NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 6; Number 3 **January 2012**

What's new this month?

- **DPP-4 inhibitors are reviewed in detail and sitagliptin (Januvia) is confirmed as the agent of choice. Designation GREEN. Linagliptin (Trajenta) is approved for use as an alternative in patients suffering from renal or hepatic impairment. Saxagliptin (Onglyza) is also approved for use. Designation GREEN (see page 3).**
- **PACEF are concerned about the limited efficacy and long-term safety of eflornithine cream (Vaniqa). Only a third of women respond to treatment and hair growth approaches pre-treatment levels within 8 weeks of discontinuation. As a result of this, eflornithine cream (Vaniqa) has been designated RED-RED (see page 8).**
- **Prescribers are reminded that doses of rosuvastatin 40mg should only be initiated under specialist supervision (see page 9).**
- **Healthcare professionals are reminded of the updated dosing recommendations for paediatric paracetamol liquids (see page 9).**
- **Domperidone may be associated with an increased risk of serious ventricular arrhythmias and sudden cardiac death (see page 10).**
- **Supply problems continue with trifluoperazine tablets 1mg and 5mg (both generic and Stelazine); liquid formulations are the preferred alternative (see page 11)**

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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. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: DECEMBER 2011 UPDATE

Drug	Indication(s)	Traffic Light Status
Aprepitant 80mg and 125mg capsules (Emend)	Licensed as an adjunct to dexamethasone and a $5HT_3$ receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy	RED
Bromfenac eye drops 900microgram/ml (Yellox)	Licensed for postoperative ocular inflammation following cataract surgery.	RED-RED

Eflornithine 11.5% cream (Vaniqa)	Licensed for the treatment of facial hirsutism in female adolescents (aged 12 to 18 years) and adult women.	RED-RED Existing patients should be allowed to continue with therapy until they or their clinician considers it appropriate to stop.
Fosaprepitant injection (Ivemend)	Licensed as an adjunct to dexamethasone and a $5HT_3$ receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy	RED
Linagliptin 5mg tablets (Trajenta)	Licensed for the treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, or triple oral therapy in combination with a sulfonylurea plus metformin.	GREEN Second line DPP-4 inhibitor approved for use in patients with renal or hepatic impairment.
Saxagliptin 2.5mg and 5mg tablets (Onglyza)	Treatment of type 2 diabetes dual therapy in combination with metformin, sulfonylurea or thiazolidinedione (glitazone)	GREEN
Sitagliptin 100mg tablets (Januvia)	Treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, sulfonlyurea or glitazone or triple oral therapy in combination with a sulphonylurea plus metformin or glitazone plus metformin or with insulin with or without metformin.	GREEN First line DPP-4 inhibitor of choice
Sitagliptin 50mg/metformin 1g (Janumet)	Treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, sulfonlyurea or glitazone or triple oral therapy in combination with a sulphonylurea plus metformin or glitazone plus metformin or with insulin with or without metformin.	GREEN First line DPP-4 inhibitor/ metformin combination product of choice.
Vildagliptin 50mg tablets (Galvus)	Treatment of type 2 diabetes dual therapy in combination with metformin, sulfonlyurea or glitazone.	RED-RED
Vildagliptin/metformin 50mg/850mg and 50mg/1g tablets (Eucreas)	Treatment of type 2 diabetes dual therapy in combination with metformin, sulfonlyurea or glitazone.	RED-RED

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or 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 secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary 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; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care.**

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.**

NEW DRUG ASSESSMENTS

REVIEW: *DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS (OR GLIPTINS)*

DPP-4 inhibitors are a new class of oral antidiabetic drug which act by preventing the inactivation of glucagon like peptide-1 (GLP-1) by dipeptidyl peptidase -4. The overall effect is to increase the circulation of active GLP-1 which in turn stimulates insulin secretion and inhibits glucagon secretion; this lowers blood glucose and improves glycaemic control in patients with type 2 diabetes. There are currently four DPP-4 inhibitors (often referred to collectively as "gliptins") with a United Kingdom (UK) product license – sitagliptin (Januvia), vildagliptin (Galvus), saxagliptin (Onglyza) and linagliptin (Trajenta). A fifth agent, alogliptin is likely to receive a UK product licence sometime during 2012/13. To date PACEF has reviewed three of the four DPP-4 inhibitors and has designated sitagliptin (Januvia) as the preferred agent for use in Lincolnshire. It is the purpose of this review to consider all new evidence emerging since the original PACEF assessments of these drugs and to consider in context the latest addition to the class, linaglitin (Trajenta).

Licensed indications

All four gliptins are licensed for use in line with the recommendations made in *NICE Clinical Guideline 87: Type 2 diabetes – the management of type 2 diabetes* (May 2009). The table below summarizes the licensed indications for each of the products:

DPP-4 inhibitor	**Licensed indication**
Linagliptin (Trajenta)	Treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, or triple oral therapy in combination with a sulfonylurea plus metformin.
Saxagliptin (Onglyza)	Treatment of type 2 diabetes dual therapy in combination with metformin, sulfonylurea or thiazolidinedione (glitazone)
Sitagliptin (Januvia) + metformin (Janumet)	Treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, sulfonlyurea or glitazone or triple oral therapy in combination with a sulphonylurea plus metformin or glitazone plus metformin or with insulin with or without metformin.
Vildagliptin (Galvus) + metformin (Eucreas)	Treatment of type 2 diabetes dual therapy in combination with metformin, sulfonlyurea or glitazone.

Summary of licensed indications plus product availability

	Oral dual therapy license	Oral triple therapy license	Licensed for use in combination with insulin ± metformin	Combination with metformin	Monitoring required	Renal license
linagliptin	√	√	No	No	No	N/A*
saxagliptin	√	No	√	No	No	Yes
sitagliptin	√	√	√	√	No	No
vildagliptin	√	No	No	√	LFTs 3 monthly for one year.	No

*No dose adjustment required in renal impairment

PACEF Comment:
Sitagliptin emerges from this comparison as the DPP-4 inhibitor with the widest range of licensed indications; a combination product with metformin (Janumet) is also available. Two recently approved license extensions for saxagliptin have extended the potential role of this product to include patients with renal impairment and use in combination with insulin. Further license extensions are pending and will remain under PACEF review.

Clinical Evidence

In short term (24 to 30 weeks), placebo controlled trials, used as monotherapy or in combination with metformin, all four of the available DPP-4 inhibitors demonstrate a broadly comparable ability to lower HbA1c. In the absence of head-to-head comparative trials, PACEF reviewed the existing trial data and concluded that it is difficult to argue for superior clinical effectiveness for any of the agents. Concerns remain around all of these agents relating to the lack of long-term safety data and lack of outcomes data.

PACEF Comment:
Evidence from existing trials confirms that all of the DPP-4 inhibitors exert a broadly comparable effect on HbA1c. In terms of percentage reduction in HbA1c, sitagliptin and vildagliptin appear to have the advantage over other agents, although this may be of limited clinical significance. NICE CG 87 states that treatment with DPP-4 inhibitors should only continue if the person has been shown to have had a beneficial metabolic response (defined as a reduction of at least 0.5 percentage points in HbA1c in six months).

Use in specific patient groups

Renal impairment

The use of oral diabetic drugs in renal impairment is particularly important as 20 to 40% of patients with diabetes will develop diabetic nephropathy and may progress to end stage renal disease (ESRD). The following table summarizes the advice on renal impairment contained in each of the product SPCs:

DPP-4 inhibitor	Advice in renal impairment
Linagliptin (Trajenta)	No dose adjustment is required in patients with renal impairment.
Saxagliptin (Onglyza)	Licensed dose of 2.5mg once daily in moderate to severe renal impairment. Manufacturer advises caution in severe impairment as clinical experience in this patient group is very limited. Saxagliptin is contraindicated in end stage renal failure.
Sitagliptin (Januvia)	For patients with mild renal impairment (creatinine clearance >50ml/min), no dose adjustment is required. Clinical experience in patients with moderate to severe renal impairment is limited and therefore use in this patient group is not recommended.
Vildagliptin (Galvus)	For patients with mild renal impairment (creatinine clearance >50ml/min), no dose adjustment is required. Use of vildagliptin is not recommended in patients with moderate or severe impairment or in haemodialysis patients with end-stage renal disease (ESRD). A license application is expected to expand the role of vildagliptin to include moderate or severe impairment or end stage renal disease at a dose of 50mg once daily.

PACEF Comment:
Linagliptin appears to be the most appropriate DPP-4 inhibitor for use in patients with renal impairment as no dose adjustment is required whatever the degree of renal failure. Alternatives include: vildagliptin (subject to license extension and dose reduction as detailed above) and saxagliptin (subject to caution in severe impairment and contra-indication in ESRD as detailed above).

Hepatic impairment

The following table summarizes the advice on hepatic impairment contained in each of the product SPCs:

DPP-4 inhibitor	Advice in hepatic impairment
Linagliptin (Trajenta)	Pharmacokinetic studies suggest that no dose adjustment is required for mild/moderate or severe liver impairment, but clinical experience in such patients is lacking.
Saxagliptin (Onglyza)	No dose adjustment is required for mild or moderate hepatic impairment. Saxagliptin should be used with caution in moderate impairment and is not recommended for use in severe impairment.
Sitagliptin (Januvia)	No dose adjustment is required in mild to moderate impairment. Sitagliptin has not been studied in patients with severe impairment.
Vildagliptin (Galvus)	Avoid in liver impairment. There have been rare reports of liver dysfunction; monitor liver function before treatment and every three months for first year and periodically thereafter. Patients should be advised to seek prompt medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue and dark urine develop; discontinue if jaundice or other signs of liver dysfunction occur.

PACEF Comment:
In patients with severe hepatic impairment, linagliptin appears to be the best treatment option, although clinical experience in this patient group is limited. Neither saxagliptin nor sitagliptin require dose adjustment in mild to moderate hepatic impairment and offer a possible alternative for those with less severe liver disease. Vildagliptin has been associated with rare cases of hepatic dysfunction and requires regular monitoring of liver function tests during the first year of treatment; it should be avoided in patients with any degree of hepatic impairment.

Cardiovascular safety

There is now a requirement from the licensing authorities, in particular the American Food and Drug Administration (FDA), for manufacturers to show that therapies for diabetes do not cause unacceptable increases in cardiovascular risk. The data for this can be derived either from pooled analysis of pre-registration trials or a planned trial measuring cardiovascular outcomes. Both saxagliptin and linagliptin had to provide this additional cardiovascular safety data prior to gaining marketing authorisation, whereas sitagliptin and vildagliptin gained product licenses before this additional requirement was necessary. A recent review of the cardiovascular safety of DPP-4 inhibitors published in *The British Journal of Cardiology* concluded that sitagliptin, saxagliptin and vildagliptin have shown no evidence of increased cardiovascular risk in trials.

The United Kingdom Prospective Diabetes Study (UKPDS) established metformin as the first line drug of choice for the treatment type 2 diabetes. In the study, metformin was shown to reduce the rates of myocardial infarction, diabetes related death and

all-cause mortality. A number of large, double-blind, randomised trials with cardiovascular end points have been set up to evaluate long-term outcomes related to all four of the DPP-4 inhibitors. Examples include the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) and the Saxagliptin Assessment of Vascular Outcomes Study (SAVOR-TIMI 53).

PACEF Comment
Current data suggests that the DPP-4 inhibitors do not appear to increase cardiovascular risk in type 2 diabetes. Large, long-term RCTs are in progress to determine whether DPP-4 inhibitors confer cardiovascular benefits and improve long-term outcomes.

Adverse effects

The adverse effect profile is similar for all DPP-4 inhibitors. There is currently insufficient data to determine whether one DPP-4 inhibitor is better tolerated than another. DPP- 4 inhibitors may increase infection rates, particularly nasopharyngitis and urinary tract infections. As a consequence, national regulatory authorities are currently monitoring infection rates associated with DPP-4 inhibitor use.

PACEF Comment:
At present there is insufficient evidence to determine whether one DPP-4 inhibitor is better tolerated than another.

Price comparison

Formulation	Dose	Cost(£)	
		Original pack	One year treatment
DPP-4 inhibitors			
Linagliptin (Trajenta)	5mg daily	£33.26 (28)	£432.38
Saxagliptin (Onglyza)	5mg daily	£31.60 (28)	£410.80
Saxagliptin (Onglyza)	2.5mg (moderate to severe renal impairment)	£31.60 (28)	£410.80
Sitagliptin (Januvia)	100mg daily	£33.26 (28)	£432.38
Sitagliptin 50mg/ metformin 1000mg (Janumet)	1 tablet twice daily	£34.56 (56)	£449.28
Vildagliptin (Galvus)	50mg twice daily (once daily if administered with sulfonlyurea)	£31.76 (56)	£412.88
Vildagliptin 50mg/ metformin 850mg (Eucreas 50/850)	1 tablet twice daily	£31.76 (60)	£381.12
Vildagliptin 50mg/ metformin 1000mg (Eucreas 50/1000)	1 tablet twice daily	£31.76 (60)	£381.12
Metformin			
Metformin 500mg	2 tablets twice daily	£0.92 (28)	£47.84
Metformin 850mg	1 tablet twice daily	£1.33 (56)	£17.29

PACEF Comment:
In context, DPP-4 inhibitors remain relatively expensive third line branded antidiabetic agents. They are comparably priced at between £381 and £449pa with saxagliptin and vildagliptin emerging as the lowest cost agents at present.

Fixed dose DPP-4 inhibitor/metformin combination products (Janumet and Eucreas) are lower in cost than the two components prescribed separately.

Summary

The table below provides a brief summary of the key characteristics of each of the DPP-4 inhibitors.

	DPP-4 inhibitor			
	linagliptin	saxagliptin	sitagliptin	vildagliptin
Dual therapy licence	√	√	√	√
Triple therapy licence	√		√	
License with insulin		√	√	
Combination + metformin		√(early 2012)	√	√
LFT monitoring				√
Use - renal impairment	√	√		
Cost/28 days	£33.26	£31.60	£33.26	£31.76

PACEF Recommendation:
After a complete review of the clinical data associated with all four of the DPP-4 inhibitors, PACEF continue to endorse sitagliptin (Januvia) as the DPP-4 inhibitor of choice. Designation: GREEN. This is due to the range of licensed indications, the availability of the sitagliptin/metformin combination product Janumet (also designated GREEN) and the comparable efficacy and tolerability of sitagliptin to all other DPP-4 inhibitors. However, linagliptin (Trajenta) undergoes minimal elimination via the renal route and is a preferable option in patients suffering from renal or hepatic impairment. Linagliptin (Trajenta) is therefore approved as the DPP-4 inhibitor of choice in these specific patient groups. Designation: GREEN. In addition, PACEF also acknowledged the license extensions around saxagliptin and the lower acquisition cost in comparison to the other DPP-4 inhibitors. As a result of this, saxagliptin (Onglyza) was also designated GREEN. PACEF is aware that further DPP-4 inhibitor license extensions will be forthcoming in 2012 and will keep this area under review. At present, vildagliptin (Galvus) and vildagliptin/metformin (Eucreas) remain RED-RED. PACEF retain significant reservations about the use of vildagliptin on the basis of the twice daily dosage, the need for LFT monitoring in the first year of treatment and the contra-indication in liver impairment and moderate to severe renal impairment.

NEW DRUG ASSESSMENTS: *APREPITANT CAPSULES (EMEND) AND FOSAPREPITANT INJECTION (IVEMEND)*

Oral aprepitant capsules (Emend) and fosaprepitant injection (Ivemend) are neurokinin receptor antagonists licensed for use in combination with a corticosteroid and a $5HT_3$ receptor antagonist for the prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy. Aprepitant is administered orally for 3 days; fosaprepitant which has been shown to be non-inferior to aprepitant is administered intravenously as a single dose.

There is evidence from three RCTs in patients receiving highly emetogenic chemotherapy and two RCTs in patients receiving moderately emetogenic chemotherapy that the regimen including aprepitant is significantly more effective than a control regimen (ondansetron plus dexamethasone).

PACEF Recommendation:
Both oral aprepitant capsules (Emend) and fosaprepitant injection (Ivemend) have been approved by ULH Drug and Therapeutics Committee for use within United Lincolnshire Hospitals only. Designation: RED. There is no role for either of these products in primary care. Any requests made to GPs across the interface to prescribe either of these products, particularly aprepitant capsules, should be refused and referred back to the specialist service involved.

RAPID DRUG ASSESSMENT: *BROMFENAC EYE DROPS 900MICROGRAM/ML (YELLOX)*

Bromfenac is a non-steroidal anti-inflammatory drug (NSAID) with efficacy similar to other NSAIDs when used in the eye drop formulation, Yellox. The product is licensed for postoperative ocular inflammation following cataract surgery. ULH Drug and Therapeutics Committee reviewed bromfenac eye drops (Yellox) at the request of their consultant opthalmologists for use in 6 to 12 week courses to treat ocular inflammation and reduce macular oedema. As this indication is outside the license for the product and there is no evidence of superiority to alternative NSAIDs this request was refused.

PACEF Recommendation:
Bromfenac eye drops 900microgram/ml (Yellox) are designated RED-RED. Any request made to a GP across the interface to prescribe this product should be refused and referred back to the specialist service involved.

RAPID DRUG ASSESSMENT: *EFLORNITHINE 11.5% CREAM (VANIQA)*

Eflornithine 11.5% cream (Vaniqa) is the first topical product licensed for the treatment of facial hirsutism in female adolescents (aged 12 to 18 years) and adult women. Supporting evidence comes from the combined results of two identically designed randomised controlled trials. Results showed that eflornithine treatment resulted in significant reduction of visible facial hair in about a third of women. However this improvement was not maintained and hair growth approached pre-treatment levels within 8 weeks of discontinuation of therapy. There is a theoretical risk that long term use may result in skin atrophy, but published trials have been too short in duration to assess this risk. Eflornithine appears to be well tolerated with few reported adverse effects, the most common being burning, stinging and tingling. Co-cyprindiol is the only other product licensed for the treatment of hirsutism. Metformin is an alternative possibility in patients with polycystic ovary syndrome (POS). Eflornithine cream is considerably more expensive than co-cyprindiol with an annual cost of £156 per year (based on use of 30g – half a tube a month) compared to £16.

PACEF Recommendation:
PACEF are concerned about the limited efficacy and long-term safety of eflornithine cream (Vaniqa). Only a third of women respond to treatment and hair growth approaches pre-treatment levels within 8 weeks of discontinuation. As a result of this, eflornithine cream (Vaniqa) is designated RED-RED. All existing patients can continue with treatment until they or their clinician consider it appropriate to stop.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (November 2011)

Lenalidomide (Revlimid): risk of second primary malignancy – update

- Clinical trials investigating the use of lenalidomide in patients with newly diagnosed multiple myeloma have shown a four-fold increased risk of secondary primary malignancy (including haematological malignancies such as acute myeloid leukaemia, Hodgkin's disease and B-cell lymphocytic leukaemias; myelodysplastic syndrome; solid tumours; and melanomas).
- There seems to be a smaller increased risk of secondary primary malignancy in patients treated with lenalidomide for relapsed or refractory melanoma (the licensed indication).

Advice for healthcare professionals:

- Use of lenalidomide in unlicensed indications is not recommended unless it takes place as part of a clinical trial.
- Patients should be carefully evaluated before and during treatment with lenalidomide using routine cancer screening for occurrence of secondary primary malignancy.
- All suspected adverse reactions should be reported via the Yellow Card Scheme.

High-dose rosuvastatin and rhabdomyolysis

- In March 2003, rosuvastatin was launched in the UK.
- Consistent with other statins, muscle toxicity was recognised as a dose-related adverse reaction, leading in rare cases to rhabdomyolysis.
- In June 2004, the Committee on Safety of Medicines issued guidance contra-indicating rosuvastatin at the highest licensed dose (40mg) in patients with predisposing risk factors for muscle toxicity.
- Specialist supervision is recommended when 40mg is initiated.

PACEF Comment:
Prescribers are reminded that doses of rosuvastatin 40mg should only be initiated under specialist supervision.

Paracetamol: reminder of updated dosing recommendations for children

- Healthcare professionals are reminded of the updated dosing recommendations for paediatric paracetamol liquids.
- Products labelled with the new recommendations are now entering the market.

Updated dosing regimens are as follows:

New Dosing Schedule

Paracetamol 120mg/5ml

Child's age	Dose	Frequency (24 hours)
2-3 months Post vaccination fever	2.5ml (60mg)	If necessary repeat after 4-6 hours
2-3 months Other causes of pain and fever if baby weighs over 4kg and was born after 37 weeks.	2.5ml (60mg)	If necessary repeat after 4-6 hours
• Do not give to babies under 2 months of age • Do not give more than 2 doses • Leave at least 4 hours between doses • If further doses are needed, talk to your doctor or pharmacist		
3-6 months	2.5ml (60mg)	4 times
6-24 months	5ml (120mg)	4 times
2-4 years	7.5ml (180mg)	4 times
4-6 years	10ml (240mg)	4 times
• Do not give more than 4 doses in any 24 hour period • Leave at least 4 hours between doses • Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist		

Paracetamol 240mg/5ml or 250mg/5ml

Child's age	Dose	Frequency (24 hours)
6-8 years	5ml (240 to 250mg)	4 times
8-10 years	7.5ml (360 to 375mg)	4 times
10-12 years	10ml (480 to 500mg)	4 times
12-16 years	10-15ml (480 to 750mg)	Up to 4 times
Adults and children over 16 years	10-20ml	Up to 4 times a day
• Do not give more than 4 doses in any 24 hour period • Leave at least 4 hours between doses • Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist • Do not give to children under the age of 6 years		

DOMPERIDONE AND POSSIBLE INCREASED CARDIAC RISK

In a letter issued on December 16th, the manufacturers of domperidone tablets (Motilium) provided new information to prescribers on the cardiac risks associated domperidone. Two epidemiological studies published in 2010 concluded that domperidone when prescribed at higher doses (>30mg/day) or in patients older than 60 years may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. The SPC for domperidone (Motilium) will be amended to reflect this; further advice from the MHRA may be forthcoming later in the year. In the meantime, prescribers need to consider the following:

- Some epidemiological studies have shown that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death.
- These risks may be higher in patients older than 60 years and in patients who receive daily oral doses of than 30mg.
- Domperidone should be used in the lowest effective dose in adults and children.
- Patients should be advised to seek prompt medical attention if symptoms such as syncope or tachyarrhythmia appear during treatment.
- Domperidone should be avoided in patients who are taking concomitant medication known to cause QT prolongation (such as ketoconazole and erythromycin).

- Caution should be exercised when using domperidone in patients who have: existing prolongation of cardiac conduction intervals (particularly QTc); patients with significant electrolyte disturbances; or patients with underlying cardiac diseases such as congestive heart failure.
- Over-the-counter domperidone, sold under the supervision of a pharmacist, should not be supplied to people with underlying cardiac disease.
- The benefits of domperidone continue to outweigh the risks.

PACEF Recommendation:
The risk of serious ventricular arrhythmias or sudden cardiac death with domperidone *may* be higher in patients over 60 and in *any* patient on a dose higher than 30mg per day. Prescribers are asked to identify and review all patients currently taking domperidone who fall into either of these categories. Particular care should be taken where patients are taking domperidone in combination with concomitant medication known to cause QT prolongation or where the person has pre-existing cardiac disease or known electrolyte disturbances. All patients currently taking domperidone at doses higher than 30mg should have their dosage reviewed and stepped down where possible. Patients over 60 years of age currently taking domperidone at any dose will need to have their treatment reviewed. As there is no clear alternative to domperidone for many of these patients, each patient will need to be evaluated individually and decisions made after a careful consideration of relative risks and benefits. In many patients, the benefits will continue to outweigh the risks as long as the risks have been minimised through dosage reduction and the elimination of potentially interacting concurrent medication. Community pharmacies should no longer sell OTC domperidone to any patient with underlying cardiac disease and questions related to this must be incorporated into the discussion with the patient/carer at the time of OTC sale.

SUPPLY UPDATE: *TRIFLUOPERAZINE TABLETS (STELAZINE)*

As readers are probably aware, both Stelazine 1mg and 5mg tablets have been in short supply since Spring/Summer 2011. As a consequence, stocks of both strengths of generic trifluoperazine tablets have also declined and there are now chronic supply problems with both strengths of trifluoperazine tablets, both generic and brand. Trifluoperazine syrup 1mg in 5ml and oral solution 5mg in 5ml remain available and are being advocated by Lincolnshire Partnership Foundation Trust as the best way to manage the current crisis.

PACEF Recommendation:
All existing patients taking trifluoperazine 1mg or 5mg tablets will need to be considered for alternative therapy or managed using the syrup or oral solution formulations. No new patients should be started on trifluoperazine. There is a significant risk of psychotic symptoms emerging rapidly where treatment is abruptly withdrawn and every effort should be made to ensure continuing supply either through the available liquid formulations or through review and use of appropriate alternative therapy.

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