NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 29th January 2015

Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Dr R Sofat	Consultant Clinical Pharmacologist, UCLH	**(Chair)***
	Dr R Fox	DTC Chair, RNOH	
	Dr M Kelsey	Whittington DTC Chair	
	Dr R Urquhart	UCLH Chief Pharmacist	
	Ms W Spicer	RFH Chief Pharmacist	
	Dr R Kapoor	Consultant Neurologist, UCLH	
	Mr T James	MEH Chief Pharmacist	
	Mr A Shah	RNOH Chief Pharmacist	
	Ms L Reeves	C&I Mental Health Trust Chief Pharmacist	
	Mr A Dutt	NHS Islington, Head of Medicines Management	
	Ms N Shah	NHS Camden, Head of Medicines Management	
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management	
	Mr TF Chan	BCF Chief Pharmacist	
	Ms P Taylor	NHS Haringey Head of Medicines Management	
	Mr J Paszkiewicz	Prescribing Advisor, NCL/NEL CSU	
	Dr L Wagman	Barnet CCG, GP	
	Dr V Thiagarasah	Enfield CCG, GP	
In attendance:	Mr D Ralph	Urology Consultant, UCLH	
	Dr E Seward	Gastroenterology Consultant, UCLH	
	Ms S Patel	GI Services Pharmacist, UCLH	
	Mr E Hindle	MEH Pharmacist	
	Ms S Ceci	Whittington Pharmacist	
	Mr M Wyke-Joseph	NMUH Pharmacist	
	Ms I Samuels	RFH Pharmacist	
	Ms S Sanghvi	UCLH Pharmacist	
	Mr P Bodalia	UCLH Pharmacist	
	Mr G Purohit	RNOH Pharmacist	
	Ms H Amer	Clinical Pharmacology Registrar, UCLH	
	Ms M Mustapha	Dietician, NMUH	
Apologies:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Prof L Smeeth	NCL JFC Vice-Chair	**(Vice-Chair)**
	Dr R Breckenridge	UCLH UMC Chair	
	Dr E Boleti	Consultant Oncologist, RFH	
	Dr A Tufail	MEH DTC Chair	
	Dr J Hurst	Consultant Chest Physician, RFH	
	Dr D Bavin	Camden CCG, GP	
	Dr C Stavrianakis	Haringey CCG, GP	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Ms E Mortty	NHS Haringey, Deputy Head of Medicines Management	
	Ms R Dallmeyer	CSU Pharmacist	
	Dr H Taylor	Whittington Chief Pharmacist	
	Ms S Drayan	NMUH Chief Pharmacist	
	Mr A Karr	NCL Procurement Consortia Chair	
	Dr P Ancliff	GOSH DTC Chair	
	Ms J Cope	GOSH Chief Pharmacist	

**Dr R Sofat chaired the meeting in the absence of Prof R MacAllister & Prof L Smeeth*

2. Minutes of the last meeting

These were accepted as accurate.

3. Matters arising

3.1 Tadalafil (*Cialis®; Eli Lilly*) for ED and post NSRP (Applicant: Mr D Ralph)

The Committee discussed the evidence for daily tadalafil and avanafil which have previously been presented at the JFC. Mr Ralph agreed with the Committee that the evidence showed equivalent efficacy for all PDE5 inhibitors whether administered daily or on a when required basis. Based on this, and the evidence previously considered, the Committee agreed that daily PDE5 inhibitors would only be appropriate for short term use post NSRP as part of the rehabilitation program. Mr Ralph agreed that sildenafil would be acceptable as a first line option, used daily for a maximum of 3 months. If after 3 months there was a lack of response, patients would be switched to intracavernosal injections. The Committee agreed that in the absence of published data the urologists should collect audit data to show benefit of daily PDE5 inhibitors over 'when required' and present this back within one year. It was further agreed that these 3 month prescriptions should be restricted to secondary care prescribing.

For erectile dysfunction there was unanimous agreement that prn sildenafil should remain first line, and that patients with lack of response who are referred to the urology service should be re-challenged with sildenafil titrating up to maximum doses. The Committee agreed that given PDE-5 inhibitors have a similar mechanism of action, there should be a maximum of two on the formulary to avoid patients cycling through multiple drugs. It was acknowledged that a second line agent is necessary for those patients that may have idiosyncratic reactions, rather than non-responders, for which, there is little evidence. Mr Ralph explained that avanafil has a preferable adverse effect profile to tadalafil and is cheaper, however could not support the removal of tadalafil altogether if avanafil was made 2nd line. The Committee heard that the tadalafil patent will expire in 2017 and would offer greater savings in the long term. Therefore the Committee agreed to recommend that avanafil not be included on the formulary and to keep sildenafil prn as 1st line and tadalafil prn as 2nd line treatments for erectile dysfunction. Mr Ralph and primary care members agreed that a joint primary/secondary care treatment pathway and process to facilitate appropriate referrals would be of great benefit to the service. It was agreed that a draft pathway should be prepared by the urologists for consideration at JFC.

4. Declarations of relevant conflicts of interest

None were declared.

5. New Medicine Reviews

5.1 Ciclosporin for Chronic Idiopathic Urticaria (Applicant: Dr S Berkovitz; Presentation: Ms S Sanghvi)

The Committee reviewed the evidence for the use of ciclosporin for chronic idiopathic urticaria (CIU), which was proposed for use as a third line agent in patients who are refractory to treatment with high-dose antihistamines and short courses of steroids. The Committee heard that this approach was in line with European and UK dermatology and immunology guidelines, although leukotriene receptor antagonists could be considered as second line before trial of ciclosporin. The Committee noted that omalizumab is licensed for CIU and a NICE TA is expected in April, however the initial published ACD suggests that omalizumab will not be recommended.

The Committee considered a randomised controlled double blind trial by Vena et al in 99 patients with CIU. The mean improvement in severity score at week 8 (primary endpoint) was 62.5% in the 16-week ciclosporin arm, 62.1% in the ciclosporin 8-week arm and 23.3% in the placebo arm ($p<0.03$ for ciclosporin vs placebo). By week 24 the results were not statistically significantly different (41.7%, 46.9% and 30.2% respectively). At week 16 there was an improvement in Dermatology Life Quality Index (DLQI) of 63.9% with 16 week ciclosporin, 68.4% with 8 week ciclosporin and 33.9% with placebo. The Committee noted several limitations of the study including lack of power calculation, no reporting of absolute values and therefore difficulty in determining clinical significance. In addition there was a lack of information regarding concomitant medication and rescue therapy, with a lower dose of cetirizine compared to usual high dose antihistamine practice.

The Committee further considered a double-blind, RCT by Grattan et al comparing ciclosporin to placebo in 29 patients with severe CIU. All patients had a positive autologous serum skin test (ASTT), previous poor response to antihistamine therapy, and 18 patients had required prednisolone courses for urticaria. Patients were randomised to receive ciclosporin 4mg/kg daily or matching placebo over 4 weeks, with concomitant cetirizine 20mg daily for all patients. At week 4 patients entered an open-label follow-up phase of the study and received ciclosporin. Patients completed a daily symptom log, upon which a weekly aggregate urticaria activity score

(UAS) was calculated (ranging from 0 to 42). Response was defined as reduction in the weekly UAS to <25% of baseline, and relapse as return of the UAS to >75% of baseline. The results showed response in 42% of patients who received ciclosporin at 4 weeks and none in the placebo arm ($p<0.05$). Absolute mean reduction in UAS from baseline at 4 weeks was 12.7 (95% CI 6.6-18.8) for ciclosporin and 2.3 (95% CI -3.3 to 7.9) for placebo ($p=0.005$). The mean reduction in VAS at 4 weeks was 3.0 (95% CI 1.5 to 4.5) for ciclosporin and 0.7 (95% CI -0.9 to 2.3) for placebo ($p=0.026$). Overall 65% of patients in the study responded to ciclosporin over week 0-8, however only 26% were still clear at 6 months. The Committee acknowledged that this was a slightly more robust study and representative of the proposed patient group, although questioned the apparent lack of long-term efficacy in managing CIU.

The Committee discussed the known toxicities associated with ciclosporin including increased risk of infections, nephrotoxicity, hepatotoxicity and malignancies; and more common adverse effects of tremor, hirsutism, hypertension and GI disturbances. The Committee heard that the proposed doses for CIU are relatively low and that most of the adverse effects are dose-dependent and responsive to dose reduction. The applicant had attached an outline of monitoring that would be conducted in CIU patients on ciclosporin.

The cost of ciclosporin is anticipated to be £660 for a 5 month course based on a 70kg patient. The Committee agreed that prescribing should be restricted to secondary care by dermatology or allergy clinic consultants.

Overall the Committee questioned the limited data which demonstrated that patients may initially improve but with a low long-term responder rate. The studies highlighted that the optimal dosing and duration of treatment still need to be defined. Despite this, the Committee recognised that for patients refractory to high dose antihistamines the disease has a significant impact on quality of life and that ciclosporin has a better level of evidence compared to other potential treatments. The Committee therefore agreed that ciclosporin should be added to the NCL formulary for CIU refractory to high dose antihistamines and steroids, pending a treatment protocol. The Committee requested that the protocol outline monitoring criteria, stopping criteria, outcomes for assessment of response and suggested a trial period on ciclosporin after which this treatment response could be assessed.

5.2 Montelukast for Chronic Idiopathic Urticaria (Applicant: Dr S Berkovitz; Presentation: Ms S Sanghvi)

In light of the application for ciclosporin, the Committee further discussed the position in therapy of the leukotriene receptor antagonist, montelukast, for CIU. The Committee heard that European and UK dermatology and immunology guidelines recommend leukotriene receptor antagonists as second line treatment for patients refractory to high dose antihistamines (and short courses of steroids) before trial of ciclosporin.

The Committee reviewed a randomised, double-blind study by DiLorenzo et al which compared the following treatments: (1) desloratadine 5mg daily, (2) desloratadine 5mg daily plus montelukast 10mg each evening, (3) montelukast 10mg each evening and (4) placebo in 160 adult patients with CIU. Disease activity was assessed via a patient self-scoring system using 4-point scales for pruritis, number of hives, size of largest hive, interference with sleep and interference with daily activities. The results showed that for each of these outcomes desloratadine monotherapy was more effective than montelukast monotherapy. The combination of desloratadine and montelukast failed to show a significant advantage over using desloratadine alone.

Based on this lack of efficacy, the Committee agreed that there was no benefit in use of montelukast for CIU and it should therefore not be included on the NCL formulary.

5.3 Moviprep for Bowel Evacuation (Applicant: Dr E Seward; Presentation Mr P Bodalia)

The Committee reviewed an application for Moviprep bowel evacuation preparation. Moviprep is a polyethylene glycol (PEG) based preparation, similar to Kleanprep. They are both non-absorbable, iso-osmotic solutions which pass through the bowel without net absorption or secretion. This is favourable compared to other bowel cleansing preparations (e.g. Picolax, Citramag) as there are no significant fluid and electrolyte shifts, and therefore a lower risk of provoking hypovolaemia and/or hyponatraemia. The Committee heard that PEG –based solutions are highly effective when taken correctly, however outside of clinical trials the efficacy of PEF-based preparations may be compromised as a result of poor compliance. The standard preparation, Klean-Prep requires total consumption of 4L of fluid, which many patients find intolerable. Moviprep is a PEG-based cleansing agent which reduces the effective volume required for consumption to 2L. It further contains ascorbic acid which has a cathartic effect and improves the taste of the formulation.

The Committee considered a randomised, single-blinded study by Worthington et al (n=65) which compared the efficacy and safety of Moviprep to Picolax in outpatients undergoing elective colonscopy. The primary end-point was the degree of bowel cleansing for each bowel segment, and whether it was necessary for the patient to return for a further colonoscopy because of insufficient cleansing of the colon. The results showed that bowel evacuation was a success (grade A or B) in 84.4% (n=27) in the Moviprep group versus 72.7% (n=24) in the Picolax group (p=0.37). Patients in the Picolax group generally found the taste better than those in the Moviprep group, however no patient in either group reported that it was very difficult to take the preparation. No patients in the Moviprep group required a repeat colonoscopy, whereas two patients in the Picolax arm did require repeat colonoscopy as a result of inadequate cleansing.

The Committee further considered a non-inferiority, randomised, controlled, blinded study by Ell et al (n=359) to assess the efficacy and safety of two PEG-based preparations; Moviprep® versus Klean-Prep. The primary end point was the degree of bowel cleansing for each bowel segment analysed by both independent expert panels and colonoscopists performing the procedure. Participants were randomised on a 1:1 ratio to receive either treatment on the evening before colonoscopy, and on the morning of the procedure; Moviprep (total of 2L) and Klean-Prep (total of 4L). Non-inferiority was defined if the lower limit of the 1-sided 97.5% CI for the difference in success rates between the two groups was less than 15%.

The results (from independent expert panel) showed that successful gut cleaning (grade A or B) was achieved in 88.9% (n=136) of Moviprep arm compared to 94.8% (n = 155) in the Klean-Prep group, resulting in a -5.9% with a lower limit of -12% on the one-sided 97.5% CI; thus showing non-inferiority. The colonoscopists that performed the procedure gave similar ratings to the blinded expert panel (89.5% versus 92.3%, respectively). With regards to the secondary end-points, there were more patients that consumed all the bowel solution in the Moviprep group compared to the Klean-Prep group ($p = 0.035$; actual figures not provided). The overall acceptability of from the participants perspective was 27.6 ± 14.8 versus 34.2 ± 19, respectively ($p < 0.025$), measured on a self-assessed VAS scale (ranging from 0 – excellent to 100 – very bad).

In terms of safety, the Committee discussed the NPSA alert from 2009 which highlighted the potential for harm associated with use of oral bowel cleansing preparations. The Committee noted that in general these solutions are well tolerated if used within guidelines and with careful consideration of the contraindications and cautions to use.

Dr Seaton reassured the Committee that at UCH clinicians are required to document and specifically exclude the contraindications, cautions and interactions from the NPSA alert for each patient before a suitable bowel evacuation agent can be selected. He further explained that the rationale for using a pegylated preparation first line is (1) a favourable safety profile (e.g. in renal, cirrhosis and heart failure patients) and (2) local audit data which demonstrates that the combination of citramag and senna results in less effective bowel cleansing and repeat colonoscopies. He outlined that first line Moviprep would initially be piloted in bowel cancer patients and the efficacy would be audited and presented locally before widespread use. Kleanprep would only be used for patients who were resistant to Moviprep and required a larger volume for bowel cleansing.

The Committee agreed that Moviprep was an appropriate first line oral bowel cleansing agent with the advantages of better safety profile, improved patient acceptability and comparable cost. It was therefore decided to add Moviprep to the NCL formulary, with use to be audited locally by gastroenterology teams.

6 NICE Biosimilar Statement

The NICE biosimilar position statement outlines that NICE will consider biosimilars within the same remit as their reference products for technology appraisals. Based on this, the Committee agreed that biosimilars would not require independent review at JFC, and that instead appropriate implementation plans should be agreed locally with clinicians.

7 Generic Pregabalin

The Committee noted the correspondence from Pfizer regarding the Lyrica® (pregabalin) pain patent.

8 Parkinson's Disease Pathway

The Committee discussed the Parkinson's Disease (PD) pathway prepared at NMUH and agreed that this would be a useful document across NCL for PD patients in primary and secondary care. However the Committee noted some variations between the document and current formularies. Mr Bodalia agreed to liaise with NCL formulary pharmacists and the PD units at Edgware Memorial Hospital to check consistency of the document. It was

further agreed that tertiary specialist care of PD e.g. apomorphine treatment would not be covered by this document.

9 Paediatric Dietetic Formulary

Ms Mustapha presented a paediatric dietetic formulary prepared at NMUH. Ms N Shah highlighted concerns regarding the lack of hierarchy, with some products considerably more expensive than others. It was agreed that Ms Mustapha should liaise with other dietetic teams across NCL primary and secondary care to produce a summarised document incorporating hierarchy of choice of products, and an indication of the level of urgency in administering the products.

10 Stable Angina Pathway

The Committee approved the amended stable angina pathway for use across NCL.

11 Local DTC Recommendations

MEH

- **Rituximab for Ocular Mucous Membrane Pemphigoid –** Approved for use in refractory patients at MEH only.

RFH

- **Thalidomide for severe arteriovenous malformation –** Approved under evaluation, for review at RFH in 6 months.
- **Ribavirin for chronic norovirus in PID –** Approved for 3 patients and then to be reviewed at RFH only.
- **Maribavir for resistant CMV infections –** Approved for 3 patients and then to be reviewed at RFH only.
- **Rituximab for orbital inflammatory disease** – Approved, for RFH only

12 Next Meeting: 26th February 2015, Room 6LM1, Stephenson House, 75 Hampstead Rd

11 Any other business

Mr Gouldstone informed the Committee that consultation documents for draft NICE guidance on diabetes contain several variations to the proposed NCL diabetes pathway that is under development. The Committee agreed to discuss this in further detail at the February meeting.