Formulary Changes

Mirabegron (Betmiga®)
Mirabegron has been approved for restricted use in NHS Fife for the symptomatic management of patients with overactive bladder syndrome.

How does mirabegron work?
Mirabegron is a beta3-adrenoceptor agonist which stimulates receptors in the bladder to enhance urine storage function. The recommended dose for most patients is 50mg once daily.

What other treatment options are there?
Alternative treatment options for overactive bladder are the antimuscarinics. Formulary choices are tolterodine (1st choice), oxybutynin XL and solifenacin.

When should mirabegron be prescribed?
The ADTC has approved mirabegron for restricted use as a 3rd choice in patients who have not responded adequately to/cannot tolerate 1st and 2nd choice formulary antimuscarinics. Mirabegron has been shown to be less likely to cause dry mouth than tolterodine. However overall discontinuation rates with mirabegron are similar. Mirabegron is not recommended for use in patients with bp >180/110mmhg.

How effective is mirabegron?
Compared to placebo, mirabegron has been shown to be more effective in three 12-week studies in reducing the mean number of micturitions and incontinence episodes over a 24 hour period. However, overall the treatment benefits compared to placebo were considered modest.

How much does it cost?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen</th>
<th>Cost per year (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirabegron tablets</td>
<td>50mg once daily</td>
<td>352</td>
</tr>
<tr>
<td>Tolterodine tablets</td>
<td>2mg twice daily</td>
<td>58</td>
</tr>
<tr>
<td>Tolterodine XL capsules</td>
<td>4mg daily</td>
<td>268 to 335</td>
</tr>
<tr>
<td>Oxybutynin prolonged release tablets (Lynel XL®)</td>
<td>5 to 20mg daily</td>
<td>165 to 660</td>
</tr>
<tr>
<td>Solifenacin tablets</td>
<td>5 to 10mg daily</td>
<td>331 to 431</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from Drug tariff July 2013 and BNF 66.

Key Messages
- Mirabegron should only be prescribed when 1st and 2nd choice Formulary antimuscarinics have been ineffective or not tolerated.
- Treatment should only be initiated/recommended by a urologist.

Lisdexamfetamine (Elvanse®)
Lisdexamfetamine has been approved as a 2nd choice treatment option for the management of children and adolescents with ADHD after failure with methylphenidate.

Atomoxetine can also be used as a 2nd line option in patients when a stimulant is considered inappropriate.

Lisdexamfetamine is classified as a Schedule 2 Controlled Drug and should be prescribed and dispensed accordingly.

NHS Fife Formulary Abbreviated List
An updated version of the abbreviated list of the Fife Formulary is now available to be downloaded from the ADTC website at www.fifeadtc.scot.nhs.uk/ or via the direct link www.fifeadtc.scot.nhs.uk/formulary/NHS%20Fife%20Formulary%20Abbreviated%20List.pdf

The abbreviated list can be saved to your PC desktop or downloaded onto mobile devices e.g. Smart phones, e-readers and tablets.

The update contains all approved formulary changes up to the end of June 2013.

The abbreviated list includes the names of medicines specifically recommended as 1st and 2nd choices or those only approved for restricted use within NHS Fife and provides an easy reference source for all prescribers and clinicians to determine recommended Formulary choices.
Formulary Changes

Linaclotide (Constella®)

Linaclotide (Constella®) has been approved for restricted use in NHS Fife for the management of patients with constipation predominant moderate to severe irritable bowel syndrome (IBS-C).

How does linaclotide work?
Linaclotide causes decreased visceral pain, increased intestinal fluid secretion and accelerated intestinal transit. The recommended dose is 290 micrograms once daily.

What other treatment options are there?
Treatments for IBS-C may include laxatives and antispasmodic agents. Off label use of a tricyclic antidepressant or a selective serotonin reuptake inhibitor may be considered if laxatives and antispasmodics are ineffective.

When should linaclotide be prescribed?
In line with SMC advice, linaclotide is approved for restricted use as a 3rd choice in patients who have not responded adequately to/ cannot tolerate laxatives, antispasmodics and antidepressants.

How effective is linaclotide?
Compared to placebo, linaclotide has been shown to be more effective in two 12-week studies in producing symptom relief and in reducing abdominal pain and discomfort.

Linaclotide was also significantly better than placebo in improving straining, bloating and stool consistency.

There is no comparative trial evidence against other treatment options.

Who can prescribe it?
Linaclotide should only be initiated by a GI specialist.

45% of patients in the clinical trials did not respond to treatment. It is therefore important that patients are reviewed after 4 weeks by a specialist to assess clinical benefit. Prescribing may be transferred to primary care at this stage if ongoing treatment is considered beneficial.

How much does it cost?
Linaclotide is considerably more expensive than alternative treatment options. The cost of one year’s treatment with linaclotide is £488 per patient.

Key Messages
- Linaclotide is only approved for use when other alternatives have been ineffective/not tolerated.
- Treatment should only be initiated by a GI specialist.
- Patient should be reviewed after 4 weeks to assess benefit and the need for continuing treatment.

Guidance Documents

The following guidance documents have been approved for use by the ADTC -

- Guidelines for Benzodiazepine Prescribing in Benzodiazepine Dependence – This guideline document has been updated and is presented in an easy to read format. The guideline is a useful reference source for any clinician dealing with patients with benzodiazepine dependence.
- Recommended Antibiotic Prophylaxis for Adult Patients Undergoing General Surgery – The guidance has been reviewed and updated and provides information on recommended antibiotic regimes and doses for different surgical procedures.

New Safety Advice - Strontium (Protelos®)

In April 2013, the MHRA issued a drug safety alert http://www.mhra.gov.uk/SafetyInformation/DrugSafetyUpdate/CON266148 relating to the prescribing of strontium ranelate (Protelos®). A review of available safety data for strontium ranelate has identified an increased risk of serious cardiac disorders, including myocardial infarction. The drug safety alert notes that -

- Strontium ranelate is now restricted to the treatment of severe osteoporosis in patients at high risk of fractures.
- Strontium ranelate should not be used in patients with: ischaemic heart disease, peripheral arterial disease; cerebrovascular disease; a history of these conditions; or in patients with uncontrolled hypertension.
- Treatment should only be initiated by a physician with experience in the treatment of osteoporosis.

In NHS Fife the 1st choice treatment options are oral bisphosphonates (alendronate and risedronate) and the 2nd choice option is s.c. denosumab.

Updated prescribing advice and a flow diagram was issued across NHS Fife in June. Further copies of the advice can obtained by contacting William John, Public Health Pharmacist on (01592) 226915.

New Safety Advice - Cilostazol (Pletal®)

The April 2013 MHRA Drug Safety Update also contained new safety advice relating to cilostazol (Pletal®). Cilostazol is used for the improvement of walking distance in patients with intermittent claudication.

Cilostazol is now contraindicated in patients with:
- unstable angina, recent myocardial infarction or coronary intervention (within 6 months)
- history of severe tachyarrhythmia
- those receiving two or more other antiplatelet or anticoagulant treatments

Patients should be reassessed after 3 months of starting cilostazol and treatment stopped if there is no clinically relevant improvement in walking distance.

It should be noted that cilostazol is non-SMC approved and is non-formulary in NHS Fife and should not be prescribed routinely for intermittent claudication.
### SMC Recommendations

**Medicines accepted for use by SMC**

**Formulary Choices** – Products that are recommended within Fife and should be used in the majority of patients.

**Restricted Use** – Products that have been approved by the SMC for a limited indication or for a niche group of patients. Appropriate for them to be prescribed for patient groups that have been approved by the SMC / Fife ADTC.

**Not Preferred** – Products that have been approved by the SMC but agreed in Fife that suitable Formulary choices are already available. These products should only be used when Formulary products have been ineffective, not tolerated or are contra-indicated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication Assessed</th>
<th>Fife ADTC Decision &amp; Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisdexamfetamine dimesylate, 30mg, 50mg &amp; 70mg capsules (Elvanse®)</td>
<td>Attention deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate.</td>
<td>Included on the Fife Formulary as a 2nd choice stimulant. 1st choice Methylphenidate 2nd choice Lisdexamfetamine Atomoxetine 3rd choice Dexamfetamine Specialist use only (until approval of Shared care Protocol, then specialist initiation/recommendation).</td>
</tr>
<tr>
<td>Mirabegron 25mg and 50mg prolonged-release tablets (Betmiga®)</td>
<td>Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.</td>
<td>Included on the Fife Formulary for the indication stated. Add to restricted list for 3rd line use only. Restricted to patients in which 1st and 2nd choice formulary antimusarinics are ineffective, not tolerated or contraindicated. Specialist initiation/ recommendation only.</td>
</tr>
<tr>
<td>Ranibizumab, 10mg/mL solution for injection (Lucentis®)</td>
<td>Treatment of visual impairment due to macular oedema (MO) secondary to branch retinal vein occlusion (BRVO) in adults.</td>
<td>Included in the Fife Formulary for the indication stated. Hospital use only.</td>
</tr>
</tbody>
</table>
| Linacotide hard capsules, 290 micrograms (Constella®)                  | Symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults.  
**SMC restriction:** linacotide is restricted for use in patients with moderate to severe IBS-C who have not responded adequately to or cannot tolerate all other suitable treatment options. | Included on the Fife Formulary. Add to restricted list for 3rd line use only. To be only used after failure/intolerance of antispasmodics, laxatives and off-label antidepressants. Specialist initiation only. |
| Saxagliptin plus metformin, 2.5mg/850mg and 2.5mg/1000mg tablets (Komboglyze®) | Adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets.  
**SMC restriction:** use in patients for whom a combination of saxagliptin and metformin is an appropriate choice of therapy and only when the addition of sulphonylureas to metformin monotherapy is not appropriate. Saxagliptin/metformin is also licensed for use in combination with insulin for the treatment of type 2 diabetes. The manufacturer’s submission related only to the use of saxagliptin and metformin in combination therefore SMC cannot recommend the use of saxagliptin/metformin in combination with insulin. | Not included on Fife Formulary because clinicians do not support formulary inclusion of the combination product. |
| Pegylated interferon alpha-2a, 135 and 180microgram/mL pre-filled syringe, 135 and 180microgram/mL pre-filled pen (Pegasys®) | In combination with ribavirin, for the treatment of chronic hepatitis C (CHC) in treatment-naïve children and adolescents five years of age and older, who are positive for serum hepatitis-C virus ribonucleic acid (HCV-RNA).  
**SMC restriction:** prescribing by specialist in paediatric infectious disease or paediatric gastroenterology. | Not included on Fife Formulary for this indication because clinicians do not support formulary inclusion. Tertiary centre use only. |
Canakinumab (Ilaris®) is not recommended for symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

Canakinumab (Ilaris®) is not recommended for treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 2 years and older of 7.5 kg or above: presenting with signs and symptoms beyond cold-induced urticarial skin rash.

Everolimus (Votubia®) is not recommended for treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications but who do not require immediate surgery.

Fluocinolone acetonide intravitreal implant (Iluvien®) is not recommended for treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies.

Ivacaftor (Kalydeco®) is not recommended for treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Vildagliptin (Galvus®) is not recommended for treatment of type 2 diabetes mellitus in adults as triple oral therapy in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control or in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

Vildagliptin/metformin hydrochloride (Eucreas®) is not recommended for treatment of type 2 diabetes mellitus in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulphonylurea or in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

Medicines not recommended by SMC

Crizotinib (Xalkori®) is not recommended for treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Abiraterone (Zytiga®) is not recommended with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

Rifampicin, isoniazid, pyrazinamide, ethambutol hydrochloride (Voractiv®) is not recommended for initial treatment of tuberculosis according to World Health Organisation (WHO) guidelines.

Tafamidis meglumine (Vyndaqel®) is not recommended for treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment.

Vincristine sulphate (Oncovin®) is not recommended for cytotoxic chemotherapy in adults with non Hodgkin lymphoma or advanced solid tumours who achieve a complete response after one or two cycles of chemotherapy to allow observation and delayed intervention.

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