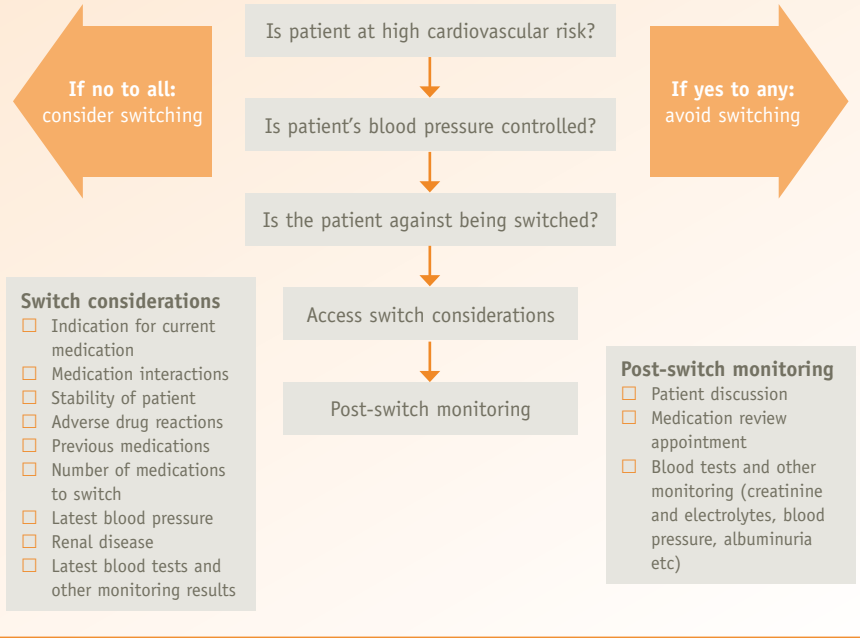
Additional resource use associated with switching antihypertensives also needs consideration. For example, a retrospective analysis of patients who received ARBs found that those who switched between ARBs incurred significantly higher annual all-cause medical costs than those who did not switch ($6286 vs. $5701, respectively; p<0.001); these costs are illustrated in Table 3.[42]

Johnston et al highlighted that although there are similarities between a branded ARB and the potential alternatives, there are also potential differences which need to be considered, such as pharmacokinetics in special populations, evidence for similar efficacy and patient outcomes and safety.[42]

The algorithm illustrated in Figure 2 has been adapted from a South Gloucestershire PCT document which provides some considerations when switching medicines. It may be used to help determine whether it is appropriate to switch a patient from their current regular ARB medication to a different generic ARB. To arrive at a rational decision about whether a switch is justified it is necessary for healthcare professionals to consider all aspects of making a switch including:

- **The current clinical status of the patient.** Is the patient's BP stable and reaching target BPs? Peter Budden also suggests that *"you need to consider what acceptable drift in BP you might allow after switching"*. *"BP can swing by 5–6mmHg at different appointments"*, he says, *"so you need to look at the patient's BP and variation over several appointments. A consistent swing (from an average set of readings) of 5mmHg, however, would be regarded as significant"*, says Peter. Consideration also needs to be given to the indication for current medication – hypertension, stroke, heart failure, diabetes, renal disease, CKD or other co-morbidities because this will impact on the indicated medicines and the

Figure 2. Selecting patients eligible for switching antihypertensives[43]



Adapted from South Gloucestershire PCT. Available at: www.sgbs-pct.nhs.uk. Date accessed: 02 February 2010.[43]

Assessing the suitability of switching patients' ARBs

Before any patient is switched, it is important to consider the suitability of a potential switch based on the issues below:

- ☐ The current clinical status of the patient
- ☐ The current medications the patient is taking
- ☐ The licensed indications of the proposed generic drug(s)
- ☐ The patient's view
- ☐ The means of equipping a patient with adequate information about their treatment to make an informed decision
- ☐ Assess the frequency of post-switch follow-up appointments and monitoring needed

Table 3. Short- and long-term resource use and costs associated with switching antihypertensives in addition to drug acquisition costs[42]

Short-term resource use associated with switch implementation

Resource type	Resource use or average direct cost[a,b] [time period after switch]
Clinic visit	1.24 x US$52.33[c] 1 x US$28.00 2 x €7.05 (US$8.64)[d] £3.70[e] (US$6.73)[d]
Laboratory tests	US$4.55 €39.12 (US$47.92)[d]
Pharmacy	
Prescription filling time	US$0.23
Setting up programme	US$1020 (fixed)
Adverse reactions	
Telephone contact	US$0.17[f]
Discarded medication	US$0.95
Office visit	US$3.21
Drug wastage	US$9.05
Explaining switch to patients	US$1.40[f] £0.32[g] (US$0.39)[d]
Indirect costs	NA

Long-term resource use arising from switching antihypertensives

Resource type	Resource use or average direct cost[a,b] [time period after switch]
Clinic visits	£5 (US$7.50)[d] increase in cost vs nonswitchers [1 year] US$115 ($28 per visit)[h] [1 year] 11% increase in visits; CA$13 (US$9.49)[d] increase in cost vs nonswitchers[i] [2 months] 18% increase in visits; CA$13 (US$9.49)[d] increase in cost vs nonswitchers[i] [2 months] 66–78% increase in visits; US$37 increase in cost vs nonswitchers [1 year]
Laboratory/diagnostic tests	US$31[h] [1 year]
Outpatient visits	35–41% increase in outpatient visits; US$20 increase in cost vs nonswitchers [1 year] US$177 increase in cost vs pre-switch [6 months]
Hospitalisation	£24 (US$36)[d] increase in cost vs nonswitchers [1 year] No significant excess in admissions vs nonswitchers [2 months] 37–42% increase in inpatient visits, US$162–185 increase in cost vs nonswitchers [1 year]
Emergency room visits	US$4[h] [1 year]
Long-term care	No significant excess in admissions vs nonswitchers [2 months]
Medication	Increase of US$28 compared with pre-switch; co-payment increased by US$9 [6 months]
Indirect costs	NA

[a]Cost given per patient unless otherwise stated. [b]Year of pricing ranges from 1989–2005. [c]The authors estimated that 24% of patients would require a second visit to adjust dosage. [d]Approximate value, based on historical exchange rate. [e]Includes time spent by general practitioner (£2.77) and time for repeat blood pressure measurements (£0.93).[f] Pharmacist's time. [g]Postage costs. [h]No control (nonswitchers) group. [i]Costs not specified but 'reflected increased number of visits to physicians'. NA, no information available.

clinical targets. *"For renal patients, we generally aim for lower target BPs (than people without renal disease) at around 130/80mmHg"*, says Peter. In addition to assessing BP *"current renal function by measuring Us and Es (urea and electrolytes) is assessed"*, adds Peter. Other tests may be needed for individual patients, such as creatinine and any therapeutic drug monitoring. Evaluation of the patient's cardiovascular risk is also important and *"a risk score is calculated for all patients"*, Peter explains. *"A variety of scoring systems are in use – I use the Framingham system, which is linked to my practice PC, or the JBS2 calculator, which is more accurate. Others may use the SCORE system and Q-RISK"*, he says. *"Patients who score above 20% would be considered to be at intermediate risk, while those scoring above 30% would be considered to be at high risk"*, says Peter. *"People with diabetes, established heart disease, renovascular disease or CKD at stage 3, 4 or 5 would be considered to be high risk (above 30%)"*, explained Peter. From Figure 2, if the total cardiovascular risk is high, or if the patient's BP is currently controlled or if they are against switching, it would not be appropriate to base a switch on cost-savings alone (Figure 2).

- **The current medications the patient is taking**. The number of medicines a patient is taking and the complexity of their regimen could influence whether a change might cause confusion for them and lead to reduced compliance. Also, the patient's past experience is important; *"a patient might have used a medication in the past"*, says Peter, and that might impact upon a decision to switch. For example, they may have experienced side-effects, such as cough with an ACEI, or the medicine might not have controlled their BP adequately. *"Idiosyncratic reactions to medicines are always possible"*, says Peter *"and these are not predictable – although within the ARBs none is any more likely to produce these than another. A contraindication for switching ARBs would be if a patient has experienced side-effects with the proposed ARB previously. However, a patient might be experiencing side-effects with their current medicine, which could be improved by switching, for example"*, he adds.

- **The licensed indications of the proposed generic drug(s)**. These should match the patient's disease requirements. All ARBs are licensed for essential hypertension, but there are some important differences with respect to individual members of the class, which could impact upon people with chronic heart failure and renal disease, as indicated in Table 2.
- **The patient's view**. Peter Budden considers it very important that *"decisions must be made in discussion with the patient, explaining the reasons for a proposed switch in their medication. This might be because it would be beneficial – or even that it might be cost-efficient. If two drugs are equally efficacious then we could agree a switch (to the cheaper version) providing the patient is informed that if the new drug appears to be less effective or if side-effects appear they can switch back"*, he says.
- **The means of equipping a patient with adequate information about their treatment to make an informed decision**. Providing information about the generic medicine and gaining the patients' agreement with the switch is in line with Government policies, giving patients the right to choose their treatments and have the necessary information to help them make treatment decisions,[44] and this is recognised as helping to maximise concordance. It will be necessary to assess whether each patient will need explanations about their medication reinforced and who will provide the repeated explanations.
- **Assess the frequency of post-switch follow-up appointments and monitoring needed**. BP, creatinine and electrolytes will usually need repeating after a switch and patient reviews will confirm whether the switch has been successful or not. Each of these has an associated cost, which needs to be taken into account.

Switching can then be considered to an agent with an appropriate indication once the patient's current clinical status is assessed. Potential savings to be made from a branded to generic switch will need to be weighed against costs of switching, such as administrative costs, providing patient information, monitoring BP and renal function, and post-switch patient review appointments. However, for ARB switches, Peter Budden says, *"we need to take a long-term, pragmatic view of prescribing. Blanket mass-switches are bad medicine. All prescribing decisions should be based upon a bespoke discussion between the patient and their GP. Mass switches cannot, therefore apply to all patients. It is better for a transition (of patients from branded products to generics) to slowly evolve (by prescribing cheaper generics to new patients) – we should be treating patients, not the budget holder'*.

Conclusions

Hypertension is a significant modifiable risk factor for numerous diseases including heart failure, myocardial infarction, stroke and worsening renal function.[18] Type 2 diabetes also contributes to cardiovascular risk, and both hypertension and diabetes are associated with,[24] and are risk factors for,[25] kidney disease. This underlines the economic and health benefits of managing hypertension to minimise microvascular and macrovascular complications. Current guidelines recommend that ACEIs or ARBs are used first line in people who are younger than 55 years. They are also indicated for people with hypertension and diabetes and/or CKD because of reno-protective effects, including halting disease progression and increasing disease regression.

Despite not being recommended as first-line agents, ARBs can have an important role to play in the treatment of specific subgroups of these patients as part of the overall antihypertensive management strategy. In particular, currently, two ARBs have an additional licensed indication for treatment of renal disease in patients with diabetes and hypertension: irbesartan[15] and losartan.[10] Trials with irbesartan demonstrated renal protection in both early and late stages of renal disease,[39,40] and in late stage only for losartan.[38]

Within the next 2 years four ARBs will have lost their patent protection and generic versions of these branded products will begin to appear in the market place. Although it might appear tempting to switch patients to the cheapest generic ARB currently available, prescribers and dispensers should remember that drug prices fall unpredictably after a branded product's patent expiry and making switches has associated costs, which are likely to erode potential savings made per prescription item. 'Hidden costs', such as staff costs for database searches to identify suitable patients; conducting patient reviews and gaining patients' agreement to switch; medical assessments and clinical chemistry screening; costs of management and implementing the switch, and costs associated with managing any adverse events or loss in patients' BP control after a switch could negate any saving or even make a switch more costly than if the patient remained on regular therapy. For the ARBs significant long-term cost savings are therefore more likely to be achieved by switching patients to the appropriate generic ARB at patent expiry of the branded product without associated switching complications and costs.

"We need to take a long-term, pragmatic view of prescribing. Blanket mass-switches are bad medicine. All prescribing decisions should be based upon a bespoke discussion between the patient and their GP."

More importantly, patients should receive individualised appropriate medication that is indicated for their clinical condition in discussion with their GP. As Peter Budden concluded, *"Blanket switches are bad medicine – a decision to switch patients' medication should be based upon treating the patient, not the budget holder"*.

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PRESCRIBING INFORMATION

APROVEL® FILM-COATED TABLETS PRESCRIBING INFORMATION See Summary of Product Characteristics prior to prescribing **PRESENTATION:** Film-coated tablets containing 150mg and 300mg irbesartan; for specific patient populations 75mg **INDICATION:** Essential hypertension. Renal disease in hypertensive Type 2 diabetic patients as part of an antihypertensive drug regimen. **DOSAGE:** Usual initial and maintenance dose is 150mg once daily with or without food. If necessary, dose can be increased to 300mg or other antihypertensives added. Thiazide diuretics have an additive effect. Correct volume and/or sodium depletion prior to administration of Aprovel. Initiation with 75mg should be considered in patients over 75 years old or on haemodialysis. In hypertensive, type 2 diabetic patients, initial dose 150mg titrated to 300mg once daily if tolerated, for treatment of renal disease. No dosage adjustment in renal impairment or mild to moderate hepatic impairment. CHILDREN: Safety and effectiveness not established. **CONTRA-INDICATIONS:** Hypersensitivity to ingredients. Pregnancy. **WARNINGS AND PRECAUTIONS:** Increased risk of severe hypotension in patients with renal artery stenosis. In patients with renal impairment, periodic monitoring of electrolytes, including potassium and creatinine serum levels is recommended. Monitoring of serum potassium in patients with heart failure or diabetes mellitus recommended. Not recommended in patients with primary aldosteronism. As with other vasodilators, use with caution in patients with aortic and/or mitral valve stenosis or obstructive hypertrophic cardiomyopathy. Caution in patients with galactose intolerance, glucose/galactose malabsorption or Lapp lactase deficiency. Not recommended during lactation. **DRUG INTERACTIONS:** Increased hypotensive effect with other antihypertensives. Potassium supplements and potassium-sparing diuretics. NSAIDs: reduced antihypertensive effect; risk of worsening renal function, especially in the elderly. Lithium: not recommended. **SIDE EFFECTS:** In clinical trials of patients with hypertension, the overall incidence of adverse events was the same as placebo. In placebo controlled trials, the following adverse drug reactions were reported: *common:* dizziness, nausea/vomiting, fatigue; *uncommon:* tachycardia, flushing, cough, chest pain, sexual dysfunction, diarrhoea, dyspepsia/heart burn. Postmarketing, there have been *rare* reports of rash, urticaria and angioedema and *very rare* reports of hyperkalaemia, headache, tinnitus, dysgeusia, abnormal liver function, hepatitis, arthralgia, myalgia, leukocytoclastic vasculitis and impaired renal function. In trials of hypertensive patients with Type 2 diabetes and renal disease, an increased incidence of orthostatic dizziness and hypotension, musculoskeletal pain and hyperkalaemia was observed. For further information, see SPC. **LEGAL CATEGORY:** POM **AUTHORISATION NUMBERS/BASIC NHS PRICE:** APROVEL 75mg (EU/1/97/046/017) £9.69 for 28 tablets APROVEL 150mg (EU/1/97/046/022) £11.84 for 28 tablets APROVEL 300mg (EU/1/97/046/027) £15.93 for 28 tablets **MARKETING AUTHORISATION HOLDER:** Sanofi Pharma Bristol-Myers Squibb **SNC FURTHER INFORMATION FROM:** Bristol-Myers Squibb Pharmaceuticals Ltd., Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex, UB8 1DH Tel: 0800-731-1736 **DATE OF P.I. PREPARATION:** January 2010

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk.

Adverse events should also be reported to Bristol-Myers Squibb Pharmaceuticals Ltd Medical Information on 0800 731 1736, medical.information@bms.com

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