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NHS
Greater East Midlands
Commissioning Support Unit

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 20 **December 2013**

What's new this month?

- **Degarelix injection (*Firmagon*) is a gonadotrophin-releasing hormone antagonist used to treat advanced hormone-dependent prostate cancer. In comparative trials it emerges as non-inferior to leuprorelin; it also induces suppression of testosterone and PSA significantly faster than leuprorelin with no evidence of a testosterone surge. As testosterone surge can be associated with temporary tumour growth, degarelix may be of particular benefit to those with spinal cord compression or severe bone pain; it may also be preferable in those with high volume, high PSA metastatic disease. Subject to these criteria and subject to the development of a care pathway covering patient selection criteria and use, degarelix injection (*Firmagon*) is designated AMBER without shared care and approved for inclusion in the *Joint Formulary* (see page 3).**
- **Medroxyprogesterone acetate subcutaneous injection 104mg/0.65ml (*Sayana Press*) is designated GREEN for long-term female contraception. It may be preferable to *Depot Provera* in those patients with bleeding disorders or on anticoagulants who are at risk of haematoma following IM injection. It may also be preferable in very obese women where conventional IM injection may not achieve sufficient depth to penetrate the muscle. Medroxyprogesterone acetate 150mg/ml injection (*Depot Provera*) remains GREEN for the same indication with both products included on the *Joint Formulary* (see page 5).**
- **Sildenafil chewable tablets 25mg/50mg/100mg (*Nipatra*) are designated RED-RED and have not been approved for inclusion in the *Joint Formulary* (see page 5).**
- **Lincolnshire Community Health Services have developed local guidelines for the diagnosis and management of heart failure. The guidance encompasses both best practice in the management of heart failure itself and in the management of symptoms commonly experienced in advanced heart failure, including palliative and supportive care. The text can be accessed either through the LCHS website or through the PACEF section of the NHS in Lincolnshire website (see page 6).**
- **A new *Infant Feeding Formulary for Cows' Milk Protein Allergy and Lactose Intolerance* has been produced and is available through the PACEF section of the NHS in Lincolnshire website (see page 6).**
- **Further evidence has emerged supporting a link between cephalosporin and quinolone use and community acquired *Clostridium difficile* infection (see page 6).**
- **Janssen, the manufacturer of ketoconazole (*Nizoral*) 200mg tablets, have confirmed their intention to discontinue the product following the suspension of the UK marketing authorisation effective from November 11th. *Nizoral* 200mg tablets were already designated RED-RED for the treatment of fungal infections prior to this product withdrawal; they have also been removed from the *Joint Formulary* for this indication. Prescribers are urged to review any remaining patients currently prescribed oral ketoconazole with a view to stopping treatment or using an alternative. Off label use for patients with Cushing's syndrome may present a problem as Janssen do not intend to continue to supply the product through a patient access scheme (see page 7).**
- **Following a local case in which a patient receiving rituximab therapy was inadvertently vaccinated against herpes zoster with *Zostavax*, clinicians are asked to be mindful of**

the contra-indications around immuno-suppressive therapy (detailed below) (see page 8).

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SUMMARY OF PACEF DECISIONS: *OCTOBER 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Aripiprazole 5mg and 10mg tablets (*Abilify*) Aripiprazole 10mg orodispersible tablets (*Abilify Orodispersible*) Aripiprazole 1mg/ml oral solution (*Abilify Oral Solution*)	For the treatment of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older.	RED Approved for inclusion in the *Joint Formulary* for this indication. NB Aripiprazole is authorized for a wider range of indications than this.
Degarelix injection (*Firmagon*)	For the treatment of advanced hormone-dependent prostate cancer	AMBER without shared care. Subject to the development of a care pathway. Approved for inclusion in the *Joint Formulary* for this indication.
Eltrombopag 25mg and 50mg (*Revolade*) tablets	For the treatment of chronic idiopathic thrombocytopenic purpura in splenectomised patients refractory to other treatments	RED
Everolimus 5mg and 10mg tablets (*Afinitor*)	For the treatment of advanced renal cell carcinoma. For the treatment of hormone receptor positive human epidermal growth factor 2 (HER-2) negative advanced breast cancer in combination with exemestane in postmenopausal women in whom breast cancer has recurred or progressed following treatment with a non-steroidal aromatase inhibitor.	RED-RED Not approved for inclusion in the *Joint Formulary* for these indications.

Ketoconazole 200mg tablets (*Nizoral*)	For the treatment of fungal infections	RED-RED Removed from the *Joint Formulary* for this indication. *Nizoral* 200mg tablets have now been discontinued by the manufacturer.
Medroxyprogesterone acetate 150mg/ml (*Depo- Provera*)	For long-term female contraception	GREEN Included in the *Joint Formulary*
Medroxyprogesterone acetate 104mg/0.65ml *(Sayana Press)*	For long-term female contraception	GREEN Approved for inclusion in the *Joint Formulary*
Sildenafil chewable tablets 25mg/50mg/100mg (*Nipatra*)	For the treatment of erectile dysfunction	RED-RED Not approved for inclusion in the *Joint Formulary*
Varicella zoster virus vaccine (*Zostavax*)	For the prevention of shingles and Post Herpetic Neuralgia (PHN) in adults > 50.	A national vaccination programme has now made varicella virus vaccine available on the NHS to those aged 70 or 79 (the first wave of a programme designed to eventually offer vaccination to those aged between 70 and 79). Varicella zoster virus vaccine (*Zostavax*) should not be prescribed outside of this age range on NHS prescription and is designated RED-RED.

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: *DEGARELIX INJECTION 80MG/120MG (FIRMAGON)*

Degarelix is a gonadotrophin-releasing hormone (GnRH) antagonist indicated for the treatment of advanced hormone dependent prostate cancer. It acts by binding to pituitary GnRH receptors thus reducing the secretion of testosterone by the testes.
Metastatic cancer of the prostate usually responds to hormonal treatment with a gonadorelin analogue aimed at depleting androgen levels. In Lincolnshire, the most commonly prescribed gonaderelin analogues are goserelin (*Zoladex*) and leuprorelin (*Prostap*).

Within the first 1 to 2 weeks of therapy, gonadorelin analogues may cause a surge of testosterone which can lead to increased Prostate Specific Antigen (PSA) levels and result in a progression of prostate cancer. In susceptible patients, this tumour flare may result in spinal compression, ureteric obstruction or increased bone pain. Concomitant use of an anti-androgen such as cyproterone acetate or flutamide for the first 3 weeks of gonadorelin analogue therapy helps to reduce this effect.

PACEF reviewed the original 12 month randomised open label parallel-group study that evaluated the efficacy and safety of degarelix in comparison to leuprorelin. Degarelix emerged as non-inferior to leuprorelin in terms of maintenance of low testosterone levels over a 1-year treatment period; it also induced sustained suppression of testosterone and PSA significantly faster than leuprorelin with no evidence of a testosterone surge. A 5 year extension to this original trial has confirmed longer-term safety and efficacy.

A cost comparison reveals the following:

Drug	Dose range	Cost (£) pa
Degarelix injection (*Firmagon*)	**240mg initially then 80mg every 28 days**	**£1,683**
Goserelin depot injection(*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 depot injection (*Zoladex*)	3.6mg every 28 days	£845
Histrelin depot SC implant (*Vantas*)	50mg every 12 months	£990
Leuprorelin acetate sustained release suspension for injection (*Prostap 3 DCS*)	11.25mg every 3 months	£902.88
Leuprorelin acetate sustained release suspension for injection (*Prostap SR DCS*)	3.75mg monthly	£902.88
Triptorelin IM injection(*Decapeptyl SR*)	11.25mg every 3 months	£828
Triptorelin IM injection (*Decapeptyl SR*)	3mg every 28 days	£897
Triptorelin IM injection (*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)

PACEF Recommendation:

Trial evidence confirms that degarelix injection (*Firmagon*) is non-inferior to leuprorelin and induces suppression of testosterone and PSA significantly faster with no evidence of a testosterone surge. As testosterone surge can be associated with temporary tumour growth, degarelix may be of particular benefit to those with spinal cord compression or severe bone pain; it may also be preferable in those with high volume, high PSA metastatic disease. Subject to these criteria and subject to the development of a care pathway covering patient selection criteria and use, degarelix injection (*Firmagon*) is designated AMBER without shared care and approved for inclusion in the *Joint Formulary*.

RAPID DRUG ASSESSMENT: *MEDROXYPROGESTERONE ACETATE 104MG/0.65ML INJECTION (SAYANA PRESS)*

Sayana Press is a new injectable formulation of medroxyprogesterone acetate with a marketing authorisation for long-term female contraception. It prevents ovulation by inhibiting the secretion of gonadotropins and is administered as a 104mg subcutaneous injection every 13 weeks. Pharmacokinetic studies have shown that *Sayana Press* and medroxyprogesterone acetate 150mg/ml injection (*Depot Provera*) are bioequivalent even though *Sayana Press* contains less medroxyprogesterone (104mg/0.65ml compared to 150mg/ml) and is given subcutaneously rather than intramuscularly. Clinical studies confirm that subcutaneous depot medroxyprogesterone is an effective method of contraception with no pregnancies reported in 16,023 women cycle exposures.

There is very little difference in price between *Sayana Press* (£6.90 per dose) and *Depot Provera* (£6.01 per dose); *Sayana Press* is given every 13 weeks, *Depot Provera* every 12 weeks. Both products are comparable in terms of adverse effects, contraindications and cautions, although more injection site reactions are reported with *Sayana Press*.

PACEF Recommendation:
Medroxyprogesterone acetate subcutaneous injection 104mg/0.65ml (*Sayana Press*) is designated GREEN for long-term female contraception. It may be preferable to *Depot Provera* in those patients with bleeding disorders or on anticoagulants who are at risk of haematoma following IM injection. It may also be preferable in very obese women where conventional IM injection may not achieve sufficient depth to penetrate the muscle. Medroxyprogesterone acetate 150mg/ml injection (*Depot Provera*) remains GREEN for the same indication with both products included on the *Joint Formulary.*

RAPID DRUG ASSESSMENT: *SILDENAFIL CHEWABLE TABLETS 25MG/50MG/100MG* (*NIPATRA*)

Sildenafil chewable tablets (*Nipatra*) are a new chewable formulation of sildenafil, the original phosphodiesterase (PDE5) inhibitor authorized for the treatment of erectile dysfunction. A cost comparison reveals that generic sildenafil is now very low cost compared to all alternatives and that sildenafil chewable tablets (*Nipatra*) are priced comparably to other premium price branded PDE5 inhibitor formulations:

Product	**Strength**	**Cost (£) (4 tablets)**
Sildenafil chewable tablets (*Nipatra*)	**25mg**	**£13.72**
Sildenafil chewable tablets (*Nipatra*)	**50mg**	**£17.02**
Sildenafil chewable tablets (*Nipatra*)	**100mg**	**£18.80**
Sildenafil tablets (generic)	25mg	£1.31
Sildenafil tablets (generic)	50mg	£1.45
Sildenafil tablets (generic)	100mg	£1.55
Sildenafil tablets (*Viagra*)	25mg	£16.59
Sildenafil tablets (*Viagra*)	50mg	£21.27
Sildenafil tablets (*Viagra*)	100mg	£23.50
Tadalafil tablets (*Cialis*)	10mg	£26.99
Tadalafil tablets (*Cialis*)	20mg	£26.99
Tadalafil tablets (*Cialis*)	2.5mg (daily)	£54.99
Tadalafil tablets (*Cialis*)	5mg (daily)	£54.99

Vardenafil tablets (*Levitra*)	5mg	£7.56
Vardenafil tablets (*Levitra*)	10mg	£14.08
Vardenafil tablets (*Levitra*)	20mg	£23.48
Vardenafil (*Levitra Orodispersible*)	10mg	£17.88

PACEF Recommendation:
Following the sildenafil patent expiry, generic sildenafil tablets are recommended as first line treatment for erectile dysfunction (subject to *Drug Tariff* restrictions). Recent price reductions in the October 2013 *Drug Tariff* have resulted in sildenafil becoming a fraction of the price of alternative premium price brands. Prescribers are encouraged to undertake a non-urgent review of patients currently taking tadalafil (*Cialis*) or vardenafil (*Levitra*) to determine whether generic sildenafil tablets present a more cost-effective option. Current usage of vardenafil 10mg orodispersible tablets (*Levitra*) in county is exceptionally low. This has suggested to PACEF that there is little or no role for sildenafil chewable tablets (*Nipatra*). In addition to this, *Nipatra* is much more expensive than generic sildenafil and comparably priced to premium price brands. As a result of this, sildenafil chewable tablets 25mg/50mg/100mg (*Nipatra*) are designated RED-RED and have not been approved for inclusion in the *Joint Formulary*.

LINCOLNSHIRE COMMUNITY HEALTH SERVICES: *CLINICAL GUIDANCE FOR THE DIAGNOSIS AND MANAGEMENT OF HEART FAILURE IN LINCOLNSHIRE* (SEPTEMBER 2013)

Lincolnshire Community Health Services have developed local guidelines for the diagnosis and management of heart failure. The guidance encompasses both best practice in the management of heart failure itself and in the management of symptoms commonly experienced in advanced heart failure, including palliative and supportive care. The document can be accessed either through the LCHS website or through the PACEF section of the NHS in Lincolnshire website (www.lincolnshire.nhs.uk).

INFANT FEEDING FORMULARY: *FOR COWS' MILK PROTEIN ALLERGY AND LACTOSE INTOLERANCE* (OCTOBER 2013)

A new *Infant Feeding Formulary* has been produced as a collaboration between PACEF and the Nutrition and Dietetic Department at ULH. The document promotes breastfeeding as the best form of nutrition for infants and provides guidance on the circumstances within which prescribing and supply of milk substitutes, such as formula milk, for babies is appropriate.

The document can be accessed through the PACEF section of the NHS in Lincolnshire website (www.lincolnshire.nhs.uk).

NEW TRIAL ASSESSMENT

COMMUNITY ASSOCIATED CLOSTRIDIUM DIFFICILE INFECTION AND ANTIBIOTICS: A META-ANALYSIS

This meta-analysis of 8 observational studies involving over 30,000 people found recent antibiotic exposure to be associated with an increased risk of community-associated *C difficile* infection (CDI). The risk differed among the different antibiotic classes, and was greatest for clindamycin, followed by quinolones and cephalosporins. Tetracyclines were not associated with an increased CDI risk.

PACEF Comment:
Most studies that have investigated the association between *Clostridium difficile* infection (CDI) and antibiotics have been in hospitalised patients or people in long term care facilities. This meta-analysis found 8 studies reporting specifically on the risk of community associated *C. difficile* infection associated with antibiotics. It reported substantial variation in the risk between classes of antibiotics. The study serves as a reminder that broad spectrum antibiotics, particularly quinolones and cephalosporins, are most strongly implicated in the causation of CDI. 'No antibiotic' or 'delayed antibiotic' strategies should be considered for a wide range of commonly occurring infections, including sore throat, acute otitis media, sinusitis and acute bronchitis. Wherever there is a choice of antibiotic, the use of an agent with a narrower spectrum of activity is preferred. Prescribers are reminded of the potential to use doxycycline (200mg stat followed by 100mg daily) when antibiotics are indicated for acute cough, sinusitis, community acquired pneumonia or acute exacerbation of COPD. *PACE Bulletin* Volume 7 Number 13 (August 2013) provides further information.

Reference:
Deshpande A et al. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. *J Antimic Chemo* 2013; 68(9):1951 – 1961.

PRODUCT DISCONTINUATION: *KETOCONAZOLE 200MG TABLETS* (*NIZORAL*)

In a letter dated November 7th 2013, Janssen, the manufacturer of ketoconazole (*Nizoral*) 200mg tablets have confirmed their intention to discontinue the product following the suspension of the UK marketing authorisation effective from November 11th. This decision follows the European Medicines Agency CHMP evaluation of the risk of liver injury (such as hepatitis, cirrhosis and liver failure) associated with ketoconazole and their conclusion that the drug should no longer be prescribed for the treatment of fungal infections (see *PACE Bulletin*, Vol 7 No 18 (October 2013).

Topical ketoconazole formulations such as ketoconazole 2% cream (*Nizoral Cream*) (available at NHS expense under the Selected List Scheme for seborrhoeic dermatitis or pityriasis versicolor) and ketoconazole 20mg/ml liquid (*Nizoral Shampoo*) (for seborrhoeic dermatitis of the scalp, dandruff, or pityriasis versicolor caused by Pityrosporum spp) will remain available. Topical ketoconazole formulations have a very low systemic absorption and may continue to be used.

Ketoconazole is sometimes used off label for patients with Cushing's syndrome. Janssen have confirmed that they will not continue to supply *Nizoral* tablets for any other indication through a patient access scheme.

PACEF Recommendation:
Ketoconazole 200mg tablets (*Nizoral*) were already designated RED-RED for the treatment of fungal infections prior to this product withdrawal; they have also been removed from the *Joint Formulary* for this indication. Prescribers are urged to review any remaining patients currently prescribed oral ketoconazole with a view to stopping treatment or using an alternative. Oral ketoconazole should not be initiated in new patients for this indication. Off label use for patients with Cushing's syndrome may present a problem as Janssen do not intend to continue to supply the product through a patient access scheme.

CONTRA-INDICATIONS AND DRUG INTERACTIONS WITH VARICELLA ZOSTER VIRUS VACCINE (*ZOSTAVAX*)

Following a local case in which a patient receiving rituximab therapy was inadvertently vaccinated against herpes zoster, clinicians are asked to be mindful of the contra-indications around immunosuppressive therapy detailed below:

Varicella zoster virus vaccine (*Zostavax*) should not be given to a person who:

- has primary or acquired immunodeficiency state due to conditions such as;
  - acute and chronic leukaemias.
  - lymphoma.
  - other conditions affecting the bone marrow or lymphatic system.
  - immunosuppression due to HIV/AIDS.
  - cellular immune deficiencies.
- is receiving immunosuppressive therapy (including high-dose corticosteroids); however *Zostavax* is not contra-indicated for use in individuals who are receiving topical/inhaled corticosteroids or in patients who are receiving corticosteroids as replacement therapy (e.g. for adrenal insufficiency).
- has an active untreated TB infection.
- is pregnant.
- has had a confirmed anaphylactic reaction to a previous dose of varicella vaccine.
- has had a confirmed anaphylactic reaction to any component of the vaccine, including neomycin or gelatine.

Therapy with low-doses of methotrexate (MTX) (<0.4mg/kg/week), azathioprine (<3.0mg/kg/day), or 6 mercaptopurine (<1.5mg/kg/day) for the treatment of rheumatoid arthritis, psoriasis, poliomyositis, sarcoidosis, inflammatory bowel disease and other conditions are not considered sufficiently immunosuppressive and are not contraindications for administration of zoster vaccine.

While MTX is excluded from the definition of contra-indicated immunosuppressive therapy, the following drugs are included:

- **moderate to high doses of steroids for longer than 2 weeks. Must be stopped 3 months before live vaccines can be administered.**
- **biologics (e.g. infliximab, rituximab, etanercept, anakinra, adalimumab, abatacept, tocilizumab, certolizumab pegol, golimumab).**
- **leflunomide.**

PACEF Recommendations:

A national vaccination programme has now made varicella zoster virus vaccine (*Zostavax*) available on the NHS to those aged 70 or 79 (the first wave of a programme designed to eventually offer vaccination to those aged between 70 and 79).
For patients aged 50 to 69, *Zostavax* holds an appropriate marketing authorisation, but use in this age group falls outside the national vaccination programme. Following a local case in which a patient receiving rituximab therapy was inadvertently vaccinated against herpes zoster, clinicians are asked to be mindful of the contra-indications around immunosuppressive therapy detailed above. Varicella zoster virus vaccine (*Zostavax*) should only be provided through the national vaccination programme; it should not be prescribed to patients outside of this age range on NHS prescription and is designated RED-RED.

References:
Department of Health, Public Health England, NHS England, Introduction of shingles vaccine for people aged 70 (Gateway Reference No: 00254) (12th July 2013).
Joint Committee on Vaccination and Immunisation, *Immunisation against infectious disease*, Chapter 28a *Shingles (herpes zoster)* (June 2013).

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

NEW ORAL ANTICOAGULANTS APIXABAN (ELIQUIS), DABIGATRAN (PRADAXA) AND RIVAROXABAN (XARELTO): RISK OF SERIOUS HAEMORRHAGE – CLARIFIED CONTRAINDICATIONS APPLY TO ALL THREE MEDICINES

The following contraindications now apply to all three new oral anticoagulants, for all doses and indications:

- A lesion or condition, if considered a significant risk factor for major bleeding. This may include:
    - current or recent gastrointestinal ulceration.
    - presence of malignant neoplasm at high risk of bleeding.
    - recent brain or spinal injury.
    - recent brain, spinal or ophthalmic surgery.
    - recent intracranial haemorrhage.
    - known or suspected oesophageal varices.
    - arteriovenous malformation.
    - vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant drug (e.g. unfractionated heparin, LMWH (e.g. enoxaparin, dalteparin, tinzaparin), heparin derivatives (e.g. fondaparinux), or oral anticoagulants (e.g. warfarin). There are exceptions such as switching therapy to or from the new OAC or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter.

Additional advice and information:

- Take special care when prescribing NOACs to patients with other conditions, procedures or treatments (e.g. NSAIDs, antiplatelet drugs) that may increase the risk of major bleeding.
- Impaired renal function may constitute a contra-indication to a NOAC or require a dose reduction; recommendations differ for the three agents.
- Consider contra-indications, warning and precautions, as well as the individual's risk factors for bleeding, before prescribing these medicines.
- Remember that there is no specific antidote available for any of the three NOACs.

PACEF Comment
Many of these issues have been raised in the various pieces of guidance relating to the use of the NOACs for different indications that have been published by PACEF in the last few months. As updated versions of each guideline are published, revised contra-indications, warnings and precautions will be included. In the meantime, prescribers are advised to be fully cognisant of each product SPC.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 292: *ARIPIPRAZOLE FOR TREATING MODERATE TO SEVERE MANIC EPISODES IN ADOLESCENTS WITH BIPOLAR DISORDER* (JULY 2013)

Key Recommendation

Aripiprazole is recommended as an option for treating moderate to severe manic episodes in adolescents with bipolar I disorder, within its marketing authorisation (that is, up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older).

Notes

- Aripiprazole (*Abilify)* is an second generation antipsychotic drug with partial dopamine D2 and D3 agonistic properties. It has a UK marketing authorisation 'for the treatment up to 12 weeks of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older'. It is also authorised for the treatment of moderate to severe manic episodes in bipolar I disorder in adults, and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.
- The recommended maintenance dosage for aripiprazole in adolescents aged 13 years and over is 10 mg once daily for a maximum of 12 weeks. Treatment should be initiated at 2 mg daily for 2 days (using aripiprazole oral solution 1 mg/ml) and titrated to 5 mg daily for 2 additional days before reaching the recommended daily dose of 10 mg.
- Aripiprazole 5mg and 10mg tablets (*Abilify*), aripiprazole 10mg orodispersible tablets (*Abilify Orodispersible*) and aripirazole 1mg/ml oral solution (*Abilify Oral Solution*) all have a potential role in this treatment regimen. There is no cost difference between the 10mg tablet and the 10mg orodispersible tablet.
- The summary of product characteristics notes that enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated and that a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects. Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring.

Alternative options

- The *BNF for Children* provides details of alternative antipsychotic drugs that can be used for the treatment of mania in bi-polar disorders in adolescents, although **none of these alternatives are licensed for use in children and adolescents.** Unlicensed alternatives include: olanzapine, risperidone and quetiapine.

Clinical evidence

- From an evaluation of two placebo controlled clinical trials involving aripiprazole in adolescent patients with moderate to severe manic episodes in bipolar 1 disorder and a network meta-analysis (including aripiprazole, olanzapine, risperidone and quetiapine), NICE have concluded that aripiprazole is as effective as other antipsychotics for acute mania and has a comparable and acceptable adverse reaction profile

Cost comparison

Drug	Daily dose	28 day cost
Aripiprazole	10mg	£96.04
Olanzapine	5mg	£1.51
	10mg	£1.86
	15mg	£2.75
	20mg	£3.15
Quetiapine	200mg twice daily	£4.37
	300mg twice daily	£6.03
Risperidone	2.5mg once daily	£2.23*
	6mg (3mg twice daily)	£2.01

*Price based on using 2mg + 0.5mg tablet.

PACEF Recommendation

Aripiprazole (*Abilify*) is currently the only antipsychotic drug with a marketing authorisation for the treatment of moderate to severe manic episodes in bipolar I disorder in adolescents (aged 13 and older). Although other unlicensed alternatives are available at a lower cost, standard MHRA advice is to use products with a UK marketing authorisation where available. As a result of this, aripiprazole 5mg and 10mg tablets (*Abilify*), aripiprazole 10mg orodispersible tablets (*Abilify Orodispersible*) and aripiprazole 1mg/ml oral solution (*Abilify Oral Solution*) are all designated RED for this indication. All initiations will be made by Child and Adolescent Mental Health Services (CAMHS). Aripiprazole should only be prescribed for up to 12 weeks for this indication; the entire course will be provided by CAMHS. These products are all approved for inclusion in the *Joint Formulary* for this indication. Please note that aripiprazole is authorized and approved for a wider range of indications than this.

NICE TECHNOLOGY APPRAISAL 293: *ELTROMBOPAG FOR TREATING CHRONIC IMMUNE (IDIOPATHIC) THROMBOCYTOPENIC PURPURA* (REVIEW OF TECHNOLOGY APPRAISAL 205) (JULY 2013)

Eltrombopag is recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated), only if:

- their condition is refractory to standard active treatments and rescue therapies, **or**
- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies

PACEF Recommendation:

Eltrombopag (*Revolade*) tablets were previously designated RED-RED for this indication in accordance with NICE TA 205 (July 2013). In response to this review and subject to NICE criteria, they are now approved for use and designated RED for this indication. The product SPC stipulates that eltrombopag treatment should remain under the supervision of a physician experienced in the treatment of haematological diseases. Eltrombopag (*Revolade*) tablets are approved for inclusion in the *Joint Formulary* for this indication.

NICE TECHNOLOGY APPRAISAL 295: *EVEROLIMUS IN COMBINATION WITH EXEMESTANE FOR TREATING ADVANCED HER2-NEGATIVE HORMONE-RECEPTOR-POSITIVE BREAST CANCER AFTER ENDOCRINE THERAPY* (AUGUST 2013)

Everolimus, in combination with exemestane, is **not recommended** within its marketing authorisation for treating postmenopausal women with advanced human epidermal growth factor receptor 2 (HER2) negative hormone-receptor positive breast cancer that has recurred or progressed following treatment with a non-steroidal aromatase inhibitor.

PACEF Recommendation:
Everolimus tablets 5mg and 10mg (*Afinitor*) are already RED-RED for the treatment of advanced renal carcinoma. They are now designated RED-RED for advanced HER2-negative hormone-receptor positive breast cancer in combination with exemestane. Everolimus tablets (*Afinitor*) are not approved for inclusion in the *Joint Formulary* for either of these indications.

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