NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 26th September 2013

In UCL Room Chadwick 2.18, Gower St, LONDON, WC1E 6BT

1. Present:	Prof L Smeeth	NCL JFC Vice Chair (Chair)
	Dr D Bavin	Camden CCG
	Dr E Boleti	Consultant Oncologist, RFH
	Mr A Dutt	NHS Islington, Head of Medicines Management
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management
	Mr TF Chan	BCFH Chief Pharmacist
	Dr R Urquhart	UCLH Chief Pharmacist
	Ms J Cope	GOSH Chief Pharmacist
	Ms W Spicer	RFH Chief Pharmacist
	Mr T James	MEH Chief Pharmacist
	Ms S Drayan	NMUH Chief Pharmacist
	Dr H Taylor	WH Chief Pharmacist
	Dr R Sofat	Clinical Pharmacologist
	Mr A Shah	RNOH Chief Pharmacist
	Ms N Shah	NHS Camden Head of Medicines Management
	Ms P Taylor	NHS Haringey Head of Medicines Management
	Dr J Hurst	RFH DTC Chair
In attendance:	Mr A Grosso	UCLP Pharmacist
	Ms K Chapman	JFC Support Pharmacist
	Ms S Sanghvi	UCLH Pharmacist
	Ms R Holland	UCLH Pharmacist
	Mr K Thakrar	UCLH Pharmacist
	Dr D Thomas	MEH Consultant Ophthalmologist
	Ms I Samuels	RFH Pharmacist
	Ms J Van Der Leer	RFH Head Respiratory Physiologist
Apologies:	Prof R MacAllister	NCL JFC Chair
	Dr R Fox	RNOH DTC Chair
	Mr G Irvine	Lay Member
	Mr A Karr	NCL Procurement Chair
	Dr R Breckenridge	UCLH DTC Chair
	Dr L Wagman	NHS Barnet CCG
	Dr A Tufail	MEH DTC Chair
	Dr M Kelsey	WH DTC Chair
	Dr M Broadbent	BCF DTC Chair
	Dr R Kapoor	UCLH Neurologist
	Dr S Bennett	Islington CCG
	Mr C Daff	Barnet Head of MM
	Ms R Dallmeyer	CSU Pharmacist
	Ms B Brese	CSU Pharmacist

Dr J Hurst was welcomed as a new member (RFH DTC Chair & Respiratory/Medicine Consultant).

2. Minutes of the last meeting

Ms N Shah noted that the funding mechanism for Botox® for Sphincter of Oddi Dysfunction was not minuted. It was advised that a business case will be required.

3. Matters arising

3.1 NOAC prescribing hierarchy

The Committee was asked to consider whether a prescribing hierarchy for the preferred selection of a NOAC should be stated within the NOAC documentation. The Committee agreed that as there was

insufficient evidence to differentiate these agents on efficacy and safety that a hierarchy should be based on cost and convenience. The following preferred ordering was agreed: (1) rivaroxaban (2) dabigatran (3) apixaban. The Committee agreed that the NOAC imitative can now go-live once the documents are amended to reflect this and are made available on the JFC website.

3.2 Preferred calcium & vitamin D preparation

Feedback from the August JFC meeting was given regarding the preferred calcium & vitamin D preparation to be used across NCL. The Committee noted that a 50% switch to Accrete® could save the five CCGs in NCL, in total, £150,000 per annum. However implementing this switch would require branded prescribing, which goes against current generic prescribing principles. A pragmatic approach was agreed whereby CCGs would raise awareness of the potential cost-saving in primary care by the ScriptSwitch system and switching will be encouraged where appropriate.

3.3 Moorfields Eye Hospital Glaucoma Guidelines

The Committee had previously discussed the proposed MEH Glaucoma Guidelines for implementation across NCL. NS asked for clarification at the July meeting regarding choice of brinzolamide drops as the first-line carbonic anhydrase inhibitor. NS pointed out that as dorzolamide has similar efficacy, and is available as a generic, this may be a more appropriate first-line agent. The Committee heard that MEH Glaucoma consultants reconsidered the pathway at their September Service meeting and unanimously voted to keep brinzolamide drops as first line despite it being the more costly option, due to increased side effects with topical dorzolamide which can reduce patient compliance and increase clinic appointments. The Committee noted the lack of underlying rigour in the evidence to support the improved tolerability of brinzolamide but agreed to accept the MEH Glaucoma Guidelines without amendment.

4. Members & applicants declarations of relevant conflicts of interest

None declared.

5. CCG-related medicine applications & reviews

5.1 Lixisenatide (Lyxumia®; Sanofi) for Type 2 Diabetes (Applicant: Dr M Cohen; Presenation: Ms S Sanghvi)

The Committee considered an application for lixisenatide injection for use in type 2 diabetics in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

The Committee heard that there are currently three other GLP-1 receptor agonists licensed in the UK; exenatide (Byetta®), exenatide modified release (Bydureon®) and liraglutide (Victoza®). These have all been shown to improve glycaemic control and have beneficial effects on weight, with a low risk of hypoglycaemia. The applicant proposed to replace exenatide as the first line GLP-1 receptor agonist when used as per NICE CG 87.

The Committee considered evidence from the GetGoal-X4, a 24 week, randomised, open-label; non-inferiority study compared the efficacy and safety of lixisenatide versus exenatide in type 2 diabetes inadequately controlled by metformin. Participants were randomised to either lixisenatide 20mcg once daily (n=318) or exenatide 10mcg twice daily (n=316).

The primary objective was a non-inferiority assessment of lixisenatide versus exenatide in HbA1c change from baseline to week 24. In this study lixisenatide demonstrated non-inferiority in HbA1c reduction based on a predefined non-inferiority criterion (≤0.4% for the upper limit of the 95% CI).

Kapitza *et al* conducted a 28 day, randomised, open-label multi-centre study to assess the pharmacodynamics of lixisenatide (n=77) once daily versus liraglutide (n=71). A standardized solid breakfast test was performed and post-prandial glucose (PPG) and other metabolic parameters were measured in patients with type 2 diabetes insufficiently controlled on metformin. The primary efficacy endpoint was the change from baseline to day 28 in the area under the plasma-glucose concentration time curve in the 4 hour period after the start of the standardised breakfast meal. From

baseline to day 28, lixisenatide provided a significantly greater reduction in PPG compared with liraglutide (-12.6 vs. -4.0h/mmol/l, respectively; p<0.0001) with regard to the breakfast meal. This is not entirely unexpected considering the different profiles of each drug: lixisenatide reaches t_{max} at 1 to 3.5 hours and liraglutide peaks at 8 to 12 hours post-dose. The maximum PPG was shown to occur 1.5 hours after the start of the meal. Mean HbA1c was reduced by 0.51% in the liraglutide group and 0.32% in the lixisenatide group, although this was only after a 28 day period. Reduction in body weight was 2.4kg in the liraglutide group compared to 1.6kg in the lixisenatide group (p<0.01).

GetGoal-L-Asia8 was a 24-week, randomised, double-blind, placebo controlled study conducted in an Asian population. Patients included in the study had type 2 diabetes and were on stable basal insulin therapy with or without a sulfonylurea and had HbA1c between 7-10%. A total of 311 subjects were randomized to receive lixisenatide titrated up to 20mcg once daily over 2 weeks (n=154), or placebo (n=157). Established doses of insulin with or without sulfonylurea were continued.

The primary end point was change in HbA1c from baseline to week 24. A 0.88% greater reduction [95% CI: -1.12% to -0.65%, p<0.001] was seen in the lixisenatide group compared to placebo. Lixisenatide also showed significant improvements compared to placebo in secondary outcomes including fasting plasma glucose, post-prandial glycaemic control and average 7-point self-monitoring plasma glucose values. The change in weight between the two groups, however, was not statistically significant (p=0.089). This may be due to the average baseline BMI of 25.3kg/m^2.

With regard to safety, the EMA recently concluded that presently available data does not confirm recent concerns over an increased risk of pancreatic adverse events with GLP-1 receptor agonists. Two large independent studies funded by the European Commission are currently underway to determine the risk profile of diabetes treatments in general including pancreatic adverse effects. These are expected to be published in 2014.

The Committee heard that the overall adverse event profile of lixisenatide is similar to other GLP-1 agonists, with GI side effects being the most common. In the GetGoal-X study of lixisenatide vs exenatide, 74 patients had adverse events that led to premature treatment discontinuation (10.4% of these in the lixisenatide group and 13.0% in the exenatide group). These discontinuations were mainly due to gastro-intestinal effects such as nausea. However, significantly fewer participants experienced nausea in the lixisenatide group (24.5% vs 35.1% p<0.05). Fewer participants also experienced symptomatic hypoglycaemia in the lixisenatide once-daily group compared with the exenatide twice-daily group (2.5% vs. 7.9%; P<0.05).

In the study by Kapitza *et al*, lixisenatide had fewer adverse events reported when compared to liraglutide (55% and 65% respectively). Fewer patients in the lixisenatide arm reported gastrointestinal side effects (36.4%) compared to the liraglutide arm (46.5%). There were no serious adverse events or symptomatic hypoglycaemia reported.

Cost and convenience were summarised for the Committee in the table below:

Drug	**Dose Regimen**	**Annual Drug Cost Per Patient (inc VAT)**
Lixisenatide	**20mcg once daily**	**£780**
Exenatide (Byetta®)	5-10mcg twice daily	£983
Exenatide Modified Release (Bydureon®)	2mg once weekly (requires reconstitution before administration and patient training)	£1144
Liraglutide (Victoza®)	1.2mg once daily	£1130

The Committee discussed the various preparations available in this class with regard to efficacy and safety, and it was agreed that the inclusion of GLP-1 receptor agonists on the Formulary should be limited to those recommended by NICE in current technology appraisals – namely liraglutide and exenatide modified-release. Therefore, the Committee could not see the value of introducing a third

GLP-1 on to the formulary so it was agreed to not recommend lixisenatide and to remove exenatide (Byetta®) from local formularies.

Adalimumab (Humira®; Abbvie) for posterior uveitis (Applicant: Dr A Rees; Presentation: Ms K Chapman)

The Committee considered an application for adalimumab sub-cutaneous injection to be added to the formulary for posterior uveitis. The applicant also asked for consideration for severe refractory anterior uveitis, based on positive initial results from the Sycamore trial currently being conducted in children with Juvenile Idiopathic Arthritis.

The Committee heard that uveitis is an inflammatory condition affecting various structures in the eye, and may occur alone or in relation to auto-immune conditions such as rheumatoid arthritis, Behcet's disease psoriasis or sarcoidosis. Patients with posterior uveitis and those with sight threatening complications of anterior uveitis usually require systemic treatment especially if the disease is bilateral. The mainstay of treatment is topical and oral corticosteroids, methotrexate or mycophenolate. Severe, refractory cases may require the administration of an anti-TNF, with the goal of preserving vision by redressing immunological tolerance and inducing drug-free remission.

The Committee heard that infliximab (IV) is currently on the MEH Formulary for this indication, however not all patients tolerate and/or respond to this biologic, and therefore a request has been made to add adalimumab to the formulary. Adalimumab is a fully human monoclonal antibody against TNFα and is delivered via sub-cutaneous injection fortnightly, which may offer cost and patient advantages. The addition of an anti-TNF can reduce steroid and oral immunosuppressant doses, which in turn can reduce side effects and improve patient compliance. Moorfields Eye Hospital is currently participating in a RCT evaluating adalimumab in uveitis.

The Committee considered evidence from Cordero-Coma *et al* who conducted a systematic review of studies assessing the use of a particular anti-TNF-α in patients with previously documented uveitis. With regard to adalimumab, a total of 420 patients with different uveitis diagnoses were included.

Using the criteria set out by the authors, current evidence shows that treatment with either infliximab or adalimumab seems to be effective for the treatment of non-infectious immune-mediated uveitis with a recommendation level of C and an evidence level of 2b for each drug. According to the Oxford Centre for Evidence-based Medicine Levels of Evidence, 2b is defined as individual cohort studies or low-quality randomised controlled trials and is a medium level of evidence. The review notes that as both infliximab and adalimumab share a similar action profile, but different routes of administration, immunogenic potential, and price, the reasons for using an individual agent should be related to non-clinical issues associated with the patient.

Diaz-Llopis *et al* conducted a prospective case series of 131 patients with refractory uveitis and intolerance or failure to respond to at least one other systemic immunosuppressive drug. Patients received 40mg of adalimumab sub-cutaneously every other week for 6 months. Uveitis was classified anatomically; 33.6% had chronic anterior uveitis, 6.9% had intermediate uveitis, 3.8% had posterior uveitis, and 43.5% had panuveitis. The remainder had combined uveitis.

During the 6 months of the study, 50 patients (38.2%) experienced reactivation of uveitis which was severe in only 9 patients (6.8%). Visual acuity improved by -0.3 log MAR (+15 letters) in 21.3% of eyes, remained stable in 75.4% of eyes and worsened by +0.3logMAR in 3.3% at the 6 month visit. At 6 months, 84.7% of patients were able to reduce at least 50% of their baseline immunosuppressant load. The mean dose of corticosteroids also decreased from 0.74 (3.50) to 0.20 (0.57) mg/kg/day ($P<0.001$). In patients who had a loss of efficacy after a prior initial response to infliximab or etanercept, a satisfactory therapeutic response was achieved with adalimumab as described in other therapeutic indications. All 131 patients with refractory uveitis of different causes showed an improvement of symptoms and a decrease in inflammatory activity.

Suhler *et al* conducted a multi-centre, open-label, Phase II prospective trial enrolling subjects with non-infectious uveitis refractory to corticosteroids and at least one other immunosuppressive medication. The efficacy and safety of adalimumab was assessed in 31 patients over 50 weeks. Week 10 responders were permitted to continue receiving adalimumab (every two weeks) for the study duration of 50 weeks.

21 patients (68%) were characterised as clinical responders at 10 weeks, and 12 of these (39%) exhibited durable response after 50 weeks. Two out of 6 patients with posterior uveitis had a durable response at 50 weeks (17% of 50 week responders). The same group conducted a similar study on infliximab, which showed a higher response rate (77% response at 10 weeks), but also higher levels of toxicity.

With regard to safety the overall rate of reported side effects with anti-TNF-α agents for the treatment of uveitis was 2.2% (26 out of 1147 patients reported). WHO reports that since 2000 there have been 509 cases of TB with infliximab and 109 with adalimumab. The chief mechanism for this is suppression of macrophage activation, which inhibits the T-cell-mediated and TNF-dependent response implicit in the response to TB infection.

In the study by Diaz-Llopis *et al*, (n=131) adalimumab was well tolerated in all patients but one during the 6 month follow up period. Minor side effects such as localised injection site pain, rash and bruising were reported, as were individual cases of fatigue, hypertension, herpes zoster, infectious mononucleosis, and reactivation of chronic hepatitis C. These patients did not discontinue the study.

Generally, published literature reports that infliximab appears to show more treatment-limiting toxicity than adalimumab.

In summary, the Committee agreed that the evidence for adalimumab in posterior uveitis is limited by lack of RCT data, differing study designs as well as by all types of uveitis being considered together meaning that evidence specifically in posterior uveitis was limited by very small patient numbers. Despite these limitations, the results show that adalimumab is effective in patients with severe refractory uveitis, with fewer side effects than infliximab. Although proposed patient numbers are small, the cost-savings with regard to the drug itself are significant (cost of medication almost halved when adalimumab is compared to infliximab). Sub-cutaneous injection is also a more convenient method of delivery compared to IV, although injections are more regular than infliximab (fortnightly versus every six weeks after initiation period).

The Committee agreed that adalimumab should be added to the NCL Joint Formulary for posterior uveitis, pending a clear protocol for cessation of treatment. The route of funding still needs to be clarified and a business case will be required.

With regard to the late application for use severe refractory anterior uveitis, the Committee agreed that the applicant should re-apply to the Committee once the relevant trial data are published.

6. Local DTC recommendations

6.1 UCLH: Cinacalcet (Mimpara®; Amgen Ltd) for primary hyperparathyroidism.

Approved for 3 patients at UCLH only and not for primary care prescribing. To be re-evaluated in 12 months and audit data to be combined with RFH audit data. The Committee agreed with this proposal.

6.2 RFH: Leuprorelin (Prostap®; Takeda) for prostate cancer

Leuprolein was recommended for use in prostate cancer (except neo-adjuvant use) at the RFH. The Committee noted that there may be a more convenient and cost-effective option available, and recommended a review of all LHRH analogues at the JFC before supporting this recommendation.

6.3 RFH: 18F – fluorocholine for PETC/CT imaging for staging of prostate cancer

Fluorocholine for PETC/CT imaging for staging of prostate cancer was recommended for use at the RFH. The Committee agreed with this recommendation.

6.4 RFH: Bosentan (Tracleer®; Actelion) for digital ulcers.

Bosentan for digital ulcers was recommended for use at the RFH. The Committee agreed with this recommendation subject to clarification with the CRG.

7. NCL-MMC/NCL-MON minutes

These minutes were provided for information. It was noted that the NCL Medicines Management Committee has changed its name to NCL Medicines Optimisation Network.

8. Post trial access of drugs used as IMPs

Ms Cope discussed the requirement for clinical trials to have a statement in the patient information leaflet outlining the access to treatments at the end of the study. At present this statement is not always available to pharmacy departments when signing-off trial protocols. The importance of this was highlighted as even though an information leaflet may state that the IMP will be available post-trial, this is not always practicable depending on availability and terms of any Patient Access Scheme, as well as the burden of delivery and other related charges.

The Committee agreed that pharmacists should be able to review and clarify the statement of IMP availability post-trial in the patient information leaflet as part of the pharmacy review of any new study.

9. Non CCG-related applications/reviews

9.1 Mannitol (Osmohale®; Pharmaxis) for bronchial challenge testing (Applicant: Dr P Dilworth; Presentation: Ms I Samuels)

The Committee reviewed an application for mannitol (MANN) to be used as an indirect osmotic bronchial challenge test for identifying hyper-responsiveness in subjects with a baseline FEV1 of 70% or more of the predicted value. It was proposed that this would replace methacholine (METC).

The Committee noted that METC is currently unlicensed and is prepared by the Pharmacy department. MANN is in capsule form so is proposed to be safer, easier and quicker to perform the test. It is also approximately half the price of the unlicensed product currently in use.

The Committee heard that 10 studies have compared these treatments in adults and children. One of the key studies by Anderson *et al* (2009) compared MANN with METC to predict exercise-induced bronchoconstriction and a clinic diagnosis of asthma. This was a multi-centre trial in 25 sites in the US. The phase III trial (funded by the company Pharmaxis) investigated the specificity and sensitivity of MANN and METC to identify exercise-induced bronchoconstriction (EIB). 509 people were enrolled (age range 6-50yrs). The clinical diagnosis of asthma was made on examination, history, skin tests, questionnaire and response to exercise. The investigators were blind to the MANN and METC results.

The prevalence of BHR was the same: for exercise (43.5%), MANN (44.8%) and METC (41.6%) with a test agreement between 62% and 69%. The sensitivity and specificity for a clinical diagnosis of asthma was 56%/73% for MANN and 51%/75% for METC. Sensitivity increased to 73% and 72 % for MANN and METC when 2 exercise tests were positive. The authors concluded that MANN and METC provided therapeutic equivalence to identify BHR, EIB, and a clinical diagnosis of asthma in a group of subjects suspected of having asthma but without a clear diagnosis. In addition to not requiring specialist equipment, the MANN test was more reproducible and took less time to perform than the METC. Only 43.5% of subjects had a positive response to exercise as defined by at least a 10% reduction in FEV1 on at least 1 of 2 challenges.

The Committee concluded that the proposal to use a cost-effective and safe product that does not require dilution by pharmacy was reasonable and therefore agreed that inhaled mannitol (Osmohale®) should be added to the formulary for bronchial challenge testing. This will replace inhaled metacholine, which will be removed from the RFH formulary.

10. Date of next meeting: 24th October 2013 (location TBC).

11. Any other Business

11.1 Low molecular weight heparins (LMWH)

Mr Grosso reminded the Committee that there is a consultation document regarding the transfer of care of LMWH on the JFC website. Comments are welcome until close of the consultation period on 4th October 2013.

11.2 Royal College of Paediatrics pain review

Ms Cope informed the Committee that a review of the pain treatment pathway has been undertaken by the Royal College of Paediatrics, in light of recent EMA recommendations regarding the use of codeine in children.

The Review highlights the importance of multi-modal pain relief, particularly after commonb surgical procedures such as tonsillectomy. A combination of regular paracetamol, ibuprofen and an adjunct opiate analgesic such as morphine is recommended. It is likely that GOSH will use morphine oral syringes as the opiate of choice.

11.3 Lucentis for diabetic macular oedema (DMO)

Ms Spicer suggested that the JFC should try and challenge the use of ranibizumab (Lucentis®) intravitreal injection in DMO as per the recently published NICE TA. Ms Spicer highlighted the significant cost-savings that would be achieved by the use of unlicensed intravitreal bevacizumab in its place. It was agreed that the views of Moorfields specialists should be sought on this in the first instance.