Lincolnshire NHS

Prescribing and Clinical Effectiveness Bulletin

Volume 2; Number 10 **July 2008**

CONTENTS

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Steps will be taken to ensure the widest possible distribution across Lincolnshire PCT and within United Lincolnshire Hospitals Trust and Lincolnshire Partnership Trust. Both paper and electronic copies will be circulated initially with a view to evolving into complete electronic distribution as soon as we are confident that all key stakeholders can access E-mail. There are also plans to make all bulletins, guidelines, formularies, new product assessments, care pathways and other PACEF publications available through the LPCT website.

SUMMARY OF PACEF DECISIONS: JUNE UPDATE

Drug	Indication	Traffic Light Status
Abatacept (Orencia) intravenous infusion	Moderate to severe rheumatoid arthritis	RED-RED
Infliximab (Remicade) intravenous infusion	For subacute manifestations of moderately to severely active ulcerative colitis	RED-RED
Omacor capsules	Hypertriglyceridaemia Secondary prevention after MI	RED-RED
Sitagliptin (Januvia) tablets	Licensed for the treatment of type 2 diabetes mellitus in combination with metformin or a thiazolidinedione when metformin or a	RED-RED

	thiazolidinedione is inadequate. Also has a license for triple therapy in combination with metformin and a sulfonylurea.	
Vildagliptin (Galvus) tablets	Licensed for the treatment of type 2 diabetes mellitus as dual oral therapy in combination with either metformin, a sulphonylurea or a thiazolidinedione (glitazone).	RED-RED
Vildagliptin/Metformin (Eucreas) tablets	Licensed for the treatment of type 2 diabetes mellitus in those unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with a combination of vildagliptin and metformin as separate tablets.	RED-RED

RED-RED: This signifies that a product is **not recommended** for prescribing in **both** primary and secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within ULHT and/or LPT **only** and has **no role in primary care**.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; in the coming months PACEF will be working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care**. Specialist initiation and shared care guidelines are not considered necessary.

OMACOR REVIEW

As you may remember from *PACE Bulletin* Vol 1 No 2, PACEF reviewed Omacor a year ago as part of our assessment of NICE Clinical Guideline 48 *MI: secondary prevention* (May 2007). In that CG, NICE recommended that patients should be advised to consume at least 7g of omega 3 fatty acids per week from two to four portions of oily fish. For patients who found oily fish unpalatable, they recommended that at least 1g daily of omega-3-acid ethyl esters in a formulation licensed for secondary prevention post MI (i.e. Omacor) should be considered for up to 4 years post MI. Having reviewed the evidence base for this recommendation PACEF decided that the case was not sufficiently compelling to justify the routine prescribing of this treatment for a significant proportion of these patients. As a result, Omacor was classified as RED-RED.

At the May meeting of PACEF, in response to an appeal from a number of ULHT cardiologists, a full review of this decision was undertaken encompassing a broad range of trials, including new trials involving Omacor as well as a broader review of the context of the decision utilizing trials demonstrating the benefits of a Mediterranean diet, oily fish diet and Maxepa. Following this review, PACEF

concluded that the bulk of the evidence base supporting this recommendation is still derived from the GISSI Prevenzione study [1]. This was an open-label randomized trial carried out in 11,324 Italian patients who had suffered an MI in the preceding 3 months. Patients were randomized to Omacor one daily; vitamin E 300mg; both or no supplement. The dose of omega-3 fatty acid corresponded to 100g of oily fish per day. The results showed a statistically significant reduction in the primary endpoint of death, non-fatal MI and non-fatal stroke. The trial was published in 1999 and data collection took place in Italy during the mid to late 90s. During this period, the use of secondary prevention measures widely in use today (e.g. statins, aspirin and beta-blockers) was much lower. Many have speculated that the positive effects of a Mediterranean diet on the trial population in combination with a much lower use of alternative secondary prevention measures is likely to have resulted in the trial over-estimating the benefits of Omacor.

The NICE Guideline Group concluded their evaluation of the GISSI-P trial with the following statement:

'The guideline development group acknowledged that this is the only major trial of omega 3 acid ethyl esters supplementation in patients within 3 months of an MI which reported a favourable impact on clinical outcome. **It was noted that a high proportion of trial participants reported eating fish at least once a week throughout the trial in both the treatment and control groups. The low percentage of participants receiving cholesterol lowering treatment at the start of the trial and its subsequent increase in both groups was also recognised.** The consensus of the group was that the results of the trial should not be dismissed and that treatment should be considered within three months of an MI, although the results could not be extrapolated to recommending initiation of supplementation beyond three months after the acute event' [2]

PACEF have made every effort to assess this study in detail on two occasions, but remain unconvinced that in isolation it justifies the widespread use of Omacor across the county in post-MI patients.

Further trials featuring Omacor were also scrutinized as part of the evaluation of this appeal. A recent study from the *European Journal of Clinical Pharmacology* looked at the impact of omega 3 fatty acid supplementation on the one-year risk of atrial fibrillation post-MI [3]. Unfortunately, PACEF had serious reservations about this study on the basis of poor study design, poorly matched treatment and control groups and lack of detail on dose, duration of treatment and even formulation used (we assume this was Omacor). The authors themselves accept these limitations in study design and acknowledge that further studies are required. A further study known as GISSI-HF has not yet been published, but will evaluate the effects of Omacor or rosuvastatin vs placebo over a three year period.

Finally, PACEF reviewed the cost-effectiveness model utilized by the NICE post-MI CG Group. The model is based on the results of GISSI-P and calculates a four year Cost per Quality Adjusted Life Year (QALY) of £15,189; this is high, but is below the NICE cost-effectiveness threshold of £20,000 per QALY. PACEF remain concerned that this figure has been determined solely from the results of a single trial that may significantly over-estimate the benefits of Omacor. Further data from additional trials that may have attenuated these benefits and given a more realistic cost per QALY were not included. It has been estimated that, if 50% of patients post-MI were initiated on Omacor, the cost to the Lincolnshire health economy could escalate over 4 years to almost £0.5M; if all patients post-MI received Omacor, this figure would double to £1M.

PACEF Recommendation:
PACEF have reviewed the evidence base for Omacor again and remain concerned over the application of the GISSI Prevenzione Study in a UK population and the poor cost-effectiveness of Omacor post MI. We entirely endorse the need for lifestyle change and support NICE advice that post MI patients should, if possible, consume two to four portions of oily fish per week. Omacor remains classified as RED-RED. It should not be prescribed in either primary or secondary care in Lincolnshire even within the context endorsed by NICE.

When advising patients on oily fish consumption, the following table detailing appropriate fish and average portion sizes may be helpful:

Fish	Amount required to provide approx 1g of EPA plus DHA per day.	Average portion size
Canned tuna	340g	I small can 130g
Fresh tuna	56-200g	1 steak 110g
Herring	56g	-
Mackerel	56-255g	1 fish 130g
Salmon	56-85g	1 fillet 140g, 1 steak 150g
Sardines	56-85g	120g small can
Trout	100g	1 fish 200g

References

1. Marchioli R. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*, Vol 354, August 7th 1999, 447- 455.

2. NICE Clinical Guideline 48 *MI: secondary prevention* (Full text), May 2007, p.50.

3. Macchia A, Monte S , Pellegrini F et al. Omega - 3 fatty acid supplementation reduces one-year risk of atrial fibrillation (AF) in patients hospitalized with myocardial infarction. *Eur J Clin Pharmacol* (accepted for publication Jan 2008)

NEW DRUG ASSESSMENT

VILDAGLIPTIN (GALVUS) AND VILDAGLIPTIN/METFORMIN (EUCREAS)

Vildagliptin is a new dipeptidyl peptidase (DPP-4) inhibitor (or gliptin) licensed for the treatment of type 2 diabetes as dual oral therapy in combination with either metformin, a sulphonylurea or a thiazolidinedione (glitazone). The drug is available as a 50mg tablet taken once or twice daily. The vildagliptin/metformin combination product (Eucreas) is licensed for those unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with a combination of vildagliptin and metformin as separate tablets. It is available as 50/850mg and 50/1000mg strengths. DPP- 4 inhibitors enhance the level of active incretin hormones, reducing blood glucose levels by increasing insulin secretion and reducing glucagon secretion. Vildagliptin is the second DDP- 4 inhibitor to come to market in the UK, the first being sitagliptin (Januvia). Sitagliptin was evaluated by PACEF in September 2007 and classified RED/RED.

PACEF reviewed six randomised double blind controlled trials featuring vildagliptin all of which were compromised by low patient numbers; all but one was limited to 24

weeks duration. In trials, vildagliptin added to established oral antidiabetic therapy (e.g. metformin, pioglitazone, gliclazide) produced small reductions in $HbA_{1c.}$ No comparative data against sitagliptin is available and long term safety data and outcomes data is lacking.

Both gliptins appear to be well tolerated with few reported adverse effects; trial data suggests that they do not cause the weight gain associated with alternative therapies. Hepatic dysfunction has been rarely associated with vildagliptin and regular liver function tests (LFTs) are recommended for the first year of treatment. The Summary of Product Characteristics (SPC) for vildagliptin states that it should be used with caution in those with mild to moderate heart failure and not used at all in those with severe heart failure. This makes vildagliptin a poor substitute if a glitazone has to be withdrawn due to emerging or existing heart failure.

NICE has excluded gliptins from the new Clinical Guideline on Type 2 DM due to late licensing and the limited evidence base; a review of the newer glucose lowering agents is expected as part of a rapid update to the guideline in February 2009. A recent Cochrane review published in April concluded that, although DPP- 4 inhibitors offer some theoretical advantages over existing therapies, lack of outcome data and concerns over the unknown effect of DPP-4 inhibition on the immune system mean that their use should be restricted until further data becomes available.

Vildagliptin at a dose of 50mg twice daily emerges as slightly lower in cost that sitagliptin and comparable in cost to a higher dose of a glitazone. The vildagliptin/metformin combination product Eucreas is no more expensive than vildagliptin prescribed alone. As with any fixed dose combination product, dose titration may prove difficult.

.

Drug	Daily dose range	Cost (£) 28 days
Vildagliptin	50mg twice daily	£31.76
Vildagliptin/metformin 50mg/850mg	1 tablet twice daily	£31.76
Vildagliptin/metformin 50mg/1000mg	1 tablet twice daily	£31.76
Sitagliptin	100mg daily	£33.36
Gliclazide	80mg twice daily	£1.36
Glipizide	max 20mg daily	£9.98
Metformin	500mg three times daily	£1.50
Metformin	850mg twice daily	£1.01
Metformin/pioglitazone 850mg/15mg	1 tablet twice daily	£31.56
Metformin/rosiglitazone 1g/2mg	1 tablet twice daily	£24.14
Metformin/rosiglitazone 1g/4mg	1 tablet twice daily	£36.96
Metformin/rosiglitazone 500mg/2mg	Max 2 tablets twice daily	£36.96
Pioglitazone	15mg daily	£24.14
Pioglitazone	30mg daily	£33.54
Rosiglitazone	4mg daily	£24.14
Rosiglitazone	8mg daily	£36.96

PACEF Recommendation:
In view of the poor quality of the trial data and the lack of long term safety and outcome data, vildagliptin (Galvus) is classified as RED-RED; vildagliptin/metformin (Eucreas) is also classified as RED-RED. Sitagliptin (Januvia) remains RED-RED. Gliptins will be subject to ongoing review by PACEF as further evidence emerges.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 140: INFLIXIMAB FOR THE SUBACUTE MANIFESTATIONS OF ULCERATIVE COLITIS (APRIL 2008)

The key recommendations are as follows:

- Infliximab is **not recommended** for subacute manifestations of moderately to severely active ulcerative colitis.
- A subacute manifestation of moderately to severely active ulcerative colitis is defined as disease that would normally be managed in an outpatient setting and does not require hospitalisation or consideration of urgent surgical intervention.

PACEF Recommendation:
Infliximab is designated RED-RED for the treatment of subacute manifestations of moderately to severely active ulcerative colitis.

NICE TECHNOLOGY APPRAISAL 141: ABATACEPT FOR THE TREATMENT OF RHEUMATOID ARTHRITIS (APRIL 2008)

The key recommendations are as follows:

- Abatacept is **not recommended** (within its marketing authorisation) for the treatment of rheumatoid arthritis (RA).
- Patients currently receiving abatacept for RA should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

PACEF Recommendation:
Abatacept is designated RED-RED for the treatment of RA.

NICE PUBLIC HEALTH PROGRAMME GUIDANCE 11: *MATERNAL AND CHILD NUTRITION* (MARCH 2008)

The key recommendations relating to medicines are as follows:

- Advise all women to take **400 micrograms of folic acid daily before pregnancy and throughout the first 12 weeks of pregnancy. Advise them about a suitable supplement (e.g. Healthy Start vitamin supplement containing folic acid, vitamins C and D). Advise them to eat foods rich in folate and folic acid.**
- The Healthy Start vitamin supplement should be offered to pregnant women eligible for the Healthy Start benefit.
- Both types of Healthy Start vitamin supplements (for women and for children aged 6 months to 4 years) should be available for distribution by healthcare

professionals to those in the Healthy Start scheme. Healthy Start vitamin supplements for women should also be available to purchase from community pharmacies.

- **For women with diabetes or a family history of neural tube defects or a previous baby with a neural tube defect, folic acid 5mg daily should be prescribed.**
- Offer information and advice on the benefits of vitamin D supplementation during pregnancy and while breastfeeding (available through the Healthy Start vitamin supplement or from community pharmacies) Those particularly at risk of vitamin D deficiency are the obese, those with limited exposure to sunlight and those of South Asian, African, Caribbean or Middle Eastern descent.
- The Drugs and Lactation Database (LactMed) and the UK Drugs in Lactation Advisory Service are advocated as supplementary information sources when prescribing or dispensing drugs to a breastfeeding mother. Appendix 5 of the *BNF* is also a useful guide.

NICE CLINICAL GUIDELINE 62: *ANTENATAL CARE – ROUTINE CARE FOR THE HEALTHY PREGNANT WOMAN* (MARCH 2008)

The key recommendations are as follows:

- At the first contact appointment the healthcare professional should give specific information on: folic acid supplements, food hygiene, lifestyle (specifically smoking cessation, recreational drug use and alcohol consumption) and all antenatal screening.
- All women should be informed at the booking appointment (ideally by 10 weeks) about the importance for their own and the baby's health of maintaining adequate vitamin D stores during pregnancy and whilst breastfeeding. Women can achieve this by taking 10 microgram of vitamin D per day (as found in the Healthy Start multivitamin supplement). Particular care should be taken in those at greatest risk (e.g. women of South Asian, African, Caribbean or Middle Eastern family origin, women who have limited exposure to sunlight [i.e. those who are predominantly housebound or who remain covered while outdoors], women who eat a diet low in vitamin D [i.e. those who consume no oily fish, eggs, meat, vitamin D-fortified margarine or breakfast cereal], women with a pre-pregnancy BMI above 30kg/m^2).
- Screening for sickle cell diseases and thalassaemias should be offered to all women as early as possible in pregnancy (ideally by 10 weeks).
- The 'combined test' (nuchal translucency, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A) should be offered to screen for Down's syndrome between 11 weeks 0 days and 13 weeks 6 days. For women who book later in pregnancy the most clinically and cost-effective serum screening test (triple or quadruple test) should be offered between 15 weeks 0 days and 20 weeks 0 days.
- A range of antenatal interventions are not routinely recommended. These include: repeated maternal weighing, breast or pelvic examination, iron or vitamin A supplementation, routine screening for Chlamydia, cytomegalovirus, hepatitis C virus, group B streptococcus, toxoplasmosis and bacterial vaginosis, routine Doppler ultrasound in low-risk pregnancies, ultrasound estimation of fetal size for suspected large babies, routine screening for preterm labour or cardiac anomalies using nuchal translucency, gestational diabetes screening using fasting blood glucose, random blood glucose, glucose challenge or urinalysis, routine fetal movement counting, routine

ausculation of the fetal heart, routine antenatal electronic cardiotocography and routine ultrasound scanning after 24 weeks.

.

NICE CLINICAL GUIDELINE 63: *DIABETES IN PREGNANCY – MANAGEMENT OF DIABETES AND ITS COMPLICATIONS FROM PRE-CONCEPTION TO THE POSTNATAL PERIOD* (MARCH 2008)

The key recommendations are as follows:

Pre-conception care

- Women with diabetes planning to become pregnant should be informed that establishing good glycaemic control before conception and continuing throughout pregnancy will reduce the risk of miscarriage, congenital malformation, stillbirth and neonatal death.
- The importance of avoiding unplanned pregnancy should be emphasized through diabetes education for women with diabetes.
- Folic acid supplements (5mg daily), self-monitoring of blood glucose, ketone testing strips (for those with type1 diabetes), monthly HBA1c, retinal assessment and renal assessment should all be offered.

Gestational diabetes

- Screening for gestational diabetes using risk factors is recommended in the healthy population. Risk factors include: BMI above 30kg/m^2, previous macrosomic baby weighing 4.5kg or above, previous gestational diabetes, family history of diabetes (first degree relative), family origin with a high prevalence of diabetes [South Asian, black Caribbean, Middle Eastern]. Women with any one of these risk factors should be offered screening.
- Do not offer gestational diabetes screening using fasting blood glucose, random blood glucose, glucose challenge or urinalysis.
- **Consider hypoglycaemic therapy for women with gestational diabetes if lifestyle changes do not maintain blood glucose targets over a period of 1 to 2 weeks or if ultrasound shows incipient fetal macrosomia at diagnosis. Regular insulin, rapid acting insulin analogues (aspart and lispro) and/or metformin and glibenclamide may be considered.**

Antenatal care (also see CG62 *Antenatal care*)

- If it is safely achievable, women with diabetes should aim to keep fasting blood glucose between 3.5 and 5.9mmol/l and 1-hour postprandial blood glucose below 7.8mmol/l during pregnancy. Fasting and 1-hour postprandial blood glucose should be tested after every meal.
- Women with insulin-treated diabetes should be advised of the risks of hypoglycaemia and hypoglycaemia unawareness in pregnancy, particularly in the first trimester.
- During pregnancy, women with suspected diabetic ketoacidosis should be admitted immediately for level 2 critical care.
- Women with diabetes should be offered antenatal examination of the four chamber view of the fetal heart and outflow tracts at 18-20 weeks.

Postnatal care

- Women who were diagnosed with gestational diabetes should be offered lifestyle advice (weight control, diet, exercise) and offered a fasting plasma glucose measurement at the 6-week postnatal check and annually thereafter.

There are also specific recommendations relating to medicines in the guideline:

- **Metformin may be used before and during pregnancy, as well as or instead of insulin. Metformin does not have a UK marketing authorisation specifically for pregnant and breastfeeding women. Informed consent should be obtained and documented.**
- **Rapid-acting insulin analogues (aspart and lispro) are safe to use in pregnancy and have advantages over soluble human insulin during pregnancy. Rapid-acting insulin analogues do not have a UK marketing authorisation specifically for pregnant and breastfeeding women. Informed consent should be obtained and documented.**
- **Isophane (NPH) insulin is the first choice long-acting insulin during pregnancy.** Evidence about the use of long-acting insulin analogues during pregnancy is limited. Neither isophane (NPH) insulin nor long-acting insulin analogues have UK marketing authorisations specifically for pregnant and breastfeeding women. Informed consent should be obtained and documented.
- **Before or as soon as pregnancy is confirmed the following drugs should be stopped (where relevant): oral hypoglycaemic agents (apart from metformin), angiotensin converting enzyme inhibitors and angiotensin-II receptor antagonists and statins. Insulin may be commenced if required and alternative antihypertensive agents should be considered.**

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: SAFETY UPDATE (MAY 2008)

RIMONABANT (ACOMPLIA): NEW ADVICE ON DEPRESSIVE REACTIONS

Rimonabant is a selective antagonist of cannabinoid type -1 receptors licensed in adults as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥30kg/m^2) or overweight patients (BMI≥ 27kg/m^2) who have associated risk factors such as a type 2 diabetes or dyslipidaemia. Psychiatric adverse drug reactions, particularly an increased incidence of depression, were identified in the original product SPC. New contraindications, added in June 2007, precluded the use in patients with a major depressive disorder or those currently taking antidepressants.

Up to the end of January 2008 1,971 individual reactions have been reported to the MHRA associated with the use of rimonabant of which 44% (876) concerned psychiatric reactions, most commonly depression and related mood disorders. The MHRA has expressed concern over the incidence of depressive reactions and has issued the following advice to healthcare professionals.

- Depressive reactions may occur in up to 10% of patients treated with rimonabant.
- Patients who have no obvious risk factors, apart from obesity itself, may be affected.
- The evidence suggests that many patients who develop such reactions will do so within 2 weeks of starting treatment.
- Rimonabant is contraindicated in patients with ongoing major depression or those taking antidepressants
- Prescribers are encouraged to take a detailed history from patients before prescribing rimonabant to assess risk factors for psychiatric reactions, particularly depression.

EXENATIDE (BYETTA): RISK OF ACUTE PANCREATITIS

Post marketing reports from the USA have raised concern over the incidence of acute pancreatitis associated with exenatide. Up to September 30th 2007, 89 reports of pancreatitis had been reported world wide, including one fatality. Since then, in November 2007, there has been a reported non-fatal case in the UK. As a result of these reports, the MHRA has issued the following to healthcare professionals:

- Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent severe abdominal pain; back pain may also be present.
- If pancreatitis is suspected, exenatide and other potentially suspect medicines should be discontinued.
- As with all new medicines, the safety of exenatide remains under close review and all suspected adverse reactions should be reported using the yellow card scheme.

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)

The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.

Stephen Gibson,
Head of Prescribing and Medicines Management,
Lincolnshire PCT
steve.gibson@lpct.nhs.uk