# Derbyshire Medicines Management Newsletter

www.derbyshiremedicinesmanagement.nhs.uk

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The purpose of the Medicines Management newsletter is to deliver succinct, evidence-based advice and information on primary care prescribing issues. Aimed at busy prescribers wanting to know key messages from the many publications in the previous month.



## 1. What's in the news

**DTB January 2017, Volume 55, number 1.**

**An update on LAMA/LABA combinations for COPD.**

Currently there are four fixed dose LABA/LAMA combinations on the market (umeclidinium/vilanterol – Anoro Ellipta, aclidinium/formoterol - Duaklir Genuair, tiotropium/olodatero – Spiolto Respimat and glycopyrronium/indacaterol – Ultibro Breezhaler), all indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. All four combinations have been shown to produce small statistically significant changes in lung function, symptom scores and rates of exacerbations compared with monotherapy to varying degrees. The clinical significance of such changes is unclear. Indirect comparisons from a number of trials suggest there is little clinical difference in efficacy between the different combinations. There is some evidence that LAMA/LABA combinations produce slightly greater changes in measures of lung function than a LABA/ICS combination and are associated with a lower risk of pneumonia.

In patients requiring a LABA and a LAMA for control of COPD, then a combination product would be more convenient. Duaklir Genuair and Ultibro Breezhaler are classified as BROWN and cost-effective compared to the individual components, whereas Anoro Ellipta and Spiolto Respimat are classified as BLACK and not commissioned for use in Derbyshire. The local COPD guidance and the place of LABA/LAMA are currently under review. The FLAME study evaluated the efficacy and safety of a LABA/LAMA (glycopyrronium/indacaterol - Ultibro) Vs LABA/ICS regimen based on patient oriented outcomes such as exacerbations. Glycopyrronium/indacaterol was shown to be non-inferior to salmeterol/fluticasone for annual rate of all COPD exacerbations and also demonstrates superiority for glycopyrronium/indacterol. There were fewer incidences of pneumonia with LABA/LAMA combination in comparison to LABA/ICS. However the study has many limitations and results should be interpreted with caution. SDCCG is currently undertaking work looking at the place of LABA/LAMA combinations over LABA/ICS in the treatment of COPD patients. Prescribers are reminded to follow local COPD guidance.

**Metformin for patients with moderately reduced kidney function.**

Metformin has previously been contraindicated in this population out of concern that those with reduced kidney function would be unable to clear metformin, resulting in an increased risk of lactic acidosis – a rare but serious complication of treatment. However, after considering the scientific literature, clinical data, epidemiological studies and clinical guidelines, the EMA concluded that patients with moderately reduced kidney function (glomerular filtration rate [GFR] 30–59mL/min) can still benefit from metformin treatment. The Agency notes that clear dosing recommendations and monitoring before and during treatment can minimise any increased risk. The EMA's new recommendations serve both to standardise the prescribing advice for metformin and, more importantly, to make this potentially beneficial hypoglycaemic agent available to more people.

Local type 2 guidance for metformin states: review the dose of metformin if the eGFR is below 45ml/minute/1.73m$^2$. Stop metformin if the eGFR is below 30 ml/minute/1.73m$^2$. Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45ml/minute/1.73m$^2$.

**Other news**

**Vitamin D supplementation to prevent acute respiratory tract infections. (BMJ 2017;356:i6583)**

Systematic review on individual participant data was undertaken to assess the overall effect of vitamin D supplementation on the risk of acute respiratory tract infection. To date RCTs of vitamin D supplementation for the prevention of acute respiratory tract infections have yielded conflicting results. The meta-analysis of individual participant data (not previously performed) for 10,933 participants in 25 RCT showed an overall protective effect of vitamin D supplementation against acute respiratory tract infections (NNT=33). Benefit was greater in those receiving daily or weekly vitamin D without additional bolus doses (NNT=20), and the protective effects against acute respiratory tract infection in this group were strongest in those with profound vitamin D deficiency at baseline (NNT=4).

**Beta-blocker for hypertension**. (Cochrane review PMID:28107561)
This is a Cochrane review (initially 2007 and updated 2013) to assess whether beta-blockers decrease the number of deaths, strokes, and heart attacks associated with high blood pressure in adults.
Current evidence suggests that initiating treatment of hypertension with beta-blockers leads to modest CVD reductions and little or no effects on mortality. These beta-blocker effects are inferior to those of other antihypertensive drugs. Further research should be of high quality and should explore whether there are differences between different subtypes of beta-blockers or whether beta-blockers have differential effects on younger and older people.
The review concluded that beta-blockers were not as good at preventing the number of deaths, strokes, and heart attacks as other classes of medicines such as diuretics, calcium-channel blockers, and ACEI. Most of these findings come from one type of beta-blocker - atenolol.

**Deleted products 2017 | MIMS online** for January 2017

| | | |
|---|---|---|
| Amoxil sachets (amoxicillin) | Asasantin Retard (aspirin/dipyridamole) | Dualtis (DHA/EPA/omega-3-acid ethyl esters) |
| Erlibelle (ethinylestradiol/levonorgestrel) | Exelon Capsules (rivastigmine) | Exelon Oral Solution (rivastigmine) |
| Micronor (norethisterone) | One Touch Comfort | Prempak-C (oestrogen/norgestrel) |
| Risperdal Quicklet (risperidone) | | |

## 2. Drug safety update primarily relating to primary care prescribing

(For more information see Drug Safety Update ) Vol 10, issue 6 January 2017

Not relevant to primary care

1. Prescribers are reminded that all patients with hepatitis C who starting therapy with direct-acting antiviral interferon-free regimens should be screened for hepatitis B infection, as these patients are at risk of reactivation of hepatitis B.
2. Patients receiving vitamin K antagonists and direct-acting antivirals (used to treat chronic hepatitis C), there is a risk of interaction, resulting in fluctuations of INR values. INR should be monitored closely and if necessary anticoagulant therapy adjusted.
3. Risk of suicidal thoughts and behaviour associated with use of apremilast( highlighted in last month's newsletter)

**Other safety news…**

**Medication Error: Citalopram Oral Drops 40mg/ml – dose prescribed in 'millilitres' instead of in 'drops'**

We have had an incident reported to us highlighting that 2 patients (nursing home residents) registered at a GP practice (using SystmOne clinical system) have been prescribed Citalopram Oral Drops 40mg/ml with dose directions of *"Take 0.5ml daily"* instead of the correct dosage instructions of *8 drops daily* (16mg oral drops = equivalent to 20mg tablet). The incorrect dosage instructions continued for 18 months in one case and 2 years for the other patient.

***Why should the dosage be in 'drops' and not in 'millilitres'?***
The dose for citalopram oral drops should be stated in drops, not in millilitres to avoid confusion for patients and also for ease of administration (doses cannot accurately be prescribed or administered by volume of the liquid). The bottle is fitted with a dropper to facilitate this and to ensure accurate dosing. Also, the oral drops should be mixed with water, orange juice or apple juice before taking or administering via a feeding tube. The resulting solution must be drunk by the patient or administered via a feeding tube immediately.

Citalopram Oral Drops 40mg/ml (citalopram hydrochloride, corresponding to 40 mg citalopram base) contain the following:
(a) 1 drop = 2 mg citalopram

(b) 1 ml = 20 drops = 40 mg citalopram

*Citalopram oral drops have approximately 25% increased bioavailability compared to the tablet formulation.*

If a patient was given a dose of 0.5ml of the citalopram oral drops, according to the number of drops in 1ml, the patient would actually be receiving a dose of 10 drops which equates to an actual dose of 20mg of the oral drop solution (equivalent to 25mg of a tablet formulation) – however, as the oral drops have an increased bioavailability compared to the tablet formulation, the dose that should be given to a patient is 16mg given as a dose of 8 drops (equivalent to 20mg given in tablet form).

*Table to show dose of Citalopram for tablet vs. oral drops:*

| Dose of Citalopram in tablet form | Equivalent dose of Citalopram in 'oral drop' dose form | Number of drops required to deliver the required dose |
|---|---|---|
| 10mg | 8mg | 4 drops |
| 20mg | 16mg | 8 drops |
| 30mg | 24mg | 12 drops |
| 40mg | 32mg | 16 drops |

Maximum dose for patients over 65 years of age is 20mg in tablet form & 16mg (8 drops) in oral drop form

Prescribers are also reminded

- The maximum dose of citalopram is 40mg daily (previously a dose of up to 60mg daily was licensed).
- The maximum dose in the elderly and in patients with reduced hepatic function is 20mg daily.
- Citalopram is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.
- Use with other medicines known to prolong QT interval is contraindicated.
- Use is cautioned in patients at higher risk of developing Torsade de Pointes, including those with congestive heart failure, recent myocardial infarction, bradyarrhythmias, or a predisposition to hypokalaemia or hypomagnesaemia due to illness or drug therapy.

## 3. Local news and GP/pharmacist queries

Query from GP practice:

**Q: What are the recommended treatments for hirsutism?**
**A: If referral is not indicated then CKS recommends the following**: https://cks.nice.org.uk/hirsutism#!scenario

- Encourage weight loss in women who are overweight or obese.
- Advise about other local methods of hair removal such as shaving and waxing
- Offer co-cyprindiol provided there are no contraindications, such as uncontrolled hypertension and current breast cancer
- Topical eflornithine (Vaniqua cream 11.5%) should only be considered for use in women where alternative drug therapy e.g. co-cyprindiol, was ineffective, not recommended, contraindicated or considered inappropriate
- Do not prescribe topical eflornithine to pregnant or breastfeeding women, or women younger than 19 years of age. (eflornithine)
- Treatment with topical eflornithine should be discontinued if no effects are seen within four months
- Treatment with topical eflornithine does not remove hairs but slows down hair growth such that users required less frequent hair removal by other methods.
- Topical eflornithine is classified as **BROWN** for facial hirsutism in women with the revised exceptionality of discontinuation after 4 months if no effects are seen.

Prescriber are reminded of the **GREEN** classification for topical eflornithine for transgender and non-binary adults. Prescribing in adults off-license in primary care is also permitted as per NHS England specialised services circular, Primary Care Responsibilities in Prescribing and Monitoring Hormone Therapy for Transgender and Non-Binary Adults. This should be done in close collaboration with the specialists at the Gender Identity Clinics.

**Other local news**
**Controlled drug for temporary patients.**
Information on prescribing of controlled drugs for temporary patients can be found on the Derbyshire medicines management website:
http://www.derbyshiremedicinesmanagement.nhs.uk/assets/Controlled_Drugs/Prescribing_CDs_for%20temporary_patients.pdf

**End life website**
New Derbyshire Alliance for End of Life web site is available through the medicines management website. Prescribing guidance for end of life care (e.g. constipation, agitation, syringe drivers etc.) can be found on the website, (http://derbyshire.eolcare.uk/). The website is a national example of best practice and collaboration.

## 4. Quality, Innovation, Productivity and Prevention (QIPP)

**Tariff watch**
Tariff Watch is a bulletin detailing key price changes in the drug tariff and is now produced on a monthly basis. The QIPP co-ordination group will review this on a regular basis.

**This Newsletter has been produced by Sadaf Qureshi – sderccg.derbyshiremedcinesmanagement.nhs.uk**

QIPP opportunities

**Carbocisteine 750mg/10ml sachets Vs Carbocisteine 250mg/5ml solution**

NHS listed price for

- carbocisteine solution £8.39 x 300ml
- carbocisteine sachets £3.85 x 15

Assuming dose of 750mg tds used for 30 days, the cost comparison of the two preparation

- Solution £37.76 per month
- Sachets £23.10 per month
- By using sachets instead of the solution there is **£14.66/month/patient** potential saving to be made

Epact data for Derbyshire for Jan – Dec 2016

| | Carbocisteine Oral Soln 250mg/5ml | | Carbocisteine Soln750mg/10ml Sach 10ml S/F | |
|---|---|---|---|---|
| **Prescriber Name** | **Total Items** | **Total Act Cost** | **Total Items** | **Total Act Cost** |
| ECCG | 164 | £2,670 | 13 | £116 |
| HCCG | 292 | £6,085 | 18 | £221 |
| NDCCG | 676 | £10,590 | 109 | £1,640 |
| SDCCG | 784 | £14,425 | 92 | £1,362 |
| | | **£33,770** | | **£3,339** |

**January**

Prescribers should note that the re-imbursement price on FP10 may not necessarily reflect the Drug Tariff price as a result of a drug shortage. These concessionary prices are set by the Department of Health to reflect actual market prices.

A concession only lasts until the end of the month in which it was granted. If there is an on-going supply problem, it is possible that a new concession will be granted by the Department of Health the following month, however this is not guaranteed

| Drug Pack | Pack size | Current months Drug tariff price | Price concession |
|---|---|---|---|
| Amitriptyline 50mg tablets | 28 | £2.77 | £3.40 |
| Buspirone 5mg tablets | 30 | £3.19 | £19.54 |
| Candesartan 2mg tablets | 7 | £1.92 | £2.25 |
| Dapsone 50mg tablets | 28 | £40.77 | £46.19 |
| Docusate 50mg/5ml oral solution sugar free (new) | 300ml | £7.99 | £7.99 |
| Exemestane 25mg tablets | 30 | £5.71 | £9.60 |
| Flecainide 100mg tablets | 60 | £10.10 | £13.50 |
| Flecainide 50mg tablets | 60 | £8.64 | £11.25 |
| Leflunomide 10mg tablets (new) | 30 | £4.69 | £8.20 |
| Leflunomide 20mg tablets (new) | 30 | £4.62 | £9.50 |
| Lorazepam 1mg tablets | 28 | £4.41 | £6.05 |
| Mirtazapine 15mg tablets | 28 | £1.19 | £5.95 |
| Mirtazapine 30mg tablets | 28 | £1.27 | £1.61 |
| Mirtazapine 45mg tablets | 28 | £1.55 | £5.95 |
| Naratriptan 2.5mg tablets | 6 | £4.21 | £24.55 |
| Nitrofurantoin 100mg tablets | 28 | £7.03 | £14.50 |
| Nitrofurantoin 50mg tablets | 28 | £11.66 | £17.50 |
| Quinagolide 75microgram tablets | 30 | £55 | £64.97 |
| Ropinirole 0.5mg tablets | 28 | £13.63 | £16.32 |
| Ropinirole 1mg tablets | 84 | £2.07 | £56.71 |
| Ropinirole 2mg tablets (new) | 28 | £2.80 | £25.00 |
| Ropinirole 5mg tablets | 84 | £3.91 | £165.00 |
| Valsartan 160mg capsules | 28 | £4.05 | £5.20 |
| Valsartan 40mg capsules | 28 | £3.31 | £4.72 |
| Valsartan 80mg capsules | 28 | £2.21 | £5.55 |
| Zolmitriptan 2.5mg tablets | 6 | £1.48 | £15.30 |
| Zolmitriptan 2.5mg orodispersible tablets sugar free (new) | 6 | £1.69 | £15.25 |

## 5. NICE evidence summaries: New medicines (relating to primary care prescribing)

None to note

## 6. Useful resources

| | |
|---|---|
| BMJ | www.thebmj.com |
| JAMA: The Journal of the American Medical Association | http://jama.ama-assn.org/ |
| The Lancet | www.thelancet.com |
| The New England Journal of Medicine | http://content.nejm.org/ |
| BMJ, JAMA and NEJM can be accessed in full-text directly through your NHS Athens Account via:<br>National Library for Health:<br>search via My Journals<br>MyAthens:<br>Via National Library for Health Resources or Local Resources.<br>Current Lancet articles are sometimes available with free registration from http://www.thelancet.com/content/register.<br>Print copies of The Lancet are available at DCGH library. | www.library.nh.uk<br><br>or<br><br>www.athens.ac.uk |
| If you have not already registered for an NHS Athens Account, please register at:<br>NB: It is recommended that you register on a Trust (NHS) PC for speedy confirmation of your username a password. Once registered, your account can be accessed from any computer with online access. | https://register.athensams.net/nhs/nhseng/ |
| UKMI<br><br>Nathnac<br>NHS evidence<br>Electronic medicines compendium<br>Clinical Knowledge Summaries<br>Medicines Prescribing Centre (Formerly NPC)<br>Medicines for children (patient information leaflets<br><br>Drugs in lactation | http://www.ukmi.nhs.uk/<br>https://www.evidence.nhs.uk/search?om=%5B%7B%22srn%22%3A%5B%22%20ukmi%20%22%5D%7D%5D<br>http://www.nathnac.org/<br>http://www.evidence.nhs.uk/<br>http://www.medicines.org.uk/emc/<br>www.cks.nhs.uk.<br>http://www.nice.org.uk/mpc/<br>http://www.medicinesforchildren.org.uk/<br><br>http://www.midlandsmedicines.nhs.uk/content.asp?section=6&subsection=17&pageIdx=1 |
| UK teratology services | http://www.uktis.org/index.html |
| Vaccine update- Vaccination newsletter for health professionals and immunisation practitioners | https://www.gov.uk/government/organisations/public-health-england/series/vaccine-update |