NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 27th November 2014

Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Prof L Smeeth	NCL JFC Vice-Chair	**(Vice-Chair)**
	Dr R Fox	DTC Chair, RNOH	
	Dr R Sofat	Consultant Clinical Pharmacologist, UCLH	
	Dr L Wagman	Barnet CCG, GP	
	Dr R Breckenridge	UCLH UMC Chair	
	Dr E Boleti	Consultant Oncologist, RFH	
	Mr T James	MEH Chief Pharmacist	
	Dr H Taylor	Whittington Chief Pharmacist	
	Mr A Shah	RNOH Chief Pharmacist	
	Ms L Reeves	C&I Mental Health Trust	
	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 C Daff	NHS Barnet, Head of Medicines Management	
	Ms E Mortty	NHS Haringey, Deputy Head of Medicines Management	
In attendance:	Ms L Woodeson	Director of Health & Wellbeing, DOH	
	Dr A Mohamed	Urology Clinical Fellow, UCLH	
	Mr E Hindle	MEH Pharmacist	
	Mr M Wyke-Joseph	NMUH Pharmacist	
	Ms R Holland	Pharmacist, UCLH	
	Ms S Sanghvi	Pharmacist, UCLH	
	Mr P Bodalia	Deputy Chief Pharmacist, RNOH	
Apologies:	Dr M Kelsey	Whittington DTC Chair	
	Dr R Urquhart	UCLH Chief Pharmacist	
	Dr A Tufail	MEH DTC Chair	
	Ms W Spicer	RFH Chief Pharmacist	
	Dr J Hurst	Consultant Chest Physician, RFH	
	Ms P Taylor	NHS Haringey Head of Medicines Management	
	Dr D Bavin	Camden CCG, GP	
	Mr TF Chan	BCF Chief Pharmacist	
	Dr C Stavrianakis	Haringey CCG, GP	
	Dr R Kapoor	Consultant Neurologist, UCLH	
	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

Mr Gouldstone confirmed that he was happy to take the Enfield type 2 diabetes pathway forward and gain stakeholder input. Ms Shah requested that revisions to the angina pathway should be reviewed at a JFC meeting prior to approval.

3. Matters arising

Nil

4. Declarations of relevant conflicts of interest

None were declared.

5. New Medicine Reviews

5.1 Daily Tadalafil (*Cialis®; Eli Lilly*) for Erectile Dysfunction (Applicant: Dr A Mohamed; Presentation: Mr P Bodalia)

The Committee reviewed the evidence for daily tadalafil for erectile dysfunction (ED) in two scenarios (1) following non nerve-sparing prostatectomy or (2) ED that has failed to respond to when-required PDE5 inhibitors (sildenafil or tadalafil).

The Committee considered the REACTT study (2014; n=423) which assessed the effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy (NSRP). Patients were randomised to tadalafil 5mg daily, tadalafil 20mg when required or placebo. The endpoint measured was the International Index of Erectile Dysfunction-EF score. This ranges from zero (very poor erectile function) to 30 (normal is considered 26-30).

At month 9, the proportion of patients achieving an International Index of Erectile Function-Erectile Function (IIEF-EF) score of ≥22 were: tadalafil once daily = 25.2%; tadalafil on demand = 19.7%; placebo = 14.2%. The difference between the two tadalafil groups was non-significant. The only statistically significant difference was between tadalafil once daily and placebo groups (p = 0.016; NNT = 10 to achieve one additional responder). At the end of the 3-month open label period (month 13.5) where all patients received tadalafil 5 mg daily, the proportion of patients from the original cohorts achieving an IIEF-EF score of ≥22 were: tadalafil once daily = 32.4%; tadalafil on demand = 33.1%; placebo = 27.0%. None of the differences were statistically significant.

These results were similar in studies by Pavlovich et al and Padma-Nathan et al for sildenafil and Montorsi et al for vardenafil. Overall the studies failed to show an advantage of once-daily dosing versus when-required dosing of PDE5 inhibitors when used to restore erectile function after NSRP. Without the benefits of once-daily dosing being demonstrated and with all PDE5 inhibitors being equally effective, the Committee agreed that in this cohort of patients, when-required dosing of sildenafil would be a suitable first line option.

The Committee noted that there was only one study by Edward et al which showed that daily tadalafil, at licensed doses, improved erectile function in men who had previously had a partial response to when-required PDE5 inhibitors. It was agreed to consider this particular trial in more detail before the next meeting to establish whether daily tadalafil would be suitable for patients with ED that has failed to respond to when required PDE5 inhibitors, and to consider a treatment pathway.

Subsequent analyses of this trial highlighted the following

- men with no response to when-required PDE inhibitors were excluded
- men with an IIEF-EF score between 17 and 26 (moderate ED; on when-required treatment) were recruited.
- of 1021 screened, 623 were randomised to one of three treatment groups; placebo, tadalafil 2.5-5 mg, or tadalafil 5 mg.
- IIEF-EF score increased by 2 units on placebo (from a baseline of 14), and by 8 in both tadalafil groups (to approximately 22)
- the absence of a concurrent group treated when-required made it difficult to fully appreciate the effect of daily tadalafil; these were men who had all responded to when required therapy and might also have increased their IIEF-EF score by 8 units
- the mean IIEF-EF score on screening was not reported, so it was not clear if daily tadalfil had improved ED beyond the effect of prior when-required PDE inhibitor.

One interpretation of this study is that men who with a partial response to when-required therapy also sustain a partial response to daily tadalafil and does not clearly establish superiority of daily tadalafil over when-required PDE inhibitors.

5.2 Ivabradine (*Procorolan®; Servier*) for Stable Angina (No Applicant; Presentation: Ms S Sanghvi)

In light of the recent SIGNIFY study and EMA recommendations the Committee reviewed the evidence for ivabradine for stable angina. In the stable angina pathway discussed at the October 2014 JFC meeting ivabradine was proposed as a last line option for inoperable patients who remain symptomatic or are unsuitable all other treatments and where lowering of heart rate would be beneficial.

The Committee considered the BEAUTIFUL study (2008; n=10,917), a phase 3, randomised, double-blind, placebo-controlled study which assessed whether the addition of ivabradine would reduce cardiovascular death and morbidity in patients with stable coronary artery disease and left-ventricular systolic dysfunction. Patients included in the study were >55 years old, with coronary artery disease, LVEF <40% and in sinus rhythm with resting heart rate ≥60bpm. Patients received either ivabradine 5mg twice daily or placebo with dose adjustment after 2 weeks to 7.5mg twice daily if HR remained ≥ 60bpm.

The primary endpoint was a composite of cardiovascular death, admission to hospital for acute MI and admission to hospital for new/worsening heart failure. The results showed that for the total population there was no significant difference with ivabradine compared to placebo in terms of the primary composite endpoint (HR 1.00; 95% CI 0.91–1.10; p= 0.94) as well as mortality, heart failure and coronary endpoints including admission to hospital for MI or coronary revascularisation. The data was also analysed for a subgroup with heart rate greater than 70bpm. In the sub-group there was no difference with ivabradine in terms of the primary endpoint (HR 0.91; 95% CI 0.81-1.04; p=0.17), mortality or heart failure. However there was a reduction in admission to hospital for MI or unstable angina (HR 0.78; 95% CI 0.62-0.97; p=0.023) and coronary revascularisation (HR 0.70; 95% CI 0.52-0.93; p=0.016).

The Committee noted that the subgroup had a very slightly higher baseline incidence of diabetes, class 3 HF and lower use of β blockers compared to the total study group. The impact of these as confounding factors is not known. In addition the study was in a population with concomitant left ventricular dysfunction where CCBs were contraindicated; the use of nitrates was relatively low and there were no reports of previous use of nicorandil or ranolazine.

The Committee discussed at length the SIGNIFY study (2014; n=19,102), a randomized, double-blind, placebo-controlled trial of ivabradine added to standard background therapy in patients with stable coronary artery disease without heart failure. In this study eligible patients had resting heart rate greater than 70 bpm and were excluded if they had left ventricular dysfunction. Patients received either ivabradine 7.5mg twice daily (5mg twice daily if ≥75 years old) or placebo. Doses could then be adjusted to 5, 7.5 or 10mg twice daily according to the heart rate and symptoms of bradycardia. The target HR for the study was 55 to 60bpm.

The primary endpoint of the study was a composite of death from cardiovascular causes and nonfatal MI. The results showed that ivabradine did not reduce incidence of cardiovascular death, nonfatal MI, coronary revascularisation or admission to hospital for heart failure compared to placebo. There were no significant differences for any of the primary or secondary outcomes including nonfatal MI, coronary revascularisation or stable angina (HR 0.97; 95% CI 0.87-1.07; p=0.53).

In the subgroup analysis of patients with activity limiting angina (CCS scale ≥II), ivabradine was associated with an increase in the composite primary endpoint of cardiovascular death or nonfatal MI (7.6% with ivabradine vs. 6.5% with placebo; HR 1.18; p=0.02). This was consistent for each of the two components of the primary endpoint. There was no significant difference in any of the secondary outcomes with ivabradine. The Committee acknowledged that there were several confounding factors including low target HR, high incidence of bradycardia, higher than recommended doses and that the primary efficacy analysis was not significant therefore the sub analysis results are just indicative.

Aside from the increased mortality signals with ivabradine in the SIGNIFY study, there was a significant increase in bradycardia (18% vs 2%) with placebo, in atrial fibrillation (5.3% vs 3.8%) and phosphenes (5.4% vs 0.5%). There was also a higher incidence of QT prolongation with ivabradine compared to placebo 1.9% vs 0.7%.

The Committee noted recent recommendations from the EMA for prescribing of ivabradine, in response to the SIGNIFY study. However, overall it was agreed that the evidence demonstrated a lack of efficacy of ivabradine in preventing cardiovascular events or mortality. The Committee expressed concern at the increased incidence of mortality and nonfatal MI with ivabradine in the subgroup with symptomatic angina as this represents the anticipated patient group. Despite the potential confounding factors, the Committee agreed that the safety risks with ivabradine outweigh the benefits and therefore agreed that ivabradine would not be added to the NCL formulary for stable angina, and should be removed from the pathway.

5.3 Formoterol & Budesonide Inhaler (Duoresp Spiromax®; Teva) for Asthma/COPD (No Applicant; Presentation Ms R Holland)

The Committee heard that DuoResp Spiromax® is a breath-actuated, dry powder, fixed dose inhaler (160/4.5, 320/9) of budesonide and formoterol fumarate dihydrate licenced for the treatment of asthma or chronic obstructive pulmonary disease (COPD).

The Committee reviewed the evidence from the European Medicines Authority (EMA) marketing authorisation document for DuoResp®, and concluded that bioequivalence was demonstrated between DuoResp Spiromax® and the reference product; Symbicort Turbohaler® at both high (320/9) and medium strengths (160/4.5). The Committee noted that low dose DuoResp® was not shown to be bioequivalent. The committee noted that there are no published 3 clinical efficacy trials, and therefore no patient outcome data is available for real-world use of DuoResp®. Mr Daff informed the Committee that Barnet CCG have been collecting patient data and will be happy to share this when it becomes available. The Committee noted that NICE guidelines for the management of asthma and COPD conclude that there are no significant differences between the many inhaled corticosteroids in terms of efficacy and safety. The Committee noted that patients should be considered individually, taking into account their therapeutic need, preference and ability to concord with treatment. The Committee agreed with NICE guidelines suggesting that the least costly device should be selected, and therefore DuoResp could be an alternative combination therapy. In terms of safety, the committee agreed that DuoResp would be expected to have the same adverse drug reactions as the reference product, Symbicort®. The reported ADRs include systemic effects of steroids and their associated issues (e.g. Cushing's syndrome, decreased bone mineral density), and can also cause; hypokalaemia, potential for a prolonged QTc interval, palpitations, headache, tremor, dizziness and oral candidiasis.

The Committee agreed that DuoResp seems a reasonable alternative to Symbicort, however noted some minor risks with its use;

- DuoResp® is licensed in adults only, potentially leading to off-label use
- DuoResp® appears similar to pMDIs in shape and design but does not require priming
- DuoResp differs in appearance to Symbicort and therefore may cause confusion if switching devices
- As DuoResp® is available as 160/4.5 and 320/9 strength there is no option for down-titrating doses

In terms of cost the Committee heard that a switch of all patients from Symbicort to DuoResp could lead to £500k savings across NCL, if only new patients were commenced on DuoResp the saving would be less but still significant.

The Committee heard from Ms Shah that there is a high use of Seretide® in Camden which is concerning due to the association between fluticasone and community acquired pneumonia. Camden CCG currently recommends that all patients should be commenced on inhalers containing beclometasone as 1st line treatment (with a spacer if necessary), moving to budesonide as second line treatment. The Committee noted that there are differing treatment pathways across NCL, and therefore varying use of combination inhalers for both asthma and COPD. Ms Holland informed the Committee that a new group called the London Respiratory Clinical Leadership Group is being set up which will review all inhalers and devices, considering efficacy, safety, and cost to generate pathways for asthma and COPD. Dr Taylor agreed to liaise with Dr Louise Restrick who is leading the Committee to confirm their position on DuoResp in treatment pathways. The Committee agreed that decisions made by the LRCLG could be brought to the JFC, inviting Dr Restrick if clarification is needed.

The Committee supported local pathways, and the local switching of patients to DuoResp in line with QIPP savings. The Committee awaits a final decision from the LRCLG before an NCL-wide switch is instigated.

6 Moorfields Prescribing Protocols

The Committee approved the updated glaucoma prescribing guidelines and ocular lubricant prescribing guidelines. Mr Hindle informed the Committee that a separate protocol for topical ciclosporin in dry eye would be brought to the next meeting.

7 Hydroxyethyl Starch Preparations

The Committee noted that the suspension of the licenses for hydroxyethyl starch (HES) solutions has been lifted. HES products are now indicated for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not sufficient, and have several new listed contraindications and warnings. The Committee agreed that the evidence for HES solutions should be reviewed at the next JFC meeting before considering addition back onto the formulary.

8 NICE AF Guidance on NOACs and Aspirin

The Committee discussed the recent NICE CG180 guidance on the management of AF. It was agreed that patients on aspirin monotherapy should be reviewed on an individual basis. The Committee supported an expansion of the use of NOACs and review of the comparative evidence, particularly relating to renal impairment. Dr Sofat agreed to lead on this and contact relevant stakeholders.

9 Local DTC Recommendations

UCLH

- **Elosulfase Alfa (Vimizim) for Morquio A Syndrome** – Not approved (approved as continuation for 2 patients only).
- **Ramucirumab for Metastatic Gastric or Gastro-oesophageal Junction Adenocarcinoma -** Approved under named patient scheme only.

RFH

- **Nitazoxanide for chronic resistant norovirus infection in PID patients –** Approved for prescribing by Immunology only.
- **Bosentan for extended use in digital ulcers** – Interim approval until NHS England policy is issued.

10 Next Meeting: 29th January 2015, Room TBC

11 Any other business

The Committee agreed that the UCLH decision to approve rituximab for myasthenia gravis under evaluation for one year (pending funding confirmation) could be extended to RFH, and encouraged collaboration in the collection of evaluation data.