Arden and Greater East Midlands Commissioning Support Unit

Arden and 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 9; Number 4 **March 2015**

What's new this month?

- **In accordance with the new NICE Clinical Guideline on the treatment of dyspepsia and gastro-oesophageal reflux disease, guidance is offered on the use of proton pump inhibitors (PPIs) in the treatment of uninvestigated dyspepsia, functional dyspepsia, GORD, severe oesophagitis and peptic ulcer disease (PUD). Guidance on *Helicobacter pylori* eradication is also updated (see page 3).**
- **Principles for the prescribing of PPI gastroprotection for those at risk of gastro-intestinal complications on non-steroidal anti-inflammatory drugs (NSAIDs) are defined. Those particularly at risk from an unopposed NSAID include: (1) those over 65; (2) those with a history of PUD or serious GI complications; (3) those taking other medicines that increase the risk of GI side effects; and (4) those with serious co-morbidity (e.g. cardiovascular disease, diabetes, renal or hepatic impairment). Appropriate doses of PPIs for gastroprotection are defined (see page 8).**
- **Two new treatments for chronic hepatitis C are assessed and approved for use: simeprevir 150mg capsules (*Olysio*) and sofosbuvir 400mg tablets (*Sovaldi*). Both are designated RED (see page 8).**
- **Following the completion of a European wide review on the risks of abnormal pregnancy associated with valproate therapy, new information and safety warnings have been issued (see page 14).**

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longer available without prescription; Aceclofenac (Preservex)- updated cardiovascular advice

SUMMARY OF PACEF DECISIONS: *FEBRUARY 2015 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Aceclofenac 100mg tablets (generic/ *Preservex*) (Almirall)	For the treatment of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*.
Idelalisib 100mg and 150mg tablets (*Zydelig*) (GileadSciences)	For use in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or *TP53* mutation in patients unsuitable for chemo-immunotherapy.	RED Approved for use through the National Cancer Drugs Fund for this indication. Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Idelalisib 100mg and 150mg tablets (*Zydelig)* (Gilead Sciences)	For use as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Isotretinoin 5mg, 10mg and 20mg capsules (*Roaccutane*, *Rizuderm*) (Roche)	For the systemic treatment of nodulo-cystic and conglobate acne, severe acne, scarring, acne which has not responded to an adequate course of systemic antibacterial or acne associated with psychological problems. For women who develop acne in the third or fourth decades of life.	**RED** Already approved for use in the *Lincolnshire Joint Formulary*.
Ivabradine 5mg and 7.5mg tablets *(Procoralan)* (Servier)	For the treatment of angina in patients in normal sinus rhythm. For mild to severe chronic heart failure.	AMBER without shared care. Already approved for use in the *Lincolnshire Joint Formulary*.
Montelukast 10mg tablets (generic)	For use as an add-on therapy in mild to moderate asthma inadequately controlled by inhaled corticosteroids and short acting beta 2 agonists. For exercise induced bronchoconstriction. For the symptomatic relief of concomitant seasonal allergic rhinitis in asthma patients.	GREEN First line leukotriene antagonist of choice. Included in the *Lincolnshire Joint Formulary* for these indications.
Simeprevir 150mg capsules *(Olysio)* (Janssen-Cilag)	For use in combination with other antivirals in the treatment of chronic hepatitis C genotype 1 or 4.	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. All of the 12 week course should be provided from secondary or tertiary care.
Sofosbuvir 400mg tablets (*Sovaldi)* (Gilead)	For use with ribavirin (with or without peginterferon alfa) for the treatment of chronic hepatitis C.	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. All of the 12 week course should be provided from secondary or tertiary care.
Ustekinumab 90mg/ml injection (*Stelara*) (Janssen)	For the treatment of moderate to severe plaque psoriasis and active psoriatic arthritis in adults.	RED Included in the *Lincolnshire Joint Formulary* for these indications.
Zafirlukast 20mg tablets (*Accolate*) (AstraZeneca)	For the treatment of asthma	AMBER without shared care. Second line after montelukast. Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. Specialist initiation only.

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 PACEF website (http://lincolnshire-

pacef.nhs.uk); follow the commissioning link to PACEF. Electronic copies 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.

Google searching can be a quick and effective way of finding back numbers of the *PACE Bulletin* relevant to a specific topic of interest. Searchers are advised to use the official version of the *Bulletin* available from the PACEF website rather than depend on a potentially unreliable draft or variant found through Google or an alternative search engine.
The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

NICE CLINICAL GUIDELINE 184 : *DYSPEPSIA AND GASTRO-OESOPHAGEAL REFLUX DISEASE* (SEPTEMBER 2014)

Common elements of care

- Offer simple lifestyle advice (e.g. healthy eating, weight reduction, smoking cessation etc).
- Avoid known precipitants associated with dyspepsia (e.g. smoking, alcohol, coffee, chocolate, fatty foods, being overweight). Raising the head of the bed and having a main meal well before going to bed may help some people.
- Encourage people who need long-term management of dyspepsia to reduce their use of prescribed medication stepwise: (1) by using the lowest effective dose or (2) by trying as needed use when appropriate or (3) by returning to self-treatment with antacid and/or alginate therapy.
- Community pharmacy provides an important function in terms of offering initial and ongoing help for people with symptoms of dyspepsia (including advice on lifestyle change, over-the counter medication, help with prescribed medicines etc)

Referral guidance for endoscopy

- For people presenting with dyspepsia together with significant acute gastro-intestinal (GI) bleeding, refer immediately (on the same day) to a specialist.
- Review medication for possible causes of dyspepsia (e.g. calcium channel blockers, nitrates, theophyllines, bisphosphonates, corticosteroids, NSAIDs). In people needing referral, suspend NSAID use.

Summary Table of NICE Recommended Interventions (for definition of low dose, full dose and high dose proton pump inhibitor (PPI) therapy see below)

	Intervention
Uninvestigated dyspepsia	Offer *H.pylori* 'test and treat' to people with dyspepsia. Offer ***full-dose*** PPI therapy for ***4 weeks***. First Line: Either generic omeprazole 40mg capsules once daily or generic lansoprazole 30mg capsules once daily Second Line: Generic pantoprazole 40mg tablets once daily If symptoms return, step down the PPI to the lowest dose needed to control symptoms. Discuss using the PPI 'as needed' enabling people to manage their own symptoms

	If there is an inadequate response to a PPI, offer an H2 receptor antagonist (e.g. ranitidine).
Functional dyspepsia (non-ulcer dyspepsia)	*H.pylori* positive Manage endoscopically determined functional dyspepsia using initial treatment for *H.pylori* , if present, followed by symptomatic management and periodic monitoring. Offer eradication therapy to people testing positive for *H.pylori*. Do not routinely offer re-testing after eradication. *H.pylori* negative If *H.pylori* has been excluded and symptoms persist, offer either a ***low-dose*** PPI or an H2RA for ***4 weeks.*** First Line: Either generic omeprazole 20mg capsules once daily or generic lansoprazole 15mg capsules once daily or generic ranitidine tablets 150mg twice daily or 300mg at night. Second Line: Generic pantoprazole 20mg tablets once daily. If symptoms continue or recur after initial treatment, offer a PPI or H2RA at the lowest possible dose to control symptoms. Discuss 'as needed' therapy. Avoid long-term, frequent dose, continuous antacid therapy as it only provides symptomatic relief in the short-term rather than prevention.
Gastro-oesophageal reflux disease (GORD)	Offer ***full-dose*** PPI for ***4 to 8 weeks***. First Line: Either generic omeprazole 40mg capsules once daily or generic lansoprazole 30mg capsules once daily Second Line: Generic pantoprazole 40mg tablets once daily. If symptoms return, step down the PPI to the lowest dose needed to control symptoms. Discuss using the PPI 'as needed' enabling people to manage their own symptoms If there is an inadequate response to a PPI, offer an H2 receptor antagonist (e.g. ranitidine).
Severe oesophagitis	Offer ***full-dose*** PPI for ***8 weeks.*** First Line: Either generic omeprazole 40mg capsules once daily or generic lansoprazole 30mg capsules once daily

	Second Line: Generic pantoprazole 40mg tablets once daily. If initial treatment for healing severe oesophagitis fails, consider a ***high- dose*** of the initial PPI, switching to another full dose PPI or switching to another high-dose PPI. First Line: Generic omeprazole 40mg capsules twice daily (licensed) or Generic esomeprazole 40mg capsules or tablets twice daily (licensed). Second Line: Generic lansoprazole 30mg capsules twice daily (unlicensed) Generic pantoprazole 40mg tablets twice daily (unlicensed). Offer a full-dose PPI long-term as maintenance treatment for people with severe oesophagitis. Preferred products as detailed above.
Peptic ulcer disease (PUD)	*H.pylori* positive Nearly all duodenal ulcers and most gastric ulcers not associated with NSAIDs are caused by *H.pylori*. Offer *H pylori* eradication therapy to people who have tested positive for *H pylori* who have PUD. For people using NSAIDs with diagnosed PUD, stop the use of NSAIDs where possible. Offer ***full-dose*** PPI or H_2RA therapy for ***8 weeks*** and, if *H.pylori* is present, subsequently offer eradication therapy. First Line: Either generic omeprazole 40mg capsules once daily or generic lansoprazole 30mg capsules once daily or generic ranitidine tablets 150mg twice daily or 300mg at night. Second Line: Generic pantoprazole 40mg tablets once daily. Offer people with gastric ulcer and *H pylori* repeat endoscopy 6 to 8 weeks after beginning treatment, depending on the size of the lesion. Offer people with PUD (gastric or duodenal) and *H.pylori*, retesting 6 to 8 weeks after beginning treatment, depending on the size of the lesion. *H.pylori* negative Offer ***full-dose*** PPI or H2RA therapy for ***4 to 8 weeks*** to people who have tested negative for *H.pylori* who are not taking NSAIDs.

	First Line: Either generic omeprazole 40mg capsules once daily or generic lansoprazole 30mg capsules once daily or generic ranitidine tablets 150mg twice daily or 300mg at night. Second Line: Generic pantoprazole 40mg tablets once daily. For people continuing to take NSAIDs after a peptic ulcer has healed, discuss the potential harm from NSAID treatment. Review the need for NSAID use at least every 6 months and offer a trial of limited 'as needed' NSAID therapy. Consider reducing the dose, substituting an NSAID with paracetamol or using an alternative analgesoic or low-dose ibuprofen (1.2g daily). In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, offer gastric protection or consider substitution with a cyclooxygenase (COX)-2-selective NSAID.
Reviewing patient care	The object should be to reduce the dose and duration of long-term PPI therapy and to increase patient responsibility for self-care 'as needed'. Offer people who need long-term management of dyspepsia symptoms an annual review of their condition and encourage them to try stepping down or stopping treatment. Where appropriate advise people to return to self-treatment 'as needed' with antacid or antacid/alginate therapy (either prescribed or purchased over the counter). Review medication for possible causes of dyspepsia (e.g. calcium channel blockers, nitrates, theophyllines, bisphosphonates, corticosteroids, NSAIDs).

NICE defined PPI doses

PPI	Full/standard dose	Low dose (on-demand dose)	High/double dose
Esomeprazole	40mg once daily	20mg once daily	40mg twice a day
Lansoprazole	30mg once daily	15mg once daily	30mg twice a day (off-label)
Omeprazole	40mg once daily	20mg once daily	40mg twice a day
Pantoprazole	40mg once daily	20mg once daily	40mg twice a day (off-label)
Rabeprazole	20mg once daily	10mg once daily	20mg twice a day

			(off-label)

***Helicobacter pylori* testing and eradication**

- Test for *H.pylori* using a carbon-13 urea breath test or a stool antigen test or laboratory-based serology where its performance has been locally validated.
- Perform re-testing for H.pylori using a carbon-13 urea breath test.
- Do not use office-based serological tests for *H.pylori* because of their inadequate performance [2014].

Eradication

First Line treatment

- Offer people who test positive for H.pylori a 7 day twice daily course of treatment with: (1) a **PPI** and (2) **amoxicillin** and (3) either **clarithromycin** or **metronidazole**. Choose the treatment regime with the lowest acquisition cost and take into account previous exposure to clarithromycin or metronidazole.

PACEF Recommendation:
The lowest cost regimens are either:
Lansoprazole 30mg twice daily plus amoxicillin 1g twice daily plus metronidazole 400mg twice daily for 7 days (£3.97) or:
Omeprazole 20mg twice daily plus amoxicillin 500mg three times a day plus metronidazole 400mg three times a day for 7 days (£3.64).

- Offer people who are allergic to penicillin a 7 day twice daily course of treatment with: (1) a **PPI** and (2) **clarithromycin** and (3) **metronidazole**.

PACEF Recommendation:
The lowest cost regimens are either:
Lansoprazole 30mg twice daily plus clarithromycin 250mg twice daily plus metronidazole 400mg twice daily for 7 days (£3.36) or:
Omeprazole 20mg twice daily plus clarithromycin 250mg twice daily plus metronidazole 400mg twice daily for 7 days (£3.14) or:
Pantoprazole 40mg twice daily plus clarithromycin 250mg twice daily plus metronidazole 400mg twice daily for 7 days (£3.31).

- Offer people who are allergic to penicillin and who have had previous exposure to clarithromycin a 7 day, twice daily course of treatment with: (1) a **PPI** and (2) **bismuth** and **(3) metronidazole** and (4) **tetracycline** [2014].

PACEF Comment:
The regimen recommended for eradication failure in the *BNF* is a two week course of a PPI (e.g. omeprazole 20mg twice daily) plus tripotassium dicitratobismuthate 120mg four times daily plus tetracycline 500mg four times daily plus metronidazole 400 to 500mg three times daily. Alternatively the patient can be referred for endoscopy and treatment based on the results of culture and sensitivity testing.

- Discuss the importance of treatment adherence with the person.

Second-line treatment

- Offer people who still have symptoms after first-line eradication treatment a 7 day, twice daily course of treatment with: (1) a PPI and (2) amoxicillin and (3)either clarithromycin or metronidazole (whichever was not used first line).

- Offer people who have had previous exposure to clarithromycin and metronidazole a 7 day, twice daily course of treatment with (1) a PPI and (2) amoxicillin and (3) a quinolone or tetracycline (whichever has the lowest acquisition cost).
- Offer people who are allergic to penicillin (and who have not had previous exposure to a quinolone) a 7 day twice daily course of treatment with (1) a PPI and (2) metronidazole and (3) levofloxacin
- Offer people who are allergic to penicillin and who have had previous exposure to a quinolone (1) a PPI and (2) bismuth and (3) metronidazole and (4) tetracycline.
- Seek advice from a gastroenterologist if eradication of *H.pylori* is not successful with second-line treatment.

NSAID-associated ulcers

Patients at high risk of developing gastro-intestinal complications with a non-steroidal anti-inflammatory drug (NSAID) include:

- those over 65 years.
- those with a history of PUD or serious GI complications.
- those taking other medicines that increase the risk of GI side effects (e.g. calcium channel blockers, nitrates, theophyllines, bisphosphonates, corticosteroids, aspirin etc).
- those with serious co-morbidity (e.g. cardiovascular disease, diabetes, renal or hepatic impairment).

PACEF Recommendation:
Where an NSAID is considered unavoidable, concurrent PPI prophylaxis should be considered in the doses tabulated below.

Recommended PPI doses for prophylaxis of gastroduodenal complications in patients who require continuous NSAID treatment

PPI	Dose
Esomeprazole	20mg once daily
Lansoprazole	15mg to 30mg once daily
Omeprazole	20mg once daily
Pantoprazole	20mg once daily

NEW TREATMENTS FOR CHRONIC HEPATITIS C

Infection with the hepatitis C virus (HCV) is a significant global problem with wide-ranging personal, societal and economic impact. HCV consists of six genotype subgroups, of which genotype 1 is the most common in the UK accounting for 40-50% of those infected. Up to 85% of patients infected with the virus go on to develop chronic infection, putting them at progressive risk of serious sequelae, including liver fibrosis, cirrhosis, hepatocellular carcinoma and death. In addition to the morbidity and mortality directly associated with liver-related disease, chronic HCV infection is also associated with increased morbidity and mortality from extrahepatic diseases, including circulatory diseases, renal diseases, autoimmune disorders, cutaneous manifestations and non-liver cancers that occur in a significant proportion of patients. CHC also has significant effects on a patient's quality of life and ability to work, and results in high medical costs which rise in line with increasing disease severity.

A combination of peginterferon alfa and ribavirin (PR) is recommended by NICE as a treatment for adults with chronic hepatitis C. NICE guidance for PR therapy applies to all six

genotypes. However, there is a high unmet need across all genotypes in the treatment of those with cirrhosis given the incremental risk of adverse events with peginterferon alfa (neutropenia, weight loss and mental health problems) plus ribavirin (anaemia and thrombocytopenia) plus a first generation protease inhibitor (PI) such as telaprevir or boceprevir.

In cirrhotic patients, although triple therapy with a PI improves treatment response, toxicity increases and discontinuation rates increase when a PI is added to peginterferon plus ribavirin compared to peginterferon plus ribavirin alone. Further concerns have been raised by a recent study of telaprevir and boceprevir in cirrhotic patients, which reported an increase in the incidence of serious adverse events and difficulties managing severe cytopenia.

NEW DRUG ASSESSMENT: *SIMEPREVIR 150MG CAPSULES (OLYSIO)*

Simeprevir 150mg capsules (*Olysio*) hold a marketing authorisation, in combination with other medicinal products, for the treatment of genotype 1 and 4 chronic hepatitis C (HCV) in adult patients with compensated liver disease (including cirrhosis).

European Association on the Study of the Liver (EASL) *Recommendations on treatment of hepatitis C* (2014) recommend the use of simeprevir as the first choice protease inhibitor in treatment of genotypes 1 and 4 in combination with pegylated interferon and ribavarin or sofosbuvir. Typical combinations as detailed in the Summary of Product Characteristics are tabulated below:

Table 1: Recommended co-administered medicinal product(s) and treatment duration for simeprevir combination therapy

Patient population	**Treatment**	**Duration**
Treatment-naïve and prior relapse patients with HCV genotype 1 or 4		
with or without cirrhosis, who are not co-infected with HIV without cirrhosis, who are co-infected with HIV	simeprevir + peginterferon alfa + ribavirin	24 weeks Treatment with simeprevir must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 12 weeks of peginterferon alfa and ribavirin.
with cirrhosis, who are co-infected with HIV	simeprevir + peginterferon alfa + ribavirin	48 weeks Treatment with simeprevir must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa and ribavirin.
Prior non-responder patients (including partial and null responders) with HCV genotype 1 or 4, with or without cirrhosis, with or without HIV co-infection	simeprevir + peginterferon alfa + ribavirin	48 weeks Treatment with simeprevir must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa and ribavirin.
Treatment-naïve, prior relapse[1] and prior non-responder[4] patients	Simeprevir + sofosbuvir (+/- ribavirin)	12 weeks

(including partial and null responders) with HCV genotype 1 or 4, with or without cirrhosis, with or without HIV co-infection		

NICE Technology Appraisal 331, *Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C (February 2015)*

NICE have recently published guidance that approves simeprevir in combination with peginterferon alfa and ribavirin within marketing authorisation as an option for treating genotype 1 and 4 chronic hepatitis C in adults.

PACEF Recommendation:
Following approval by United Lincolnshire Hospitals Drug and Therapeutics Committee and in response to NHS England Specialised Commissioning Policy and NICE guidance, simeprevir 150mg capsules (*Olysio*) are approved for use; designation RED and included within the *Lincolnshire Joint Formulary* for this indication. The usual dosage regime is one 150mg capsule once daily for 12 weeks. All of the 12 week course will be provided through secondary or tertiary care. Any approaches to GPs with requests to prescribe this treatment should be declined.

NEW DRUG ASSESSMENT: *SOFOSBUVIR 400MG TABLETS (SOVALDI)*

Sofosbuvir 400mg tablets (*Sovaldi*) is a nucleide prodrug, a direct acting antiviral, indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults. Studies have demonstrated the achievement of sustained viral response (SVR) in a substantial proportion of patients associated with a wide range of benefits, including decreased all-cause mortality and liver complications, improved health related quality of life and reduced healthcare utilisation. The current interferon based treatment regimens offer the prospect of a cure for some, but are not successful in a substantial proportion of patients. In addition, many patients are excluded from treatment due to contraindications or their inability or unwillingness to tolerate current therapies. Current therapy options for CHC are also associated with significant side effects, adverse drug interaction profiles and the potential for the development of treatment-resistant viral mutations leading to treatment failure.

The table below summarizes the range of treatment combinations available for the treatment of specific CHC genotypes:

Patient population	**Treatment**	**Duration**
Patients with genotype 1, 4, 5 or 6 CHC	Sofosbuvir + ribavirin + peginterferon alfa	12 weeks
	Sofosbuvir + ribavirin Only for use in patients ineligible or intolerant to peginterferon alfa.	24 weeks
Patients with genotype 2 CHC	Sofosbuvir + ribavirin	12 weeks
Patients with genotype 3 CHC	Sofosbuvir + ribavirin + peginterferon alfa	12 weeks
	Sofosbuvir + ribavirin	24 weeks
Patients with CHC awaiting liver transplantation	Sofosbuvir + ribavirin	Until liver transplantation

NICE Technology Appraisal 330: Sofosbuvir for treating chronic hepatitis C (February 2015)

NICE have recently published Technology Appraisal 330: *Sofosbuvir for treating chronic hepatitis C* (February 2015) and their guidance is tabulated below:

Genotype	Sofosbuvir in combination with peginterferon alfa and ribavirin	Sofosbuvir in combination with ribavirin
Adults with genotype 1 HCV	Recommended	Not recommended
Adults with genotype 2 HCV	Not licensed for this population	Treatment naïve, only recommended for those intolerant to or ineligible for interferon. Recommended for those who are treatment experienced.
Adults with genotype 3 HCV	Treatment naïve, only recommended for those with cirrhosis. Recommended for those who are treatment experienced.	Treatment naïve, only recommended for people with cirrhosis who are intolerant to or ineligible for interferon. For treatment experienced, only recommended for people with cirrhosis who are intolerant to or ineligible for interferon.
Adults with genotype 4, 5 or 6 HCV	Only recommended for those with cirrhosis.	Not recommended.

NICE define treatment naïve people as those who have not had treatment for chronic hepatitis C. Treatment experienced people are defined as those who have not responded adequately to interferon-based treatment.

PACEF Recommendation:

Following approval by United Lincolnshire Hospitals Drug and Therapeutics Committee and in response to NHS England Specialised Commissioning Policy and NICE TA330, sofosbuvir 400mg tablets (*Sovaldi*) are approved for use; designation RED and included within the *Lincolnshire Joint Formulary* for these indications (subject to NICE restrictions). The usual dosage regime is one 400mg tablet once daily for 12 weeks. All of the 12 week course will be provided through secondary care or tertiary care. Any approaches to GPs with requests to prescribe this treatment should be declined.

RAPID DRUG ASSESSMENT: *ZAFIRLUKAST 20MG TABLETS (ACCOLATE)*

Zafirlukast (*Accolate*) is a highly selective and potent oral peptide leukotriene antagonist licensed for the treatment of asthma. PACEF have previously evaluated the two leukotriene antagonists available in the UK and have approved montelukast as the preferred agent due to the availability of a lower cost generic. ULH Drug and Therapeutics Committee reviewed the comparative evidence between montelukast and zafirlukast in response to a consultant request for zafirlukast to be made available as a second line oral leukotriene antagonist for patients unresponsive or only partially responsive to montelukast.

Comparative data between montelukast and zafirlukast is scarce, although one study showed both drugs to offer statistically significant improvements in quality of life scores. There is no data available to support any contention that one of these agents is potentially superior to another.

A cost comparison reveals that zafirlukast is significantly more expensive than montelukast:

	Dose	Cost (28 days)
Montelukast 10mg tablets (generic)	10mg once daily in the evening	£2.20
Zafirlukast 20mg tablets (*Accolate*) (AstraZeneca)	20mg twice daily	£17.75

Montelukast is also licensed for a wider range of indications including both prophylaxis of asthma and the symptomatic relief of seasonal allergic rhinitis in patients with asthma

PACEF Recommendation;
Following this review, montelukast is confirmed as the leukotriene antagonist of choice. This is due to: (1) a lack of comparative evidence between montelukast and zafirlukast that confirms zafirlukast to be superior in any way; (2) montelukast being once daily compared to twice daily zafirlukast; (3) montelukast having a wider range of licensed indications; (4) montelukast being significantly lower in price than zafirlukast when prescribed generically. Prescribers are reminded that montelukast 10mg tablets are designated GREEN and already appear on the *Lincolnshire Joint Formulary* as the preferred oral leukotriene antagonist. Nonetheless, PACEF were in support of a specialist request for zafirlukast to be available as a second line agent for patients unresponsive or only partially responsive to montelukast. As a result of this zafirlukast 20mg tablets (*Accolate*) are designated AMBER without shared care and approved for use through the *Lincolnshire Joint Formulary* for second line use by specialist initiation only.

NICE TECHNOLOGY APPRAISAL 328: *IDELALISIB FOR TREATING FOLLICULAR LYMPHOMA THAT IS REFRACTORY TO TWO PRIOR TREATMENTS* (TERMINATED APPRAISAL) (DECEMBER 2014)

NICE were unable to make a recommendation about the use of idelalisib for the treatment of follicular lymphoma refractory to 2 prior lines of treatment because no evidence submission was received from the manufacturer, Gilead Sciences.

Idelalisib (*Zydelig*) is licensed for use as monotherapy for the treatment of adults with follicular lymphoma (FL) that is refractory to two prior lines of treatment. It is also licensed for use in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL).

Idelalisib is currently one of the drugs funded through the National Cancer Drugs Fund for the treatment of relapsed/ refractory CLL.

PACEF Recommendation:
In response to NICE TA 328, idelalisib 100mg and 150mg tablets (*Zydelig*) are designated RED-RED for the treatment of adults with follicular lymphoma (FL) refractory to two prior lines of treatment. The product is already available through the NCDF for the treatment of relapsed/refractory CLL and is designated RED and included in the *Lincolnshire Joint Formulary* for this indication.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (DECEMBER 2014)

IVABRADINE (*PROCORALAN*) IN THE SYMPTOMATIC TREATMENT OF ANGINA: RISK OF CARDIAC SIDE EFFECTS—NEW ADVICE TO MINIMISE RISK

The MHRA have issued further advice on the use of ivabradine (*Procoralan*) which is currently licensed for the treatment of angina and heart failure.

The SIGNIFY study was a large randomised placebo controlled trial involving 19,102 coronary artery disease patients without heart failure. Ivabradine treatment did not demonstrate a beneficial effect on the primary outcome of cardiovascular disease or non-fatal myocardial infarction. Further subgroup analysis showed a small, statistically significant improvement in both of these outcomes associated with ivabradine compared with placebo. There was also a higher incidence of bradycardia in the ivabradine group.
To minimise the risk of cardiovascular events and severe bradycardia associated with ivabradine, the MHRA have issued the following advice:

New advice for healthcare professionals:

- In the symptomatic treatment of patients with chronic stable angina, ivabradine should only be started if the patient's resting heart rate is above or equal to 70 beats per minute.
- Ivabradine should be discontinued if the symptoms of angina do not improve within 3 months.
- Do not prescribe ivabradine with other medicines that cause bradycardia, such as verapamil, diltiazem, or strong CYP3A4 inhibitors.
- Prior to treatment initiation or when considering titration, the heart rate should be monitored frequently, including serial heart rate measurements, ECG or ambulatory 24 hour monitoring.
- The risk of atrial fibrillation is increased in patients treated with ivabradine. Monitor patients regularly for the occurrence of atrial fibrillation. If atrial fibrillation develops during treatment, carefully reconsider whether the benefits of continuing ivabradine treatment outweigh the risks.
- Consider stopping ivabradine if there is no or only limited symptom improvement after 3 months

All prescribers are reminded that:

- Ivabradine is indicated to treat symptoms of chronic angina in patients unable to tolerate or with a contraindication to beta-blockers. It can also be used in combination with beta-blockers in patients for whom an optimal beta-blocker dose is not enough
- The recommended starting dose is 5 mg twice daily; do not exceed the maximum maintenance dose of 7.5 mg twice daily.
- Down-titrate the dose if resting heart rate decreases persistently below 50 beats per minute or if the patient experiences symptoms of bradycardia. The dose can be down-titrated to 2.5 mg twice daily if necessary
- Stop ivabradine treatment if the resting heart rate remains below 50 beats per minute or symptoms of bradycardia persist

ISOTRETINOIN (ROACCUTANE): REMINDER OF POSSIBLE RISK OF PSYCHIATRIC DISORDERS - WARN PATIENT AND FAMILY; MONITOR PATIENTS FOR SIGNS OF DEPRESSION

Isotretinoin (*Roaccutane*, *Rizuderm*) is licensed for the treatment of severe acne resistant to systemic antibacterials and topical therapy. There have been reports of psychiatric disorders in patients taking isotretinoin (e.g. depression, anxiety, and, rarely suicidal ideation and suicide). The MHRA have conducted a review and, although the results were inconclusive, it considered that there was sufficient evidence to support the current warnings in the summary of product characteristics.

The following advice has been issued to all health care professionals:

- Isotretinoin should only be prescribed by or under the supervision of a consultant dermatologist with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.
- Patients and their families should be warned that isotretinoin may cause psychiatric disorders such as depression, anxiety, and, in rare cases, suicidal thoughts.
- When prescribing isotretinoin to patients with a history of depression, the potential benefits should be balanced against the possible risk of psychiatric disorders.
- All patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Stopping isotretinoin may not be enough to alleviate symptoms and further psychiatric or psychological evaluation may be necessary.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: DRUG SAFETY UPDATE (JANUARY 2015)

MEDICINES RELATED TO VALPROATE: RISK OF ABNORMAL PREGNANCY OUTCOMES

Following the completion of a European wide review on the risks of abnormal pregnancy associated with valproate therapy, new information and safety warnings have been issued. Valproate products include: sodium valproate, valproic acid (e.g. *Epilim*) and valproate semisodium (e.g. *Depakote*).
A letter has been sent from the MHRA dated 21st January to all health care professionals informing them of the following issues:

- Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases).
- Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated.
- Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.
- The benefits of valproate treatment must be balanced against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.
- Healthcare professionals must ensure that all female patients are informed of and understand:
    - the risks associated with valproate during pregnancy.
    - the need to use effective contraception.
    - the need for regular review of treatment.

- the need to rapidly consult if planning a pregnancy or becoming pregnant.

Risk of abnormal pregnancy outcomes
Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines. Data suggest that when valproate is taken for epilepsy with other medicines, the risk of abnormal pregnancy outcomes is greater than when valproate is taken alone.

The risk of congenital malformations is approximately 10 % while studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking, and/or walking, have low intellectual abilities, poor language skills and memory problems. Intelligence quotient (IQ) measured in a study of 6 years old children with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD). Given these risks, valproate for the treatment of epilepsy or bipolar disorder should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated).

Treatment during pregnancy
If a woman with epilepsy or bipolar disorder who is treated with valproate plans a pregnancy or becomes pregnant, consideration should be given to alternative treatments.
If valproate treatment is continued during the pregnancy:

- the lowest effective dose should be used and the daily dose should be divided into several small doses to be taken throughout the day - the use of a prolonged release formulation may be preferable to other treatment forms.
- specialised prenatal monitoring should be initiated in order to monitor the development of the unborn, including the possible occurrence of neural tube defects and other malformations.
- folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies; however the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Reclassification of valproate
Valproate is now a black triangle medicine and is subject to additional monitoring. Any suspected side effects must be reported via the Yellow Card scheme (www.gov.uk/yellowcard).

Information resources
The MHRA have produced a guide for health care professionals and a valproate booklet for patients. Both of these can be accessed from the web address below.
https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes

PACEF Comment
All valproate products are currently classed as AMBER without shared care (i.e. approved for prescribing in primary care following initiation by or on the advice of a specialist).

USTEKINUMAB (*STELARA*): RISK OF EXFOLIATIVE DERMATITIS

Ustekinumab injection (*Stelara*) is licensed to treat moderate to severe plaque psoriasis and active psoriatic arthritis in adults for whom other non-biological systemic therapies have proved insufficiently effective. The MHRA have received reports of exfoliative dermatitis in patients being treated with ustekinumab for plaque psoriasis. Symptoms reported included widespread erythema, scaling, itching, and skin exfoliation. In some cases, skin exfoliation occurred without other symptoms of exfoliative dermatitis. In many cases, patients were hospitalised as a result of their symptoms.

When using ustekinumab to treat plaque psoriasis or active psoriatic arthritis:

- be alert for signs and symptoms of exfoliative dermatitis or erythrodermic psoriasis
- start appropriate treatment promptly if a patient develops widespread erythema and skin exfoliation
- stop ustekinumab treatment if you suspect exfoliative dermatitis caused by an adverse drug reaction to ustekinumab
- tell patients to report symptoms of exfoliative dermatitis or erythrodermic psoriasis (e.g. increased redness and shedding of skin over a larger area of the body) to their doctor promptly
- continue to report suspected adverse drug reactions to ustekinumab or any other medicines on a Yellow Card www.gov.uk/yellowcard

MYCOPHENOLATE MOFETIL (CELLCEPT) AND MYCOPHENOLIC ACID: RISK OF HYPOGAMMAGLOBULINAEMIA AND RISK OF BRONCHIECTASIS

Mycophenolate mofetil (brand leader: *CellCept*) is licensed in combination with ciclosporin and corticosteroids to prevent acute transplant rejection in patients receiving renal, cardiac, or hepatic transplants. It is also used off-label in other specialties, such as rheumatology, gastroenterology, respiratory medicine, and dermatology.

Hypogammaglobulinaemia

A review by European regulators concluded that mycophenolate mofetil in combination with other immunosuppressants can cause hypogammaglobulinaemia in adults and children, which can be associated with recurrent infections. Switching from mycophenolate mofetil to an alternative immunosuppressant resulted in serum immunoglobulin G (IgG) levels returning to normal in some cases.

Bronchiectasis

The review also concluded that mycophenolate mofetil in combination with other immunosuppressants can cause bronchiectasis in adults and children (sometimes years after starting mycophenolate mofetil treatment). The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect of MPA on the lungs. Patients who developed bronchiectasis usually presented with a persistent productive cough and, in some cases, recurrent upper or lower respiratory tract infections. The diagnosis was confirmed by high resolution computed tomography of the chest. In some of these cases, switching from mycophenolate mofetil to another immunosuppressant improved respiratory symptoms. Mycophenolate mofetil is also known to cause pulmonary fibrosis

When using mycophenolate mofetil or any other medicine containing mycophenolic acid (MPA) as its active ingredient:

- measure serum immunoglobulin levels if recurrent infections develop.

- in cases of sustained, clinically relevant hypogammaglobulinaemia, consider appropriate clinical action. Take into account the potent cytostatic effects of MPA on B-lymphocytes and T-lymphocytes.
- consider bronchiectasis or pulmonary fibrosis if patients develop persistent respiratory symptoms, such as cough and dyspnoea.
- continue to report suspected adverse drug reactions to mycophenolate mofetil, medicines containing MPA, or any other medicines on a Yellow Card www.gov.uk/yellowcard.

ORAL DICLOFENAC NO LONGER AVAILABLE WITHOUT PRESCRIPTION

When prescribing or dispensing diclofenac, consider that:

- oral diclofenac must not be sold without prescription.
- a recall has been issued for non-prescription diclofenac.
- the prescribing advice for diclofenac was updated in June 2013
- topical formulations of diclofenac (e.g. gel and cream) remain available for sale over the counter.

ACECLOFENAC (PRESERVEX): UPDATED CARDIOVASCULAR ADVICE IN LINE WITH DICLOFENAC AND COX-2 INHIBITORS

Aceclofenac (*Preservex*) is a non-steroidal anti-inflammatory drug (NSAID) licensed for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Aceclofenac has little pharmacological activity itself; its main mode of action is through its metabolites which include diclofenac and 4'-hydroxy diclofenac.
In June 2013 the MHRA issued new contraindications and warnings for diclofenac. This was after a review by European regulators concluded that the risk of arterial thrombotic events (myocardial infarction; stroke) with diclofenac is greater than with other non-selective NSAIDs and similar to the COX-2 inhibitors. There are limited data available regarding the arterial thrombotic effects of aceclofenac. The treatment advice for aceclofenac has been updated in line with diclofenac and COX-2 inhibitors. This was based on aceclofenac's structural similarity to diclofenac and its metabolism to diclofenac.

The MHRA have issued the following advice to health care professionals:

When using aceclofenac to relieve pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis:

- consider that aceclofenac is now contraindicated in patients with established:
    - ischaemic heart disease
    - peripheral arterial disease
    - cerebrovascular disease
    - congestive heart failure (New York Heart Association, NYHA, classification II-IV)
- switch patients with these conditions to an alternative treatment at their next routine appointment.
- only start aceclofenac treatment after careful consideration of any significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

PACEF Comment
Prescribers are reminded that aceclofenac 100mg tablets (generic/*Preservex*) are designated RED/RED and are not included in the *Lincolnshire Joint Formulary*.

Diclofenac remains a GREEN drug, but is only approved for use in patients for whom ibuprofen or naproxen are deemed to be insufficiently effective, poorly tolerated or inappropriate.

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