Lincolnshire Prescribing and Clinical Effectiveness Bulletin

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Summary of PACEF decisions from November 2017 PACE Short (Vol 12 No 2)

Device, Dressing or Drug	**Indication(s)**	**Traffic Light and *Joint Formulary* Status**
Dymista nasal spray	For the treatment of patients with allergic rhinitis not responding to intranasal corticosteroid alone or in combination with oral antihistamine in line with the BSACI guidance.	Amber 2 Approved for inclusion on to the Joint Formulary Initiation to be at request of ENT specialists.
Lecicarbon A suppositories	1) Patients with neurogenic bowel dysfunction (secondary to spinal injury) 2) Patients with anorectal dysfunction, either due to anatomical abnormality or anorectal dysynergy -	Amber 2 Approved for inclusion onto the joint for use only for the specific patient group as requested by ULHT gastroenterology service.
Epistatus 10mg in 1ml oromucosal solution – Midazolam as maleate	Licensed as a 10mg/ml 1ml oral syringe licensed only for use in children and adolescents aged 10 to less than 18 years of age.	Amber 2 Approved for inclusion onto the formulary as an option for the treatment of prolonged seizures both within its licensed indications and also unlicensed for the for the treatment of prolonged seizures in adults.
Salofalk brand of mesalazine foam enema	The Asacol brand of mesalazine foam enema has been recently discontinued.	Amber 2 Approved for inclusion on Joint formulary Salofalk brand of mesalazine foam enema as a replacement, classing it as AMBER 2.
Roflumilast (Daxas) 500mcg tablets	It is licensed for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.	NICE TA 461 recommended use of Roflumilast for the treatment of chronic obstructive pulmonary disease. Reviewed and re-designated as Amber 2.

Other news

MEDICINES AND HEALTHCARE REGULATORY AGENCY (MHRA): DRUG SAFETY UPDATE (October 2017)

Methylprednisolone injection (Solu-Medrone) 40mg may contain trace amounts of milk proteins
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Rapid Drug Assessment Dymista nasal spray.

This is a combination nasal spray consisting of an antihistamine component azelastine and a corticosteroid fluticasone, licensed for the relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient. Each spray contains 137 micrograms azelastine hydrochloride and 50 micrograms fluticasone propionate, the usual dose is one spray in each nostril twice daily (morning and evening).
This has previously been reviewed by PACEF and not approved for use. Reasons cited were lack of comparative trial data against other nasal corticosteroid and oral antihistamine treatments, lack of long term efficacy and safety data and the prohibitively high cost of Dymista compared to alternative therapies.
A request had been made from United Lincolnshire Ear Nose and Throat service to review formulary status of Dymista, since use of a combination topical antihistamine with intranasal corticosteroid is now recommended with the 2017 revision of included within the British Society of Allergy and Clinical Immunology (BSACI) guideline for the diagnosis and management of allergic and non-allergic rhinitis

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- The British Society of Allergy and Clinical Immunology (BSACI) guideline for the diagnosis and management of allergic and non-allergic rhinitis, revised 2017 suggests that the combination of a topical antihistamine with intranasal corticosteroid should be used in patients when symptoms remain uncontrolled on topical antihistamine or intranasal corticosteroid monotherapy or on a combination of oral antihistamine plus intranasal corticosteroid.
- Dymista is the only combination product available and evidence suggests that it improves symptom control compared with either of the two components administered separately.
- It is licensed for use in adults and adolescents (12 years and older).
- Since PACEF last reviewed the combination therapy the cost of the product has been reduced and it is now cheaper than the individual ingredients administered

separately, although still significantly more expensive when compared with alternative intranasal corticosteroids and oral antihistamines.

Cost comparison table (formulary approved products in bold)

Product	dose	Cost (£)
Dymista (fluticasone propionate / azelastine)	1 spray each nostril twice daily	£14.40 (120 doses)
Beclometasone 50mcg/dose	2 sprays each nostril twice daily	£2.63 (200)
Budesonide nasal spray 64mcg/dose	2 sprays each nostril every morning or 1 spray each nostril twice daily.	£4.77 (120)
Fluticasone furoate 27.5mcg/spray	2 sprays each nostril daily Maintencae 1 spray , each nostril daily	£6.44 (120)
Mometasone furoate 50mcg/dose	2 sprays both nostrils daily.	£1.79 (140)
Triamcinolone 55mcg/dose	2 sprays per nostril once daily. Maintenace 1 spray per nostril once daily.	£7.39 (120)
Azelastine 0.1%	1 spray each nostril twice daily.	£10.50 (150)
Cetirizine 10mg tablet	1 tablet daily	£0.70 (30)
Loratadine 10mg tablet	1 tablet daily	£0.74 (30)

- PACEF approved Dymista for the treatment of patients per month with allergic rhinitis not responding to intranasal corticosteroid alone or in combination with oral antihistamine in line with the BSACI guidance. To be designated as AMBER 2.

Rapid Drug Assessment Lecicarbon A suppositories

Lecicarbon A suppositories contain sodium dihydrogen carbonate (0.5g per suppository) and sodium dihydrogen phosphate (0.680g per suppository) . It is a rectal laxative licensed for constipation and for bowel evacuation prior to surgery or diagnostic procedures.

- Lecicarbon A were launched in UK in 2014 via a well-established use application via an incoming Mutual Recognition Procedure from Germany to the UK. It has been on the German market for approximately 80 years.
- PACEF reviewed Lecicarbon A in September 2014 and Lecicarbon C in July 2015. In view of the lack of comparative data against alternatives and the relatively high cost, both formulations were not approved for use and were designated RED-RED.
- The ULHT gastroenterology service had requested that Lecicarbon A be reviewed again to be reserved for the treatment of patients with neurogenic bowel dysfunction (secondary to spinal injury) and patients with anorectal dysfunction, either due to anatomical abnormality or anorectal dysynergy.

- This treatment will only be used when standard oral or rectal therapies have been tried and are either ineffective or poorly tolerated, prior to moving on to more expensive and less locally available treatment modalities.
- For this group of patients the dosage regime would be one suppository when required to relive symptoms up to 2 per day with an average dose of 2 – 3 per week
- One pack of 10 Lecicarbon A suppositories costs £8.20, with a month's treatment therefore costing approximately £10.00.
- PACEF approved the request designating Lecicarbon A suppositories as an AMBER 2 drug for use only for the specific patient group as requested.

Rapid Drug Assessment Epistatus Midazolam (as maleate) 10mg in 1ml oromucosal solution

Epistatus has recently become licensed as a single dose of 10mg packaged in a single dose oral syringe intended for administration to the buccal cavity. Previously Epistatus as only been available as unlicensed medicine strength 10mg/ml available in a 5ml multidose bottle.

- The current preferred first-line product when buccal midazolam is indicated is Buccolam which is midazolam hydrochloride in a strength of 5mg/ml available in the following doses: 2.5mg,5mg,7.5mg and 10 mg. Buccolam is licensed for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years).
- The unlicensed formulation of Epistatus has previously been included on the Lincolnshire formulary, classed as AMBER 2 as a treatment option when buccal midazolam is indicated, for the treatment of prolonged, acute, convulsive seizures and the Buccolam formulation was not considered an appropriate choice.
- Epistatus – midazolam maleate is now licensed as a 10mg/ml 1ml oral syringe licensed only for use in children and adolescents aged 10 to less than 18 years of age. It is available in packs of one syringe whereas Buccolam is available in packs of four doses.
- Lincolnshire formulary advice is that due to serious concerns regarding the risk of confusion between different midazolam formulations all liquid midazolam preparations should be prescribed by brand. However scrutiny of prescribing data shows that the majority of prescribing is generic.

Cost comparison table

product	strength	Pack size	Cost (£)
Epistatus (Midazolam maleate)	**10mg/ml**	**1ml syringe)**	**£45.76 Cost per dose £45.76**
Buccolam (Midazolam Hydrochloride)	**2.5mg/0.5ml (yellow label)**	**4 x 0.5ml**	**£82.00 Cost per dose £20.50**
Buccolam (Midazolam Hydrochloride)	**5mg/1ml (blue label)**	**4 x 1ml**	**£85.50 Cost per dose £21.38**
Buccolam (Midazolam Hydrochloride)	**7.5mg/1.5ml (purple label)**	**4 x 1.5ml**	**£89.00 Cost per dose £22.25**

Buccolam (Midazolam Hydrochloride)	**10mg/2ml (orange label)**	**4 x 2ml**	**£91.50 Cost per dose £22.87**

- Cost per dose Epistatus is more expensive than the equivalent does of Buccolam. However it is available in half the volume , so could be a more appropriate choice for some patients.
- Midazolam oral solution is not included within the Drug tariff list of approved specials and imported unlicensed medicines which means that there is no agreed fixed price for the product and the price charged will vary depending on where the product has been sourced.
- Taken from recent ePACT data the cost of Midazolam liquid special 50mg/5ml varies from £60.00 to £230.65 for 5ml.
- PACEF approved Epistatus 10mg in 1ml oromucosal solution as an option for the treatment of prolonged seizures both within its licensed indications for use in children and adolescents aged 10 to less than 18 years of age and also unlicensed for the for the treatment of prolonged seizures in adults. Classed as AMBER 2.
- All clinicians should be reminded that all buccal midazolam should be prescribed by brand. To further minimise risk doses should always be prescribed in both mg and mL to minimize the risk of wrong dose errors.
- There are currently no buccal midazolam preparations which are licensed in those age over 18 years. However following the MHRA guidance on the use of unlicensed medicines using a licensed medicine "off label" for an unlicensed indication is preferable than using an unlicensed product and therefore both Buccolam & Epistatus oral solutions do provide a safer option for adults rather than a totally unlicensed product.

Rapid Drug Assessment Salofalk brand of mesalazine foam enemas

Following discontinuation of the Asacol brand of mesalazine, there was a need to review alternative mesalazine foam enemas.

- The Salofalk brand of mesalazine foam enemas are licensed for the treatment of active, mild ulcerative colitis of the sigmoid colon and rectum. It is intended to treat an acute episode and usually treatment would not be expected to extend beyond a 4-6 week period.
- Salofalk costs £30.17 for 14 doses compared to the previous cost of Asacol enemas which were £26.72.
- PACEF approved the Salofalk brand of mesalazine foam enema as a replacement, classing it as AMBER 2.

Review of PACEF decision Roflumilast

NICE TA 461 recommending the use of Roflumilast for the treatment of chronic obstructive pulmonary disease was published on 26th July 2017. The recommendations from the NICE TA were subsequently reviewed by PACEF and roflumilast was designated as RED – hospital only for the management of this condition.
Respiratory consultants from United Lincolnshire Hospital Trust (ULHT) have requested that this decision is reviewed, citing that the treatment would be appropriate for prescribing in primary care following specialist initiation. PACEF approved the request re-designating Roflumilast as an AMBER drug.

NICE TA 461 recommendations are:
1.1 Roflumilast, as an add-on to bronchodilator therapy, is recommended as an option for treating severe chronic obstructive pulmonary disease in adults with chronic bronchitis, only if:

- the disease is severe, defined as a forced expiratory volume in 1 second (FEV1) after a bronchodilator of less than 50% of predicted normal, and
- the person has had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid.

1.2 Treatment with roflumilast should be started by a specialist in respiratory medicine.

- Roflumilast (Daxas, AstraZeneca) is an orally administered long-acting selective phosphodiesterase-4 enzyme inhibitor. It is licensed for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.
- The recommended dose is 500 micrograms (one tablet) roflumilast once daily. Roflumilast may need to be taken for several weeks to achieve its effect.
- Roflumilast is not considered a high cost treatment with a month's treatment costing £37.71 for 30 days supply.
- The TA stipulates initiation of treatment should be by a specialist in respiratory medicine, but there is no reference to continued prescribing and supply remaining with the specialist service.
- There is no specific requirement for monitoring associated with the therapy except for general advice to monitor a patient's weight as a common adverse effect reported with the therapy is decreased appetite, diarrhoea, headache, insomnia, nausea, weight loss.
- ULHT based respiratory consultants will recommend initiation of treatment by GPs and then will review in 3-6 months to decide if we are to continue it long term.

MEDICINES AND HEALTHCARE REGULATORY AGENCY (MHRA): DRUG SAFETY UPDATE (October 2017)

Methylprednisolone injectable medicine containing lactose (Solu-Medrone 40mg): do not use in patients with cow's milk allergy.

Solu-Medrone may contain trace amounts of milk proteins. Do not use in patients with a known or suspected milk allergy to cow's milk.

The MHRA have issued the following advice to healthcare professionals.

- Solu-Medrone 40mg uses lactose produced from cow's milk as an excipient and may contain trace amounts of milk proteins; other strengths of Solu-Medrone do not contain lactose.
- Serious allergic reactions have been reported in patients allergic to cow's milk proteins.
- Do not use in injectable methylprednisolone medicines that contain lactose in patients with a known or suspected allergy to cow's milk.
- If a patient's symptoms worsen or any new allergic symptoms occur, allergic reaction to cow's milk proteins should be suspected, stop administration of the product and treat the patient's condition accordingly.

Gabapentin (Neurontin): risk of severe respiratory depression.

Gabapentin has been associated with a rare risk of respiratory depression even without concomitant opioid medicines. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of nervous system (CNS) depressants and elderly people might be of higher risk of experiencing respiratory depression. Dose adjustments might be necessary in these patients.

The MHRA has issued the following advice for health care professionals:

- Be aware of the risk of CNS depression, including severe respiratory depression, with gabapentin.
- Consider whether dose adjustments might be necessary in patients at higher risk of respiratory depression.
- Report any suspected adverse reactions on a yellow card.

Isotretinoin (Roaccutane):rare reports of erectile dysfunction and decreased libio

Cases of sexual dysfunction, predominately erectile dysfunction and decreased libido, have been reported rarely in patients taking oral isotretinoin, indicated for severe acne.

Isotretinoin is currently included on the Lincolnshire Joint Formulary as a RED drug with the responsibility of prescribing and supply for this product being retained by specialist hospital based dermatology services.

The MHRA has issued the following advice for health care professionals:

- Be aware of reports of sexual side effects, in patients taking oral isotretinoin, indicated for severe acne.
- The exact incidences of these adverse reactions are unknown but considering the number of patients in the UK taking the medicine, reports are understood to be rare.
- Report any suspected adverse reactions on a yellow card.

Clozapine: reminder of potentially fatal risk of intestinal obstruction, faecal impactation and paralytic ileus.

If constipation occurs during treatment with clozapine (Clozaril, Denzapine, Zaponex) it is vital that it is recognised and actively treated.

Clozapine is included as a RED drug on the Lincolnshire formulary. All prescribing, supply and monitoring associated with this therapy is the responsibility of specialist mental health services provided by the Lincolnshire Partnership Foundation Trust (LPFT)

The MHRA has issued the following advice for health care professionals:

- The antipsychotic drug clozapine has been associated with varying degrees of impairment of intestinal peristalsis; this effect can range from constipation, which is very common, to very rare intestinal obstruction, faecal impaction and paralytic ileus.
- Exercise care in patients currently receiving other drugs known to cause constipation (especially those with anticholinergic properties, patients with a history of colonic disease or lower abdominal surgery and in patients aged 60 years or older.
- Clozapine is contraindicated in those with paralytic ileus
- Advise patients to report constipation immediately
- Actively treat any constipation that occurs.

NICE Update

NICE Technology Appraisal	Guidance	PACEF recommendation
TA 471 Eluxadoline for treating irritable bowel syndrome with diarrhoea	Eluxadoline is recommended as an option for treating irritable bowel syndrome with diarrhoea in adults only if: • the condition has not responded to other pharmacological treatments (for example, antimotility agents, antispasmodics, tricyclic antidepressants) or • pharmacological treatments are contraindicated or not tolerated, and • it is started in secondary care. Eluxadoline treatment should be reviewed at 4 weeks and stopped if there is inadequate relief of the symptoms of irritable bowel syndrome with diarrhoea.	Designated as AMBER 2 appropriate for prescribing in primary care following initiation by secondary care. Secondary care services will also be responsible for ensuring patients are assessed for initial response and treatment only continued if adequate relief obtained.
NICE TA 480 Tofacitinib for moderate to severe rheumatoid arthritis	Tofacitinib, either with methotrexate, or as monotherapy, is recommended as an option for treating active rheumatoid arthritis in adults if certain criteria are met.	Designated RED and approved for use through the Lincolnshire Joint Formulary for this indication.
TA 483 Nivolumab for previously treated squamous non-small-cell lung cancer	Nivolumab is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic squamous non-small-cell lung cancer in adults after chemotherapy, only if: •nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and •the conditions in the managed access agreement are followed	Designated RED and approved for use through the Lincolnshire Joint Formulary for this indication
TA 484 Nivolumab for previously treated non-squamous non-small-cell lung cancer	Nivolumab is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic non-squamous non-small-cell lung cancer in adults after chemotherapy, only if: •their tumours are PD-L1 positive and •nivolumab is stopped at 2 years of uninterrupted treatment, or earlier in the event of disease progression, and •the conditions in the managed access agreement are followed.	Designated RED and approved for use through the Lincolnshire Joint Formulary for this indication
NICE TA 485 Sarilumab for moderate to severe rheumatoid arthritis	Sarilumab, either with methotrexate, or as monotherapy, is recommended as an option for treating active rheumatoid arthritis in adults if certain criteria are met.	Designated RED and approved for use through the Lincolnshire Joint Formulary for this

		indication
TA 486 Aflibercept for treating choroidal neovascularisation	Aflibercept is recommended, within its marketing authorisation, as an option for treating visual impairment because of myopic choroidal neovascularisation in adults, only if the company provides aflibercept with the discount agreed in the patient access scheme	Aflibercept approved as a RED drug to be used in line with recommendations. NICE have stated that ranibizumab is also a treatment option for the same condition. NICE state that the least costly drug should be used taking into account administration costs, dose and cost of the drugs.

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