NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 30th October 2014

Roberts Building, Room 421, UCL

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Dr M Kelsey	Whittington DTC Chair	
	Dr R Urquhart	UCLH Chief Pharmacist	
	Mr A Dutt	NHS Islington, Head of Medicines Management	
	Ms N Shah	NHS Camden, Head of Medicines Management	
	Dr R Fox	DTC Chair, RNOH	
	Dr R Sofat	Consultant Clinical Pharmacologist, UCLH	
	Dr C Stavrianakis	Haringey CCG, GP	
	Dr L Wagman	Barnet CCG, GP	
	Dr D Bavin	Camden CCG, GP	
	Mr TF Chan	BCF Chief Pharmacist	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Dr E Boleti	Consultant Oncologist, RFH	
	Mr T James	MEH Chief Pharmacist	
	Dr R Kapoor	Consultant Neurologist, UCLH	
	Ms P Taylor	NHS Haringey Head of Medicines Management	
In attendance:	Dr H Amer	Clinical Pharmacology Registrar, UCLH	
	Mr E Hindle	MEH Pharmacist	
	Ms K Nwosu	NMUH Pharmacist	
	Mr M Wyke-Joseph	NMUH Pharmacist	
	Dr M Ozkor	Consultant Cardiologist, UCLH	
	Dr C Bourantas	Consultant Cardiologist, UCLH	
	Mr P Wright	Lead Cardiology Pharmacist, UCLH	
	Dr T Wagner	Consultant, Nuclear Medicine, RFH	
	Dr R Mizoguchi	Consultant Neurologist, RFH	
	Ms R Holland	Pharmacist, UCLH	
	Ms S Sanghvi	Pharmacist, UCLH	
	Mr A Katira	Medical Student	
	Mr P Bodalia	Deputy Chief Pharmacist, RNOH	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Dr H Taylor	Whittington Chief Pharmacist	
	Mr A Shah	RNOH Chief Pharmacist	
	Dr A Tufail	MEH DTC Chair	
	Ms W Spicer	RFH Chief Pharmacist	
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management	
	Dr J Hurst	Consultant Chest Physician, RFH	
	Dr R Breckenridge	UCLH UMC Chair	
	Ms R Dallmeyer	CSU 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	

2. Minutes of the last meeting

Ms N Shah questioned whether GPs would be expected to continue prescriptions for pregabalin for neuropathic pain. The Committee agreed that these were suitable for continued prescribing in primary care provided they were initiated by the agreed specialist consultants in line with the strict initiation criteria.

3. Matters arising

3.1 Amyvid for Alzheimer's Disease

The Committee reviewed the Amyvid (florbetapir 18-F) scan for diagnosis of Alzheimer's Disease (AD) at the September JFC meeting and considered it to be a useful research tool and biomarker for studies. However, due to the low specificity and sensitivity in the prediction of AD and the unlikely impact on clinical management of patients, it was agreed not to include florbetapir 18-F on the NCL formulary. Dr Wagner and Dr Mizoguchi appealed against this decision and informed the Committee that they wished to use Amyvid to differentiate between different types of dementia, primarily between AD and frontal temporal lobe dementia (FTD). The Committee expressed concern that amyloid plaques are not a definitive diagnostic tool and that false positive results can occur, for example in patients with cerebral amyloid angiopathy. The Committee also questioned whether differentiation between these types of dementia would result in altered progression or treatment pathway. The Committee requested clinical evidence demonstrating utility of the Amyvid test in differentiating between AD and FTD and the impact on the treatment pathway before reconsideration at JFC.

3.2 Angina Pathway

The Committee reviewed the UCLH pathway for management of stable angina and requested that it be revised to reflect the treatment hierarchy for nitrates, nicorandil, ivabradine and ranolazine, taking cost-effectiveness into consideration. Regarding ivabradine, the recent Signify trial had detected a signal for harm in patients with stable coronary disease. It was decided to defer accepting ivabradine as a treatment for angina until further review. Ranolazine was previously reviewed at JFC and accepted for use at BCF, however it was agreed that ranolazine could be added to the NCL JFC formulary strictly for symptomatic angina patients as a potential add-on treatment when patients are inadequately controlled or intolerant to all other therapies (beta blockers, calcium channel blockers, nitrates and nicorandil) and are not suitable for revascularisation. Dr Bavin questioned the duration and 80mg dose of atorvastatin in the pathway and it was agreed that the specific dose would be removed as a lower dose may be more appropriate for some patient groups.

4. Declarations of relevant conflicts of interest

None were declared.

5. New Medicine Reviews

5.1 Hydrocortisone MR (Plenadren; ViroPharma Ltd) for Adrenal Insufficiency (Applicant: Prof M Bouloux; Presentation: Ms S Sanghvi)

The Committee reviewed an application for hydrocortisone modified release tablets (Plenadren) for the second line treatment of adrenal insufficiency in adults who are identified by consultant endocrinologists as having sub-optimal treatment with immediate release hydrocortisone.

The Committee reviewed the open-label, randomised crossover trial by Johansson et al in 64 adults with primary adrenal insufficiency. Patients were randomised to a single dose of Plenadren or immediate release hydrocortisone in three divided doses for 12 weeks and then switched over for a further 12 weeks. The mean total serum cortisol area under the curve was approximately 20% lower with Plenadren compared to immediate release hydrocortisone. Plenadren achieved higher morning levels compared to the immediate release preparation but lower afternoon and evening levels. It partly mimicked the physiological release of cortisol but did not replicate the gradual increase before wakening or the small daytime spikes associated with eating. The authors suggested that the lower bioavailability may be beneficial for patients who suffer adverse events from over-substitution with glucocorticoid, however the Committee agreed that this could also be achieved by adjusting the doses of immediate release hydrocortisone. There were small reductions in both weight and blood pressure with Plenadren compared to immediate release hydrocortisone, which although statistically significant were noted to be small in absolute terms and may be attributed to the lower bioavailability of Plenadren.

The Committee noted that the frequency and type of adverse effects are similar between Plenadren and hydrocortisone IR. The most common reported adverse events were nasopharyngitis, fatigue, gastroenteritis, headache and vertigo. Patients initially started on Plenadren reported increased adverse effects during the first

8 weeks of treatment, likely due to the relative under-substitution compared to immediate release hydrocortisone.

The Committee acknowledged that a once daily dose is more convenient for patients, but agreed that adherence to treatment is generally high in patients with adrenal insufficiency due to the symptoms caused by non-compliance. In terms of cost, based on a 20mg daily dose immediate release hydrocortisone costs £103 whereas Plenadren costs £240 per patient per month. The company have a PLEDGE scheme to reduce cost burden, however this only applies for the first six months.

In summary the Committee agreed that Plenadren only partly achieves a physiological pattern of cortisol release and any improvements in metabolic profile or adverse events could be achieved by reducing the dose of immediate release hydrocortisone, in line with the lower bioavailability of Plenadren. Taking into consideration the higher cost and lack of data showing benefit over immediate release preparations, the Committee agreed that Plenadren would not be included on the NCL formulary.

5.2 Fondaparinux (Arixtra; Aspen) for Management of ACS (Applicant: Dr M Ozkor; Presentation: Dr H Amer)

The Committee reviewed an application for fondaparinux as first-line anticoagulant for treatment of NSTEACS in adults for whom PCI is not indicated. Fondaparinux is a selective inhibitor of activated Factor X (Xa) which is recommended by NICE and the European Society of Cardiology for acute anticoagulation in unstable angina and NSTEMI.

The Committee reviewed the OASIS 5 study (n=20,078), a randomised, double-blind, double-dummy trial in which fondaparinux was compared to enoxaparin in patients with ACS. The Committee noted that fondaparinux was non-inferior to enoxaparin in terms of the primary efficacy endpoint of death, MI or refractory ischaemia at 9 days; 579 patients (5.8%) in the fondaparinux group vs 573 (5.7%) in the enoxaparin group (HR 1.01; 95% CI 0.90 to 1.13). At 30 days there was a trend towards a lower rate of death, myocardial infarction or refractory ischaemia with fondaparinux compared than with enoxaparin (8.0% vs. 8.6%; hazard ratio , 0.93; 95% CI, 0.84-1.02) and of the composite of death or MI (6.2%; HR, 0.90;95%CI, 0.81-1.01). These differences were due to a significant reduction in mortality with fondaparinux (2.9% vs. 3.5% with enoxaparin; hazard ratio, 0.83; 95 percent CI 0.71-0.97; p=0.02).

The primary safety objective in the OASIS 5 study was to determine whether fondaparinux was superior to enoxaparin in preventing major bleeding. Major bleeds were halved in the fondaparinux group: 2.2% vs 4.1% with enoxaparin (HR 0.52; 95% CI 0.44 to 0.61; p<0.001). Fondaparinux was associated with a lower incidence of fatal bleeds (7 vs 22), p=0.005) and severe bleeding according to TIMI criteria (70 vs.126; HR 0.55; 95%CI, 0.41- 0.74; P< 0.001). Larger differences in the rates of minor bleeding were observed (1.1% in the fondaparinux group vs. 3.2% in the enoxaparin group) so that the rates of total bleeding were substantially lowered with fondaparinux than with enoxaparin (3.3% vs 7.3%; HR 0.44; 95% CI 0.39- 0.50).

The Committee heard that fondaparinux is more convenient as it as single daily dose which is not weight based. In terms of cost fondaparinux is comparable to costs of LMWHs and may offer savings for some Trusts depending on the LMWH on formulary.

The Committee discussed risks associated with a switch to fondaparinux from LMWH, including the risk of co-prescribing both fondaparinux and LMWH and lack of familiarity. It was agreed that these issues could be managed locally at Trusts with training and a robust implementation plan. The Committee also agreed that patients with renal impairment (CrCL<20mL/min) or extremes of weight should be managed on an individual basis.

In summary, the Committee agreed that in light of the demonstrated non-inferiority to LMWH in terms of efficacy, and safer bleeding profile, fondaparinux should be the first-line anticoagulant for treatment of NSTEACS across NCL.

5.3 Solifenacin and Tamsulosin (Vesomni; Astellas) for Lower Urinary Tract Symptoms (Applicant: Dr S Chitale; Presentation: Ms R Holland)

The Committee reviewed an application for Vesomni, a fixed dose combination (FDC) of solifenacin 6mg and tamsulosin 0.4mg for the treatment of male patients with moderate to severe lower urinary tract symptoms (LUTS) secondary to bladder outflow obstruction and/or overactive bladder. It was proposed as a 3rd line option

for patients who remain symptomatic after 1st line oxybutynin and tamsulosin, and 2nd line tolterodine and tamsulosin.

The Committee reviewed the SATURN study, a 12-week double blind phase two dose finding study (n=937) in men with LUTS. This study looked at FDC tamsulosin 0.4mg in combination with solifenacin 3, 6 or 9mg versus tamsulosin 0.4mg monotherapy, solifenacin 3, 6 or 9mg monotherapy or placebo. The primary outcome was the change in baseline total international prostate symptom score (IPSS), which was noted to be small in all groups, and not dissimilar from placebo. There was no significant difference between tamsulosin monotherapy and FDC study arms, although FDC-6 and FDC-9 showed a greater efficacy than FDC-3.

The Committee further reviewed the NEPTUNE study, a randomised, double-blind, parallel group placebo-controlled phase three trial in 1,334 men with storage and voiding symptoms of LUTS. The trial assessed efficacy of FDC of solifenacin 6mg plus tamsulosin 400mcg (n=339), FDC solifenacin 9mg plus tamsulosin 400mcg (n=327) compared with tamsulosin 400mcg monotherapy (n=327) and placebo (n=341). The mean reduction from baseline in total IPSS was 5.4 in the placebo arm, 6.2 in the tamsulosin monotherapy arm, 7.0 in the FDC-6 arm and 6.5 in the FDC-9 arm. The Committee noted with interest the lack of significant difference between the tamsulosin monotherapy IPSS (absolute difference of 0.3 to 0.8 on a 35 point scale) and total urgency and frequency score (TUFS) compared to the FDC, particularly with the higher dose of solifenacin (9mg) within the FDC-9 arm. The study showed little clinical benefit in the addition of solifenacin to tamsulosin, particularly at higher doses. In the long-term extension phase of the NEPTUNE study (n=1199) reductions in both total IPSS (-9.0 points) and TUFS (-10.1 points) were maintained. The mean IPSS quality of life score was reduced by 1.9 points from “mostly dissatisfied” (4.1, SD 1.1) to “mostly satisfied” (2.1, SD 1.4).

In terms of safety the Committee were informed that the adverse event profile of each individual drug is similar and the synergism of dosing does not appear to have an effect on adverse drug events, with the most frequently reported treatment-related adverse effects being dry mouth, constipation, dyspepsia, abdominal pain, dizziness, blurred vision, fatigue and ejaculation disorders.

The Committee noted that there are no published trials comparing solifenacin and tamsulosin administered concurrently, versus the FDCs. Although FDCs are designed to simplify medication regimens and improve adherence, the published studies for Vesomni did not report data regarding adherence to treatments. The Committee agreed that for symptomatic conditions such as LUTS adherence is likely to be high and that FDC do not allow for flexibility in dosing. In terms of cost, Vesomni at £36.62 per month is cheaper than tamsulosin and solifenacin given separately but still significantly more expensive compared to immediate release antimuscarinics (oxybutynin IR and tolterodine IR) and oxybutynin MR.

The Committee concluded that there were little data showing advantage of Vesomni over monotherapy with tamsulosin in terms of efficacy, and that the cheaper antimuscarinics used in combination with tamsulosin may be considered where dual therapy was required. The Committee therefore agreed not to include Vesomni on the NCL formulary.

6 Retigabine Audit Data

Ms Sanghvi shared the results of an audit of retigabine conducted by the epilepsy consultants at NHNN on the background of an MHRA safety update in July 2013. The audit of all patients on retigabine showed poor retention rate due to adverse effects and lack of efficacy. At the request of the neurologists, retigabine will now be restricted at UCLH to prescriptions from the lead consultant from the audit only. It remains on the formulary in line with the positive NICE technology appraisal 232 until this guidance is amended and updated. The JFC commended the robust audit approach and agreed that the results should be shared with epilepsy experts at individual Trusts for consideration of formulary position of retigabine locally.

7 Home Oxygen Ordering Guide

This item was deferred to the next meeting.

8 Camden DMARD Guideline

The Committee reviewed the Camden DMARD guideline and agreed that it was very useful as a generic tool for GPs. Dr Urquhart mentioned some concerns and comments from the gastroenterology team at UCLH and agreed to forward these to Ms N Shah. Overall the Committee approved use of the Camden document pending changes in accordance with the clinicians’ comments but agreed that it would also be helpful to have a more specific and detailed shared care document across NCL. Until this is in place it was agreed to approve both the generic Camden guideline across NCL and other shared care protocols to support specific conditions.

9 Type II diabetes treatment pathway – Camden, Enfield and Islington

The Committee reviewed diabetes treatment pathways produced by Camden, Enfield and Islington. It was agreed that the CCG Medicines Management teams would work together to produce a single, simplified pathway for NCL and engage with diabetologists for input before bringing back to the JFC for approval.

10 Local DTC Recommendations

UCLH

- **Rituximab for Myasthenia Gravis** - Approved under evaluation (pending approval of treatment protocol and funding pathway) for UCLH only
- **Rituximab for Stiff Person Syndrome** - Approved under evaluation (pending approval of treatment protocol and funding pathway) for UCLH only
- **Subcutaneous Immunoglobulin for MMN and CIDP –** Approved under evaluation for UCLH only

MEH

- **Juvederm Ultra 3 and 4, hyaluronic acid dermal fillers for orbital reconstruction and volume deficiency** – Approved for Adnexal service at MEH only
- **Lidocaine 3.5% eye gel (Akten) for local anaesthesia in strabismus surgery** – Approved for MEH only

RFH

- **Simeprevir for Hepatitis C** – Approved for patients with secured funding at RFH only
- **Ipilimumab for melanoma** – Approved as per NICE TA as first line therapy for melanoma at RFH
- **Pembrolizumab for melanoma** – Approved under compassionate access program with further review when data become available – for RFH only
- **Miglustat for Neiman Pick Disease type C** - approved in line with specialist national guidelines at RFH only

11 Next Meeting: 27th November 2014, Room TBC

12 Any other business

Nil