North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 30 June 2016
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Dr R Sofat	UCLH, Consultant Clinical Pharmacologist	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr C McGuinness	Patient Partner	
	Ms K Landeryou	Patient Partner	
	Mr T James	MEH, Chief Pharmacist	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr M Kelsey	WH, Chair DTC	
	Ms W Spicer	RFL, Chief Pharmacist	
	Ms H Taylor	WH, Chief Pharmacist	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Dr R Fox	RNOH, DTC Chair	
	Ms L Reeves	C&I, Chief Pharmacist	
In attendance:	Mr J Minshull	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Mr A Barron	NCL JFC, Support Pharmacist	
	Mr K Thakrar	UCLH, Formulary Pharmacist	
	Ms H Mehta	NMUH, Formulary Pharmacist	
	Mr E Hindle	MEH, Formulary Pharmacist	
	Ms A Fakoya	NEL CSU, Assistant Director Acute Services	
	Ms H Amer	UCLH, Clinical Pharmacology Registrar	
Apologies:	Dr V Thiagarasah	Enfield CCG, GP	
	Prof D Robinson	UCLH, Consultant in Respiratory Medicine	
	Prof L Smeeth	NCL JFC Vice-Chair	
	Mr I Man	WH, Interim Deputy Chief Pharmacist	
	Mr TF Chan	RFL, Deputy Chief Pharmacist	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr R Breckenridge	UCLH, DTC Chair	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Dr C Cooper	Islington CCG, GP	

3. Minutes of the last meeting

Section 6.1 was updated to state that nivolumab (compassionate use) for locally advanced or metastatic PD-L1 positive non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy will be used at both UCLH and RFL.

The minutes were otherwise accepted as an accurate record of the meeting.

4. Matters arising

Mr Atkinson (NMUH) will appeal the JFC decision about Collatamp for osteomyelitis. It has come to light since the application was discussed that other Trusts in NCL are using Collatamp or similar product. This was not identified before the meeting because some Pharmacies are not supplying this medical device.

5. Declarations of relevant conflicts of interest

No conflicts of interest relevant to the agenda were declared by the Committee members.

6. Local DTC recommendations / minutes

6.1 Approved by DTC

DTC site	Month	Drug	Indication	JFC outcome
C&I	Dec 15	Paliperiodone long-acting injection	Schizophrenia where long-acting injection (LAI) is indicated. Restricted to patients responding and tolerating risperidone who require dose above 50mg risperidone LAI or who are unable to comply/tolerate fortnightly injections	Added to NCL Joint Formulary
RFL	May 16	Tacrolimus modified release (Envarsus)	Immunosuppression in Liver and Renal Transplant Recipients where Advagraf would otherwise be indicated (Envarsus replaces Advagraf)	RFL only

6.2 Deferred approved by DTC

DTC site	Month	Drug	Indication	JFC outcome
WH	Apr-16	Lipegfilgrastim	Prevention of neutropenic sepsis for patients are allergic to filgrastim or do not want daily injections due to needle phobia or there are difficulties arranging district nursing visits and the patient is unable to self-administer	Deferred

Representatives from UCLH and RFL discussed that usage of pegylated G-CSFs was very low following availability of biosimilar filgrastim. Subsequently UCLH and RFL did not wish to use lipegfilgrastim. The WH minutes described exceptional use only (2 patients per annum). Ms H Taylor explained that lipegfilgrastim would be used by Whittington Community Services to avoid five separate visits to patients' homes to administer G-CSF. The Committee requested further clarification from WH as to the eligibility criteria for lipegfilgrastim and requested input from other Trusts and Community Providers in NCL as to their current management of these patients.

Action: Mr Barron to request clarification from WH and seek input from other Trusts and Community Providers

7. New Medicine Reviews

7.1 Naltrexone for cholestatic itch (Applicant: Dr D Sadigh, WH)

The Committee reviewed an application for the use of naltrexone in intractable pruritus due to cholestatic liver disease [off-label indication]. The application did not include pruritus due to cholestasis in pregnancy, therefore data on this were not considered as part of the discussion. Pruritic itch is associated with complex physiology and many potential mechanisms, hence the range of pharmacological treatments, including antihistamines and cholestyramine, an anion exchange resin.

Naltrexone, an opioid receptor antagonist, has been proposed as a treatment for pruritus following recognition that activation of mu-opioid receptors often resulted in analgesia together with pruritus. Rifampicin has also been proposed as a treatment for pruritus and is already used at RFL third line in this indication (after cholestryramine and ursodeoxycholic acid). The application from WH requests that naltrexone be made available as a second-line treatment for symptomatic relief of intractable pruritus when both non-sedating and sedating antihistamines and cholestyramine have failed, with use restricted to gastroenterology.

The Committee noted guidance from the American Association for the Study of Liver Diseases (AASLD) on the management of pruritus in Primary Biliary Cirrhosis, which advises that bile acid sequesterants (e.g. cholestyramine) should be used as first-line therapy. Alternatives for pruritus refractory to bile acid sequesterants include rifampicin (150 mg to 300 mg BD) and naltrexone (50 mg daily).

A systematic review and meta-analysis (Xander et al., 2013) was discussed by the Committee, as it provided evidence for efficacy and safety of different drugs in pruritus in palliative care, including non-malignant liver disease. The review identified two small, short-term RCTs comparing naltrexone to placebo in cholestatic pruritus (16 to 20 patients followed for up to 4 weeks). A third study considered the effect of naltrexone on uraemic pruritus compared to placebo. In pooled analysis, naltrexone statistically significantly reduced the visual analogue scale (VAS) score for pruritus when compared to placebo treatment (MD -2.1, 95% CI: -2.91 to -1.37, p<0.0001). None of these studies assessed secondary outcomes for quality of life, patient satisfaction or depression. Patients continued to take their standard medicines during these studies.

The review also compared rifampicin to placebo in cholestatic pruritus, concluding that rifampicin showed a statistically significant reduction compared to standard treatment in a pooled analysis of three, short-term cross-over studies. The reduction in VAS showed a MD -3.05 (95% CI: -3.34 to -2.76, p=0.003), in favour of rifampicin. All three of these studies were short-term, cross-over trials (7 to 28 days).

The Committee discussed that there are a range of adverse effects listed for naltrexone, with an adverse event associated withdrawal rate of 12/92 patients identified in the meta-analysis. Naltrexone is not suitable for any patient receiving endogenous opiate treatment, as it will cause opioid withdrawal. It was commented that rifampicin also has a long list of adverse effects and should be used cautiously in patients with impaired liver function. Dr Kelsey commented that using rifampicin for non-infectious indications poses a risk of encouraging resistance, therefore should not be used in preference to naltrexone.

In summary, the Committee agreed that for patients with cholestatic pruritus, both rifampicin and naltrexone may be effective treatments based on the findings of these small, short-term studies. Although the overall treatment effect with rifampicin was greater than that with naltrexone, the Committee was concerned about the adverse liver effects of rifampicin and wanted to support antimicrobial stewardship. Therefore naltrexone should be added onto the NCL Joint Formulary as a third-line agent, after cholestyramine and antihistamines, and before rifampicin.

Decision: Approved
Prescribing: GP Prescribing following initiation by Gastroenterologist or Hepatologist
Tariff status: In tariff
Funding: GP and Hospital prescribing budget
Fact sheet or shared care required: No
Audit required: No

7.2 Sirdupla™ inhaler alternative to Seretide Evohaler (Applicant: Mr C Daff, Barnet CCG)

The Committee discussed an application to include Sirdupla inhaler (a metered dose combination of fluticasone propionate and salmeterol) on the formulary to support a move away from prescribing Seretide® Evohalers. Moving from Seretide® Evohaler (which contains the same ingredients) to Sirdupla has the potential to save a significant amount of money for the local health economy. It was noted that this combination of drugs is not included in the NCL Adult Asthma Inhaler Choice Guidance, yet it represents a significant proportion of prescribing of inhaled corticosteroids and long-acting beta agonist.

Sirdupla inhalers are 25% less expensive than the equivalent strength of Seretide Evohaler, and remain less expensive even when a commercially sensitive rebate scheme for Seretide Evohaler is taken into account. Additionally, not all CCGs subscribe to pharmaceutical rebate schemes. Prescriptions for Seretide Evohaler and generic fluticasone/salmeterol inhalers (which are priced according to the Seretide Evohaler price in the Drug Tariff) account for approximately three quarters of prescriptions for this drug

combination, therefore recommending routine use of the cheaper alternative in NCL represents the opportunity for a significant saving. Seretide (and generic fluticasone/salmeterol) make up approximately 50% of all ICS/LABA combination inhalers prescribed nationally.

It was discussed whether the MHRA's decision to recognise Sirdupla as bioequivalent to Seretide® Evohaler gave the Committee confidence that patients would respond adequately to Sirdupla inhalers. The Committee acknowledged that the MHRA has considered two pharmacokinetic (PK) and two pharmacodynamic (PD) phase I studies comparing Sirdupla inhaler to Seretide Evohaler in healthy adults. The Committee agreed that it has no justification for not accepting the MHRA study requirements. The MHRA did not require the manufacturers of Sirdupla to conduct any new clinical studies as the regulatory agency treated this as a hybrid application, rather than a new drug application. It was noted that the Seretide Evohaler and Sirdupla inhaler are licensed for different age groups (Sirdupla inhalers are licensed only for use in adults). It was noted that neither Seretide Evohaler nor Sirdupla are licensed for use in patients with COPD, though it is known that many COPD patients currently receive Seretide Evohaler.

The following key concerns were addressed:

- Because the majority of prescriptions are written generically in NCL, it is likely that a significant number of patients are already being switched between Seretide and Sirdupla MDIs, therefore there is a need for organisations to take a proactive approach to ensure patients are supported to manage their new inhalers.
- Switching inhalers can be detrimental to asthma outcomes if the patient is not supported properly. The Committee endorsed the need for health care professionals involved in the patient's asthma care (including nurses, GPs and pharmacists) to explain to the patient the similarities and differences between the original inhaler and their new inhaler. Organisations should factor in the cost of additional patient contact when estimating savings achievable by using Sirdupla inhaler. The Patient Partners agreed that prompting an opportunity for a holistic review of asthma would be beneficial. Previous inhaler switches have involved a change in drug, therefore have been more difficult to manage.
- The Committee supported the RCP National Review of Asthma Deaths (NRAD) recommendation that a structured assessment of inhaler technique should be conducted and documented regularly as part of the annual asthma review in an attempt to prevent poor asthma control.
- CCGs should communicate with community pharmacists to remind them of their responsibility to check inhaler technique when a new device is dispensed. Community Pharmacies can also provide patients with additional support through either a targeted Medicines Use Review, or the New Medicine Scheme.
- Branded prescribing of combination inhalers would prevent inadvertent switching between Sirdupla and Seretide Evohaler.
- The Responsible Respiratory Prescribing Group were consulted on this application and advised the Committee that any patient contact with an appropriate HCP can be used as an opportunity to promote medication review, smoking cessation and flu jab. It may be identified during review that steroid dose reduction is appropriate, which would have financial (40 to 48% saving) and patient benefits by exposing them to less ICS.

In summary, the Committee considered that the MHRA process for determining bioequivalence of inhalers should be accepted, thus Sirdupla can be considered equivalent to Seretide Evohaler. It was agreed that patients should always be provided with information about their inhalers whenever a device or drug is changed; this is the responsibility of any health care professional involved in the prescribing or dispensing or inhaler medicines. Sirdupla inhalers should be included on the NCL Joint Formulary.

Decision: Approved
Prescribing: Primary and secondary care
Tariff status: In-tariff
Funding: GP prescribing budget
Fact sheet or shared care required: No
Audit required: No

7.3 Ribavirin for chronic hepatitis E (Applicant: Dr Westbrook, RFL)

The Committee discussed an application for ribavirin for the treatment of chronic hepatitis E in immunosuppressed individuals [off-label indication].

The Committee reviewed the evidence from a single case series of 59 patients with solid organ transplants were treated with ribavirin monotherapy; 34 patients (58%) had persistently positive serum HEV RNA tests for 6 months, 20 patients (34%) for 3 to 6 months and 5 patients (8%) for <3 months.

Ribavirin was initiated at a median dose of 600mg per day (range, 29 to 1200mg) for a median of 3 months (range, 1 to 18). Immunosuppressive medications were not discontinued during treatment and their doses were not changed substantially except in 5 patients who discontinued mycophenolic acid after undergoing a blood transfusion for severe anaemia.

Of the 59 patients who initiated ribavirin, 1 was lost to follow-up and 1 withdrew from treatment due to psychiatric reasons. At the end of therapy, 56 of the 57 patients had HEV clearance. Of the 56 patients, 10 patients had HEV recurrence, therefore the 6 month SVR was 78% (46 of 59 patients). At a median follow-up of 25 months, none of the 46 patients developed recurrence. Of the 10 patients who had a recurrence, 6 were retreated; 5 of these patients were retreated with longer courses and 4 of them had a SVR. No episodes of acute rejection were observed during ribavirin therapy. The key adverse effect of ribavirin was a significant reduction in haemoglobin (Hb) from a median of 13.4g/dL to 11.6g/dL despite an increase in erythropoietin use from 25% to 54%. Seven patients required a blood transfusion.

As chronic hepatitis E is a rare condition the prescribing and supply of ribavirin should be restricted to secondary care. Patient numbers are expected to be low (approximately 7 per annum across NCL) with a total annual budget impact of £1,740.

The Committee heard from Dr MacDonald that there are no commercial incentives to fund a randomised controlled trial of ribavirin in hepatitis E therefore the absence of such a trial is unlikely to resolve over time. The protocol developed at RFL provides a pragmatic approach to treatment; reduction of immunosuppression where possible and then treating with ribavirin if the viral load does not fall, or no change in serological status, or worsening of LFTs after 6 months. Serum hepatitis E RNA levels would be monitored at least monthly for 24 weeks, then liver function enzymes would be monitored to detect recurrence. Dr Kelsey was supportive of the application as there are no suitable alternatives for this rare condition.

In summary, the Committee agreed that ribavirin for chronic hepatitis E viraemia in immunosuppressed individuals should be included on the NCL Joint Formulary. The Committee agreed that the drug should be restricted to Hepatologists.

Decision: Approved
Prescribing: Secondary care prescribing only; restricted to Hepatologists
Tariff status: In tariff
Funding: Hospital budgets
Fact sheet or shared care required: N/A
Audit required: No

8. Guidelines

8.1 Antihyperglycaemic agents for Type 2 Diabetes

The Committee reviewed the guideline for antihyperglycaemic agents (including oral agents and glucagon-like peptide-1 receptor agonists [GLP-1RA]) which was developed jointly by the Camden IPU, Barnet IPU and JFC Support, and has undergone multiple rounds of consultation with stakeholders across NCL. Five issues were discussed.

Some clinicians requested the guideline includes concurrent use of sodium-glucose cotransporter-2 inhibitors (SGLT2-i) and GLP-1RAs which is not supported by randomised controlled trials. Dr Rosenthal agreed there was no evidence to support the combination and given the concerns of diabetic ketoacidosis (DKA) with the SGLT2-i drugs it was important to prescribe in line with the current evidence base.

Some stakeholders requested that all patients prescribed sulphonylureas should be encouraged to self-monitor blood glucose levels before driving or operating machinery, however other reviewers stated intensive monitoring was intrusive and unnecessary. The Committee heard from Dr Rosenthal that the risk of hypoglycaemia in patients with Type 2 diabetes is lower than for patients with Type 1 diabetes however the DVLA would revoke a patient's driving license if they have suffered one episode of severe hypoglycaemia. Severe hypoglycaemia occurs in patients who have lost their awareness of hypoglycaemia which is a consequence of recurrent episodes of mild hypoglycaemia. Patients should be informed when

initiating a sulphonylurea to report any hypoglycaemia to their GP who may recommend an alternative antihyperglycaemic agent or self-monitoring. The Committee noted that the guideline links to the Diabetes UK 'Safe Driving Tips' webpage however should also include a prompt for GPs to recommend that patients report any hypoglycaemia. Furthermore, routine testing for all patients taking a sulphonylurea is unnecessary.

The Committee discussed whether linagliptin for patients with poor renal function should be included in the guideline. It was noted that linagliptin had been rejected by JFC in 2014 for this indication, in part because sitagliptin (the first choice dipeptidyl peptidase 4 inhibitor [DPP4-i] in NCL) at reduced doses is licensed at every stage of renal impairment. The Committee heard that cardiovascular safety data for linagliptin is not expected until 2018 which is considered to be particularly relevant following the FDA warnings of an increased risk of heart failure with some drugs in the class (saxagliptin and alogliptin) which was not identified with sitagliptin. The Committee heard from Dr Rosenthal that in clinical practice, patients' eGFR may fluctuate between 25 to 40mL/min/1.72m^2 which is dependent on hydration. The dose of linagliptin is independent of renal function therefore has practical advantages in that the eGFR does not need to be monitored so frequently. The Committee heard that the alternative to linagliptin might be to use sitagliptin 25mg however this risks under-dosing some patients who have a true renal function >30mL/min/1.72m^2. GP members advised that having a single drug on the formulary within each class was advantageous. The Committee also heard sitagliptin was the first DPP4-i to come off patent, therefore unless there was a compelling reason to adopt linagliptin, sitagliptin should be the preferred agent.

The Committee discussed whether only one SGLT2-i drug should be recommended on the NCL Guideline noting that all SGLT2-i drugs have received positive endorsement by NICE (Technology Appraisal Guidance), therefore all will remain on formulary. The Committee heard that all three drugs in class were similar with minor differences in efficacy (HbA1c, BP and weight), post-marketing adverse effects and renal dosing. Empagliflozin is the only SGLT2-i with cardiovascular safety data however was also the last to market with the least amount of experience. The Committee heard from Dr Rosenthal that there was very little data at this point in time to differentiate between the three drugs, however in the future a front runner may emerge at which point the formulary choice should be revisited.

It was questioned whether the guideline should include Bydureon (exentatide MR) which is expected to be removed from the formulary 6 month after clinicians have familiarised themselves with dulaglutide (an alternative once-weekly GLP-1RA approved by JFC in January 2016). It was agreed that the guideline should be published without Bydureon as new patients were likely to be initiated on dulaglutide. The Committee confirmed that current patients prescribed Bydureon would not be switched to dulaglutide.

In camera, the Committee agreed with the clinical expert that the combination of SGLT2-i and GLP-1RA should not be included in the guideline, that the guideline should include advice for GPs to inform patients taking sulphonylureas to report any hypoglycaemia, and for all SGLT2-i drugs to be included on the formulary (without ranking). The Committee also discussed that there was no new data to support linagliptin use since the 2014 JFC decision. Furthermore sitagliptin had a wide therapeutic index therefore patients with renal function varying between 25 to 40mL/min/1.72m^2 were unlikely to experience complications. It was also noted that the American Diabetes Association recommended sitagliptin and linagliptin in patients with renal dysfunction. The Committee acknowledged dosing was simpler with linagliptin, however were not satisfied that this benefit would translate to improved patient outcomes nor that it outweighed the disadvantages in terms of unknown cardiovascular risk or the incremental cost when sitagliptin comes off patent. The Committee agreed to remove any reference to linagliptin from the guideline.

8.2 Insulin for Type 2 Diabetes

The Committee reviewed a guideline for insulin in adults with Type 2 Diabetes. The guideline had been reformatted and updated in line with outcomes from the initial JFC review in October 2015. It was confirmed that Toujeo (insulin glargine 300iU/mL) was not on the NCL Joint Formulary and the wording in section '7.5 Longer acting basal insulin analogues' should be updated to improve clarity.

8.3 Sacubitril valsartan position statement

The Committee heard from Dr Amer that a position statement had been developed to standardise the place in therapy of sacubitril valsartan and to promote safe initiation and up-titration by specialists, appropriate transition of care (from specialist to GP) and provide clear monitoring requirements.

The place in therapy is consistent with European Society of Cardiology guidance as third line treatment for patients with heart failure with reduced ejection fraction who remain symptomatic post ACEi+BB and

MRA. This positioning is at the same level of consideration as CRT and ICD devises. The consensus opinion of cardiologists in North London was that only patients with BNP levels consistent with the inclusion criteria of the PARADIGM-HF clinical study, and a recent echocardiogram should be offered sacubitril valsartan.

A GP Fact Sheet has been developed to support primary care colleagues. It was requested that advice is provided on how to manage a patient who develops renal impairment whilst taking sacubitril valsartan. It should also be made clearer that specialists should initiate and up-titrate the dose before transferring care to GPs.

9. Methotrexate for unlicensed indications

The Medicines Optimisation Network is working to create a single shared care document for methotrexate that could be used by all Trusts and CCGs for sharing care. This process has highlighted that methotrexate is used for various indications at different Trusts, some of which may be unlicensed. Methotrexate has often been on the formulary for these indications for many years and the specialists feel it is part of standard practice.

Camden CCG highlighted that when methotrexate had been discussed at their Medicines Management Committee meeting, GPs were uncomfortable taking on prescribing for unlicensed indications for which they didn't know there was a satisfactory evidence base.

The Committee acknowledged that for many indications, the published evidence may be limited, but could be backed up by professional opinion. From a governance perspective, the evidence base has already been approved by the local DTCs as satisfactory; therefore reappraising the evidence at the JFC would not be a good use of time.

It was agreed that the list of indications for which methotrexate is being used in NCL should be augmented with information on the grade of evidence. This should be represented at the JFC.

Action: Mr Thakrar to update the paper with information about the grade of evidence for each indication and bring to the July JFC.

10. NCL MON Meeting Minutes 10 March 2016

This item was included for information only. Any questions should be directed to Mr Sandhu.

11. JFC Work-plan

This item was included for information only. Any questions should be directed to Mr Minshull.

12. Next meeting

Thursday 28th July 2016, Room 6LM1, Stephenson House, 75 Hampstead Rd.

13. Any Other Business

Mr Sandhu requested that our statement on conflicts of interest in the minutes be updated to clarify that we are referring only to conflicts relevant to that meeting which haven't been declared previously. The Committee agreed.