Greater East Midlands Commissioning Support Unit in association with
Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services,
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Prescribing and Clinical Effectiveness Bulletin

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What's new this month?

- **Ingenol mebutate gel (*Picato*) is an effective treatment for non-hyperkeratotic and non-hypertrophic actinic keratosis of the face, scalp, trunk and extremities. Despite the lack of comparative data against alternative treatments, a Cochrane review has concluded that ingenol mebutate is of similar efficacy to diclofenac 3% sodium hyaluronate 2.5% gel, fluorouracil 5% cream and imiquimod 5% cream (*Aldara*). In addition, the much shorter treatment period, with ingenol mebutate is potentially more convenient for patients. As a result of this, ingenol mebutate gel 0.015% and 0.05% (*Picato*) is designated GREEN and has been approved for inclusion in the *Joint Formulary* (see page 4).**
- **Estradiol/nomegestrol 1.5mg/2.5mg tablet (*Zoely*), a new combined oral contraceptive pill, is designated RED-RED and has not been approved for inclusion in the *Joint Formulary* (see page 5).**
- **Both latanoprost 50 microgram/ml (0.005%) preservative-free single dose eye drops (*Monoprost*) and bimatoprost 300 microgram per ml (0.03%) preservative-free single dose eye drops (*Lumigan*) are approved for use and are included in the *Joint Formulary*. Designation: AMBER without shared care (see page 6).**
- **Dapagliflozin (Forxiga) 5mg and 10mg tablets are designated GREEN and approved for inclusion in the *Joint Formulary* subject to NICE criteria (i.e. combination therapy with metformin and combination therapy with insulin). Certain licensed indications remain RED-RED (i.e. monotherapy and triple therapy with metformin and a sulfonylurea) (see page 8).**
- **Mirabegron (*Betmiga*) has been approved by NICE for the treatment of symptoms of overactive bladder in people for whom antimuscarinics are contraindicated or clinically ineffective or have unacceptable side effects. Within these criteria and contraints, mirabegron 25mg and 50mg tablets (*Betmiga*) are designated GREEN and approved for inclusion in the *Joint Formulary*. Further guidance on the place of mirabegron in the management of urinary incontinence will be issued following the publication of the updated NICE Clinical Guideline in September 2013 (see page 13).**
- **Diclofenac is now contra-indicated in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure (NYHA classification II to IV). Patients with these conditions should be switched to an alternative treatment at their next routine appointment (see page 16).**

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SUMMARY OF PACEF DECISIONS: *JULY 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Bevacizumab intravenous infusion (*Avastin*)	For the first line treatment of advanced epithelial ovarian, fallopian tube or primary peritoneal cancer in combination with carboplatin and paclitaxel	RED-RED Not approved for inclusion in the *Joint Formulary* for this indication.
Bevacizumab intravenous infusion (*Avastin*)	For use in combination with gemcitabine and carboplatin for treating people with the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.	RED-RED Not approved for inclusion in the *Joint Formulary* for this indication.
Bimatoprost 300microgram/ml preservative-free single dose eye drops (*Lumigan*)	For use as monotherapy or as an adjunct to beta-blockers in chronic open-angle glaucoma or ocular hypertension	AMBER without shared care Approved for inclusion in the *Joint Formulary*
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	RED-RED for monotherapy. Not approved for inclusion in the *Joint Formulary* for this indication.

	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.	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.
Estradiol valerate / dienogest combined oral contraceptive pill (*Qlaira*)	Oral contraception	RED-RED Not approved for inclusion in the *Joint Formulary*.
Estradiol hemihydrate 1.5mg / nomegestreol acetate 2.5mg combined oral contraceptive pill (*Zoely*)	Oral contraception	RED-RED Not approved for inclusion in the *Joint Formulary.*
Ingenol mebutate gel (*Picato*) 150 microgram/g (0.015%) 500 microgram/g (0.05%)	Non-hyperkeratotic and non-hypertrophic actinic keratosis	GREEN Approved for inclusion in the *Joint Formulary*
Latanoprost 50microgram/ml preservative-free single dose eye drops (*Monoprost*)	Open angle glaucoma, ocular hypertension	AMBER without shared care Approved for inclusion in the *Joint Formulary*
Loxapine inhalation (*Adusave*)	For adults with mild to moderate agitation associated with schizophrenia and bipolar disorder. The product has yet to be launched in the UK.	RED-RED Not approved for inclusion in the *Joint Formulary.*
Mirabegron 25mg and 50mg sustained release tablets (*Betmiga*)	For the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence in adult patients with overactive bladder (OAB) syndrome.	GREEN Approved for inclusion in the *Joint Formulary.* Reserved for those in whom antimuscarinics are contraindicated or clinically ineffective or have unacceptable side effects.
Ranibizumab (*Lucentis*) intravitreal injection	Treatment of neovascular (wet) age-related macular degeneration. Treatment of visual impairment due to diabetic macular oedema Treatment of visual impairment due to macular oedema secondary to branch or central retinal vein occlusion.	RED. Included in the *Joint Formulary* RED. Included in the *Joint Formulary* RED. Approved for inclusion in the *Joint Formulary*.
Tafluprost 15microgram/ml preservative-free single dose eye drops (*Saflutan*)	For use as monotherapy or as an adjunct to beta-blockers in open-angle glaucoma or ocular hypertension	AMBER without shared care. Included on 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

NEW DRUG ASSESSMENT: INGENOL MEBUTATE GEL (*PICATO*)

Ingenol mebutate gel (*Picato*) is indicated for the cutaneous treatment of non-hyperkeratotic non-hypertrophic actinic keratosis in adults. Actinic keratoses are common sun-induced skin lesions which have a small potential to progress to invasive squamous cell carcinomas; only 2% of actinic keratosis progress to skin cancer. The product is available in two strengths: 150 micrograms/gram (0.015%) for the treatment of lesions of the face or scalp and 500 micrograms/gram (0.05%) for treating lesions on the trunk or extremities.

In four phase III, double-blind, randomised, vehicle-gel controlled trials of patients with actinic keratosis, ingenol mebutate gel was associated with significantly higher rates of complete lesion clearance in the treatment area, compared with the vehicle gel. In a pooled analyses of these studies, the percentages of patients with complete clearance of lesions after treatment with ingenol mebutate gel were 42.2% (face/scalp studies) and 34.1% (trunk/extremities studies), compared with 3.7% and 4.7% respectively of patients receiving vehicle gel. These studies demonstrate that ingenol mebutate gel is significantly more effective than placebo and confirm the different strengths of the product required in the treatment of lesions of the face or scalp (150micrograms/gram) and the trunk or extremities (500 micrograms/gram). There are no published studies comparing ingenol mebutate gel with any other active treatment for actinic keratosis.

The table below reveals the short duration of ingenol mebutate therapy (2 to 3 days) compared to the much longer periods of treatment required with alternatives:

	Marketing authorisation	**Directions**	**Cost**
Ingenol mebutate 150 microgram/g gel (*Picato*)	Non-hyperkeratotic and non-hypertrophic actinic keratosis of the face or scalp	Apply once daily to the affected area for 3 consecutive days.	3 x 0.47g tubes £65.00
Ingenol mebutate 500 microgram/g gel (*Picato*)	Non-hyperkeratotic and non-hypertrophic actinic keratosis of the trunk or extremites	Apply once daily to the affected area for 2 consecutive days.	2 x 0.47g tubes £65.00
Diclofenac 3%/ sodium hyaluronate 2.5% gel (*Solareze*)	Actinic keratoses	Apply to the affected area twice daily for 60 to 90 days	50g - £38.30 100g - £76.60
Fluorouracil 5% cream (*Efudix*)	Superficial pre-malignant and malignant skin lesions	Apply once or twice daily for three to four weeks	40g - £32.90
Fluorouracil 0.5%/salicylic acid 10% solution (*Actikerall*)	Slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) in immunocompetent patients	Apply once daily for up to 12 weeks.	25ml - £38.30
Imiquimod 5% cream (*Aldara Cream*)	Actinic keratoses when cryotherapy or other topical treatment options are less appropriate	Apply three times a week at bedtime for 4 weeks followed by a 4 week treatment free period followed by a further 4 weeks' treatment if necessary	12 sachets - £48.60 Maximum one sachet per application
Imiquimod 3.75% cream (*Zyclara*)	Non-hyperkeratotic and non-hypertrophic actinic keratosis of full face or balding scalp when other topical treatment options are less appropriate	Apply once daily at bedtime for 2 weeks repeat once after a 2 week treatment free period.	28 sachets - £113.00 Maximum 2 sachets per application

A Cochrane review considered the efficacy and safety of these treatments for actinic keratosis and concluded that diclofenac 3%/ sodium hyaluronate 2.5% gel, fluorouracil 5% cream, imiquimod 5% cream (*Aldara*) and ingenol mebutate gel had similar efficacy, but adverse events and cosmetic outcomes varied between treatments.

The most common side effects with topical ingenol mebutate are pain, pruritis and irritation at the site of application appearing up to two weeks after first application. The short duration of therapy means that these effects are often most apparent after the course of treatment

has ended; this may improve adherence to therapy. Ingenol mebutate appears to be better tolerated than some of the other treatments; a higher proportion of patients completed ingenol mebutate therapy in trials compared to completion rates with imiquimod 5% cream and fluorouracil 0.5%/salicylic acid 10% solution. Although the adverse effects reported are similar to those reported with other treatments and affect most patients, the shorter duration of treatment with ingenol mebutate may be preferable and adverse effects seem to resolve quickly.

PACEF Recommendation:
PACEF are convinced that ingenol mebutate gel (*Picato*) is an effective treatment for non-hyperkeratotic and non-hypertrophic actinic keratosis of the face, scalp, trunk and extremities. Despite the lack of comparative data against alternative treatments, a Cochrane review has concluded that ingenol mebutate is of similar efficacy to diclofenac 3% sodium hyaluronate 2.5% gel, fluorouracil 5% cream and imiquimod 5% cream (*Aldara*). In addition, the much shorter treatment period with ingenol mebutate is potentially more convenient for patients. As a result of this, ingenol mebutate gel 0.015% and 0.05% (*Picato*) is designated GREEN and has been approved for inclusion in the *Joint Formulary*. Local guidelines on the treatment of actinic keratosis are in the process of being reviewed. More guidance on the place of ingenol mebutate gel in therapy will be issued later in the year.

RAPID DRUG ASSESSMENT: ESTRADIOL HEMIHYDRATE 1.5MG /NOMEGESTROL ACETATE 2.5MG COMBINED ORAL CONTRACEPTIVE PILL (*ZOELY*)

Estradiol/nomegestrol 1.5mg/2.5mg tablet (*Zoely*) is a newly launched combined oral contraceptive (COC), the first containing the estradiol/nomegestrol combination. Estradiol is a synthetically produced estrogen identical to natural human estrogen; nomegestrol acetate is structurally similar to natural human progesterone, has a strong affinity for the progesterone receptor and has no oestrogenic, androgenic, glucocorticoid or mineralocorticoid activity. *Zoely* is the second COC to reach the market containing estradiol; the first was *Qlaira* (currently RED-RED, see *PACE Bulletin* Vol 3 No 13 (December 2009)).

Supporting evidence for *Zoely* comes from two small clinical trials. The first of these was a randomised open label comparative study that confirmed *Zoely* as having similar contraceptive efficacy to an ethinyloestradiol/ drospirenone containing COC (e.g. *Yasmin*). This is the only comparative study currently available. The second randomised controlled trial compared *Zoely* administered in a 24 days on 4 days off pattern with a conventional COC administered in a 21/7 pattern in 76 French women aged between 18 and 38. This trial showed that the shorter pill-free interval with *Zoely* was associated with a greater inhibition of follicular growth and a shorter withdrawal bleed than the 21/7 regimen. This suggests the possibility of increased contraceptive efficacy and fewer withdrawal symptoms. As a result of this, *Zoely* is packaged in a 28 tablet pack containing 24 active tablets and four yellow tablets containing lactose; the product is taken continually each month without a pill-free interval.

In theory, as estradiol directly mimics naturally produced estrogen, it should have a better profile in terms of fewer adverse effects and improved efficacy over synthetic estrogens. In practice, there is no compelling clinical evidence to suggest any such benefits in comparison to any of the alternative estrogens contained in other COCs. The Faculty of Sexual and Reproductive Healthcare (FSRH) statement on *Zoely* concluded that until further data is available it must be assumed that the indications and contraindications are the same as for other COCs.

In terms of cost, *Zoely* is a lot more expensive than most alternative products:

Combined Pill	Cost (£) per 3x21 pack (unless stated)
Estradiol 1.5mg/nomegestrol 2.5mg	
Zoely	£16.50 (3 x 28)
Ethinyloestradiol 30mcg/levonorgestrel 150mcg	
Rigevidon	£1.89
Microgynon 30	£2.82
Microgynon 30 ED	£2.99 (3 x28)
Ovranette	£2.20
Ethinyloestradiol 20mcg/desogestrel 150mcg	
Gedarel 20/150	£5.98
Mercilon	£7.67
Ethinyloestradiol 30mcg/desogestrel 150mcg	
Gedarel 30/150	£4.93
Marvelon	£6.45
Ethinyloestradiol 30mcg/drospirenone 3mg	
Yasmin	£14.70
Ethinyloestradiol 20mcg/gestodene 75mcg	
Millinette 20/75	£6.37
Femodette	£8.85
Sunya	£6.62
Ethinyloestradiol 30mcg/gestodene 75mcg	
Millinette 30/75	£4.85
Femodene	£6.73
Femodene ED	£7.10 (3x28)
Katya	£5.03
Ethinylestradiol 35mcg/norgestimate 250mcg	
Cilest	£7.16
Triphasic ethinyloestradiol levonorgestrel 30/50 (6 tabs) 40/75 (5 tabs) 30/125 (10 tabs)	
TriRegol	£2.87
Logynon	£3.82
Logynon ED	£4.00 (3x28)
Estradiol containing Estradiol + dienogest	
Qlaira	£25.18 (3 x 28)

PACEF Recommendation

The evidence supporting the use of estradiol 1.5mg/nomegestrol 2.5mg tablets (*Zoely*) is confined to two small scale short duration clinical trials. In consequence, the benefits of using an estrogen that so closely mimics natural estrogen remain theoretical rather than clinically proven. In addition to this, *Zoely* is significantly more expensive than ethinyloestradiol containing equivalents. As a result of this, estradiol/nomegestrol 1.5mg/2.5mg tablet (*Zoely*) is designated RED-RED and has not been approved for inclusion in the *Joint Formulary*.

RAPID DRUG ASSESSMENTS: LATANOPROST 50 MICROGRAM/ML (0.005%) (*MONOPROST*) AND BIMATOPROST 300 MICROGRAM/ML (0.03%) (*LUMIGAN*) PRESERVATIVE FREE SINGLE DOSE EYE DROPS

Latanoprost 50 microgram/ml (0.005%) preservative-free single dose eye drops (*Monoprost*) and bimatoprost 300 microgram per ml (0.03%) preservative-free single dose eye drops (*Lumigan*) are newly launched prostaglandin analogue eye preparations licensed for use in open angle glaucoma and ocular hypertension. Both products are already approved for use as multi-dose preservative containing formulations and appear on the *Joint Formulary*. Previously, the tafluprost 15 microgram/ml preservative free single dose formulation (*Saflutan*) was the only preservative-free product available. A cost comparison reveals that both the latanoprost and bimatoprost formulations are lower in cost than the tafluprost formulation with the latanoprost product being the lowest cost option:

Product	Pack Size	Cost
Bimatoprost 300microgram/ml preservative-free single dose eye drops (*Lumigan*)	30 x 0.4ml	£13.75
Latanoprost 50microgram/ml preservative-free single dose eye drops (*Monoprost*)	30 x 0.2ml	£8.49
Tafluprost 15microgram/ml preservative-free single dose eye drops (*Saflutan*)	30 x 0.3ml	£17.41

PACEF Recommendation:
Both latanoprost 50 microgram/ml (0.005%) preservative-free single dose eye drops (*Monoprost*) and bimatoprost 300 microgram per ml (0.03%) preservative-free single dose eye drops (*Lumigan*) are approved for use and are included in the *Joint Formulary*. Designation: AMBER without shared care.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 283: *RANIBIZUMAB FOR TREATING VISUAL IMPAIRMENT CAUSED BY MACULAR OEDEMA SECONDARY TO RETINAL VEIN OCCLUSION* (MAY 2013)

Ranibizumab is recommended as an option for treating visual impairment caused by macular oedema:

- following central retinal vein occlusion **or**
- following branch retinal vein occlusion only if treatment with laser photocoagulation has not been beneficial, or when laser photocoagulation is not suitable because of the extent of macular haemorrhage **and**
- only if the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 274.

PACEF Recommendation:
Ranibizumab (*Lucentis*) is approved for use for the treatment of visual impairment due to macular oedema secondary to branch or central retinal vein occlusion. It is designated RED and approved for inclusion in the *Joint Formulary* for this indication.

NICE TECHNOLOGY APPRAISAL 284: *BEVACIZUMAB IN COMBINATION WITH PACLITAXEL AND CARBOPLATIN FOR FIRST-LINE TREATMENT OF ADVANCED OVARIAN CANCER* (MAY 2013)

Bevacizumab in combination with paclitaxel and carboplatin is **not recommended for first-line treatment of advanced ovarian cancer** (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV epithelial ovarian, fallopian tube or primary peritoneal cancer). People currently receiving bevacizumab for first-line treatment of advanced ovarian cancer should be able to continue treatment until they and their clinicians consider it appropriate to stop.

PACEF Recommendation:
Bevacizumab (*Avastin*) intravenous infusion is designated RED-RED for the first line treatment of advanced epithelial ovarian, fallopian tube or primary peritoneal cancer in combination with carboplatin and paclitaxel. It is not approved for inclusion in the *Joint Formulary* for this indication.

NICE TECHNOLOGY APPRAISAL 285: *BEVACIZUMAB IN COMBINATION WITH GEMCITABINE AND CARBOPLATIN FOR TREATING THE FIRST RECURRENCE OF PLATINUM-SENSITIVE ADVANCED OVARIAN CANCER* (MAY 2013)

Bevacizumab in combination with gemcitabine and carboplatin is **not recommended for treating people with the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer)**. People currently receiving bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer should be able to continue treatment until they and their clinician consider it appropriate to stop.

PACEF Recommendation:
Bevacizumab (*Avastin*) intravenous infusion is designated RED-RED for treating people with the first recurrence of platinum-sensitive advanced ovarian cancer (in combination with gemcitabine and carboplatin) and is not approved for inclusion in the *Joint Formulary* for this indication.

NICE TECHNOLOGY APPRAISAL 286: *LOXAPINE INHALATION FOR TREATING ACUTE AGITATION AND DISTURBED BEHAVIOURS ASSOCIATED WITH SCHIZOPHRENIA AND BIPOLAR DISORDER* (TERMINATED APPRAISAL) (MAY 2013)

NICE is unable to recommend the use in the NHS of loxapine inhalation for treating acute agitation and disturbed behaviours associated with schizophrenia and bipolar disorder because no evidence submission was received from the manufacturer of the technology.

PACEF Recommendation:
Loxapine inhalation (*Adusave*) is designated RED-RED for the treatment of adults with mild to moderate agitation associated with schizophrenia and bipolar disorder.

NICE TECHNOLOGY APPRAISAL 288: *DAPAGLIFLOZIN (FORXIGA) IN COMBINATION THERAPY FOR TREATING TYPE 2 DIABETES* (JUNE 2013)

Dapagliflozin (Forxiga) is recommended as combination therapy in the management of type 2 diabetes in the following circumstances:

- in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP- 4) inhibitors in NICE Clinical Guideline 87: *Type 2 diabetes- the management of type 2 diabetes* (May 2009) (see below).
- in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes

Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended in treating type 2 diabetes (except as part of a clinical trial).

People currently receiving dapagliflozin in a dual or triple therapy regimen that is not recommended for them as above should be able to continue treatment until they or their clinician considers it appropriate to stop.

Notes

Marketing Authorisation

Dapagliflozin (*Forxiga*) is a sodium–glucosecotransporter-2 (SGLT-2) inhibitor that works by blocking the reabsorption of glucose from the proximal tubule of the kidney, leading to increased excretion of excess glucose in the urine. This effect is dependent upon baseline glycaemic control and the renal filtration rate but is independent of insulin. Dapagliflozin is the first SGLT-2 inhibitor to gain a UK marketing authorisation; it is indicated 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.

It is licensed to be used at a dose of 10mg daily.
Due to limited therapeutic experience in patients aged 75 years and older and concerns over the use of dapagliflozin in those with deteriorating or compromised renal function, initiation of dapagliflozin therapy in those aged 75 and older is contra-indicated.

Combination therapy with metformin

Data from placebo controlled trials confirms that dapagliflozin is effective at reducing HbA1c, reducing systolic blood pressure and facilitating weight loss. There is evidence supporting the combination use of dapagliflozin with metformin. NICE reviewed a meta-analysis of trials utilizing dapagliflozin in combination with metformin and concluded that dapagliflozin as an add-on therapy provides similar glycaemic control to other antidiabetic agents but may result in greater weight loss. There is no direct comparator data of dapagliflozin against other treatment options such as the DPP-4 inhibitors (gliptins), thiazolidinediones (glitazones) or GLP-1 analogues. No clinical evidence was provided by the manufacturer on the use of dapagliflozin as an add-on therapy to sulfonylureas.

PACEF Comment:
NICE have endorsed dapagliflozin as an add-on therapy to metformin, but have not made any recommendations on dual sulfonylurea/dapagliflozin therapy due to insufficient clinical evidence.

Lack of outcomes data

None of the trials reviewed by NICE evaluated dapagliflozin in terms of patient outcomes; there is no evidence, at present, that dapagliflozin has any effect on macrovascular complications, although NICE were prepared to accept the link between weight reduction, , systolic blood pressure reduction, HbA1c reduction and improvement in intermediate to longer term clinical outcomes.

PACEF Comment:
Subject to contra-indications, dapagliflozin may have a role in combination with metformin in patients who are overweight or in whom further weight loss would be beneficial.

Combination therapy with insulin

In addition to the data relating to add-on therapy with metformin, NICE also reviewed two short duration placebo controlled trials looking at dapagliflozin as an add-on therapy with insulin. Within this context, dapagliflozin demonstrated improvement in HbA1c, an increased proportion of patients achieving HbA1c target levels, change in body weight (i.e. weight loss despite concurrent insulin), reduction in BP and a reduction in the proportion of patients reporting hypoglycaemia. In addition, dapagliflozin also enabled a reduction in insulin dose in some patients.

NICE Pathway *Blood-glucose-lowering therapy for type 2 diabetes* (June 2013).

NICE recommend dapagliflozin as an alternative to DPP-4 inhibitors at the dual therapy step of the pathway originally published in NICE Clinical Guideline 87: *Type 2 diabetes- the management of type 2 diabetes* (May 2009). Most recently NICE have published the NICE Pathway entitled *Blood-glucose-lowering therapy for type 2 diabetes* (June 2013). In this pathway, metformin is recommended first line where HbA1c is $\geq$ 6.5% or agreed target after a trial of lifestyle interventions. At this step sulfonylurea monotherapy can be considered as an alternative if the patient is not overweight, or metformin is not tolerated or is contraindicated or if a rapid therapeutic response is required because of hyperglycaemic symptoms.
If HbA1c remains $\geq$ 6.5% despite monotherapy with one of these options, dual therapy is advocated. At this stage metformin-dapagliflozin dual therapy could be considered as an alternative to metformin-DPP-4 inhibitor dual therapy.

According to NICE, DPP-4 inhibitors should be considered in combination with metformin when control of blood glucose remains or becomes inadequate (HbA_{1c} $\geq$ 6.5% or other higher level agreed with the individual). At this stage:

Consider adding a DPP-4 inhibitor instead of a sulfonylurea as second-line therapy to first-line metformin if:

- The person is at significant risk of hypoglycaemia or its consequences (e.g. older people, those working in certain jobs [i.e. working at heights or with heavy machinery] or people in certain social circumstances [i.e. those living alone]) or
- The person does not tolerate a sulfonylurea or a sulfonylurea is contra-indicated.
- Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_{1C} in six months).
- A DPP-4 inhibitor may be preferable to a thiazolidinedione (pioglitazone) if: (1) further weight gain would cause or exacerbate significant problems associated with high body weight; (2) a thiazolidinedione is contraindicated; or (3) the person has previously had a poor response to a thiazolidinedione. Where either a DPP-4 inhibitor or a thiazolidinedione is suitable, the choice of treatment should be based on patient preference.

PACEF Comment:
PACEFs interpretation of TA288 is that dapagliflozin could be considered for dual therapy with metformin as an alternative to a sulfonylurea if (1) the person is at a significant risk of hypoglycaemia or its consequences (rendering a sulfonylurea inappropriate; or (2) the person does not tolerate a sulfonylurea or a sulfonylurea is contra-indicated; or (3) further weight gain would cause or exacerbate significant problems associated with high body weight; or (4) a thiazolidinedione or DPP-4 inhibitor is considered inappropriate or contra-indicated. Only continue dapagliflozin therapy if the patient has a beneficial metabolic response (i.e. a reduction of at least 0.5 percentage points in HbA_{1C} in six months).

If, despite dual therapy, HbA1c remains ≥ 7.5% or agreed target, the NICE Pathway advocates triple therapy. However, TA 288 specifically states that dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended except as part of a clinical trial.

PACEF Comment:
There is insufficient clinical evidence to support the use of dapagliflozin as part of a triple therapy combination with metformin and a sulfonylurea.

At the end of the NICE Diabetes Pathway on Blood-glucose-lowering therapy, intensifying the insulin regimen with additional drugs is advocated. NICE TA288 supports the consideration of dapagliflozin within this context.

PACEF Comment:
NICE have endorsed dapagliflozin as an add-on therapy to insulin with or without other antidiabetic drugs. PACEF support this view and recommend dapagliflozin as an alternative to pioglitazone as add-on therapy to insulin in those patients where further weight loss or the prevention of additional weight gain would be of benefit. Although the NICE TA allows for combination dapagliflozin/insulin therapy with or without other oral antidiabetic drugs, the main evidence supporting combination dapagliflozin/insulin therapy is in conjunction with metformin.

Cost Comparison

A cost comparison of dapagliflozin with alternative second and third line therapies reveals that dapagliflozin is more expensive than DPP-4 inhibitors or pioglitazone and is the most expensive option in terms of dual therapy with metformin:

	Daily dose	28 day cost
Dapagliflozin 5mg and 10mg tablets (*Forxiga*)	**5-10mg daily (lower dose may be needed in combination with sulfonylurea or insulin)**	**£36.59**
DPP-4 inhibitors (plus combinations)		
Sitagliptin tablets 25mg, 50mg and 100mg (Januvia)	100mg once daily	£33.26
Sitagliptin/metformin 50mg/1g tablets (*Janumet*)	One tablet twice daily	£33.26
Saxagliptin 5mg tablets (*Onglyza*)	5mg once daily	£31.60
Saxagliptin/metformin 2.5mg/850mg tablets (*Komboglyze*)	One tablet twice daily	£31.60
Saxagliptin/metformin 2.5mg/1000mg tablets (*Komboglyze*)	One tablet twice daily	£31.60
Linagliptin 5mg tablets (*Trajenta*)	5mg daily	£33.26
Linagliptin/metformin 2.5mg/850mg tablets (*Jentadueto*)	One tablet twice daily	£33.26
Linagliptin/metformin 2.5mg/1 gram tablets (*Jentadueto*)	One tablets twice daily	£33.26
Vildagliptin 50mg tablets (*Galvus*)	50mg twice daily	£31.76
Vildagliptin/metformin 50mg/850mg tablets (*Eucreas*)	One tablet twice daily	£33.98
Vildagliptin/metformin 50mg/1 gram (*Eucreas*)	One tablet twice daily	£33.98
Glitazone (plus combinations)		
Pioglitazone 15mg tablets (generic)	One tablet daily	£2.12
Pioglitazone 30mg tablets (generic)	One tablet daily	£2.77
Pioglitazone/metformin	One tablet twice daily	£35.89

15mg/850mg tablets (*Competact*)		
Biguanides		
Metformin 500mg and 850mg tablets (generic)	500mg-850mg two to three times daily	£1.80 to £2.70
Metformin modified release tablets	1gram twice daily (maximum dose)	£8.52
Sulfonylureas		
Gliclazide 80mg tablets (generic)	**One tablet daily**	**£1.08**
Glimepiride 2mg or 4mg tablets (generic)	**One tablet daily**	**£1.16 to £1.30**

Compared to dapagliflozin, the DPP- 4 inhibitors have the advantage of fixed dose combination products with metformin priced at the same price as the individual DPP-4 inhibitor prescribed alone. This makes dapagliflozin/ metformin therapy even more expensive in comparison to DPP-4 inhibitor/metformin combination treatments.

PACEF Comment:
Dapagliflozin costs, on average, £5.20 per patient per month more than sitagliptin taking into account the higher cost of the product and the lack of a combination product with metformin.

Use in renal impairment

The summary of product characteristics for dapagliflozin states that it is not recommended for use in people with moderate to severe renal impairment (patients with a creatinine clearance rate of less than 60 ml/min or an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2) because its efficacy is dependent upon renal function. In terms of its use in combination with metformin, dual therapy with metformin is also contraindicated in patients with an eGFR of 30ml/minute/1.73m^2 and should be used with caution in those with a eGFR less than 45ml/ minute/1.73m^2. The manufacturer recommends that renal function should be monitored prior to the start of treatment and at least once a year; more frequent monitoring than this (i.e. 2 to 4 times a year) is advised if the patient is classed as having moderate renal impairment. Additional renal monitoring is also advised if concomitant medicines are prescribed which may reduce renal function. Dapagliflozin therapy needs to be discontinued when renal function deteriorates.

PACEF Comment
Dapagliflozin must not be prescribed in patients with moderate to severe renal impairment (CrCl < 60ml/min or eGFR <60ml/minute/1.73m^2. Some of the DPP-4 inhibitors are a much better option within this context. PACEF recently approved linagliptin for use in patients with renal impairment as it undergoes minimal elimination via the renal route. Sitagliptin is also now available in lower dose formulations of 50mg, which can be given once daily if the eGFR is 30-50ml/minute/1.73m^2, and 25mg once daily, if the eGFR is less than 30ml/minute/1.73m^2. Saxagliptin can also be used at a lower dose of 2.5mg once daily in moderate to severe renal impairment.

Adverse effects

From the SPC, the adverse effects associated with dapagliflozin include:

- Very common – hypoglycaemia associated with combination use with sulfonylureas or insulin.
- Common – vulvovaginitis, balanitis and related genital infections, urinary tract infections, back pain, dysuria, polyuria, dyslipidaemia and haematocrit increases.

- Uncommon – vulvovaginal pruritus, volume depletion, thirst, constipation, hyperhiatosis, nocturia and increases in serum creatinine and urea.

Of particular concern are the common reports of urinary tract and genital infections, particularly in women.

PACEF Comment:
There is limited long-term safety data with dapagliflozin and at this stage it is difficult to judge its relative safety in comparison to alternative treatments. Due to its mechanism of action, dapagliflozin increases glucose excretion into the urine. This increased concentration of glucose in the urine is likely to be associated with the increased risk of genital urinary infections; dapagliflozin may not be an appropriate treatment choice in patients prone to such infections.

PACEF Recommendations:
In line with NICE guidance, dapagliflozin (*Forxiga*) is approved for use as part of dual therapy with metformin as detailed in the NICE Pathway for *Blood glucose lowering therapy for type 2 diabetes* (June 2013) (i.e. if HbA1c remains ≥ 6.5% despite monotherapy). In addition, dapagliflozin is also recommended in combination with insulin further down the pathway. PACEF support this view and recommend dapagliflozin as an alternative to pioglitazone as add-on therapy to insulin in those patients where further weight loss or the prevention of additional weight gain would be of benefit. The NICE TA allows for combination dapagliflozin/insulin therapy with or without other oral antidiabetic drugs, although the main evidence supporting combination dapagliflozin/insulin therapy is in conjunction with metformin. Dapagliflozin is not recommended for monotherapy, nor as part of triple therapy with metformin and a sulfonylurea. Due to limited therapeutic experience in patients aged 75 years and older and concerns over the use of dapagliflozin in those with deteriorating or compromised renal function, initiation of dapagliflozin therapy in those aged 75 and older and those with moderate to severe renal impairment is contra-indicated. Within these constraints, dapagliflozin (Forxiga) 5mg and 10mg tablets are designated GREEN and approved for inclusion in the *Joint Formulary* subject to NICE criteria. Certain licensed indications remain RED-RED (i.e. monotherapy and triple therapy with metformin and a sulfonylurea).

NICE TECHNOLOGY APPRAISAL 290: *MIRABEGRON FOR TREATING SYMPTOMS OF OVERACTIVE BLADDER* (JUNE 2013)

Mirabegron is recommended as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinics are contraindicated or clinically ineffective or have unacceptable side effects.

Notes

Marketing Authorisation

Mirabegron is a beta-3 adrenoceptor agonist which activates beta -3 adrenoreceptors located in the detrusor muscle of the bladder causing relaxation of the bladder muscle during the storage phase of the micturition cycle. This improves the storage capacity of the bladder and decreases voiding frequency. It is the first beta-3 adrenoceptor agonist to have a UK marketing authorisation which covers its use for the symptomatic treatment of urgency,

increased micturition frequency and/or urgency incontinence in adult patients with overactive bladder (OAB) syndrome.

Clinical effectiveness and tolerability

Three main pivotal trials SCORPIO, ARIES and CAPRICORN compared mirabegron at varying doses against placebo and, in SCORPIO, against an active comparator, tolterodine; the main safety trial was TAURUS.

The trials compared a range of doses of mirabegron with placebo or an active control tolterodine in patients with over active bladder. Mirabegron was found to be more effective than placebo in terms of reduced micturitions and reduced episodes of incontinence in 24 hours. From the placebo controlled trials, the main licensed dose of 50mg daily was defined, reduced to 25mg daily in renal and hepatic impairment. The trials comparing mirabegron with tolterodine were not powered to evaluate the superiority or non-inferiority of one drug over another. Nonetheless, mirabegron showed a significantly lower incidence of dry mouth than tolterodine.

The main trials were all of 12 weeks duration. NICE were happy to accept such short-term data on the basis that the effectiveness of any therapeutic intervention in OAB is normally assessed after 3 months. However, the short-term nature of the data gives no insight into long-term safety.

There are also no direct comparator trials with any active treatment other than tolterodine. Network studies provided by the manufacturer to NICE conclude that mirabegron 50mg is comparably effective to most other treatments, although solifenacn seesm to be more effective in terms of reducing the number of micturations in 24 hours and reducing the frequency of incontinence episodes in 24 hours. The same analysis revealed that all antimuscarinics had a higher risk of dry mouth than mirabegron and that mirabegron was statistically less likely to be cause constipation than solifenacin 5mg and 10mg, fesoterodine 8mg and trospium chloride 60mg.

Adverse effects

Mirabegron is not associated with the same incidence of antimuscarinic side effects (e.g. dry mouth and constipation) at that seen with the antimuscarinics. However, mirabegron is not without side effects:

- Common – urinary tract infections, tachycardia
- Uncommon - vaginal infections, cystitis, palpitations, atrial fibrillation, dyspepsia, gastritis , urticarial, rash, rash macular, rash papular, pruritus, joint swelling, vulvovaginal pruritus, increase in blood pressure, changes to liver enzymes.
- Rare – lip and eyelid oedema, leukocytoclastic vasculitis, purpura.

Mirabegron is associated with an increased risk of urinary infection, vaginal infection and cystitis which might potentially limit its usefulness in patients susceptible to these conditions.

Contraindications to treatment.

Antimuscarinics are contraindicated in people with myasthenia gravis, significant bladder outflow obstruction or urinary retention, narrow angle glaucoma, severe ulcerative colitis, toxic megacolon and in gastrointestinal obstruction or intestinal atony. There are additional specific contraindications cited for individual drugs. In the SPC for mirabegron the only stated contraindication is hypersensitivity to mirabegron or any of the excipients in the dosage form. Mirabegron has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis), those with severe hepatic

impairment (Child-Pugh Class C) and those with severe uncontrolled hypertension. As a result of this, its use is not recommended in these patient populations.

Mirabegron, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in the mirabegron studies and the effects of mirabegron in these patients remains unknown and caution must be exercised in these patient groups.

Position in treatment pathway

Current PACEF guidance recommends generic immediate release oxybutynin tablets first-line with the sustained release formulation advocated as a second line option for those intolerant of immediate release oxybutynin. Alternative second and third line options to oxybutynin include solifenacin, tolterodine both immediate release and sustained release and trospium sustained release. NICE are due to publish a Clinical Guideline on the management of urinary incontinence in women in September 2013; this is a partial update of guidance issued in 2006.

Cost comparison (formulary products are in bold)

Drug	**Daily dose**	**28 day cost**
Mirabegron SR tablets 50mg (*Betmiga*)	50mg once daily	£29.00
Antimuscarinics		
Oxybutynin 5mg tablets (generic)	**5mg three times daily**	**£4.70**
Oxybutynin 5mg tablets (*Cystrin*)	5mg three times daily	£21.99
Oxybutynin 5mg tablets (*Ditropan*)	5mg three times daily	£12.82
Oxybutynin sustained release (*Lyrinel XL*)	**5mg to 20mg once daily**	**£12.85 - £51.40**
Oxybutynin transdermal patch (*Kentara*)	3.9mg/24 hours 1 patch twice weekly	£27.20
Tolterodine 2mg tablets (generic)	**2mg twice daily**	**£4.36**
Tolterodine 2mg tablets (*Detrusitol*)	2mg twice daily	£30.56
Tolterodine 4mg SR capsules (*Detrusitol XL*)	**4mg daily**	**£25.78**
Tolterodine 4mg SR capsules (*Neditol XL*)	**4mg daily**	**£12.89**
Darifenacin tablets (*Emselex*)	7.5mg-15mg daily	£20.90
Fesoterodine SR tablets (*Toviaz*)	4-8mg daily	£25.78
Propiverine 15mg tablets (*Detrunorm*)	15mg 2-3 times daily	£18.00 -£27.00
Propiverine 30mg modified release capsules (*Detrunorm XL*)	30mg once daily	£24.45
Solifenacin tablets (*Vesicare*)	**5mg-10mg daily**	**£25.78 - £33.52**
Trospium chloride 20mg tablets (generic)	20mg twice daily	£24.27
Trospium chloride 20mg tablets (*Regurin*)	20mg twice daily	£24.27
Trospium 60mg sustained release caps (*Requrin XL*)	**60mg once daily**	**£23.05**

PACEF Recommendation:

Mirabegron (*Betmiga*) has been approved by NICE for the treatment of symptoms of overactive bladder in people for whom antimuscarinics are contraindicated or clinically ineffective or have unacceptable side effects. In terms of clinical effectiveness, NICE have concluded that mirabegron is similarly effective to other antimuscarinic drugs. However, it seems to be better tolerated than antimuscarinics with a lower incidence of dry mouth; it also seems to cause less constipation than solifenacin, fesoterodine and trospium chloride. From the currently available data there do not appear to be many known contraindications to mirabegron and as a result, it would seem to be a reasonable alternative for the majority of patients in whom the use of antimuscarinics is contraindicated. Mirabegron is not recommended in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis), those with severe hepatic impairment (Child-Pugh Class C) and those with severe uncontrolled hypertension. Within these criteria and contraints, mirabegron 25mg and 50mg tablets (*Betmiga*) are designated GREEN and approved for inclusion in the Joint Formulary. Further guidance on the place of mirabegron in the management of urinary incontinence will be issued following the publication of the updated NICE Clinical Guideline in September 2013.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (JUNE 2013)

Diclofenac: new contraindications and warnings after a European-wide review of cardiovascular safety

- The European Medicines Agency's Pharmacovigilance Risk Assessment Committee has recently concluded that the arterial thrombotic risk with diclofenac is similar to that for the selective COX-2 inhibitors (etoricoxib and celecoxib).
- Increased risk of heart attack and stroke is particularly associated with long-term use of high doses of diclofenac and in patients already at high risk.
- This new advice for diclofenac applies to systemic formulations (tablets, capsules , suppositories and injections) , but not topical (gel and cream) formulations.
- A recent meta-analysis has concluded that of 1000 patients taking diclofenac for a year, three more will have major vascular events than placebo.
- Diclofenac is now contra-indicated in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure (NYHA classification II to IV). Patients with these conditions should be switched to an alternative treatment at their next routine appointment.
- Naproxen and low-dose ibuprofen are considered to have the most favourable thrombotic CV safety profiles of all non-selective NSAIDs.
- Diclofenac is available to buy over-the-counter in pharmacies at low doses (up to 75mg/day) for short-term use only (3 days).
- Pharmacists are asked to ensure that patients with established CVD or those with significant risk factors for CV events are excluded from purchasing these products.
- Patients should be advised to seek medical advice if they need to take diclofenac for longer than 3 days.
- Patients should be advised to take only one NSAID at a time.
- An information sheet for patients has been produced and is available from the MHRA website.

PACEF Recommendation:
Diclofenac is now contra-indicated in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure (NYHA classification II to IV). Patients with these conditions should be switched to an alternative treatment at their next routine appointment.

Cyproterone acetate with ethinyloestradiol (co-cyprindiol) – balance of benefits and risks remains positive

- Cyproterone with ethinyloestradiol (co-cyprindiol/ *Dianette)* is licensed as a second line treatment for women with severe acne or moderately severe hirsutism.
- A Europe wide review set up to address concerns about the risk of venous thromboembolism has concluded that the balance of benefits and risks with co-cyprindiol remains positive.
- Co-cyprindiol can be used in women of reproductive age for the treatment of (1) skin conditions related to androgen sensitivity (e.g. severe acne with or without seborrhoea) and (2) hirsutism. It should only be used when topical therapy or systemic antibiotics has failed.
- Co-cyprindiol is an effective contraceptive, but should not be used solely for this function. Use of co-cyprindiol concurrently with a combined hormonal contraceptive can substantially increase the risk of VTE and is contra-indicated.
- The VTE risk with Dianette is similar to that with contraceptives containing desogestrel, gestodene or drospirenone. Co-cyprindiol has 1.5 to 2 times the VTE risk of levonorgestrel containing pills.

Oral retinoids: pregnancy prevention – reminder of measure to minimise teratogenic risk

- The risk of foetal malformation with oral retinoids is extremely high, even when used at a low dose or for a short time during pregnancy.
- Examples of oral retinoids include isotretinoin (*Roaccutane*) for severe acne, alitretinoin (*Toctino*) for adults with severe chronic hand eczema and acitretin (*Neotigaso*n) for severe extensive resistant psoriasis, palmo-plantar pustular psoriasis, congenital ichthyosis and Darier's disease (keratosis follicularis).
- All women must be made aware of the teratogenic risks before starting therapy.
- Women of child-bearing potential should have pregnancy excluded before starting treatment.
- Pregnancy test results must be documented 3 days or less before the prescription is issued (minimum sensitivity 25mIU/mL).
- While taking these medicines, one – or preferably two – complementary forms of contraception should be consistently used.
- Contraception should start 1 month before treatment, continue throughout and until the retinoids have left the patient's system (i.e. one month after stopping isotretinoin or alitretinion or at least 2 years after stopping treatment with acitretin). Acitretin has a substantially longer half-life and duration of effect
- Prescription of oral retinoids should be limited to 30 days treatment
- The prescription should be dispensed within 7 days of issue.

PACEF Comment:
All three oral retinoids can only be prescribed by Consultant Dermatologists and are designated RED.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (JULY 2013)

Codeine for analgesia: restricted use in children because of reports if morphine toxicity

- Codeine is converted to morphine in the liver by the CYP2D6 enzyme. Many genetic variations of CYP2D6 significantly affect the extent to which codeine is converted to morphine in different individuals. People can be classified as poor, intermediate, extensive or ultra-rapid metabolisers.
- Poor metabolisers convert very little codeine to morphine and have little or no pain relief (7 to 10% of Caucasians)
- Extensive or ultra-rapid metabolisers have an excessive amount of morphine in their blood which can result in severe side effects (29% of African or Ethiopian people are ultra-rapid metabolisers).
- A European review of the safety of codeine –containing medicines licensed for pain relief in children was triggered by three fatalities and one life-threatening case of respiratory depression in children given codeine after tonsillectomy or adenoidectomy in the treatment of obstructive sleep apnoea.
- The review concluded that codeine-containing medicines should only be used in children older than 12 where other painkillers such as paracetamol or ibuprofen have proved insufficient.
- Codeine is now contra-indicated in all children younger than 18 years undergoing tonsillectomy or adenoidectomy for sleep apnoea.
- Codeine is also contra-indicated in all patients known to be ultra-rapid metabolisers.
- It should not be used by breastfeeding mothers as it passes through the breast milk to the baby.
- Codeine is not recommended in children whose breathing might be compromised (e.g. those with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures).

Retigabine (*Trobalt*): indication restricted to last-line use and new monitoring requirements after reports of pigment changes in ocular tissue, skin, lips or nails

- Retigabine (*Trobalt*) should only be used as an adjunctive treatment for drug resistant partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy where other appropriate drug combinations have proved inadequate or have not been tolerated.
- Pigment changes (discolouration) of ocular tissue (including the retina) have been reported in two long-term clinical studies. Blue grey discolouration of the nails, lips or skin have also been identified with a frequency of >1/10 patients after prolonged therapy (defined as very common).
- All patients who are currently taking retigabine should be reviewed at the next routine (non-urgent) appointment. Patients should be informed of the risk and the balance of risks and benefits reassessed.
- A comprehensive ophthalmic examination should be done at the start of treatment and at least 6 monthly thereafter while treatment is ongoing.

PACEF Recommendation:
Retigabine (*Trobalt*) remains AMBER but with additional safety warnings on the *Joint Formulary* and emphasis of last-line position.

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