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

Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 12 **July 2013**

What's new this month?

- ***Dymista*** **nasal spray, a new combination antihistamine (azelastine hydrochloride) and corticosteroid (fluticasone propionate) nasal spray licensed for the treatment of perennial and seasonal allergic rhinitis, has been designated RED-RED (see page 3).**
- **Fluticasone furoate 27.5 microgram nasal spray (*Avamys*) now represents an appropriate third line nasal steroid in preference to more expensive products such as mometasone 50 microgram nasal spray (*Nasonex*), triamcinolone acetonide 55 microgram nasal spray (*Nasacort*) and fluticasone propionate 50 microgram nasal spray (*Flixonase*). As a result of this, fluticasone furoate 27.5 microgram nasal spray (*Avamys*) has been re-designated from RED-RED to GREEN. Where a fluticasone preparation is indicated fluticasone furoate nasal spray (*Avamys*) should be preferred (see page 3).**
- **Fluticasone propionate 50 microgram nasal spray (*Flixonase*) is now prohibitively expensive in comparison to alternative nasal steroid preparations and should no longer be initiated in new patients. Existing patients can continue on *Flixonase* until they or their clinician consider it to be appropriate to stop or change to a lower cost alternative. For new patients, fluticasone propionate 50 microgram nasal spray (*Flixonase*) should be considered to be RED-RED (see page 3).**
- **After reports of a number of patient incidents from around the country, prescribers are reminded of the risk of confusion between midazolam 5mg/ml oromucosal solution (*Buccolam*) (licensed for the treatment of prolonged acute convulsive seizures in children from the age of 3 months to 18 years) and the unlicensed alternative, midazolam 10mg/ml buccal solution (*Epistatus*). In order to minimize this confusion, all liquid midazolam preparations should be prescribed by brand and doses should always be prescribed in both mg and mL to minimize the risk of wrong dose errors (see page 5).**
- **An updated version of the shared care guideline *Methylphenidate, atomoxetine, dexamfetamine and lisdexamfetamine in the management of Attention Deficit Hyperactivity Disorder* has been published (see page 6).**
- **Following a review of the evidence base, PACEF remain unconvinced of the benefits of combination memantine and acetylcholinesterase inhibitor use in the treatment of Alzheimer's disease. As a result of this, combination therapy is not recommended and will not be endorsed in the forthcoming update to the shared care guideline (see page 6).**
- **NICE have now approved omalizumab injection (*Xolair*) as an add-on therapy to improve control of asthma in children aged 6 to 11 with severe persistant IgE mediated allergic asthma. This means that the product is now available for children aged 6 and over, adolescents and adults within the terms of its marketing authorisation and NICE guidance. It is for specialist use only and is designated RED (see page 7).**
- **Following publication of updated General Medical Council good practice guidance on prescribing and managing medicines and devices, advice is given on dealing with patient requests for specific treatments and improving patient adherence with therapy (see page 11).**

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SUMMARY OF PACEF DECISIONS: *JUNE 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Abatercept intravenous infusion (*Orencia*)	For use in combination with methotrexate (MTX) for the treatment of moderate to severe active RA in adults whose disease has responded inadequately to previous therapy with one or more DMARDS including MTX or a tumour necrosis factor inhibitor (anti-TNF).	RED
Beclometasone 50 microgram nasal spray (generic or *Beconase*)	For perennial and seasonal allergic rhinitis.	GREEN Included in the Joint Formulary First line nasal steroid of choice
Budesonide 64 microgram nasal spray (generic or *Rhinocort Aqua*)	For perennial and seasonal allergic rhinitis.	GREEN Included in the Joint Formulary Second line nasal steroid of choice
Canakinumab injection (*Ilaris*)	For the symptomatic treatment of adult patients with frequent gouty arthritis attacks when NSAIDs and colchicine are contraindicated, not tolerated or inadequate and when repeated courses of corticosteroids are inappropriate.	RED-RED
Fluticasone furoate 257 microgram nasal spray (*Avamys*)	For allergic rhinitis.	GREEN Approved for inclusion in the Joint Formulary Third line nasal steroid of choice
Fluticasone propionate 50 microgram nasal spray (*Flixonase*)	For seasonal allergic rhinitis and perennial rhinitis	RED-RED Not approved for inclusion in the Joint Formulary Existing patients should be allowed to continue until they or their clinician consider it to be appropriate to stop or change to a lower cost alternative.

Fluticasone propionate/ azelastine hydrochloride 50 microgram/ 137 microgram nasal spray (*Dymista*)	For perennial and seasonal allergic rhinitis.	RED-RED Not approved for inclusion in the Joint Formulary
Midazolam oromucosal solution 5mg/ml (*Buccolam*).	Licensed for the treatment of prolonged acute convulsive seizures in children from the age of 3 months to 18 years.	AMBER All new patients requiring liquid midazolam for this indication should be initiated on midazolam oromucosal solution 5mg/ml (*Buccolam*). Liquid midazolam formulations should only be initiated on specialist advice; no formal shared care guideline is required. **To avoid confusion liquid midazolam preparations should always be prescribed by brand and doses should always be prescribed in both mg and mL.** Included in the Joint Formulary.
Midazolam buccal liquid 10mg/ml (*Epistatus*)	Unlicensed product used for the emergency treatment of status epilepticus as a second line alternative to rectal diazepam.	AMBER Existing patients can continue using this therapy, although new initiations should be for licensed midazolam oromucosal solution 5mg/ml (*Buccolam*). Liquid midazolam formulations should only be initiated on specialist advice; no formal shared care guideline is required. **To avoid confusion liquid midazolam preparations should always be prescribed by brand and doses should always be prescribed in both mg and mL.** Learning Disabilities Services continue to use *Epistatus* in adult patients to avoid confusion arising from *Buccolam* packaging and information leaflets. Included in the Joint Formulary.
Mometasone 50 microgram nasal spray (*Nasonex*)	For seasonal allergic and perennial rhinitis.	GREEN Included in the Joint Formulary Third line alternative nasal steroid to fluticasone furoate (*Avamys*)
Omalizumab injection (*Xolair*)	For use as an add-on therapy to improve control of asthma in adults and adolescents 12 years and over and children aged 6 to 11 with severe persistant IgE mediated allergic asthma	RED Included in the Joint Formulary
Pirfenidone 267mg capsules (*Esbriet*)	For mild to moderate idiopathic pulmonary fibrosis in adults.	RED
Tolvaptan 15mg/30mg tablets (*Samsca*)	For the treatment of adults with hyponatremia secondary to inappropriate antidiuretic hormone secretion.	RED-RED Not approved for inclusion in the Joint Formulary

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS in Lincolnshire website (www.lincolnshire.nhs.uk). Follow the commissioning link to PACEF.

NEW DRUG ASSESSMENT: FLUTICASONE PROPIONATE/AZELASTINE HYDROCHLORIDE 50 MICROGRAM/137 MICROGRAM NASAL SPRAY (*DYMISTA*)

Dymista nasal spray is a new combination antihistamine (azelastine hydrochloride) and corticosteroid (fluticasone propionate) nasal spray. It holds a UK marketing authorisation for perennial and seasonal allergic rhinitis.

PACEF reviewed a meta-analysis of three trials comparing the fluticasone/azelastine combination nasal spray with the individual components and placebo in 3,398 adults and adolescents with moderate to severe seasonal allergic rhinitis. From these combined results the fluticasone/azelastine combination emerged as significantly superior to placebo and to fluticasone propionate or azelastine hydrochloride prescribed as monotherapy in terms of reduced nasal and ocular symptom scores. All three active treatments were significantly better than placebo.

In a second smaller scale randomized controlled trial, the fluticasone/azelastine combination nasal spray emerged as significantly superior to separate components and placebo in terms of total nasal symptom score. Both the meta-analysis and the trial reflect short-term use (14 days) leaving unresolved questions around longer-term efficacy and safety. The main adverse effects associated with the use of *Dymista* are epistaxis, headache, unpleasant taste and unpleasant smell sensations. There is no comparative data against any other intranasal preparations or any oral antihistamine.

A cost comparison against alternatives reveals the following:

Drug	**Daily dose**	**Cost (£) (doses)**
Fluticasone propionate/ azelastine hydrochloride 50 microgram/ 137 microgram nasal spray (*Dymista*)	1 spray into each nostril twice daily	£ 18.91 (120)
Azelastine hydrochloride 0.1% nasal spray (*Rhinolast*)	1 spray into each nostril twice daily	£10.50 (150)
Fluticasone propionate 50 microgram nasal spray (*Flixonase*)	1 spray into each nostril twice daily	£11.01 (150)
Beclometasone 50 microgram nasal spray (generic)	2 sprays into each nostril twice daily	£2.33 (200)
Beclometasone 50 microgram nasal spray (*Beconase*)	2 sprays into each nostril twice daily	£2.19 (200)
Beclometasone 50 microgram nasal spray (*Nasobec*)	2 sprays into each nostril twice daily	£3.06 (200)
Budesonide 64 microgram nasal spray (generic)	1 spray into each nostril twice daily	£3.85 (120)
Budesonide 64 microgram nasal spray (*Rhinocort Aqua*)	1 spray into each nostril twice daily	£3.49 (120)
Fluticasone furoate 27.5 microgram nasal spray (*Avamys*)	2 sprays into each nostril once daily reducing to 1 spray each nostril daily.	£6.44 (120)
Mometasone 50 microgram nasal spray (Nasonex)	2 sprays into each nostril once daily	£7.68 (140)
Triamcinolone acetonide 55 microgram nasal spray (*Nasacort*)	2 sprays per nostril once daily	£7.39 (120)
Sodium cromoglicate 2% nasal spray (*Vividrin Spray*)	1 spray into each nostril four to six times a day	£9.85 (15ml)
Sodium cromoglicate 4% nasal spray (*Rynacrom Spray*)	1 spray into each nostril two to four times a day	£17.07 (22ml)

Drug	**Daily dose**	**Cost (30 days)**
Cetirizine 10mg tablets	One tablet daily	£1.13
Loratadine 10mg tablets	One tablet daily	£1.12

PACEF Recommendations:

PACEF were concerned about the lack of trial data comparing *Dymista* with a nasal corticosteroid plus an oral antihistamine (e.g. loratadine 10mg tablets or cetirizine 10mg tablets). They were also concerned about the lack of long-term efficacy and safety data and the prohibitively high cost of *Dymista* in comparison to lower cost alternatives. Even compared to fluticasone propionate nasal spray (*Flixonase*) and azelastine nasal spray (*Rhinolast*) prescribed separately, Dymista is marginally more expensive dose for dose. As a result of this, fluticasone propionate/ azelastine hydrochloride 50 microgram/ 137 microgram nasal spray (*Dymista*) is designated RED-RED.

PACEF also took the opportunity to review the full range of nasal steroids for perennial and seasonal allergic rhinitis and to update local guidance. Beclometasone 50 microgram nasal spray (generic or *Beconase*) is the lowest cost nasal steroid and remains the first line product of choice. Combination therapy with an oral antihistamine, such as cetirizine 10mg or loratadine 10mg, would be significantly lower in cost than *Dymista.* Similarly, budesonide 64 microgram nasal spray (generic or *Rhinocort Aqua*) is also comparatively low cost and represents an appropriate second line choice that would still be low cost in combination with an oral antihistamine. After a price reduction, fluticasone furoate 27.5 microgram nasal spray (*Avamys*) now represents an appropriate third line nasal steroid in preference to more expensive products such as mometasone 50 microgram nasal spray (*Nasonex*), triamcinolone acetonide 55 microgram nasal spray (*Nasacort*) and fluticasone propionate 50 microgram nasal spray (*Flixonase*). As a result of this, fluticasone furoate 27.5 microgram nasal spray (*Avamys*) has been re-designated from RED-RED to GREEN. Where a fluticasone preparation is indicated fluticasone furoate nasal spray (*Avamys*) should be preferred. Fluticasone propionate 50 microgram nasal spray (*Flixonase*) is now prohibitively expensive in comparison to alternative nasal steroid preparations and should no longer be initiated in new patients. Existing patients can continue on *Flixonase* until they or their clinician consider it to be appropriate to stop or change to a lower cost alternative. For new patients, fluticasone propionate 50 microgram nasal spray (*Flixonase*) should be considered to be RED-RED.

PRESCRIBE OROMUCOSAL MIDAZOLAM SOLUTION BY BRAND

Early in 2012 PACEF assessed midazolam 5mg/ml oromucosal solution (*Buccolam*), the first licensed preparation for the treatment of prolonged acute convulsive seizures in children from the age of 3 months to 18 years. This preparation is available in pre-filled syringes in several doses (2.5mg, 5mg, 7.5mg and 10mg). Previously, the only option for these patients was an unlicensed midazolam 10mg/ml liquid formulation known as *Epistatus*. The launch of a *licensed* midazolam oromucosal solution provided a preferred option in infants, children and adolescents at risk of acute convulsive seizures in epilepsy. As a result of this, midazolam 5mg/ml oromucosal solution (*Buccolam*) was designated AMBER for this indication and became the preferred preparation. At the time of launch, the Medicines and Healthcare products Regulatory Agency (MHRA) expressed concern about the risk of confusion between the newly licensed product and the different strengths of established unlicensed alternatives and issued guidance to prescribers through the *Drug Safety Update*. All of this was covered in *PACE Bulletin* Vol 6 No 5 (February 2012).

Since the launch of *Buccolam* there have been several incidents reported nationally in which *Buccolam* and *Epistatus* have been used interchangeably. In some cases the patient has received the wrong brand and strength of midazolam resulting in a potential loss of seizure control. Following discussion at Lincolnshire Partnership Trust Medicines Management Committee and PACEF, local guidance is expanded and clarified as follows:

PACEF Recommendation:
Midazolam 5mg/ml oromucosal solution (*Buccolam*) is licensed for the treatment of infants, children and adolescents at risk of acute convulsive seizures in epilepsy and is designated AMBER without shared care for this indication. As a licensed product, *Buccolam* is now the buccal midazolam formulation of choice and should be preferred in all new patients. Serious concerns remain regarding the risk of confusion between the unlicensed product, midazolam buccal solution (*Epistatus*) (10mg/ml), and midazolam 5mg/ml oromucosal solution (*Buccolam*). In order to minimize this confusion, all liquid midazolam preparations should be prescribed by brand and doses should always be prescribed in both mg and mL to minimize the risk of wrong dose errors. An analysis of Lincolnshire primary care prescribing patterns has revealed that the majority of midazolam oromucosal solution is still prescribed generically. Prescribers are reminded that this constitutes an unacceptable risk and that all patients currently prescribed oromucosal midazolam should be identified and all prescriptions changed to reflect the required brand. LPFT Learning Disability Service have expressed their intention to continue to use midazolam buccal solution (*Epistatus*)(10mg/ml) as the majority of their patients are adults and the packaging and information leaflets provided with *Buccolam* presents a potential risk of confusion as they emphasize that the product is only licensed for use in children. Where *Epistatus* continues to be preferred it must be prescribed by brand with doses designated clearly in mg and mL. *Epistatus* continues to be designated AMBER without shared care within this context.

SHARED CARE GUIDELINES

PACEF have reviewed and approved an updated version of the following shared care guideline:

Methylphenidate, atomoxetine, dexamfetamine and lisdexamfetamine in the management of Attention Deficit Hyperactivity Disorder (ADHD)

The updated SCG includes the new ADHD treatment lisdexamfetamine *(Elvanse)* which has been approved for use by PACEF and was detailed in *PACE Bulletin* Vol 7 No 11 (July 2013). Prescribers are reminded that this SCG covers the initiation of treatment in children and adolescents, but not adults. However, it can be used to cover the ongoing therapy of patients over 18 years of age who were initiated on therapy as children or adolescents.

Copies of the guideline are available from www.lincolnshire.nhs.uk. Further information and advice is available from Cathy Johnson, our Interface Lead Pharmacist (Tel: 01205 366273 ext 230 or email to cathy.johnson@gemcsu.nhs.uk)

USE OF MEMANTINE AND ACETYLCHOLINESTERASE INHIBITOR COMBINATION THERAPY IN THE TREATMENT OF ALZHEIMER'S DISEASE

As part of a review of the shared care guideline relating to the treatment of Alzheimer's disease (AD), PACEF undertook a review of the evidence base for combination memantine and acetylcholinesterase inhibitor (AChEI) treatment. Currently licensed AChEIs include donepezil, galantamine and memantine with generic donepezil preferred first line.

As part of NICE TA217 *Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease* (March 2011), NICE reviewed the trial evidence for combination therapy and concluded that it offered no additional benefit beyond monotherapy in terms of cognitive, functional, behavioural or global outcomes. PACEF reviewed a range

of trials, systematic reviews and meta-analyses, some considered by NICE and some published since, and were unable to confirm any additional benefit from adding memantine into existing AChEI therapy or vice versa. One new trial comparing memantine plus a stable dose of an AChEI with an AChEI plus placebo showed no additional benefit from the combination on cognitive, functional, behavioural or global outcomes. Another new trial concluded that there were cognitive improvements, but was less convincing in relation to other outcomes. Specialist opinion from LPFT suggests that despite the lack of hard evidence the addition of a second treatment to monotherapy can confer a visible clinical benefit. Conversely, a patient can visibly deteriorate if the AChEI component is withdrawn from combination therapy with memantine.

PACEF Recommendation:
PACEF remain unconvinced as to the benefits of combination memantine and AChEI use in the treatment of AD. As a result of this, combination therapy is not recommended and will not be endorsed in the forthcoming update to the shared care guideline. Any request to prescribe combination therapy is outside the terms of the shared care guideline and should be referred back to the initiating specialist. Combination therapy is recognized within the *Maudsley Prescribing Guidelines*, although further research is required to establish the benefits more clearly. As a result, this decision will be kept under review.

NICE TECHNOLOGY APPRAISAL 278: *OMALIZUMAB FOR TREATING SEVERE PERSISTENT ALLERGIC ASTHMA (APRIL 2013)*

Omalizumab is recommended as an option for treating severe persistent allergic IgE mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:

- who need continuous or frequent treatment with oral corticosteroids (defined as four or more courses in the previous year) and
- only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.

Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta 2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids and smoking cessation if clinically appropriate.

Notes

Omalizumab (Xolair) is a monoclonal antibody that binds to IgE. It has a marketing authorisation as an add-on therapy to improve control of asthma in adults and adolescents 12 years and over and children aged 6 to 11 with severe persistant IgE mediated allergic asthma who have:

(1) a positive skin test or in vitro reactivity to a perennial aeroallergen.
(2) reduced lung function (FEV_1 less than 80% in adults and adolescents).
(3) frequent daytime symptoms or night-time awakenings.
(4) multiple documented severe exacerbations despite daily high-dose inhaled corticosteroids plus a long-acting inhaled $beta_2$ agonist.

16 weeks after the start of omalizumab therapy, physicians should assess how effective the treatment is; treatment should only continue in patients whose asthma has markedly improved.

Omalizumab therapy should be initiated and monitored in a specialist centre by a physician experienced in the diagnosis and treatment of severe persistent asthma.

It is given subcutaneously every 2 or 4 weeks with the dosage determined according to pre-treatment IgE serum concentration and body weight. The dose is 75 to 600mg every 2 or 4 weeks up to a maximum dose of 600mg every 2 weeks. The estimated annual cost ranges from £1665 per patient (75mg every 4 weeks) to £26,640 per patient (600mg every 2 weeks).

PACEF Recommendation:
Omalizumab injection (*Xolair*) was previously designated RED-RED for children aged 6 to 11 with severe persistant allergic asthma in response to NICE TA201 (October 2010). Following this review omalizumab injection (*Xolair*) is now designated RED for this indication. The product is already designated RED for the prophylaxis of severe persistent allergic asthma in adults and children over 12 in accordance with NICE TA133 (November 2007).

NICE TECHNOLOGY APPRAISAL 279: *PERCUTANEOUS VERTEBROPLASTY AND PERCUTANEOUS BALLOON KYPHOPLASTY FOR TREATING OSTEOPOROTIC VERTEBRAL COMPRESSION FRACTURES* (APRIL 2013)

Percutaneous vertebroplasty, and percutaneous balloon kyphoplasty without stenting, are recommended as options for treating osteoporotic vertebral compression fractures only in people:

- who have severe ongoing pain after a recent, unhealed vertebral fracture despite optimal pain management **and**
- in whom the pain has been confirmed to be at the level of the fracture by physical examination and imaging.

NICE TECHNOLOGY APPRAISAL 280: *ABATACEPT FOR TREATING RHEUMATOID ARTHRITIS AFTER THE FAILURE OF CONVENTIONAL DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS* (APRIL 2013)

Abatacept in combination with methotrexate (MTX) is recommended as an option for treating rheumatoid arthritis (RA) in adults whose disease has responded inadequately to 2 conventional disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, only if:

- it is used in accordance with the recommendations for other biological DMARDs in NICE TA 130, *Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis*
- **and** the manufacturer provides abatacept with the discount agreed in the patient access scheme.

Notes

Abatercept intravenous infusion (*Orencia*) has a marketing authorisation for use in combination with MTX for the treatment of moderate to severe active RA in adults whose disease has responded inadequately to previous therapy with one or more DMARDS including MTX or a tumour necrosis factor inhibitor (anti-TNF).

Abatercept is administered as a 30 minute IV infusion given at week 0, week 2, week 4 and then every 4 weeks. Fourteen infusions are needed in the first year and thirteen infusions in subsequent years. For a person weighing 60 to 100kg the cost is £12,700 in the first year

and £11,800 in subsequent years. The patient access scheme is likely to reduce these costs by an undisclosed amount.

PACEF Recommendation:
Abatercept intravenous infusion (*Orencia*) continues to be designated RED within the terms of the NICE TA and its marketing authorisation.

NICE TECHNOLOGY APPRAISAL 281: *CANAKINUMAB FOR TREATING GOUTY ARTHRITIS ATTACKS AND REDUCING THE FREQUENCY OF SUBSEQUENT ATTACKS* (TERMINATED APPRAISAL) (APRIL 2013)

NICE is unable to recommend the use in the NHS of canakinumab for treating gouty arthritis attacks and reducing the frequency of subsequent attacks because no evidence submission was received from the manufacturer.

The manufacturer did not make an evidence submission to NICE as it will not be promoting canakinumab for this indication in the UK.

PACEF Recommendation:
Canakinumab injection (*Ilaris*) holds a marketing authorisation for the symptomatic treatment of adult patients with frequent gouty arthritis attacks when NSAIDs and colchicine are contraindicated, not tolerated or inadequate and when repeated courses of corticosteroids are inappropriate. In response to this TA, the product is designated RED-RED.

NICE TECHNOLOGY APPRAISAL 282: *PIRFENIDONE FOR TREATING IDIOPATHIC PULMONARY FIBROSIS* (APRIL 2013)

Pirfenidone is recommended as an option for treating idiopathic pulmonary fibrosis only if:

- the person has a forced vital capacity (FVC) between 50% and 80% predicted and
- the manufacturer provides pirfenidone with the discount agreed in the patient access scheme.

Treatment with pirfenidone should be discontinued if there is evidence of disease progression (a decline in per cent predicted FVC of 10% or more within any 12 month period).

PACEF Recommendation:
Pirfenidone 267mg capsules (*Esbriet*) hold a marketing authorisation for mild to moderate idiopathic pulmonary fibrosis in adults. They can only be initiated subject to specialist assessment and ongoing review of disease progression and are designated RED.

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

Tolvaptan (*Samsca*): risk of liver injury

Tolvaptan (*Samsca*) is a selective vasopressin V2 receptor antagonist holding a marketing authorisation for the treatment of adults with hyponatremia secondary to inappropriate antidiuretic hormone secretion. Drug-induced liver injury has been observed in clinical trials

designed to investigate the potential use of tolvaptan in patients with autosomal dominant polycystic kidney disease. This indication requires doses higher than those normally used for the treatment of hyponatraemia. As a result of these findings, the MHRA have recommended that liver function tests should be done in patients receiving tolvaptan who report signs or symptoms of liver injury (e.g. fatigue, anorexia, right abdominal discomfort, dark urine or jaundice)

PACEF Recommendation:
Tolvaptan 15mg/30mg tablets (*Samsca*) have been evaluated by PACEF and designated as RED-RED (see *PACE Bulletin* Vol 6 No 8 (May 2012)). Local monitoring has confirmed that there is currently no GP prescribing of the product in county. Any requests from tertiary or secondary care centres to prescribe this drug should be refused.

Thalidomide: risk of second primary malignancies

Thalidomide is licensed in combination with melphalan and prednisolone as a first-line treatment for those with multiple myeloma who are over 65 years of age and who are ineligible for high dose chemotherapy. In November 2011 the MHRA highlighted the risk of second primary malignancies developing associated with a drug closely associated with thalidomide, lenalidomide (*Revlimid*). Most recently, data had emerged suggesting an association between thalidomide when used in combination with melphalan and prednisolone and second primary malignancies.

The MHRA advises that, before initiating treatment with thalidomide, the likely benefit of treatment needs to be taken into account against the risk of developing acute myeloid leukaemia and myelodysplastic syndromes.

PACEF Comment:
Both thalidomide 50mg capsules (*Thalidomide Celgene*) and lenalidomide capsules 5/10/15/25mg (*Revlimid*) are designated RED within authorised indications. Lenalidomide is approved by NICE for use in combination with dexamethasone for the treatment of multiple myeloma in patients who have received two or more prior therapies. Thalidomide is approved by NICE for use with melphalan and prednisolone as an option for the first line treatment of multiple myeloma. All prescribing and monitoring of lenalidomide and thalidomide should be the responsibility of secondary or tertiary care.

Liothyronine 20 microgram tablets: continuity of supply and potential need for patient monitoring

There are currently problems with the supply of liothyronine 20 microgram tablets from the manufacturer, Amdipharm Mercury. The only other product available is an unlicensed product imported from Europe that may not be bioequivalent to the licensed formulation.

The MHRA have issued the following advice to healthcare professionals:

- Prescribers should be alert to the possibility that a change in a patient's symptoms and thyroid stimulating hormone (TSH) status may be attributable to switching between the licensed and unlicensed products.
- Patients who experience a significant change in symptoms should have their TSH levels reviewed and their dose adjusted accordingly.
- Patients particularly susceptible to changes in bioavailability that might require close monitoring are pregnant women, especially those in their first trimester, and patients with heart disease.

- In a small number of patients prescribed liothyronine long term (usually in combination with levothyroxine), thyroid function tests should be repeated 1-2 months after every change in preparation to ensure the target TSH level has been maintained.

GENERAL MEDICAL COUNCIL: *GOOD PRACTICE IN PRESCRIBING AND MANAGING MEDICINES AND DEVICES* (FEBRUARY 2013)

The recently published GMC guide on *Good Practice in Prescribing and Managing Medicines and Devices* makes some helpful statements in relation to issues that are often raised through PACEF.

Q What do I do if a patient demands a specific therapy by name?

If a patient asks for a treatment that the doctor considers would not be of overall benefit to them, the doctor should discuss the issues with the patient and explore the reasons for their request. If, after discussion, the doctor still considers that the treatment would not be of overall benefit to the patient, they do not have to provide the treatment. But they should explain their reasons to the patient, and explain any other options that are available, including the option to seek a second opinion.

Q How do I deal with a patient who is poorly compliant with therapy?

Each medication review should confirm that the patient is taking their medicines as prescribed and should include a check that medicines are still needed, effective and tolerated. This may be particularly important following a hospital stay or changes to medicines following a hospital or home visit. Also consider whether requests for repeat prescriptions received earlier or later than expected may indicate poor adherence, leading to inadequate therapy or adverse effects (paragraph 58).

Some patients do not take medicines prescribed for them or do not follow the instructions on the dose to take or the time medicines should be taken. Try to understand the reasons for this and address them by providing reassurance and information and by negotiating with the patient to reach agreement on an appropriate course of treatment that they are able and willing to adhere to (paragraph 29).

PACEF Comment:
In November 2010, the York Health Economics Consortium and The School of Pharmacy, University of London published *Evaluation of the Scale, Causes and Costs of Waste Medicines.* This report estimated the gross cost of unused prescription medicines in primary and community care in 2009 to be in the region of £300M pa in England with around half being economically recoverable. A significant contribution to reducing wasted medicines could be made in primary care by improving patient adherence to medicines. Evidence suggests that some patients continue to collect repeat prescriptions for medicines that they have no intention of taking. Increasing patient involvement in decision making around their medicines and realistic negotiated agreements between the prescriber and the patient can help to improve this. Better integration of community pharmacy provided services such as the New Medicines Scheme and Medicines Use Reviews can also help to support patients to improve adherance with therapy.

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