North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 31 August 2017
Suite A (1st Floor), Maple House, 149 Tottenham Court Rd, W1T 7BN

Present:	Dr R Sofat	UCLH, DTC Chair	**(Chair)**
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Mr T Dean	Patient Partner	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms S Ceci	WH, Formulary Pharmacist	
In attendance:	Mr A Barron	NCL JFC, Support Pharmacist	
	Mr J Minshull	NCL JFC, Support Pharmacist	
	Dr Korlipara	UCLH, Consultant Neurologist	
	Dr Saifee	UCLH, Consultant Neurologist	
	Ms S Sumaria	UCLH, Senior Clinical Pharmacist	
	Dr Balakrishnan	RFL, Consultant Microbiologist	
	Prof P Wilson	UCLH, Consultant Microbiologist	
	Dr Murray	RFL, Consultant Gastroenterologist	
	Dr Parisi	UCLH, Consultant Gastroenterologist	
Apologies:	Dr R MacAllister	NCL JFC Chair	
	Prof L Smeeth	NCL JFC Vice-Chair	
	Ms W Spicer	RFL, Chief Pharmacist	
	Mr S Richardson	WH, Chief Pharmacist	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr M Kelsey	WH, Chair DTC	
	Dr A Bansal	Barnet CCG, GP Clinical Lead Medicines Management	
	Ms K Landeryou	Patient Partner	
	Ms L Reeves	C&I, Chief Pharmacist	
	Dr P Hyatt	NMUH, DTC Chair	
	Dr S Shaw	RFL, DTC Chair	
	Prof A Tufail	MEH, DTC Chair	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Mr T James	MEH, Chief Pharmacist	
	Dr V Thiagarasah	Enfield CCG, GP Clinical Lead Medicines Management	
	Dr R Fox	RNOH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Mr P Bodalia	UCLH, Principal Pharmacist	

2. Meeting observers

The Chair welcomed Mr MF Chowdhury (NEL CSU, Senior Prescribing Advisor), Ms S Chauhan (Islington CCG, Prescribing Advisor) and Mr J Flor (WH, Formulary Pharmacist) as observers to the meeting.

The Chair informed the Committee that Ms S Ceci (WH, Formulary Pharmacist) is going on secondment and therefore will no longer be involved with formulary in NCL. The Committee thanked Ms Ceci for her hard work in supporting the collaborative nature of the JFC, and wished her the very best for her future career.

3. Minutes of the last meeting

Mr Sandhu noted a couple of typos in the minutes. The minutes were otherwise accepted as an accurate reflection of the July meeting.

4. Matters arising

4.1 Idebenone for Duchenne Muscular Dystrophy (EAMS)

This item was deferred until the next meeting.

4.2 Ixazomib in multiple myeloma (pre-NICE; zero-cost scheme)

Mr Minshull informed the Committee that subsequent to the JFC ratifying the ixazomib compassionate use scheme across NCL for patients with multiple myeloma, NHS England London Region has written to Trusts informing them that they do not support this "free of charge" scheme, and that no new patients should be started on ixazomib under this scheme. Patients who have already started on ixazomib can continue until it is no longer required. NHS England will review this position when the NICE Technology Appraisal for ixazomib is published.

NHS England decided not to endorse this "free of charge" scheme because the potential enhanced efficacy achieved by adding ixazomib to lenalidomide and dexamethasone may result in an increase in the number of cycles of therapy of lenalidomide a patient receives. As NHS England would be paying for lenalidomide during this period, this would result in a cost increase to the NHS which has not been through formal commissioning approval and has not had a formal cost-effectiveness assessment (i.e. through NICE).

Mr Minshull advised the Committee that he has already contacted the applicant who requested use of ixazomib, as well as all NCL formulary pharmacists, to inform them that ixazomib "free of charge" scheme should not be used for new patients. Mr Minshull advised the Committee that they should be mindful of this NHS England decision when considering future FOC schemes.

5. Declarations of relevant conflicts of interest

There were no declarations of interest

6. Local DTC recommendations / minutes

6.1 Under evaluation at local DTC

DTC site	Month	Drug	Indication	JFC outcome
RFL	Aug-17	Ketamine (oral)	Acute pain unresponsive to opiates (inpatient use only; initiation by Pain team consultant or consultant Anaesthetist)	Decision: Under evaluation at RFL only[†] Prescribing: Secondary care only Tariff status: In tariff Funding: Secondary care Fact sheet or shared care required: No

[†] The Committee noted the supportive evidence base for unlicensed oral ketamine for acute pain was very limited and extrapolated from other types of pain or intravenous ketamine. Ms I Samuel agreed to circulate the RFL protocol to Dr S Ishaq who agreed to support RFL in the development of a data collection form. The outcome of the RFL evaluation was relevant to all Trusts and should be heard at JFC.

7. New Medicine Reviews

7.1 Opicapone for Parkinson's Disease (Applicant: Dr Korlipara, UCLH)

The committee reviewed an application for the use of opicapone as a second-line COMT inhibitor, for patients with end-of-dose motor fluctuations/OFF periods who do not respond to, or tolerate entacapone.

Opicapone is a third in class catechol-O-methyl transferase (COMT) inhibitor; entacapone is the first-line choice which is available generically or part of a combination product. Tolcapone, the second COMT inhibitor is on formulary in NCL however no patients receive treatment due to the very intensive liver monitoring required to mitigate the risk of severe liver toxicity.

The committee reviewed 14- to 15-week, double-blind, placebo- and active-controlled RCT of opicapone as an adjunct to levodopa in people with Parkinson's disease experiencing end-of-dose motor fluctuations (n=600). Patients were randomised to 3 doses of opicapone (5mg, 25mg and 50mg once daily), placebo or entacapone. The primary outcome was mean change from baseline to study end in absolute time in the OFF state, assessed by daily paper participant diaries. Results supported non-inferiority of opicapone vs. entacapone with a mean difference in the OFF state of −20.5 minutes (95% CI: −56.9 to 15.8 minutes) in favour of opicapone. The secondary endpoint 'Patient global impression' was superior with opicapone vs. entacapone however may have occurred by chance (repeat testing). Nearly all outcomes suggest a small improvement of opicapone vs. entacapone however none of these differences were statistically significant. The narrative of a small improvement is supported by the Phase I data which found opicapone had a higher COMT inhibitor activity resulting in higher levodopa C_{min} with opicapone than entacapone.

With regards to safety, opicapone had numerically lower rate of 'treatment-emergent adverse effects leading to discontinuation' and 'serious treatment-emergent adverse effects' than either placebo or entacapone. There is no known risk of liver toxicity suggesting it is safer than topicapone.

The Committee discussed the limitations of the non-inferiority study; principally that the proposed positioning (for patient who had previously failed entacapone) was inconsistent with the trials (for patients who were entacapone naïve) and the unexplainably high mean total OFF time (6.5 hours) at baseline in the study population with moderate PD.

Dr Korlipara agreed that the cohort intended from treatment were excluded from the pivotal study, however did not agree that a comparison with entacapone was helpful as all patients would have had an inadequate response, or intolerant to entacapone. Given the proposed place in therapy, relevant comparators were 'no additional treatment' leaving patients poorly controlled or 'invasive therapies' such as deep brain stimulation. Case studies were presented of two patients who obtained significant benefit after starting opicapone.

In camera, it was noted that AWMSG had issued a 'not recommended' statement for opicapone following a non-submission from the manufacturer; this suggested the manufacturer were unable to build a cost-effective argument in favour of its use. The evidence base for approving opicapone was weaker than that for tolcapone however tolcapone is associated with intensive LFT monitoring and is therefore not a useful addition of the formulary. The Committee heard from Mr Dean that the lack of alternative pharmacological options in this class should favour opicapone's addition to the formulary; the Committee was sympathetic to the need for a second COMT inhibitor for patients who experience idiosyncratic reactions to or do not respond to entacapone, but acknowledged that this was not consistent with the current evidence base. The Committee agreed an evaluation period was required to establish whether PD symptoms could be improved by initiating opicapone following an inadequate response or intolerance to entacapone. The evaluation should be limited to centres providing invasive therapies as this is real-world comparator. The PD Pathway required specific consultation before being approved for use. The evaluation form should be approved by the JFC Chair and the results from the evaluation presented back to JFC in September 2018.

Decision: Approved under evaluation
Prescribing: Primary and secondary care
Tariff status: In tariff
Funding: Secondary and primary care
Fact sheet or shared care required: No

7.2 Safinamide for Parkinson's Disease (Applicant: Dr Saifee, UCLH)

The Committee reviewed an application for safinamide, a highly-selective, reversible MAO-B inhibitor, as an option in the management of Parkinson's Disease (PD) with disabling peak dose dyskinesias. It was noted that the applicant had produced a pathway detailing treatment options in PD, which positioned

safinamide after optimising the dose of current medicines (inc dopamine agonists, levodopa, and MAOB inhibitors); consideration of fractionating or lowering the levodopa dose; or addition of amantadine. The Committee noted that the manufacturer claims safinamide acts at the voltage-gated sodium channels, and modulates glutamate release, in addition to its dopaminergic effects. However it was noted that the SPC highlights that the extent to which the non-dopaminergic effect contributes to its efficacy has not been fully established and therefore the Committee felt it appropriate to focus on the medicine's MAOB inhibitor activity.

The Committee reviewed two double-blind, randomised, 24-week, placebo-controlled trials (both used mean change in daily total "on" time with no or non-troublesome dyskinesias as the primary end point), and one blinded, 18-month follow up study (primary end-point of mean change in Dyskinesia Rating Scale (DRS) during "on" time). Mr Minshull also presented data during the meeting from a post-hoc analysis from the follow-up study, which has stratified patients based on presence or absence of dyskinesia at baseline, in order to report the categorical impact of safinamide treatment on their DRS score. The Committee was interested to note that patients with disabling peak-dose or biphasic dyskinesias were excluded from both clinical trials, and were therefore also not included in the follow-on study.

When considering the two RCTs, the Committee noted that both were associated with a statistically and modest clinically significant improvement in the primary efficacy outcome of improvement in total daily "on" time with no or with minor dyskenesias ranging between 30 minutes and 1 hour. For study 016 (Borgohain *et al* 2014), the mean change in total daily "on" time with no or non-troublesome dyskinesia was +0.55 hours (95% CI 0.12 to 0.99, p=0.013) for safinamide 100 mg vs. placebo; and +0.51 hours (95% CI 0.07 to 0.94, p=0.0223) for safinamide 50 mg vs. placebo. Schapira *et al* 2017 found a mean change in daily "on" time without troublesome dyskinesias of +0.96 hours (95% CI 0.50 to 1.36 hours; p<0.001) for safinamide vs. placebo.

The Committee reviewed the findings of an extension study to the first double-blind RCT (Borgohain *et al* 2014), which followed patients for an additional 18 months of treatment; patients remained randomised to the treatment they had first been allocated to. As the extension study excluded any patients who had experienced a clinically significant side-effect or a significant deterioration in motor symptoms during the initial double-blind trial, it is possible it represented an enriched sample of patients which may overestimate the tolerability and efficacy of active treatment. This study failed to meet its primary efficacy endpoint (mean change from baseline in the Dyskinesia Rating Scale (DRS) during "on" time: LS mean difference safinamide 50 mg/day vs. placebo -0.51 [95% CI -1.32, 0.29; p=0.2125]; safinamide 100 mg/day vs. placebo –0.59 [95% CI -1.4, 0.21; p=0.1469]). For a cohort of patients with a mean DRS > 4 at baseline, LS mean change in DRS score from baseline was -1.5 [95% CI -2.33 to -0.11; p=0.0317] with safinamide 100 mg daily, but as this was a secondary end-point, the Committee did not consider this to be a policy defining outcome.

Further post-hoc analysis of the Borgohain *et al* (2014) extension study as reported by Cattaneo *et al* (2015) was presented at the meeting. A sub-group analysis of patients with a baseline DRS>0 and no change to levodopa dose demonstrated that a decrease in DRS score was not statistically significantly more likely in patients on either dose of safinamide when compared to placebo. For subgroup who had baseline DRS>0 and may or may not have had a change to levodopa dose, safinamide 100 mg vs. placebo was statistically significantly more likely to result in a decrease in DRS (59.8%, vs. 42.3%; p=0.0153). However, the Committee was not convinced by this post-hoc, secondary endpoint that had been identified in a study that failed to meet its primary efficacy end-point.

The Committee considered the findings from an in-house meta-analysis based on a Cochrane Review conducted in 2010 (before the safinamide studies were conducted). The analysis identified that the OR of experiencing dyskinesias when in a safinamide trial was greater than that reported in the three other MAOB inhibitor trials included (OR 1.54 [95% CI 0.92 to 2.58] and 2.75 [95% CI 1.58 to 4.80] in safinamide trials, vs. OR=0.94 [0.49 to 1.80] for other MAOBI trials). This challenges the hypothesis that safinamide is more tolerable in terms of dyskinesias. It was noted that the EPAR for safinamide challenges the claim in the SETTLE study that safinamide as a beneficial effect on dyskinesia, as this is not proven in the data.

Dr Saifee explained to the Committee that the cohort included in the pathway for safinamide represents a small group of patients with disabling dyskinesias. Advanced therapies (such as intestinal duodopa, deep brain stimulation) would otherwise be considered at this stage, but these are not always suitable for patients, either because of patient preference or contraindications. Dr Saifee drew the Committee's attention to the improvements in mean PDQ-39 score (a scale measuring patient-reported health related quality of life) that were seen as a secondary end-point in the RCTs, though failed to show statistical significance at the 50 mg dose in both of the Borgohain studies. The proportion of patient with an

improvement on CGI-C was statistically significantly greater for safinamide than for placebo, except for the cohort receiving safinamide 100 mg in the Borgohain extension study. Dr Saifee informed the Committee that reductions in "off" time would be beneficial for the health economy because "off" time is associated with a longer stay in hospital.

The Committee was conscious that although safinamide is another MAOB-I, because it is recently marketed, it is priced higher than generic selegiline and rasagiline. The additional monthly cost of treating each patient with safinamide was between £59 (vs. selegiline) and £67 (vs. rasagiline). The Committee noted that an application had not been made by the company to the AWMSG, which suggested there may be lack of confidence in the cost-effectiveness of this therapy.

In summary, the Committee was not convinced that the evidence discussed provided proof that safinamide would be beneficial for patients with disabling peak dose dyskinesias because they had been excluded from the RCTs. The Committee considered safinamide to be a MAOB-I "me too" drug, therefore they wanted proof of additional benefit over treatment with selegiline or rasagiline, which wasn't seen in the trials. The Committee did not think it appropriate to make policy defining decisions based on the quality of life data presented, as these came from secondary endpoints and should be considered hypothesis generating.

Decision: Not approved

7.3 Ceftazidime-avibactam for carbapenemase producing Gram-negative organisms (Applicant: Dr Balakrishnan, RFL)

The Committee reviewed an application for ceftazidime-avibactam to treat infections caused by non-MBL carbapenemase producing aerobic Gram negative organisms where treatment options are limited to colistin, fosfomycin and tigecycline including (but not limited to) complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and hospital acquired pneumonia (HAP).

The Committee heard the available evidence finds ceftazidime-avibactam non-inferior to doripenem (a carbapenem not licensed in the UK) for cUTI and non-inferior to meropenem for cIAI and HAP despite numerically lower 'clinical cure' probabilities. The application does not propose to use ceftazidime-avibactam empirically therefore the licensing studies were of limited value, other than to confirm penetration into urinary tract, abdomen and lungs. Relevant *in vitro* data show ceftazidime-avibactam to have proven activity against KPC and OXA carbapenemases which differentiates it from ceftolozane-tazibactam. Ceftazidime-avibactam has no activity against MBL carbapenemases. Given the difficulty in treating KPCs and OXAs, ceftazidime-avibactam should be restricted for these isolates. Resistance to ceftazidime-avibactam has already been observed.

The use of ceftazidime-avibactam was supported by the BSAC/HIS/BIA Working Party guidelines and other NCL microbiologists, namely Dr Kelsey (WH) and Prof Wilson (UCLH).

The Committee noted the budget impact was impossible to estimate as experience with ceftolozane-tazibactam suggests treatment duration is variable (7 days to several months) and the relevant comparators varied on an individual basis. JFC recently approved a similar antibiotic, ceftolozane-tazobactam, which has revealed significant affordability concerns (£173,000 to treat 9 patients in NCL in 10 months).

In camera, the Committee approved the use of ceftazidime-avibactam for the following indication: Multi-resistant carbapenemase producing Gram-negative organisms that have proven susceptibly to ceftazidime-avibactam and where the only alternative active agents, if any, are limited to colistin, tigecycline and fosfomycin, which cannot be used due to resistance or intolerance - Microbiology recommendation only.

Decision: Approved
Prescribing: Secondary care only
Tariff status: In tariff
Funding: Secondary care
Fact sheet or shared care required: No

7.4 Glecaprevir / pibrentasvir (Maviret) and Sofosbuvir / velpatasvir / voxilaprevir (Vosevi) for the treatment of chronic hepatitis C virus

The Committee approved Maviret and Vosevi in line with the NHS England Hepatitis C rate card. Maviret replaces Sovaldi + ribavirin as the preferred choice for GT2 and replaces Epclusa for GT3, GT5 and GT6. Using a naïve comparison, efficacy and safety were similar for Maviret compared with Sovaldi and Epclusa. Vosevi was added as a new treatment option for GT5 and GT6.

Decision: Approved
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: NHSE
Fact sheet or shared care required: No

8. Inflammatory bowel disease biologic pathway (Crohn's and Ulcerative colitis) - Dr Murray (RFL) and Dr Parisi (UCLH)

The Committee, Dr Murray and Dr Parisi agreed a NCL Inflammatory Bowel Disease working group was required to progress with the pathway. The workgroup would have the secretarial support of JFC.

The following points were approved by the Committee:

- Crohn's disease pathway
    - Anti-TNFs are the first-line agents for patients with Crohn's disease. Ustekinumab should be available for more unusual cases where anti-TNF may not be preferred; such as in for patients with history of cancer, or frequently travel, or compliance concerns
    - Vedolizumab and ustekinumab would be available for patients who are not eligible for anti-TNF or have failed anti-TNFs. Ustekinumab is likely to be the preferred agent, but will also be agreed within the workgroup
    - An evidence review was required to establish whether adalimumab and ustekinumab should be available for fistulating Crohn's disease. This evidence review would be reviewed at JFC.
    - Infliximab response should be reviewed at 12 weeks, not 6 weeks as specified in the product license
    - Vedolizumab should not be dose escalated; this should be made explicit in the guideline
    - A paper was required for submission to Commissioners to confirm whether NICE intended ustekinumab to be used every 8 weeks for patients who lose response on dosing every 12 weeks
    - Commissioners agree that dose escalated anti-TNF for Crohn's disease is included within the relevant NICE TAs.
    - All issues relating to dose-escalation, treatment duration and the number of lines of commissioned treatments were referred to the NCL Inflammatory Bowel Disease working group
- Ulcerative colitis pathway
    - Golimumab was not a preferred first-line agent for patients with UC as it will be more expensive than biosimilar adalimumab (expected 2018) and biosimilar infliximab and offers no therapeutic advantages
    - An evidence review was required to establish vedolizumab or anti-TNF is the preferred first-line agent for patients with UC
    - Infliximab for acute exacerbations of severely active UC should not be conditional on a patient being contraindicated to ciclosporin therapy. This reflects current practice and can be supported with the introduction of biosimilar infliximab
    - A rapid dosing schedule of infliximab was approved for patients who experience an inadequate response to the first-dose (i.e. off-label use of infliximab with the three dose induction administered over 4 weeks rather than 6 weeks)
    - Adalimumab for acute exacerbations of severely active UC should not be included in the pathway
    - The working group should consider whether a 10 weeks or 14 week review date is suitable for vedolizumab
    - Vedolizumab should not be dose escalated; this should be made explicit in the guideline
    - All issues relating to dose-escalation, treatment duration, the number of lines of commissioned treatments and the place in therapy of surgery were referred to the NCL Inflammatory Bowel Disease working group

9. Adrenaline Auto-Injector – MHRA safety update

Mr Minshull advised the Committee that the MHRA had recently released a Drug Safety Update advising healthcare professionals to prescribe two adrenaline auto-injectors and encourage patients to carry them at all times. Healthcare professionals should also ensure patients and their carers are trained to use the device they are prescribed, and that training devices can be obtained from the appropriate manufacturer.

Ms Taylor highlighted there is a significant risk of waste from adrenaline auto-injectors, particularly if schools are asking for multiple devices for each child that needs them. It was noted that from the 1 October 2017, schools will be allowed to hold adrenaline auto-injectors for use in an emergency, without requiring a named prescription. It was proposed that schools should be encouraged to buy stock in line with this legislation change, rather than to hold individual patient supplies. Dr Stuart commented that any drive to encourage schools to stock adrenaline auto-injectors should not detract from encouraging older children to carry two devices of their own at all times.

10. DMARD Monitoring Quick Reference

Mr Minshull presented a DMARD Quick Reference Guide that had been produced as collaboration between Camden CCG and UCLH.

It was noted that leflunomide has been removed from the NCL Red List and therefore should be included in the next version of the DMARD Monitoring Quick Reference.

The Committee discussed arrangements for ophthalmic monitoring within six months for in patients started on hydroxychloroquine. It was highlighted that, as UCLH does not have an ophthalmology service, patients would need to be referred to the RFL; as the hospital has been asked to minimise consultant to consultant referrals it is current practice to ask the GP to make the onward referral to ophthalmology. There was uncertainty around which Trusts in NCL have both rheumatology and ophthalmology services and would therefore not need to make external consultant-to-consultant referrals. It was noted that some community ophthalmologists may have the required equipment and training to perform the necessary assessment.

Ms Clarke highlighted that following five years of treatment with hydroxychloroquine, further ophthalmology examinations are required; this additional cost has created uncertainty about the cost-effectiveness of this intervention. As a result, the British Society of Rheumatologists is reviewing this.

Action: Quick Reference document approved. Mr Sandhu to inform CCG contracting teams that it is likely there will be an increase in consultant to consultant referrals if UCLH rheumatologists refer patients directly to ophthalmology. Mr Minshull find out how Rheumatologists are currently ensuring patients receive necessary ophthalmology assessments and that these assessments are being actioned appropriately.

11. JFC Work plan

This item was included for information only. JFC outstanding actions are now included on this tracker with the prefix ‘OA’. Any questions should be directed to Mr Barron.

12. Next meeting

Monday 18 September 2017, G12 Council Room, South Wing, UCL, Gower St. WC1E 6BT