LOTHIAN PRESCRIBING BULLETIN

Supporting prescribing excellence - informing colleagues in primary and secondary care

Issue No. 62

July 2013

In this issue …

Apixaban: LJF second choice for non-valvular AF

Apixaban has been added to the LJF as second choice to warfarin for the prevention of thromboembolic complications in patients with non-valvular atrial fibrillation (NVAF) with one or more additional stroke risk factors. Three new oral anticoagulants (NOACs) have been accepted for use within NHS Scotland for NVAF patients by the SMC as cost-effective in comparison to warfarin. The NOACs have advantages over warfarin, in particular no need for INR testing and a lower risk of life threatening (specifically intracranial) bleeding. There is consensus in Lothian within Cardiology, Haematology and Stroke Medicine that apixaban offers the most favourable risk-benefit ratio of the three NOACs for this indication.

Healthcare Improvement Scotland guidance concludes that patients with good INR control (time in therapeutic range ≥ 60%) should continue on warfarin.[1] Clinicians should consider changing poorly controlled patients to a NOAC unless there is a clear and correctable cause for poor control, e.g. drug interaction or non-compliance.

The clinical evidence for the NOACs is compelling. The table below shows a summary of the trial findings. Each of the NOACs was compared to warfarin in separate large scale randomised trials in NVAF patients. In all the trials, the risk of thromboembolic events was lower with the NOAC (statistically significant for apixaban and high dose dabigatran). Apixaban and low dose dabigatran were associated with significantly fewer bleeding complications than warfarin. All the drugs demonstrated a reduction in risk of intracranial bleeding, with apixaban demonstrating the largest benefit, a 58% risk reduction (p<0.001). Apixaban was also the only drug to show a statistically significant reduction in overall mortality though there were strong trends for the other two drugs.

Guidance for switching patients to and from warfarin, managing the anticoagulant effect in patients who require surgical interventions and management of bleeding is available from the apixaban SPC and additional local guidance will be available soon.

Key messages:

- **Warfarin remains the anticoagulant of choice for atrial fibrillation patients with additional stroke risk factors who have good INR control; patients with poor INR control can be converted to apixaban**
- **Usual dose is 5mg twice daily; patients with two or more of the following should receive the lower dose of 2.5mg twice daily: age >80 years, body weight <60kg, creatinine >133micromol/L**
- **Apixaban, in common with the other NOACs, has a rapid onset of action; patients will be fully anticoagulated within 3 hours of their first dose**
- **There is no specific reversal agent; minor bleeding can be managed by stopping the drug and the anticoagulant effect should wear off 24 to 48 hours after the last dose**
- **Remember to inform the lab when sending blood samples for clotting tests if patient has been taking a NOAC.**

Summary of Evidence

	dabigatran High Dose	rivaroxaban	apixaban
Pharmacological Action	Direct Thrombin Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor
Trial Evidence	RE-LY	ROCKET-AF	ARISTOTLE
Trial Design	Open Label	Double Blind	Double Blind
Primary Outcome	P = 0.001	P = 0.12	P = 0.01
Mortality Reduction	P = 0.051	P = 0.073	P = <0.05
Major Bleeding	Similar to warfarin	Similar to warfarin	Less than warfarin

Reference

1. Healthcare Improvement Scotland, Statement for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrilation. April 2012. www.healthcareimprovementscotland.org (Accessed 13 June 2013)

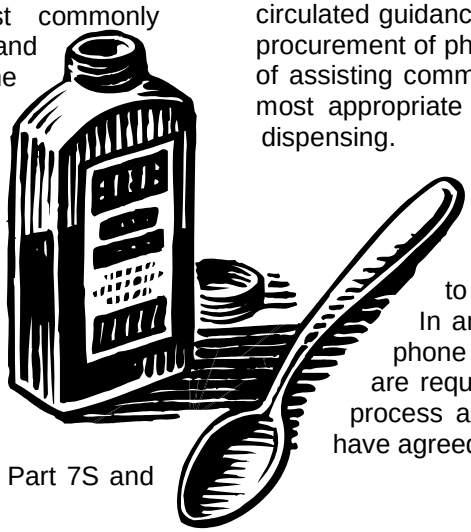
Thanks to Dr Dave Northridge, Consultant Cardiologist and Ms Marjory Neill, Cardiology Pharmacist.

Procurement of unlicensed medicines in primary care

NHS Lothian currently spends approximately £220,000 per month on unlicensed medicines, including special preparations and imported unlicensed medicines. These medicines have not been assessed for safety and efficacy in the UK by the Medicines and Healthcare products Regulatory Authority (MHRA) and therefore carry greater potential liability for the prescriber. The NHS Lothian policy states that licensed medicines will be used where possible. Unlicensed medicines should only be used if clearly justified and the clinical and pharmaceutical benefits are considered to outweigh the risks involved. The prescriber is professionally accountable for this judgement, and may be called upon to justify their actions.[1]

Part 7S Scottish Drug Tariff

On 1st February 2013 the Scottish Drug Tariff was updated to include a new section, Part 7S. This lists reimbursement prices for the most commonly prescribed special preparations and imported unlicensed medicines.[2] The Scottish Government document PCA(P)(2013)4 outlines the background to the introduction of the tariff and to a new reimbursement process for community pharmacy contractors.[3] For any unlicensed preparation outwith Part 7S of the tariff, the community pharmacy contractor must contact the Health Board for **reimbursement authorisation** for the product.



The reasons behind the introduction of Part 7S and the reimbursement process are to:

- Focus prescribers on ensuring that the prescribing of an unlicensed preparation is appropriate
- Encourage community pharmacy contractors to seek out the most cost-effective source of a preparation consistent with the care needs of the patient concerned
- Provide greater transparency around costs involved for all parties
- Clarify the role of NHS Boards in ensuring value for money in the dispensing process of these preparations
- Streamline claim arrangements for both dispensers and Practitioner Services Division.

NHS Lothian Community Pharmacy Reimbursement Authorisation Process

In July and again in October 2012, NHS Lothian circulated guidance to community pharmacies on the procurement of pharmaceutical specials, with the aim of assisting community pharmacists in procuring the most appropriate and cost-effective preparation for dispensing.

In light of PCA(P)(2013)4, the NHS Lothian guidance was updated and circulated in February to all community pharmacy premises. In an attempt to reduce the number of phone calls that community pharmacists are required to make and to speed up the process as much as possible, NHS Lothian have agreed to pre-authorise some products.

Authorisation **must be sought** from NHS Lothian Pharmacy Services before ordering an unlicensed product if it is:

- NOT included in Part 7S of the drug tariff
- NOT included in the NHS Lothian unlicensed product guide[4], or
- NOT available from an NHS manufacturing unit (Tayside Pharmaceuticals, Greater Glasgow & Clyde, Moorfields).

For more information about the NHS Lothian unlicensed medicine prescribing and procurement process please contact your local Primary Care Pharmacist.

References

1. NHS Lothian Policy for the use of unlicensed (and off-label) medicines in NHS Lothian. http://intranet.lothian.scot.nhs.uk/NHSLothian/NHSLothian/BoardCommittees/AreaDrugTherapeutics/Documents/Policy%20for%20the%20use%20of%20unlicensed%20(and%20off-label)%20medicines%20in%20NHS%20Lothian%20-%20Version%202.pdf (Accessed 13 June 2013).
2. The Scottish Drug Tariff: Part 7S. ISD Scotland. www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Scottish-Drug-Tariff/Drugs-and-Preparations-with-Tariff-Prices.asp (Accessed 13 June 2013).
3. Pharmaceutical Services Reimbursement of Special Preparations and Imported Unlicensed Medicines. NHS Circular: PCA(P)(2013)4. The Scottish Government. January 2013 www.sehd.scot.nhs.uk/pca/PCA2013(P)04.pdf (Accessed 13 June 2013).
4. Appendix 3, Procurement and Reimbursement of Pharmaceutical Specials in Community Pharmacy. NHS Lothian. February 2013.

Thanks to Ms Dawn Owen, Primary Care Pharmacist.

Lothian Joint Formulary update

Gluten-free products – CHILD section

***NEW* formulary section**

As stated in Issue 56 (July 2012) of the LPB, a paediatric section has been developed to further support the implementation of the NHS Lothian gluten-free foods prescribing policy and patient pathway. It includes information on:

- diagnosis and management of paediatric patients with gluten intolerance
- the amount of gluten-free products that may be required in a month (number of units)
- the unit value for a range of gluten-free products
- first and second choices for staple products: bread, rolls, bread mix, flour, pasta, crackers, pizza base
- recommended products, which are consistent with the adult gluten-free formulary where possible

Prescriptions for gluten-free foods should not be issued until diagnosis has been confirmed and the child assessed by a paediatric dietitian (as even a short period of gluten avoidance will mask the diagnosis).

Out of stock!

There have been recent instances of commonly used products being in short supply. A prescriber may reasonably expect that when a prescription is tendered for dispensing that the item should be supplied in a timely fashion. There have, however, been occurrences in the past 12 months of products going completely out of stock.

The background causes can be summarised as follows:

- Minor supply hiatus, quite often resolved within a couple of weeks
- Manufacturer batch quality assurance failure
- Licensing issue (variable in effect)
- Raw material shortage (rare but significant)
- Licence suspended: alternative product must be found.

Manufacturers will not always explain why there is a product shortage. In the case of generic products, whilst up to 15 companies may market a product, it is not unusual for only three or four concerns to turn the raw material as a powder into tablets and capsules. This does mean that if one company has a supply failure, pressure will be placed on the remaining companies. This has led in the past to these companies raising prices, which has impacted on the sale price rising above the dug tariff reimbursement price. This does not normally affect the overall supply process, as the product is still available.

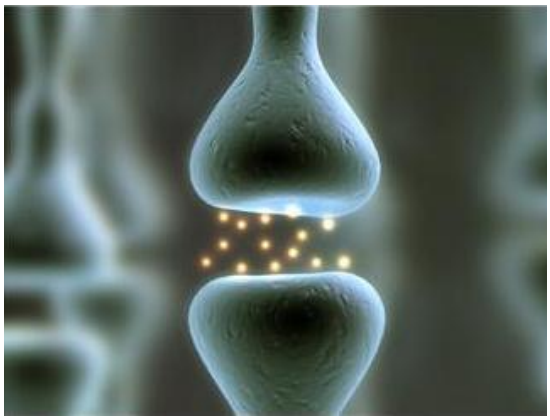
Amendment of reimbursement arrangements covers generic products and the drug tariff price. There are a number of options open where the actual reimbursement price is less than the current invoice price at point of sale. These arrangements are mediated between Community Pharmacy Scotland and National Services Scotland, with oversight from the Scottish Government.

Clinical activity in modifying patient treatment is when the prescribed medicine is not available and each situation has to be assessed on an individual basis. With this in mind options may include:

- Consideration of the expected date of resolution of the product shortage
- Prescribing of a therapeutically equivalent product on a temporary or long-term basis
- An imported version *(This is not always an option; there are also enhanced clinical liabilities for both prescriber and pharmacist in this situation; imports are not licensed in the UK and are invariably more expensive than UK versions)*
- Complete appraisal of treatment if appropriate.

Thanks to Don Page, Technical Services Pharmacist, Clinical Advisory Group, ISD National Services NHS Scotland.

Clozapine-induced constipation: be alert for early signs



Although now well established in the management of treatment-resistant schizophrenia, clozapine differs from other antipsychotics in its greater affinity for the dopamine D_4 receptor. It also acts at the serotonin, alpha-adrenergic, histamine H_1 and cholinergic receptors.[1] It is through the combination of these actions that its side-effects can be largely understood. The risk of neutropenia, a complication occurring in 3% of those on clozapine therapy, is commonly recognised.[2] However, a mandatory monitoring programme is in place to monitor full blood count.[3] Other risks such as seizure, myocarditis and significant gastrointestinal effects are perhaps under recognised and more common.

It has been observed that an increased number of referrals to the Department of Psychological Medicine, Royal Infirmary of Edinburgh, were associated with the prescribing of clozapine. Gastrointestinal complications were evident in a number of cases and, following correspondence with colleagues throughout Scotland, it would appear that this is a widespread concern. We would like to highlight the potential effects of clozapine on the gastrointestinal tract. Reports of constipation are estimated anywhere between 15-60%.[4,5] This is an unpleasant, dangerous and potentially fatal, complication of treatment. Throughout the literature there are reports of patients on clozapine presenting with bowel obstruction, perforation, toxic megacolon and ischaemia, which have all been associated with increased morbidity and mortality.[6,7,8] The number of deaths resulting from such complications is likely to be higher than that associated with the more closely monitored neutropenia.[9]

A case review of patients seen by liaison psychiatry at Royal Infirmary of Edinburgh suggested that 50% of patients referred on clozapine treatment had signs and symptoms of constipation which may well have been implicated in their presentation to hospital. In a number of cases, clozapine treatment had been ceased on admission. This carries the risk of rebound psychosis where patients experience a rapid deterioration in their mental state on suddenly stopping treatment.[10]

As a consequence of the risks associated with constipation, as well as those of rebound psychosis, we suggest that all clinicians be alert for early signs of constipation in this patient group. Constipation should be treated early with advice around diet and fluid intake, laxatives and early recognition of the more serious complications.

Key messages:

- **Constipation is a very common and potentially serious side-effect of clozapine treatment**
- **Patients should be routinely asked about bowel function**
- **Early recognition and treatment is important to prevent complications**
- **Fluid intake and dietary advice should be routinely given to patients taking clozapine.**

References

1. Kane J *et al*. Arch Gen Psychiatry 1988;*45(9)*:789-96.
2. Cohen D *et al.* J Clin Psychiatry 2012;*73(10)*:1307-12.
3. Clozapine Handbook. Pharmacy Services & Royal Edinburgh and Associated Services. NHS Lothian. 3rd Edition, June 2010.
4. Young CR *et al*. Schizophrenia Bulletin 1998;*24(3)*:381-391.
5. Centorrino F *et al.* J Clin Psychopharmacol 1994;*14*:119-25.
6. New Zealand Medicines and Medicinal Devices Safety Authority 2007;*28(1)*:7.
7. Townsend G, Curtis D. BMC Psychiatry 2006;*6*:43.
8. Flanagan RJ, Ball RY. Forensic Science International 2011;*206(1-3)*:e31-e36.
9. De Hert M *et al.* BMC Gastroenterology 2011;*11*:37.
10. Witharana D, Basu A. The Psychiatrist 2011;*35*:155.

Thanks to Dr Deborah Cooper, CT3 in Psychiatry, REH.

Supplement: National Therapeutic Indicators 2013

Supplement: Recent SMC and Lothian Formulary Committee Recommendations

The supplements can be accessed via the LJF website www.ljf.scot.nhs.uk in 'Prescribing Bulletins'.

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