LOTHIAN PRESCRIBING BULLETIN

Supporting prescribing excellence - informing colleagues in primary and secondary care

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Lothian Joint Formulary amendments – respiratory section

CFC-free Clenil Modulite® - inhaled steroid of choice

Patients should now be switched to CFC-free beclometasone dipropionate (BDP) inhalers. Supplies of CFC-containing BDP inhalers are expected to be unavailable by the middle of 2008 and the drug tariff price has increased over the last few months.

The switch from a CFC-containing BDP inhaler should be to a CFC-free BDP preparation in the first instance. When prescribing a CFC-free BDP MDI, the MHRA recommends prescribing by brand name to ensure the patient receives the correct dose and preparation. There are currently two branded CFC-free BDP MDIs available, but they have different potencies.

BDP is first choice inhaled steroid because it is as effective as, and less expensive than, alternative steroid inhalers at standard equivalent doses. However, it is not licensed for use in COPD.

The Lothian Formulary Committee has recommended that CFC-free Clenil Modulite® is now first choice inhaled steroid in Lothian. Clenil Modulite® is equipotent to, and available in the same strengths as, generic BDP MDIs. It is licensed for use in adults and children. See www.ljf.scot.nhs.uk for full prescribing advice regarding the switch to CFC-free BDP inhalers.

- **Prescribe Clenil Modulite® by brand name.**
- **Pharmacists receiving a generic prescription for a BDP MDI must establish which branded product should be dispensed.**

Patients requiring a breath-actuated BDP inhaler, due to inability to use an MDI, can be switched to a BDP dry powder inhaler. Although QVAR® is the only CFC-free breath-actuated preparation available, it is not recommended in Lothian because it is not equipotent to CFC-containing breath-actuated inhalers and switching might increase clinical risk.

Symbicort® SMART® - is it clever?

The Scottish Medicines Consortium accepted Symbicort® SMART® (budesonide/formoterol), for use in adults, in the regular treatment of asthma where use of a combination - inhaled corticosteroid and long-acting beta$_2$-agonist (LABA) - is appropriate. SMART® is an acronym for Symbicort® Maintenance And Reliever Therapy, suggesting that the Symbicort® inhaler can be taken as regular maintenance treatment and also as needed in response to symptoms. It is a regimen, and not an inhaler called Symbicort® SMART®.

A recent update to the BTS/SIGN guideline advised that it was not clear if the use of Symbicort® SMART® was superior to the conventional use of inhaled steroids and LABA (**www.sign.ac.uk**). A revision to the guidelines is scheduled for publication early 2008.

The Symbicort® SMART® regimen was recently reviewed by Formulary Committee (FC) and classified as **'not preferred for use in Lothian as suitable alternatives exist'** for the following reasons:

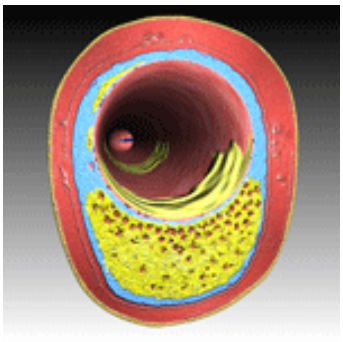
- safety issues relating to patients potentially taking large doses of corticosteroids and LABA if using excessive quantities of the inhaler
- concerns about the possibility of patients not being in possession of a short acting beta$_2$-agonist for use in the event of a severe acute exacerbation.

The place in therapy in Lothian of Symbicort® SMART® will be reviewed when the next BTS/SIGN guidelines are published.

Revised Lothian Lipid Guideline - February 2008

The Lothian Lipid Guideline has been revised in the light of reports from three national bodies (JBS 2, SIGN 97 and NICE TA 132)[5,6,3] and now includes advice on primary prevention cardiovascular disease (CVD). The advice arising from these comprehensive reviews confirms our belief that:

- statins can provide clinical benefits to patients with existing CVD (in secondary prevention)
- uncertainty remains about the cost effectiveness of statins in primary prevention.



A one-page summary of the latest Lothian Lipid Guideline is enclosed with this bulletin and a longer, more detailed version can be accessed on the LJF website www.ljf.scot.nhs.uk.

Primary prevention:

- establish CVD risk level preferably with computer programme, such as **http://cvrisk.mvm.ed.ac.uk/calculator.htm**
- if CVD risk > 20% discuss reduction of risk factors
- the most cost effective strategy is management of smoking, BP and cholesterol in that order
- there is uncertainty about cost effectiveness of drug treatment and therefore only generic statins can be recommended
- escalation of treatment to achieve a target level is not recommended
- ezetimibe is not recommended in primary prevention

Secondary prevention and diabetes:

- all patients should be considered for statin therapy, there is no cholesterol threshold for treatment
- target remains total cholesterol < 5mmol/L
- ezetimibe is appropriate treatment for patients intolerant of a statin or when a statin is contraindicated

Key message:

Generic simvastatin remains the drug of choice for lowering cholesterol.

MHRA reviews the safety of fibrates

Fibrates have been used to lower blood lipid levels since the 1970s, but have largely been superseded by statins. SIGN advise that fibrates can be considered for treatment of hypertriglyceridaemia and/or low HDL cholesterol, and may be required in combination with statins for mixed dyslipidaemia. The diminishing role of fibrates, and concerns with respect to safety and clinical benefit, prompted the MHRA to recently conduct a risk-benefit review.[7]

Five large trials were examined by the MHRA, and significant lipid lowering effects were observed. This was associated with a trend towards a decrease in non-fatal cardiovascular events, significant only for gemfibrozil. However, slightly higher mortality was seen overall in patients receiving fibrates, although gemfibrozil had a non-significant mortality benefit. There is an increased risk of myopathy and rhabdomyolysis when statins and fibrates are combined, and the review found no robust evidence for combining these agents in situations where statins alone proved inadequate.

In severe hypertriglyceridaemia, fibrates were considered the treatment of choice.

The MHRA advises that combination therapy with a statin and fibrate should be used with caution. **Concomitant use of gemfibrozil and a statin should be avoided.** In addition:

- fibrates should only be considered as first-line therapy in patients with isolated severe hypertriglyceridaemia
- for patients with mixed hyperlipidaemia, fibrates may only be used when a statin or other effective treatment is contraindicated or not tolerated
- in primary hypercholesterolaemia, gemfibrozil may be considered, but only when a statin or other effective treatment is contraindicated or not tolerated.

The Lothian Lipid Guideline recommends that fibrates should be initiated on specialist advice.

Ezetimibe - what is its place in therapy?

Guidance on the clinical effectiveness and cost effectiveness of ezetimibe has now been provided by several specialist groups; notably the Scottish Medicines Consortium[1], the Drug and Therapeutics Bulletin[2], and the National Institute for Health and Clinical Excellence (NICE)[3]. In addition, information from the ENHANCE trial[4] was recently released. Studies have shown that ezetimibe lowers cholesterol.

NICE advise that ezetimibe is an option for patients who are unable to take a statin because of contraindications, or who are intolerant to statin therapy. NICE also suggest that ezetimibe is an option in conjunction with a statin when cholesterol is not appropriately controlled on a statin alone.

The place in therapy of ezetimibe was recently discussed by Lothian Formulary Committee (FC) in the light of the NICE guidance. The evidence and the data on cost effectiveness were discussed and the FC concluded that there is a place in therapy for ezetimibe but to a limited degree. FC advise that ezetimibe should be reserved for secondary prevention in those patients who are unable to take a statin because of contraindications or who are intolerant of a statin. FC do not recommend ezetimibe in primary prevention.

Key messages:

- **Ezetimibe is not recommended in primary prevention of CVD.**
- **Ezetimibe should be reserved in secondary prevention for patients who are unable to take a statin because of contraindications, or who are intolerant of a statin.**

Why is the FC advice more restrictive than NICE about the use of ezetimibe?

It would appear that NICE was persuaded that the clinical outcomes of ezetimibe treatment would be similar to those of statins and the evidence for cost effectiveness was based on this assumption. The FC felt that equivalent clinical outcomes could not be assumed, as:

- ezetimibe has a different mode of action and is not a statin. It is an intestinal absorption blocker and inhibits the absorption of dietary and biliary cholesterol. Therefore it cannot be argued that there is a statin class effect.
- there is no evidence that ezetimibe has any effect on cardiovascular morbidity and mortality. The NICE conclusions were reached without any clinical outcome data for ezetimibe.

Since the NICE report was published new evidence has emerged from the ENHANCE trial. In this 2-year trial of 720 patients with familial hypercholesterolaemia, the primary outcome was change in the thickness of the walls of the coronary arteries. Secondary outcomes were the incidence of cardiovascular events. The study found that the speed at which arteries thickened with plaque almost doubled in those taking ezetimibe and simvastatin compared to those taking simvastatin alone, although the difference was not statistically significant. It was also found that the combination of drugs containing ezetimibe made no difference to the incidence of heart attacks or strokes. In summary, there remains no evidence at present that ezetimibe has beneficial clinical outcomes. Therefore the FC suggests limiting the prescribing of ezetimibe until there is evidence of clinical outcomes.

References

1. Ezetimibe (Ezetrol®) for primary hypercholesterolaemia. Scottish Medicines Consortium (SMC) Advice 61/03. September 2003. www.scottishmedicines.org.uk
2. Ezetimibe - a new cholesterol-lowering drug. Drug and Therapeutics Bulletin 2004 (September);*42*(9):65-7. http://dtb.bmj.com
3. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. Technology appraisal TA132. National Institute for Health and Clinical Excellence. November 2007. www.nice.org.uk
4. Effect of Combination Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients With Heterozygous Familial Hypercholesterolemia (ENHANCE). Unreported cholesterol data released by company. British Medical Journal 2008 (26 January);*336*:180-1. www.bmj.com
5. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005;*91*;1-52. http://heart.bmj.com
6. Risk estimation and the prevention of cardiovascular disease. Guideline 97. Scottish Intercollegiate Guidelines Network. NHS Quality Improvement Scotland. February 2007. www.sign.ac.uk
7. Fibrates: new prescribing advice. Drug Safety Update November 2007;*1*(4). Medicines and Healthcare products Regulatory Agency. www.mhra.gov.uk

Varenicline - take care when prescribing

Varenicline (Champix®▼) is marketed as an aid to smoking cessation. Following a Europe-wide review, varenicline product information for prescribers and patients is to be updated to contain warnings that depression has been reported in patients taking varenicline who are trying to stop smoking, and that symptoms of depression may include suicidal thoughts and behaviour[1].

The Medicines and Healthcare products Regulatory Agency (MHRA) have also asked health professionals to note that:

- patients should not drive until they know whether varenicline affects their driving ability, and
- prescribers should also be aware that stopping smoking (with or without medication) may affect the metabolism of some medicines, for which adjustment of the dose may be essential (e.g. insulin, warfarin)[2].

As with all new medicines (black triangle ▼) the MHRA continues to encourage prescribers and patients to report all suspected adverse reactions on the internet at www.yellowcard.gov.uk (MHRA), Yellow Card Centre Scotland www.yccscotland.scot.nhs.uk or using the forms at the back of the BNF.

Lothian Joint Formulary recommendations
www.ljf.scot.nhs.uk

Step 1: smoking cessation support based on assessment of patient's motivation to quit

Step 2: nicotine replacement therapy (NRT)
First choice: continuous therapy (patch) + cessation support
Second choice: intermittent therapy (lozenges/gum) + cessation support

Step 3: **bupropion** + cessation support

Varenicline may be an alternative to bupropion as a component of a smoking cessation support programme. Trials show it appears to have fewer drug interactions and contraindications than bupropion, but the efficacy and safety in patients with significant co-morbidity is unclear. It should be prescribed for a maximum of 12 weeks only.

References

1. Varenicline: safety update. Drug Safety Update. February 2008;*1*(7). Medicines and Healthcare products Regulatory Agency. www.mhra.gov.uk
2. Varenicline: possible effects on driving; psychiatric illness. Drug Safety Update December 2007;*1*(7). Medicines and Healthcare products Regulatory Agency (MHRA). www.mhra.gov.uk

Drug and Therapeutics Bulletin now available online
http://dtb.bmj.com/

The online 'DTB' is now available by logging in with an Athens password. You can obtain an Athens password via the NHS Education for Scotland elibrary www.elib.scot.nhs.uk.

No licence for prescribing co-proxamol

All licences for co-proxamol have now been withdrawn due to safety and efficacy concerns. Co-proxamol products are now unlicensed, with a significantly increased cost. Co-proxamol will be subject to 'Pay and Report' for January to June 2008 dispensing, to notify health boards of prescribing. Thereafter, it will be classed as 'named patient'. Please switch patients to an alternative analgesic now.

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