NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 29th May 2014

In Chadwick 2.18, Gower Street, UCL

1. Present:	Prof R MacAllister	NCL JFC Chair
	Dr R Urquhart	UCLH Chief Pharmacist
	Mr A Shah	RNOH Chief Pharmacist
	Mr A Dutt	NHS Islington, Head of Medicines Management
	Dr R Breckenridge	UCLH UMC Chair
	Ms N Shah	NHS Camden, Head of Medicines Management
	Ms P Taylor	NHS Haringey Head of Medicines Management
	Mr TF Chan	BCF Chief Pharmacist
	Dr R Sofat	Consultant, UCLH
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management
	Dr R Fox	DTC Chair, RNOH
	Mr C Daff	NHS Barnet, Head of Medicines Management
In attendance:	Dr H Ruschen	Consultant, MEH
	Mr E Hindle	MEH Pharmacist
	Dr D Patel	Consultant, RFH
	Dr M Cohen	Consultant, BCF
	Ms S Ceci	Pharmacist, WH
	Ms I Samuel	Pharmacist, RFH
	Mr K Thakrar	Pharmacist, UCLH
	Dr A Grosso	Pharmacist, UCLP
	Dr F Bennett	Registrar, UCLH
	Dr M George	Registrar, UCLH
	Ms R Holland	Pharmacist, UCLH
	Ms A Moore	Pharmacist, UCLH
	Ms S Sanghvi	Pharmacist, UCLH
	Mr P Bodalia	RNOH Deputy Chief Pharmacist
Apologies:	Dr L Wagman	Barnet CCG, GP
	Mr A Karr	NCL Procurement Chair
	Dr P Ancliff	GOSH DTC Chair
	Dr D Bavin	Camden CCG, GP
	Dr E Boleti	Consultant, RFH
	Dr J Hurst	Consultant, RFH
	Ms W Spicer	Chief Pharmacist, RFH
	Ms J Cope	GOSH Chief Pharmacist
	Ms R Dallmeyer	CSU Pharmacist
	Prof L Smeeth	NCL JFC Vice-Chair
	Mr T James	MEH Chief Pharmacist
	Ms S Drayan	NMUH Chief Pharmacist
	Dr M Kelsey	WH DTC Chair

2. Minutes of the last meeting

The minutes of the last meeting were accepted as accurate.

3. Matters arising

3.1 Pregabalin Position Statement

The Committee agreed that an interim primary care advice statement regarding the neuropathic pain pathway should be sent to relevant stakeholders while Dr Breckenridge arranges a meeting with stakeholders to discuss the proposed prescribing pathway.

3.2 Overactive Bladder Syndrome (OAB) Guideline

Dr Breckenridge informed the Committee that he will write a letter to the UCLH consultants in response to their concerns concerning the draft JFC OAB guidelines. Prof MacAllister noted that the specialists wished to adhere strictly to the guidance contained in CG171.

4. Members declarations of relevant conflicts of interest

None were declared.

5.1 Dexmedetomidine (Orion) for Sedation in the ICU Setting (Applicant: Dr K Agyare, Presentation: Mr P Bodalia)

The Committee reviewed the selective alpha-2-receptor agonist dexmedetomidine for sedation of adult ICU patients. The Committee heard that dexmedetomidine was recently reviewed at the March RNOH DTC but not recommended as an alternative option to midazolam and propofol for (1) patients requiring a sedation level of 0 to -3 on the Richmond Agitation-Sedation Score (RASS) scale, (2) patients with a history of 'difficult to wean from sedation to extubation' following use of midazolam/propofol, (3) patients who are highly agitated or with delirium, (4) patients who will require ventilation for longer than 24 hours.

The Committee reviewed two phase III, multi-centre, randomised, double-blind, non-inferiority studies of similar design published by Jakob et al. Dexmedetomidine was compared to propofol in PRODEX (n=498) and to midazolam in MIDEX (n=500), both in ICU patients requiring continuous light-moderate sedation as part of mechanical ventilation. Dexmedetomidine was shown to be non-inferior to both propofol [OR 0.97 95% CI 0.89-1.04] and midazolam [OR 1.09 95% CI 0.99-1.19] in maintaining light-to-moderate sedation (RASS 0 to -3) without rescue medication. There was however no advantage in reduction of duration of mechanical ventilation compared with propofol (p=0.24). Although the time to extubation was shorter with dexmedetomidine compared to midazolam (p=0.01) and propofol (p=0.04) the Committee noted that this endpoint was multifactorial and not necessarily exclusively related to sedation. There was also no significant difference in length of ICU stay or hospital stay with dexmedetomidine compared to propofol or midazolam. Although there were statistically significant increases in ability to communicate pain, ability to arouse and ability to cooperate with care (all measured via visual analogue scales [VAS]) the Committee questioned whether these differences translated to a clinically significant improvement.

Regarding safety, the Committee noted a higher discontinuation rate in general due to lack of efficacy with dexmedetomidine compared to midazolam and propofol. There was a similar incidence of neurocognitive disorders between dexmedetomidine and midazolam but fewer compared to propofol. Importantly the Committee noted that patients receiving dexmedetomidine reported more events of hypotension (20.6% vs 11.6%) and bradycardia (14.2% vs 5.2%) compared to midazolam. A significantly higher number of patients also reported first-degree AV block compared with propofol (3.7% vs 0.8%).

In summary, the Committee could not find a clinically significant advantage over midazolam or propofol to justify the higher cost of dexmedetomidine (£400 per patient compared to £10-40) and remained concerned with higher discontinuation rates and its adverse effect profile. Based on these factors, the Committee ratified the RNOH decision that dexmedetomidine should not be included on the NCL formulary for sedation in the ICU setting.

5.2 Dexmedetomidine (Orion) for Conscious Sedation in Ophthalmic Surgery (Applicant: Dr H Ruschen, Presentation: Mr P Bodalia)

The Committee further reviewed dexmedetomidine for conscious sedation in ophthalmic surgery, an off-label indication. The Committee reviewed a randomised, double-blind trial by Alhashemi et al comparing dexmedetomidine to midazolam in 44 adult patients undergoing elective cataract surgery. The Committee questioned the high mean dose of 80 micrograms of dexmedetomidine in the study, which would contribute to the lower heart rate, lower mean arterial blood pressure and longer post anaesthetic recovery and time to discharge seen with dexmedetomidine compared to midazolam. In a similar study by Apan et al (n=90) with a mean dose 19 micrograms of dexmedetomidine the safety profile was similar to midazolam with a lower mean VAS pain score in the dexmedetomidine group ($p<0.05$).

The Committee also reviewed a randomised, single-blind study by Ghali et al (n=60) comparing dexmedetomidine to propofol (±alfentanil). It was noted that dexmedetomidine had similar outcomes to propofol in terms of haemodynamic effects and time to discharge from the recovery unit ($p=0.08$) but was associated with a significantly longer time from start of infusion to target sedation level ($p=0.001$), significant increase in respiratory rate and no clinically relevant difference in satisfaction from the surgeon or patient.

Overall the Committee considered dexmedetomidine to be comparable to midazolam and propofol (± alfentanil) in achieving and maintaining conscious sedation (RSS of 3) during ophthalmic day-case surgery but were concerned with the limited data and conflicting results regarding clinical advantages (time to target sedation, patient/surgeon satisfaction, time to discharge from recovery room) over currently available agents. Dr Ruschen explained that it would primarily be useful for patients undergoing surgery close to the macula to enable them to be sedated whilst remaining completely still. Currently these patients are not sedated or require a general anaesthetic. The Committee were unconvinced that current evidence was robust enough to support this indication. Therefore it was agreed that dexmedetomidine would not be added to the formulary for sedation in ophthalmic surgery.

6 DPP-IV inhibitors for Type II Diabetes (Applicant: Dr M Barnard/Dr M Cohen; Presentation: Dr F Bennett)

The Committee reviewed the DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) in response to an application for sitagliptin to be the first-line DPP-4 inhibitor and linagliptin to be available for patients with severe or end-stage renal disease. The Committee were informed that there are a lack of head to head studies between the DPP-4 inhibitors, however current evidence suggests similar glucose-lowering efficacy, weight-neutral effects and safety profiles when used as monotherapy or in combination with other hypoglycaemic drugs. Direct comparisons with other oral antidiabetic therapies have shown slightly less HbA1c reduction than metformin and similar HbA1c reductions to thiazolidinediones (TZD) and sulphonylureas (SU), with the advantages of no weight gain compared to TZD and SU, fewer hypoglycaemic episodes compared to SU and better tolerability compared to TZD. Studies comparing DPP-4 inhibitors to GLP-1 receptor agonists (liraglutide, exenatide) demonstrated that GLP-1 receptor agonists are more effective in lowering blood glucose and weight but are also associated with increased GI side effects, higher cost and parenteral route.

The Committee considered the major cardiovascular and safety studies of DPP-4 inhibitors and found no significant differences between the DPP-4 inhibitors in tolerability profiles. The Committee noted that the long-term cardiovascular studies EXAMINE and SAVOR-TIMI 53 have shown that alogliptin and saxagliptin are neutral in terms of cardiovascular safety. The only significant increase in incidence relative to placebo was for heart failure with saxagliptin, which requires further studies. The Committee reviewed the conflicting evidence relating to pancreas-related adverse events and noted the conclusions of the MHRA and EMA investigations that prescribers should follow recommendations in product literature and counsel patients about symptoms of acute pancreatitis. Overall DPP-4 inhibitors had a low hypoglycaemia risk, similar to TZD and metformin, and favourable GI tolerability profile compared to metformin and GLP-1 agonist. Current limited data indicate similar incidence of cancer to placebo and conflicting data regarding incidence of upper respiratory tract or urinary tract infections.

The Committee considered evidence for use of DPP-4 inhibitors in kidney disease and noted that they are largely renally excreted (75-85%) with the exception of linagliptin which only has 5% excretion via the renal route. Although linagliptin would not require dose adjustment in renal disease, the Committee noted that all the DPP-4 inhibitors have been studied in patients with renal impairment and are licensed for use with appropriate dose reductions. The limited data indicates that DPP-4 inhibitor (appropriately dose reduced) are well tolerated and provide effective glucose control in patients with renal impairment compared to placebo or

SU. Considering the other DPP-4 inhibitors are licensed in renal disease (with dose reductions) the Committee could not see an advantage for switching patients to linagliptin, and therefore this agent was not approved.

Overall the Committee agreed that sitagliptin should be the sole DPP-4 on the NCL formulary.

7 GLP-1 Agonists for Type II Diabetes (Lixisenatide Appeal) (Applicant: Dr D Patel/ Dr M Cohen; Presentation: Mr K Thakrar)

Dr Patel and Dr Cohen presented an appeal for the use of the GLP-1 agonist lixisenatide in type 2 diabetes. The Committee previously agreed that the inclusion of GLP-1 agonists on the formulary should be limited to those recommended by NICE in technology appraisals (liraglutide and exenatide modified release). The Committee discussed the available options and concluded that the only advantage of including lixisenatide on the formulary would be cost savings in comparison to existing GLP-1 agonists rather than clinical outcomes. The Committee considered it unlikely that consensus across NCL would be achieved to use lixisenatide first line for cost savings, and taking into account the preferable weight loss and reduction in HbA1c with the NICE approved GLP-1 agonists agreed that lixisenatide should remain non-formulary.

8 Type II Diabetes Treatment Pathway

The Committee reviewed a proposed treatment pathway produced by Camden CCG for type II diabetes and agreed that it should be sent out for consultation to NCL stakeholders after minor amendments.

9 Parkinson's Disease Treatment Pathway

This item was deferred to the next meeting pending modification due to pre-meeting stakeholder comments.

10 Mesalazine preperations

The Committee noted the potential for significant cost savings associated with using Octasa®. A formulary bulletin, GP letter and patient information leaflet were ratified for use across NCL and are to be made available to Trusts and CCGs.

11 MHRA Patient Safety Alerts

Ms Shah informed the Committee of a recent MHRA patient safety alert 'Improving medication error incident reporting and learning' and requested a list of Medication Safety Officers for NCL. The Committee agreed that the strategy to meet the actions in the alert should be decided on an individual organisation basis, with collaboration via the existing network of medication safety pharmacists. It was agreed that each organisation would submit a short report outlining their current status and action plan, for discussion at the NCLMON.

12 Local DTC Recommendations

UCLH: Ecilizumab for atypical haemolytic uraemic syndrome. Approved pending NICE guidance in July 2014 and confirmation of ongoing funding thereafter. This decision was ratified by the Committee

UCLH: Moxibustion for foetal version in breech presentation. The Committee did not consider this to be a medicine and therefore was not under the remit of the JFC.

NMUH: Guanethidine monosulfate for complex regional pain syndrome. Removed from the formulary following advice from the Royal College of Physicians and a negative Cochrane review. This decision was ratified by the Committee.

MEH: Intracameral bevacizumab in trabeculectomy. Decision deferred.

RNOH: Midodrine for anejaculation in men with spinal cord injury. Decision deferred.

13 NCL-MMO Minutes

The NCL-MMO minutes were included for information.

14 Date of next meeting: There will no longer be a meeting in June due to apologies. Please release the date (26th June 2014) from your diaries.

15 Any other business

Ms Samuel informed the Committee that the business cases for anti-TNF maintenance therapy in Crohn's and ulcerative colitis are in progress and will be submitted to the CSU shortly on behalf of NCL Trusts.

Dr Grosso informed the Committee that the business case for tocilizumab as monotherapy in rheumatoid arthritis is complete and will be submitted to the CSU shortly on behalf of NCL Trusts.