NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 23rd May 2013

in the Chadwick Building; 2.18 Lecture Theatre, UCL Building, Gower St

1. Present:	Prof R MacAllister	NCL JFC Chair
	Mr A Dutt	NHS Islington, Head of Medicines Management
	Ms P Taylor	NHS Haringey, Head of Medicines Management
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management
	Mr TF Chan	BCFH Chief Pharmacist
	Ms N Shah	NHS Camden, Head of Medicines Management
	Mr A Karr	NCL Procurement Chair
	Mr C Daff	MHS Barnet, Head of Medicines Management
	Dr R Urquhart	UCLH Chief Pharmacist
	Mr G Irvine	Lay Member
	Ms S Drayan	NMUH Chief Pharmacist
	Mr A Shah	RNOH Chief Pharmacist
	Mr T James	MEH Chief Pharmacist
	Dr A Jones	Consultant Oncologist, RFH/UCLH
	Dr H Taylor	WH Chief Pharmacist
	Dr DBavin	Camden CCG
	Dr L Wagman	NHS Barnet, CCG
	Dr E Boleti	Oncologist, RFH
In Attendance:	Dr A Grosso	UCLP Pharmacist
	Mr K Thakrar	UCLH Formulary Pharmacist
	Ms K Chapman	MEH Formulary Pharmacist
	Ms S Sanghvi	UCLH Pharmacist
	Ms R Holland	UCLH Pharmacist
	Dr A Mier	BCFH Respiratory Consultant
	Ms L Luk	BCFH Formulary Pharmacist
	Ms I Samuels	RFH Formulary Pharmacist
	Dr H Fitz Clarence	UCLH Rheumatology Consultant
Apologies:	Prof L Smeeth	NCL JFC Vice Chair
	Dr R Fox	RNOH DTC Chair
	Dr A Tufail	MEH DTC Chair
	Dr M Kelsey	WH DTC Chair
	Ms W Spicer	RFH Chief Pharmacist
	Dr C Stavrianakis	NHS Haringey, CCG
	Ms S Beecham	CSU Support (IFRs)
	Dr S Bennett	NHS Islington CCG
	Dr W Zermansky	NHSHaringey CCG
	Dr P Hyatt	NMUH DTC Chair

2. Minutes of the last meeting

The previous meeting minutes were accepted as accurate.

3. Matters arising

3.1 NOAC pathway

Mr Daff informed the Committee that the new oral anti-coagulant (NOAC) pathway was further discussed at a CCG network meeting on 1st May 2013. This meeting was attended by a haematology consultant and a secondary care anti-coagulation pharmacist. In essence, details of the pathway have now been agreed by both primary and secondary care representatives and this pathway, along with the accompanying paperwork, will be trialled for one year after which point it will be reviewed. It was

also agreed that GPs and consultants can refer eligible patients to their local anticoagulant clinic for a two-month initiation of a NOAC after which prescribing will be continued in primary care.

4. Members & applicants declarations of relevant conflicts of interest

Ms P Taylor declared attending an advisory board for Almirall.

5. Medicine applications &reviews

5.1 Aclidinium inhaler (Eklira®; Almirall) for COPD

The Committee reviewed an application for the recently launched inhaled long-acting anti-muscarinic agent, aclidinium, for the treatment of chronic obstructive pulmonary disease (COPD). The Committee noted that NICE CG101 recommends that people with stable COPD who remain breathless or have exacerbations despite use of as required short-acting bronchodilators, should be offered long acting bronchodilators, such as a tiotropium, or a long-acting beta-adrenoceptor agonist for maintenance.

The Committee were informed that there are no published studies directly comparing aclidinium with tiotropium but that such a trial has been conducted which is only available as a poster presentation. As such, this poster was not submitted as evidence to support the case for aclidinium.

The Committee reviewed evidence from a single 24-week [ATTAIN] and a single 12-week [ACCORD I] trial. Both were Phase III randomised, placebo-controlled trials of similar design. The primary endpoint in both studies was the change from baseline in morning trough forced expiratory volume in one minute [FEV_1]. A statistically significant improvement was seen in the primary end points of both studies. In ATTAIN, the change from baseline trough (morning pre-dose) FEV_1 at week 24 was significantly greater with aclidinium compared with placebo, with a mean improvement of 128mL (95% CI: 85-170; p<0.0001). In ACCORD I, the change from baseline trough FEV_1 at week 12 was significantly greater with aclidinium than placebo with a mean improvement of 124mL (95% CI: 83-164; p<0.0001). These differences are at the level considered to be clinically relevant (minimum clinically important difference is *circa* 100 ml).

Both studies reported results related to health status (SGRQ and TDI). However, only the results from the ATTAIN study was powered to detect a treatment difference for these endpoints. At week 24 in the ATTAIN study, aclidinium produced statistically significant improvements over placebo in baseline-adjusted mean SGRQ total score (–3.8±1.1 units, p<0.001 and –4.6±1.1 units, p<0.0001 respectively). Both studies did not have the statistical power to detect a difference in exacerbations, and it was agreed that the positive results reported in the trials need to be confirmed in further trials.

With regard to safety, as noted by the applicant, aclidinium appears to have fewer anti-cholinergic adverse effects compared with tiotropium. In both the ATTAIN and ACCORD I studies, incidence of anti-cholinergic adverse events in the aclidinium arm was low (<2% for any event) and similar to placebo. Discontinuation rates due to adverse events in the aclidinium and placebo arms were comparable and low (3.0% and 4.0% in ATTAIN; 3.7% and 3.8% in the ACCORD I trial, respectively). Rates of serious adverse events for aclidinium and placebo were also comparable (5.6% vs 5.5% in ATTAIN; 3.2% vs 2.2% in ACCORD I, respectively). However the Committee noted that the trials were of a relatively short duration and that patients with unstable cardiac conditions were excluded from both studies; and these conditions may be affected by the anti-cholinergic mechanism of action of aclidinium. Therefore, the summary of product characteristics cautions use in patients with a myocardial infarction during the previous 6 months, unstable angina, newly diagnosed arrhythmia within the previous 3 months, or hospitalisation within the previous 12 months for heart failure (New York Heart Association classes III and IV).

The most frequently reported adverse events were headache (6.6%) and nasopharyngitis (5.5%).

In terms of convenience the Committee noted that aclidinium inhaler is a multi-dose breath-actuated inhaler that does not require the manual addition of a capsule by patients each day, as is the case with tiotropium and glycopyrronium inhalers. Aclidinium needs to be inhaled twice a day compared to once a day for tiotropium and glycopyrronium, and three to four times a day for ipratropium.

The Committee noted that the cost of aclidinium is less than that of tiotropium but slightly higher than glycopyrronium.

The Committee heard that aclidinium may have a place in therapy for patients who cannot tolerate tiotropium due to anti-cholinergic side effects, or cannot manipulate the inhaler device. However, the Committee noted that only 0.2% of patients withdrew from tiotropium therapy in its licensing trials and that tiotropium has a higher incidence of anti-cholinergic adverse events when compared to ipratropium (absolute risk increase of 6%). Ipratropium is also available a metered dose inhaler (MDI) device for patients unable to use the tiotropium inhaler system.

The Committee also discussed in detail the potential implications of the loss of market exclusivity for tiotropium in 2015 and when a generic (and at what price) might become available. It was agreed that it was too early to form a clear view on these issues at present.

In summary, after taking a vote (see any other business) the Committee considered the evidence for the efficacy and safety of aclidinium insufficient to support addition to the formulary, when comparisons were made with existing medications. For the specific indication that aclidinium had a role when tiotropium caused anti-cholinergic adverse effects, the Committee thought that ipratropium was a much cheaper option.

5.2 Glycopyrronium inhaler (Seebri®; Novartis) for COPD

The Committee also considered inhaled glycopyrronium for COPD in the absence of a submitted application for completeness. Glycopyrronium is another recently launched long-acting anti-muscarinic with indications similar to aclidinium and tiotropium.

The Committee reviewed the two Phase III trials [GLOW 1 & 2] which showed superiority compared to placebo (GLOW 1 &2) and non-inferiority to tiotropium (GLOW 2). The duration of treatment was 26 weeks in GLOW 1 and 52 weeks in GLOW 2. The primary endpoint was trough FEV_1 at week 12 for both studies. The absolute difference in the 12-week trough FEV_1 was 108mL in GLOW1 and 97mL in GLOW 2 compared to placebo ($p<0.001$ in both studies). In GLOW 2 the increase in trough FEV_1 compared with placebo was 83mL for tiotropium. The Committee thus noted that both drugs failed to reach differences considered to be clinically relevant by NICE. There were no statistically significant differences between tiotropium and glycopyrronium for primary or secondary outcomes.

With regard to safety, the Committee heard that the percentage of patients reporting adverse events was similar between groups in both studies. The most common anti-cholinergic adverse event reported with glycopyrronium in both studies was dry mouth (2.4%). It was also noted that the EMA found that atrial fibrillation was reported more frequently with glycopyrronium compared with placebo. However, when they considered adjudicated electrocardiogram (ECG) recordings, the number of patients with a new or worsening ECG finding of atrial fibrillation was similar for glycopyrronium bromide and placebo, Nevertheless, the SPC advises that cardiac outcomes should be monitored closely post-marketing.

In terms of convenience, the Committee noted that glycopyrronium, like tiotropium is a once daily capsule inhaler. The Committee considered that whilst once daily dosing is more convenient, patients with dexterity issues with tiotropium may also have issues with the glycopyrronium capsule inhaler.

Glycopyrronium was noted to be less expensive than both aclidinium and tiotropium.

In summary, the Committee considered the case for adding glycopyrronium inhaler unconvincing to support addition to the formulary. It was cheaper than tiotropium but otherwise there were no clear advantages. The current cost advantage might not extend beyond 2015 when tiotropium becomes generic. It had the unknown safety risk of any new drug. Were it available alongside tiotropium, it

was likely that it would be offered to patients who had not found tiotropium to be satisfactory, a patient group for which there is no evidence of efficacy or safety, and this would merely add to the overall drug spend on anti-cholinergic drugs for COPD (currently running at £1.8M per annum in NCL).

The Committee thought it worth considering whether it would be possible to switch patients from tiotropium to glycopyrronium. This could accrue savings of potentially £300,000 per annum in NCL. The Committee would welcome the views of the respiratory community on this. Any proposal for a therapeutic switch would need to accommodate the possibility of back-switching to tiotropium if a cheaper generic version became available.

5.3 Tiotropium inhaler (Spiriva®; Boehringer) for COPD

The Committee also reviewed inhaled tiotropium for COPD, as it is currently the anti-cholinergic of choice. The patent for Spiriva® is due to expire in 2015, however the Committee heard that inhaler devices are difficult to duplicate, so it may be longer before a generic product becomes available and the price reduction could be limited.

The Committee heard that UCLH Use of Medicines Committee decided not to include tiotropium onto the UCLH Formulary in both 2005 and 2009 based on a detailed evaluation of the clinical evidence. Tiotropium was only later added to the UCLH formulary as a second-line inhaled anti-cholinergic to support a subsequent sector-wide approved COPD prescribing guideline.

It was highlighted that 20,000 ipratropium inhalers were prescribed across NCL last year at a cost of £200K as compared to 46,000 tiotropium inhalers at a cost in excess of £1.8M.

Strontium ranelate (Protelos®; Servier) for osteoporosis

The Committee discussed a recent MHRA Drug Safety Bulletin regarding strontium ranelate. A review of available safety data for strontium ranelate has raised concern about its cardiovascular safety beyond the already recognised risk of venous thromboembolism (VTE). An analysis of randomised controlled trial data has identified an increased risk of serious cardiac disorders, including myocardial infarction (RR 1.6 compared with placebo [95% CI 1.07-2.38].

The MHRA has now restricted strontium ranelate to treatment of severe osteoporosis in postmenopausal women at high risk of fracture. The MHRA also state that it should not be used in patients with ischaemic heart disease, peripheral artery disease, cerebrovascular disease, a history of these conditions, or in patients with uncontrolled hypertension. Furthermore, patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should only be treated with strontium ranelate after careful consideration. The MHRA recommends that healthcare professionals should review affected patients at a routine appointment.

The Committee heard that UCLH plans to send letters to each patient currently prescribed strontium ranelate for osteoporosis, as well as their GP, advising a review of the appropriateness of treatment in light of the MHRA safety warning.

The Committee noted that it was not clear in the MHRA warning whether or not patient age is considered to be a risk-factor for cardiovascular disease. This was considered important as with age as a risk factor, very few post-menopausal patients would be suitable for treatment with strontium ranelate.

Annual zoledronic acid infusions were discussed by the Committee as a potential alternative treatment for some patients. It was noted, however, that many patients that currently use strontium ranelate do so as they are unable to tolerate [oral] bisphosphonates.

The Committee agreed to contact the MHRA for confirmation on whether age was considered as a risk factor by the MHRA and for a clearer definition of “severe” osteoporosis. Therefore the decision on the place in therapy of strontium ranelate in light of the MHRA warning was deferred to the next meeting.

5.4 Fluticasone/Formoterol inhaler (Flutiform®; Napp Pharmaceuticals) for asthma

The Committee reviewed an application for inhaled Flutiform® for asthma. Flutiform® is the first combination inhaler of this type and is delivered by a MDI. It is licensed for the regular treatment of asthma where the use of a combination product (inhaled corticosteroid and long-acting beta-agonist) is appropriate.

The Committee reviewed evidence from a non-inferiority study by Bodzenta-Lukaszyk et al (n=620) indicating that Flutiform® is non-inferior to comparable doses of fluticasone and formoterol administered concomitantly via separate inhalers. There were no significant differences in terms of lung function measured by FEV_1, percentage of rescue-medication free days, asthma symptom scores and percentage of symptom-free days. Side effects profiles and tolerability were also similar between the two groups.

Evidence was also reviewed comparing Flutiform® and Seretide® in an open-label, randomised, non-inferiority study by Bodzenta-Lukaszyk et al (n=202). The primary outcome measure was change in FEV_1 between baseline and week 12. The results showed the Flutiform® inhaler to be non-inferior to the Seretide® inhaler. The main difference between the two treatments at week 12 was -0.061L [(95%CI -0.161 to 0.040) p<0.007]. There was also no significant difference between the two groups in the secondary end-points of use of rescue medication, number of asthma exacerbations, lung function tests, and asthma symptom scores. It was noted that the study was not sufficiently powered to detect non-inferiority for secondary outcomes.

With regard to safety, both treatment groups displayed similar safety and tolerability profiles with an adverse event rate of 23.8% in both groups, the majority of which were infections including oral candidiasis. The Committee noted that Flutiform® is not currently licensed for children and therefore the decision to include on the formulary would be for adolescents and adults with asthma.

The Committee discussed at length whether the use of single component inhalers rather than combination inhalers would be appropriate, as this would be cost-saving at minimal inconvenience to patients. BTS and NICE guidance recommend the use of fixed-dose combination inhalers, because recent clinical trials of combination inhaler therapy have used fixed-dose combination inhalers rather than individual inhalers. NICE also recommends that cost be taken into account when considering inhaler therapy. The Committee also noted the significant cost-savings available if Flutiform® was used instead of Seretide® in asthma.

In summary, the Committee agreed that the use of Flutiform® in any new patients requiring a combination ICS and LABA should be supported. Patients currently stable on a combination inhaler should not be required to change therapy. The Committee noted that whilst data are limited for this new combination inhaler, the individual components have had wide use in asthma therapy to date with proven long-term safety and efficacy profiles.

The Committee also noted that significant cost-savings were available as a result of a switch from Seretide® 250 Evohaler to Seretide® 500 Accuhaler (circa £250K per annum for the five CCGs in NCL). It was agreed that a frequently asked questions [and answers] (FAQ) document should first be drafted for consideration by the JFC on this subject.

6. Local DTC recommendations

6.1 UCLH: Imiquimod for actinic keratosis (AK) and basal cell carcinoma (BCC)

Imiquimod was recommended for use in AK and BCC as a second-line agent at the UCLH UMC. The Committee agreed with this recommendation pending receipt of a treatment algorithm.

6.2 RFH: Interferon alpha for Behcet's disease

Interferon alpha for Behcet's disease was accepted for a single patient at the RFH only. This use was also subject to a six-month follow-up review.

6.3 RFH: Infliximab for CRION

Infliximab for chronic relapsing inflammatory optic neuropathy (CRION) was accepted for a single patient at the RFH only. This use was also subject to a six-month follow-up review.

6.4 NMUH: Moxifloxacin for MDRTB, CAP & acute exacerbations of chronic bronchitis

Moxifloxacin for multi-drug resistant tuberculosis (MDRTB), community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis was recommended by the NMUH DTC. The Committee agreed that moxifloxacin use in CAP and chronic bronchitis should be restricted to microbiology approval only.

6.5 MEH: Sterimar – nasal douche following endonasal dacryocystorhinostomy

Sterimar nasal douche following endonasal dacryocystorhinostomy was recommended by the MEH DTC. The Committee agreed with this recommendation pending a review of the current practice of the now UCLH Royal Ear Nose & Throat Hospital (RNTNE).

6.6 MEH: Sugammadex for emergency reversal of rocuronium

Sugammadex for emergency reversal of rocuronium neuromuscular blockade was recommended by the MEH DTC. The Committee agreed that sugammadex should be restricted to [infrequent] emergency use only.

6.7 MEH: Natamycin 5% drops (US licensed Natacyn®) for fungal keratitis

Natamycin 5% drops (UKunlicensed Natacyn®) for fungal keratitis was recommended by the MEH DTC. The Committee agreed with this decision.

7. Generic zoledronic acid

The Committee were informed that branded zoledronic acid 4mg (licensed for reduction of bone damage in advanced malignancies) has lost market exclusivity and less expensive generic versions are now available in the UK; however zoledronic acid 5mg (licensed for osteoporosis) has been subject to a legal challenge and the position of generic equivalents remains unclear. Due to the considerable cost differences, in the absence of a generic 5mg being available, the Committee agreed that two (off-label) 4mg zoledronic acid vials could be used to obtain a 5mg dose for high volume centres.

8. NCL-MMC minutes

Not available for this meeting.

9. NICE TA update

The NICE publication document was included for information only.

10. CDF update

The updated Cancer Drug Fund (list) was Included for information only. The Committee agreed not to routinely review cancer therapies newly added onto the CDF.

11. Date of next meeting

27th June 2013. Moorfields Eye Hospital Boardroom. 2nd Floor Learning Centre, 15 Ebenezer St, N1

12. Any other Business

12.1 Denosumab

Dr Boleti asked the Committee for assistance with implementing NICE TA265 with respect to the use of denosumab in bone metastasis. In essence, as denosumab is not PbR-excluded, Trusts are not currently financed to make this treatment available through the PbR system. It was agreed that a pathway determining the proposed place of denosumab therapy should first be brought to the Committee and that this may help with the necessary commissioning discussions that are required for this agent.

12.2 JFC voting

It was apparent that the decision-making [voting] rules for making Committee recommendations were not clear when the initial vote relating to aclidinium resulted in a tied outcome (six for and six against a positive recommendation). The following voting arrangements were therefore agreed:

First, only Committee members (see section 1) are entitled to vote or have an input into actual decision-making and any votes offered from non-members are not eligible to be counted. Second, the voting options should be clearly specified prior to the voting taking place and members should be able to suggest other voting options (if applicable) before voting is cast. Third, the chair is not to participate in the initial vote but will provide a casting vote in the event of a tie.