Greater East Midlands Commissioning Support Unit in association with
Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services,
United Lincolnshire Hospitals Trust and Lincolnshire Partnership Foundation Trust

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 21 **December 2013**

MERRY CHRISTMAS AND HAPPY NEW YEAR TO ALL OUR READERS

What's new this month?

- **The European Committee on Medicinal Products for Human Use (CHMP) has undertaken a safety review of metoclopramide and confirmed the already well documented risk of neurological effects, such as short-term extrapyramidal disorders and longer-term tardive dyskinesia; these risks are increased at high doses or with long-term treatment. In response to this, the MHRA have issued guidance that potentially reduces the range of authorized indications, clearly defines maximum doses in both adults and children and recommends metoclopramide for short periods only (up to 5 days). Once the findings of the CHMP are implemented across Europe, and marketing authorisations change, metoclopramide will no longer be indicated for the long-term relief of symptoms such as dyspepsia, heartburn, flatulence, sickness, regurgitation of bile and pain associated with chronic conditions such as gastroparesis (delayed gastric emptying), dyspepsia, and gastro-oesophageal reflux disease. Prescribers are advised to review all patients taking long-term metoclopramide at their next routine (i.e. non-urgent) medical appointment with a view to discontinuing therapy wherever possible. Where a prokinetic agent is still thought to be indicated, domperidone is now preferred; this and other alternative treatment strategies are detailed in the text. A small number of patients on long-term metoclopramide for chronic conditions, such as gastroparesis, may be insufficiently responsive to alternatives and may wish to continue on treatment. Such patients should be informed of the unlicensed status of the product, the maximum recommended dose and the potential risks of continuing long-term; a record of this consultation should be made in the patient's notes. Subject to agreement between the patient and the clinician, metoclopramide may be continued, although this is likely to be necessary in only a small number of patients. Metoclopramide remains GREEN for short-term use within authorized indications and doses (as detailed in the text). New patients should only be initiated on longer-term therapy on the advice of a gastroenterologist: designation AMBER without shared care. Existing patients on long-term metoclopramide should be reviewed (see page 4).**
- **Following a review, PACEF have approved all three of the gonadorelin analogues in all formulations, goserelin implant (*Zoladex/Zoladex LA*), leuprorelin injection (*Prostap SR DCS/Prostap 3 DCS*) and triptorelin injection (*Decapeptyl SR*), for inclusion in the *Joint Formulary*. All products are designated AMBER without shared care within authorized indications (see page 7).**

- **Both clopidogrel oral solution 75mg in 5ml and clopidogrel oral suspension 75mg in 5ml are high cost unlicensed specials and should not be prescribed. Both products are designated RED-RED. Neither of these products is approved for inclusion in the *Joint Formulary*. Where a patient with swallowing difficulties requires clopidogrel, generic clopidogrel 75mg tablets can be dispersed in water or crushed and mixed with water prior to administration (see page 9).**
- **A recent systematic review has provided new safety data on dapagliflozin (*Forxiga*) (see page 10).**
- **In order to maximise the financial impact of the montelukast patent expiry, prescribers are asked to ensure that all prescribing of montelukast is generic from now on. Montelukast should be considered to be the preferred leukotriene receptor antagonist within authorised indications; it is designated GREEN and included in the *Joint Formulary*. Zafirlukast 20mg tablets (*Accolate*) are designated RED-RED and are not included in the *Joint Formulary* (see page 11).**

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SUMMARY OF PACEF DECISIONS: *NOVEMBER AND DECEMBER 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Clopidogrel oral solution 75mg in 5ml	An unlicensed liquid formulation of a widely used antiplatelet agent	RED-RED Not approved for inclusion on the *Joint Formulary*.
Clopidogrel oral suspension 75mg in 5ml	An unlicensed liquid formulation of a widely used antiplatelet agent	RED-RED Not approved for inclusion on the *Joint Formulary*.
Crizotinib 200mg and 250mg capsules (*Xalkori*)	For use in second and subsequent line anaplastic lymphoma kinase fusion non-small cell lung cancer	RED Approved for inclusion in the *Joint Formulary* for this indication.
Dapagliflozin 5mg and 10mg tablets (Forxiga)	For use in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control either as: • monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. • or add-on combination therapy with other glucose-lowering agents, including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.	RED-RED for monotherapy. Not approved for inclusion in the *Joint Formulary* for this indication. GREEN for dual therapy with metformin and combination therapy with insulin. Approved for inclusion in the *Joint Formulary* for these indications RED-RED for triple therapy with metformin and a sulfonylurea. . Not approved for inclusion in the *Joint Formulary* for this indication.

Goserelin implant with syringe applicator 3.6mg (*Zoladex*)	For breast cancer and prostate cancer	AMBER without shared care. Included in the Joint Formulary.
Goserelin implant with syringe applicator 10.8mg (*Zoladex LA*)	For prostate cancer	AMBER without shared care. Included in the *Joint Formulary.*
Leuprorelin acetate sustained release suspension for injection 3.75mg (*Prostap SR DCS*)	For prostate cancer	AMBER without shared care. Included in the *Joint Formulary.*
Leuprorelin acetate sustained release suspension for injection 11.25mg (*Prostap 3 DCS*)	For prostate cancer	AMBER without shared care. Included in the *Joint Formulary.*
Metoclopramide tablets 10mg (generic/*Maxolon*) Metoclopramide oral solution 5mg in 5ml	For the symptomatic treatment of nausea and vomiting, including that associated with acute migraine.	GREEN Included in the *Joint Formulary.* Should only be used short-term (up to 5 days); dose should not exceed the maximum recommended dose (see text).
Metoclopramide tablets 10mg (generic/*Maxolon*) Metoclopramide oral solution 5mg in 5ml	For the treatment of chronic conditions such as gastroparesis, dyspepsia, and gastro-oesophageal reflux disease.	AMBER without shared care. New patients should only be initiated on the advice of a gastroenterologist. Existing patients should be reviewed at the next routine appointment with a view to stopping therapy wherever possible. Where the decision is taken to continue long-term metoclopramide, the patient should be aware of the unlicensed status of the drug, the maximum recommended dose and the risks of long-term use. Included in the *Joint Formulary.*
Montelukast 4mg and 5mg chewable tablets and 4mg granules	Add on therapy in mild to moderate asthma inadequately controlled by inhaled corticosteroids and short-acting beta 2 agonists. Alternative to low-dose inhaled corticosteroids for children with mild persistent asthma who do not have a recent history of serious asthma attacks and who are incapable of using inhaled steroids. Exercise induced broncho-constriction .	GREEN Included in the *Joint Formulary*. Prescribe generically.
Montelukast 10mg tablets	Add on therapy in mild to moderate asthma inadequately controlled by inhaled corticosteroids and short-acting beta 2 agonists. Exercise induced broncho-constriction . Symptomatic relief of concomitant seasonal allergic rhinitis in asthma patients.	GREEN Included in the *Joint Formulary*. Prescribe generically.
Ocriplasmin intravitreal injection (*Jetrea*)	For the treatment of vitreomacular traction.	RED Approved for inclusion in the *Joint Formulary.*
Triptorelin intramuscular injection 3mg (*Decapeptyl SR*)	For locally advanced non-metastatic prostate cancer as an alternative to surgical castration, metastatic prostate cancer, as an adjunct to radiotherapy in high risk localised or locally advanced prostate cancer	AMBER without shared care. Approved for inclusion in the *Joint Formulary.*
Triptorelin intramuscular injection 11.25mg (*Decapeptyl SR*)	For locally advanced non-metastatic prostate cancer as an alternative to surgical castration, metastatic prostate cancer, as an adjunct to radiotherapy in high risk localised or locally advanced prostate cancer	AMBER without shared care. Approved for inclusion in the *Joint Formulary.*
Triptorelin intramuscular injection 22.5mg (*Decapeptyl SR*)	For locally advanced non-metastatic prostate cancer as an alternative to surgical castration, metastatic prostate cancer, as an adjunct to radiotherapy in high risk localised or locally advanced prostate cancer	AMBER without shared care. Approved for inclusion in the *Joint Formulary.*
Zafirlukast 20mg tablets (*Accolate*)	Treatment of asthma	RED-RED Not approved for inclusion in the *Joint Formulary.*

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 in Lincolnshire website (www.lincolnshire.nhs.uk); follow the commissioning link to PACEF. Electronic copies of both the *PACE Bulletin* and our sister publication *PACE Shorts* (a short summary of the *PACE Bulletin*) are circulated to a wide readership via email. If you are not currently on our distribution list and wish to receive regular copies of PACEF publications please contact Sandra France on sandra.france@gemcsu.nhs.uk.

The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

METOCLOPRAMIDE – RISK OF NEUROLOGICAL ADVERSE EFFECTS

The European Medicines Agency Committee on Medicinal Products for Human Use (CHMP) have re-examined the conclusions of their review of the risks and benefits of metoclopramide and have concluded that the risks of metoclopramide therapy outweigh the benefits in conditions requiring high-dose or long-term treatment.
The review confirmed the already well-known risk of neurological effects, such as short-term extrapyramidal disorders (involuntary movements often involving the head and neck), and tardive dyskinesia (uncontrollable movements such as grimacing and twitching). The risk of short-term neurological effects is higher in children, although tardive dyskinesia is reported more often in the elderly; these risks are increased at high doses or with long-term treatment. Very rare cases of serious effects on the heart or circulation, particularly after injection, were also identified as part of the review.

The implications of this are that metoclopramide:

- should only be authorised for short-term use (defined as up to 5 days).
- should not be used in children below 1 year of age.
- should only be used in children over 1 as a second line treatment (after other treatments have been considered or tried) for the prevention of delayed nausea and vomiting after chemotherapy and for the treatment of post-operative nausea and vomiting.
- should only be used in adults for the prevention of postoperative nausea and vomiting; radiotherapy-induced nausea and vomiting; delayed (but not acute) chemotherapy-induced nausea and vomiting; and for symptomatic treatment of nausea and vomiting, including that associated with acute migraine (where it may also improve the absorption of oral analgesics).
- should no longer be prescribed for chronic conditions such as gastroparesis, dyspepsia or gastro-oesophageal reflux disease, nor as an adjunct in surgical and radiological procedures.
- should not be prescribed above the maximum recommended dose. In children the recommended dose is 0.1 to 0.15mg per kg body weight repeated up to three times a day. In adults the recommended dose is 10mg up to three times a day.
- should no longer be prescribed in high strength formulations such as metoclopramide hydrochloride injection in strengths above 5mg/ml or oral liquids in strengths above 1mg/ml. Oral liquid formulations and errors associated with their use have been linked to overdose in children. Where an oral liquid formulation is prescribed it should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy. Oral liquids containing more than 1mg/ml will be withdrawn from the market.

Metoclopramide: Revised Indications

The table below illustrates the changes to authorized indications that are likely to be made in response to this review:

Approved Indications	**Indications No Longer Approved**
Children over 1 year of age: As a second choice treatment for the prevention of delayed nausea and vomiting after chemotherapy or for the treatment of post-operative nausea and vomiting.	Children over 1 year of age: Should not be used long-term (i.e. longer than 5 days) or above maximum recommended dose (see above).
Adults: For the prevention of postoperative nausea and vomiting; radiotherapy-induced nausea and vomiting; delayed (but not acute) chemotherapy-induced nausea and vomiting; and symptomatic treatment of nausea and vomiting, including that associated with acute migraine (where it may also improve the absorption of oral analgesics).	Adults: Should not be used long-term (i.e. longer than 5 days) or above maximum recommended dose (see above). e.g. For the treatment of chronic conditions such as gastroparesis, dyspepsia, and gastro-oesophageal reflux disease. e.g. For use as an adjunct in surgical and radiological procedures.

The EMA CHMP reviewed published studies and meta-analyses on the efficacy of metoclopramide and analysed reports of adverse drug reactions. From this they concluded that:

- Metoclopramide is effective in the treatment of nausea and vomiting associated with acute migraine; doses above 10mg do not increase efficacy. Metoclopramide increases gut motility and may improve the absorption of concurrently administered oral analgesics in the acute setting.
- There is no evidence of consistent benefit to support the use of metoclopramide in gastroparesis, GORD and dyspepsia, all of which are chronic conditions that require long-term treatment that increases the risk of chronic neurological side effects.
- There is also no evidence to support a role for metoclopramide as an adjunct in surgical and radiological procedures.
- Extrapyramidal disorders are reported 6 times more frequently with children than with adults; they are also more likely to occur after several doses and early in treatment. Elderly patients on longer-term treatment are most at risk from potentially irreversible tardive dyskinesia. Extrapyramidal disorders account for nearly half of all reported adverse effects with metoclopramide.
- Serious cardiovascular reactions are very rare and mainly associated with intravenous formulations given to patients with underlying risks of cardiac disease.

Possible alternatives

The only alternative prokinetic drug on the UK market is domperidone. Domperidone does not cross the blood brain barrier and has not been associated with dystonic reactions or tardive dyskinesia; it has been shown to be as effective as metoclopramide in terms of gastric emptying. However, domperidone has been associated with arrhythmias due to prolongation of the QT interval and should be used with caution in patients who have existing prolongation of cardiac conduction intervals (particularly QTc) or significant electrolyte disturbance or underlying cardiac disease, such as congestive heart failure, and in patients who are known to be taking prescribed medicines for these conditions; this is a particular risk in patients older than 60 years and in those taking oral doses of more than 30mg daily. Domperidone should also be avoided in patients taking concomitant medicines

that prolong the QT interval such as erythromycin. A European safety review of domperidone is in progress and is likely to report soon. Where domperidone is initiated, it should be at the lowest effective dose.

In particular, alternative approaches to the treatment of dyspepsia, GORD and gastroparesis need to be considered. Where GORD or dyspepsia do not respond to a second month of a full dose proton pump inhibitor (PPI) or an alternative PPI, the NICE Clinical Knowledge Summary recommends a trial of either a H2 receptor antagonist or domperidone. Within this context domperidone should be used either on demand (i.e. when symptoms occur) or intermittently (i.e. a 2 to 4 week course when symptoms recur).

In gastroparesis, unresponsive to removal of any iatrogenic causes, prokinetic agents remain the mainstay of therapy. Both domperidone and metoclopramide are of equivalent efficacy in reducing symptoms, with domperidone now preferred. For patients for whom domperidone is not appropriate, alternative options are very limited. For example, low dose erythromycin (250 to 500mg three times daily for up to four weeks) is of some benefit, but it is unlicensed for this indication and long-term efficacy is limited by tachyphylaxis.

Future role for long-term metoclopramide?

A small number of patients on long-term metoclopramide for chronic conditions, such as gastroparesis, may be insufficiently responsive to alternatives and may wish to continue on treatment. In addition, patients at increased risk of arrhythmias due to prolongation of the QT interval (e.g. those with underlying cardiac disease) are likely to be inappropriate for domperidone and may require alternative therapy. Patients identified as needing to continue on metoclopramide should be informed of the unlicensed status of the product and the potential risks of continuing long-term; a record of this consultation should be made in the patient's notes. Subject to agreement between the patient and the clinician, metoclopramide may be continued, although this is likely to be necessary in only a small number of patients. Metoclopramide remains GREEN for short-term use within authorized indications and doses. New patients requiring longer-term therapy should only be initiated on the advice of a gastro-enterologist; designation AMBER without shared care. Existing patients on long-term therapy are subject to review as detailed above.

PACEF Recommendations:
The European Committee on Medicinal Products for Human Use (CHMP) has undertaken a safety review of metoclopramide and confirmed the already well documented risk of neurological effects, such as short-term extrapyramidal disorders and longer-term tardive dyskinesia; these risks are increased at high doses or with long-term treatment. In response to this, the MHRA have issued guidance that potentially reduces the range of authorized indications, clearly defines maximum doses in both adults and children and recommends metoclopramide for short periods only (up to 5 days). Once the findings of the CHMP are implemented across Europe, and marketing authorisations change, metoclopramide will no longer be indicated for the long-term relief of symptoms such as dyspepsia, heartburn, flatulence, sickness, regurgitation of bile and pain associated with chronic conditions such as gastroparesis (delayed gastric emptying), dyspepsia, and gastro-oesophageal reflux disease. Prescribers are advised to review all patients taking long-term metoclopramide at their next routine (i.e. non-urgent) medical appointment with a view to discontinuing therapy wherever possible. Where a prokinetic agent is still thought to be indicated, domperidone is now preferred; this and other alternative treatment strategies are detailed in the text. A small number of patients on long-term metoclopramide for chronic conditions, such as gastroparesis, may be insufficiently responsive to alternatives and may wish to continue on treatment. Such patients

should be informed of the unlicensed status of the product, the maximum recommended dose and the potential risks of continuing long-term; a record of this consultation should be made in the patient's notes. Subject to agreement between the patient and the clinician, metoclopramide may be continued, although this is likely to be necessary in only a small number of patients. Metoclopramide remains GREEN for short-term use within authorized indications and doses (as detailed in the text). New patients should only be initiated on longer-term therapy on the advice of a gastroenterologist: designation AMBER without shared care. Existing patients on long-term metoclopramide should be reviewed.

References:
European Medicines Agency, *EMA confirms changes to use of metoclopramide* (25th October 2013) (www.ema.europa.eu)
Trent Medicines Information Service, *Rapid Communication Metoclopramide: restrictions in use* (December 2013)

REVIEW OF GONADORELIN ANALOGUES

Following a full review, PACEF have approved all three of the gonadorelin analogues, goserelin (*Zoladex/Zoladex LA*), leuprorelin (*Prostap SR DCS/Prostap 3 DCS*) and triptorelin (*Decapeptyl SR*), for inclusion on the *Joint Formulary*.

Licensed indications

The table below summarizes the range of different formulations available, the licensed indications and frequency of injections:

Drug and Dose	**Goserelin 3.6mg**	**Leuprorelin 3.75mg**	**Triptorelin 3mg**	**Triptorelin 3.75mg**	**Goserelin 10.8mg**	**Leuprorelin 11.25mg**	**Triptorelin 11.25mg**	**Triptorelin 22.5mg**
Brand Name	***Zoladex***	***Prostap SR***	***Decapeptyl SR***	***Gonapeptyl Depot***	***Zoladex LA***	***Prostap 3 DCS***	***Decapeptyl SR***	***Decapeptyl SR***
Form	**Implant in prefilled syringe # needle size can be a problem**	**Powder plus solvent in prefilled syringe**	**Powder for suspension with diluent**	**Powder for suspension with vehicle in pre-filled syringe**	**Implant in prefilled syringe # needle size can be a problem**	**Powder plus solvent in prefilled syringe**	**Powder for suspension with diluent**	**Powder for suspension with diluent**
Injection frequency	**28 days**	**Monthly**	**4 weekly**	**28 days**	**12 weekly**	**3 monthly**	**3 monthly**	**6 monthly**
Licensed uses								
CaP metastatic	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
CaP locally advanced alternative to castration	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
CaP adjuvant treatment to radiotherapy	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
CaP neo adjuvant prior to radiotherapy	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**
CaP adjuvant treatment to radical prostatectomy	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Endometriosis	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**No**
Uterine fibroids	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**	**No**	**No**
Advanced breast	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**

cancer								
Early breast cancer	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Precocious puberty	**No**	**No**	**No**	**Yes**	**No**	**No**	**Yes**	**No**
Endometrial thinning	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Assisted reproduction	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Endometrial preparation prior to intrauterine surgical procedures	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**

Cost comparison

Drug	Dose range	Cost (£) pa
Goserelin implant with syringe applicator 10.8mg (*Zoladex LA*) plus Cyproterone	10.8mg every 12 weeks plus 200mg daily in 2-3 divided doses for 5-7 days before initiation and continue for 3-4 weeks	£1,018.33 plus £58.00 (28 days) Total - £1,076.33
Alternative gonadorelin analogues		
Goserelin implant with syringe applicator 3.6mg (*Zoladex*)	3.6mg every 28 days	£845
Histrelin depot SC implant (*Vantas*)	50mg every 12 months	£990
Leuprorelin acetate sustained release suspension for injection 11.25mg (*Prostap 3 DCS*)	11.25mg every 3 months	£902.88
Leuprorelin acetate sustained release suspension for injection 3.75mg (*Prostap SR DCS*)	3.75mg monthly	£902.88
Triptorelin intramuscular injection 11.25mg (*Decapeptyl SR*)	11.25mg every 3 months	£828
Triptorelin intramuscular injection 3mg (*Decapeptyl SR*)	3mg every 28 days	£897
Triptorelin intramuscular injection 22.5mg (*Decapeptyl SR*)	22.5mg every 6 months	£828
Triptorelin SC injection (*Gonapeptyl*)	3.75mg every 28 days	£1061.97
Alternative anti-androgens		
Flutamide 250mg tablets commence 3 days prior to GA and continue for 3 weeks	250mg three times daily	£44.21 (28 days)
Bicalutamide 50mg tablets commence 3 days prior to GA and continue for 3 weeks	50mg daily	£2.36 (28 days)

Conclusions

(1) Review of the evidence suggests that all three of the gonadorelin analogues are broadly similar in terms of safety and effectiveness in the treatment of prostate cancer. All three are licensed and are approved for inclusion in the *Joint Formulary* for the range of prostate cancer related indications.

(2) In addition, goserelin (*Zoladex*) is also licensed for the treatment of breast cancer at a dose of 3.6mg every 28 days. As the other two agents do not hold this marketing authorisation, goserelin (*Zoladex*) is approved for inclusion on the *Joint Formulary* for this indication.

(3) Goserelin 3.6mg and 10.8mg (*Zoladex* and *Zoladex LA*) are both administered as an implant through a prefilled syringe. The size of the needle involved can prove off-putting and painful for some patients; alternative preparations, such as leuprorelin

(*Prostap*) and triptorelin (*Decapeptyl*), which have a smaller needle and are less painful, may be preferred.

(4) Injection frequency is an issue for both clinicians and patients. All three products are available in three monthly injections within licensed indications (i.e. goserelin 10.8mg (*Zoladex LA*), leuprorelin 11.25mg (*Prostap 3 DCS*) and triptorelin 11.25mg (*Decapeptyl SR*)). Triptorelin is also available as a 22.5mg 6 monthly injection which offers greatest convenience for both the clinician and the patient (*Decapeptyl SR*).

(5) The cost comparison reveals that triptorelin IM injection 3mg, 11.25mg and 22.5mg (*Decapeptyl SR*) is currently the most cost-effectiveness gonadorelin analogue within authorized indications.

(6) Most of the gonadorelin analogue prescribing initiated in county is led by secondary care urologists. Current local prescribing preferences are for goserelin (*Zoladex*/*Zoladex LA*) and leuprorelin (*Prostap 3 DCS*/*Prostap SR DCS*).

PACEF Recommendations:
Following review, all three of the gonadorelin analogues in all available formulations are approved for inclusion in the *Joint Formulary* and designated AMBER without shared care. Prescribers should consider licensed indications, frequency of injection and cost-effectiveness when making a product selection.

NEW DRUG AND NEW FORMULATION ASSESSMENTS

RAPID DRUG ASSESSMENTS: *UNLICENSED CLOPIDOGREL ORAL SOLUTION 75MG IN 5ML AND CLOPIDOGREL ORAL SUSPENSION 75MG IN 5ML*

Clopidogrel oral solution 75mg in 5ml and oral suspension 75mg in 5ml are unlicensed specials designed for use in patients for whom clopidogrel is indicated but where the conventional tablet formulation presents difficulties, predominantly due to problems with swallowing. Within this context, liquid formulations can be more convenient for patients, carers and nursing staff. Both of these unlicensed liquid formulations of clopidogrel are listed in the specials section (Part VIIIB) of the *Drug Tariff*:

	Minimum volume	Cost per dose
Clopidogrel 75mg in 5ml oral solution	150ml	£2.33 (£69.80 per 150ml bottle)
Clopidogrel 75mg in 5ml oral suspension	100ml	£12.02 (£240.36 per 100ml bottle)
Clopidogrel 75mg tablets (generic)		£0.06 (£1.71 for 28 tablets)
Clopidogrel 75mg tablets (*Plavix*)		£1.19 (£35.64 for 30 tablets)

A cost comparison reveals that both formulations are exceptionally high cost in comparison to generic clopidogrel 75mg tablets and even clopidogrel (*Plavix*) 75mg tablets. As an alternative to prescribing a special liquid formulation, generic clopidogrel tablets can be dispersed in water or crushed and mixed with water.

PACEF Recommendation:
Both clopidogrel oral solution 75mg in 5ml and clopidogrel oral suspension 75mg in 5ml are high cost unlicensed specials and should not be prescribed. Both products are designated RED-RED. Where a patient with swallowing difficulties requires clopidogrel, generic clopidogrel 75mg tablets can be crushed and mixed with 10ml of water prior to administration. Neither clopidogrel oral solution 75mg in 5ml nor clopidogrel oral suspension 75mg in 5ml is approved for inclusion in the *Joint Formulary*.

NEW TRIAL ASSESSMENT

NEW SAFETY DATA ON DAPAFLIGLOZIN (*FORXIGA*)

A systematic review of 58 studies (n=16,407) compared sodium glucose co-transporter 2 (SGLT2) inhibitors with placebo or other medicines in the treatment of type 2 diabetes. Dapagliflozin (*Forxiga*) is currently the only SGLT2 inhibitor with a UK marketing authorisation; 21 of the studies reviewed involved dapagliflozin.

All of the SGLT2 inhibitors reduced HbA1c levels compared with placebo and all showed a comparable reduction to other anti-diabetic drugs; favourable effects on blood pressure and weight were also reported with SGLT2 inhibitors.

In terms of adverse effects, SGLT-2 inhibitors significantly increased the risk of UTIs, genital tract infections and hypotension. An increase in the incidence of renal adverse events and fractures was observed in patients with moderate renal impairment in comparison to placebo. Nine cases each of bladder cancer and breast cancer were reported in patients treated with dapagliflozin (the expected rate of bladder cancer in an age-matched population is 2 cases). This numerical imbalance may be due to detection bias as a result of more frequent urinalysis. Breast cancer was diagnosed between days 6 to 334 of the study which is much shorter than the 5 years' exposure usually regarded as necessary for breast cancer to be detectable.

PACEF Comment:
Dapagliflozin (*Forxiga*) has been designated GREEN by Lincolnshire PACEF subject to NICE criteria (i.e. it is an option to use as dual oral therapy and as an add-on to insulin treatment, but not as monotherapy or triple oral therapy). This systematic review emphasizes the common side effects of dapagliflozin, including urinary and genital infections (linked to increased concentrations of urinary glucose) and hypotension (resulting from diuresis). Dapagliflozin is not recommended for use in people 75 years and older due to limited experience and it is contraindicated for use in people with moderate to severe renal impairment (eGFR less than 60ml/min) because its efficacy is dependent upon renal function. Long term safety data are lacking. The higher than expected number of reports of bladder and breast cancer are under investigation and have contributed to the American Food and Drug Administration (FDA) refusing a US licence application from the manufacturer.

Reference:
Vasilakou D et al., Sodium-glucose co-transporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. *Ann Intern Med* 2013; 159: 262 – 274

GENERIC MONTELUKAST PREPARATIONS ARE NOW AVAILABLE

Since July 2013, all formulations of montelukast have been available as low cost generic products and a significant cost differential has opened up between generic montelukast and the originator brand, *Singulair*. Similarly generic montelukast is now significantly lower in cost than the competitor product, zafirlukast (*Accolate*) (see cost comparison below):

Drug	Dose	Cost (28 days)
Montelukast 4mg chewable tablets	4mg once daily in the evening	£2.35
Montelukast 5mg chewable tablets	5mg once daily in the evening	£2.66
Montelukast 4mg granules	4mg sachet once daily in the evening	£3.88
Montelukast 10mg tablets	10mg once daily in the evening	£2.66
Montelukast 4mg chewable tablets (*Singulair Paediatric*)	4mg once daily in the evening	£25.69
Montelukast 5mg chewable tablets (*Singulair Paediatric*)	5mg once daily in the evening	£25.69
Montelukast 4mg granules (*Singulair Paediatric Granules)*	4mg sachet once daily in the evening	£25.69
Montelukast 10mg tablets (*Singulair*)	10mg once daily in the evening	£26.97
Zafirlukast 20mg tablets (*Accolate*)	20mg twice daily	£17.75

It has been estimated that the generic savings resulting from the montelukast patent expiry will reduce prescribing costs in Lincolnshire in year by over £600,000.

The calculated savings for each of the Lincolnshire Clinical Commissioning Groups are tabulated below:

CCG	**In year savings from montelukast patent expiry**
Lincolnshire East CCG	£255,400
Lincolnshire West CCG	£164,601
South Lincolnshire CCG	£118,569
South West Lincolnshire CCG	£79,004

PACEF Recommendation:
In order to maximise the financial impact of the montelukast patent expiry, prescribers are asked to ensure that all prescribing of montelukast is generic from now on. Montelukast should be considered to be the preferred leukotriene receptor antagonist within authorised indications; it is designated GREEN and included in the *Joint Formulary*. Zafirlukast 20mg tablets (*Accolate*) are designated RED-RED and are not included in the *Joint Formulary*.

NICE TECHNOLOGY APPRAISAL 296: *CRIZOTINIB FOR PREVIOUSLY TREATED NON-SMALL-CELL LUNG CANCER ASSOCIATED WITH AN ANAPLASTIC LYMPHOMA KINASE FUSION GENE* (SEPTEMBER 2013)

Crizotinib is not recommended within its marketing authorization, that is, for treating adults with previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer.

PACEF Recommendation:
Despite the unfavourable outcome of this NICE Technology Appraisal, crizotinib 200mg and 250mg capsules (*Xalkori*) have been approved for use in second and subsequent line anaplastic lymphoma kinase fusion non-small cell lung cancer (NSCLC) through the National Cancer Drugs Fund. As a result of this Crizotinib 200mg and 250mg capsules (*Xalkori*) are designated RED for this indication. It is approved for use on the *Joint Formulary*.

NICE TECHNOLOGY APPRAISAL 297: *OCRIPLASMIN FOR TREATING VITREOMACULAR TRACTION* (OCTOBER 2013)

Ocriplasmin is recommended as an option for treating vitreomacular traction in adults, only if:

- an epiretinal membrane is not present
  and
- they have a stage II full-thickness macular hole with a diameter of 400 micrometres or less **and/or**
- they have severe symptoms.

PACEF Recommendation:
Ocriplasmin (*Jetrea*) is a highly specialized drug administered by intravitreal injection and is designated RED. It is approved for use on the *Joint Formulary*.

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