NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 18th October 2012
in the Board Room, Floor 3, UCLP Building, Tottenham Court Road

Present:	Prof R MacAllister	RM	NCL JFC Chair
	Dr R Urquhart	RU	UCLH Chief Pharmacist
	Prof A Hingorani	AH	UCLH Clinical Pharmacologist
	Mr A Dutt	AD	NHS Islington, Head of Medicines Management
	Ms S Drayan	SD	NMUH Chief Pharmacist
	Mr A Shah	AS	RNOH Chief Pharmacist
	Prof A Jones	AJ	UCLH & RFH Consultant Oncologist
	Dr E Boleti	EB	RFH Consultant Oncologist
	Dr M Kelsey	MK	WH Consultant Microbiologist
	Mr P Gouldstone	PG	NHS Enfield, Head of Medicines Management
	Dr A Jolly	AJ	BMJ Health Economics
	Dr N Trevor	NT	BMJ Health Economics
	Dr A Tufail	AT	MEH DTC Chair
	Mr T James	TR	MEH Chief Pharmacist
	Dr N Losseff	NL	NCL Medical Director
	Ms N Shah	NS	NHS Camden, Head of Medicines Management
	Ms W Spicer	WS	RFH Chief Pharmacist
	Mr C Daff	CD	NHS Barnet, Head of Medicines Management
	Ms P Taylor	PT	NHS Haringey, Head of Medicines Management
	Dr P Ancliff	PA	GOSH DTC Chair
	Mr M Broadbent	MB	BCF DTC Chair
	Ms L Reeves	LR	C&I Mental Health Chief Pharmacist
	Mr G Irvine	GI	Lay member
	Dr D Bavin	DB	NHS Camden, CCG
	Dr H Taylor	HT	WH Chief Pharmacist
	Dr R Fox	RF	RNOH DTC Chair
	Dr W Zermansky	WZ	NHS Haringey, CCG
In Attendance:	Dr A Grosso	AG	UCLP Lead Pharmacist
	Mr K Thakrar	KT	UCLH Formulary Pharmacist
	Ms I Samuel	IS	RFH Formulary Pharmacist
	Ms C Kwok	CK	UCLP Board Secretary
	Ms C Gates	CG	UCLH Haematology Pharmacist
	Dr D Mack	DM	RFH Consultant Microbiologist
Apologies:	Dr L Wagman	LW	NHS Barnet, CCG
	Mr A Karr	AK	NCL Procurement Chair
	Mr TF Chan	TC	BCF Chief Pharmacist
	Dr H Hughes	HH	NCL Medical Director
	Ms P Shah	PS	NCL Pharmacist
	Prof L Smeeth	LS	NCL JFC Vice Chair
	Dr B Goldacre	BG	Psychiatrist Representative

1. Members & meeting observers

The chair welcomed the applicant and observers to the meeting.

2. Minutes of the last meeting

These were accepted as accurate.

3. Matters arising

3.1 Updated Membership list

An updated membership list was circulated for information.

3.2 Member nominations and observers

The Committee discussed whether members should provide nominations in the event of being unable to attend a JFC meeting. The Committee agreed that this should not be endorsed as it would likely lead to fewer attendances from core members. Due to space constraints, it was also agreed that all observers should consult with AG before attending.

3.3 Updated Terms of Reference

An updated Terms of Reference was circulated following an update after discussion at the last meeting. LW had noted that agreement of shared care criteria was not included. The Committee agreed to include a statement on shared care and then approved the document.

3.4 Appeals process

AG informed the Committee that he has secured a reciprocal arrangement with the Guy's, King's, Lewisham and St Thomas' (GKLT) JFC. In essence, they have agreed to hear our appeals and the NCL JFC will hear their appeals. The Committee agreed that the first appeal should still come to this Committee, however further appeals will be directed to the external Committee. AG agreed to draft a formal appeals procedure for consideration at the next meeting.

3.5 Application forms

AG informed the Committee that the NCL Application Form still requires some agreement on the level of financial information that should be captured by an individual Trust applicant. AG and PS are working through the current [draft] form to ensure all realistic fields are included. AG informed the Committee that both the current [draft] NCL form and individual hospital DTC forms are all acceptable in the interim.

4. Members declaration of conflicts of interest

Dr Trevor informed the Committee that she has worked on NICE Technology Appraisals for some of the new oral anticoagulants (NOAC). The Committee did not consider this a conflict of interest.

5. New Oral Anti-coagulants (NOAC) NCL Position Statement

The Committee reviewed a "position statement" detailing patient eligibility criteria for the new oral anticoagulants (NOAC) for the prevention of stroke and systemic emboli in patients diagnosed with non-valvular atrial fibrillation (AF) at increased risk of stroke. The Committee approved the content of the statement. It was noted that a sector-wide policy was still required that details the prescribing, monitoring and transition arrangements for these agents. Preferences for a one-month and three-month hospital care stabilisation were suggested. The Committee agreed to review this in detail upon receipt of a draft document. The Committee discussed the pros and cons of having equal Formulary positioning of the two licensed NOACs. AH explained that these agents are used for a number of indications and that any formulary decision must consider use in other indications. AH also informed the Committee that an indirect network meta-analysis comparing dabigatran and rivaroxaban in AF revealed little clinical difference between these agents. It was agreed that both agents should be available, in case of intolerance or contra-indication, but that a preferential NOAC should be determined in order to try and decrease the risk of medication error due to their different dosing schedules. It was also agreed that this decision should also be based solely on the price of these agents. AG agreed to liaise with other centres in London to see if others would mirror this decision so as to increase the economy of scale. AG also agreed to liaise with AK and other colleagues at The London Procurement Programme (LPP) regarding the primary care procurement process.

6. Low Molecular Weight Heparins (LMWH)

NS raised concerns about patients being discharged from hospitals and their ongoing treatment with LMWHs. The concerns were largely related to limited information available to the GPs with regards to monitoring and duration

of treatment in a relatively small cohort of patients e.g. intravenous drug users. AD also noted that GPs are, on occasion, asked to prescribing LMWHs as bridging therapy prior to a surgical/interventional procedure. NL, CG and AG agreed to liaise outside of the meeting and to report back progress at the next meeting.

7. New medicine applications

7.1 Fesoterodine (*Toviaz®; Pfizer*) for Overactive bladder syndrome

Applicant (Trust)	Presented by	Outcome
Dr D Wood (UCLH) Dr R Oliver (RFH)	AG	Not approved

The Committee considered fesoterodine, an anti-muscarinic agent, for the treatment of symptoms associated with overactive bladder (OAB) syndrome. The Committee were informed that 10 different anti-muscarinic preparations are available in the UK with oxybutynin, solifenacin and tolterodine being the most common on individual hospital formularies. Fesoterodine is a pro-drug and is metabolised to exactly the same principal active metabolite as tolterodine (5-hydroxymethyl tolterodine [5-HMT]). The main difference appears to be in the mechanism of metabolism; fesoterodine is rapidly metabolised by plasma esterases whereas tolterodine is broken down by hepatic cytochromes (CYP4502D6). Festoterodine is undetectable in the plasma and all its anti-muscarinic effects are attributable to 5-HMT. The Committee heard only about 7% of patients are considered to be poor metabolisers of tolterodine and that the phenotype of these patients are not predictable. Importantly, the Committee noted that in the SPC of tolterodine there is a statement confirming that the 5-hydroxymethyl derivative metabolite exhibits a pharmacological profile similar to that of the parent compound, so that in poor metabolisers, tolterodine remains as effective as in good metabolisers.

The Committee reviewed all eight trials submitted with the application, however focused on the three randomised double-blinded trials that incorporated an active comparator arm (Kaplan et al 2010, Chapple et al 2007, Herschorn et al 2010). All three of these trials had a broadly similar design, comparing fesoterodine and tolterodine over a 12-week duration. The Committee were informed that the mean baseline severity across the three trials for urinary urge incontinence (UUI) was 2.5 episodes per 24 hours; number of voids was 12 per 24 hours; and number of nocturnal voids was 2 per night.

The Committee heard that although a statistically significant advantage was reported, the absolute clinical advantage in favour of fesoterodine appeared small. For example, the reduction in number of voids per 24 hours per patient was no greater than 0.2 of an episode. The Committee noted that this is in comparison to the baseline levels which were in the region of 12 episodes in a 24 hour period. The Committee were also informed that the absolute advantage of using fesoterodine over tolterodine regarding UUI episodes per 24 hours per patient was no greater than 0.4 of an episode (mean baseline was in the region of 2.5 episodes per 24 hours). Similarly, the Committee could find no clear advantage of using fesoterodine over tolterodine in nocturnal voids. In the safety domain, festoterodine perfomed consistently and significantly less favourably to tolterodine for the main adverse events, namely dry mouth, constipation and headache. For example, dry mouth rates were almost double for festoterodine as compared to tolterodine (16% vs 28%; 13% vs 28%; 17% vs 34%). The Committee were informed that tolterodine (also manufactured by Pfizer) has just lost market exclusivity and that generic formulations are now available at 75% of the price of branded anti-muscarinics. The Committee were informed that the annual expenditure on anti-muscarinics in NCL is *circa* £2.6m. Regarding quality of life, again numerical inspection of the absolute outcomes reveal only very minor numerical advantages for total health-related quality of life and bothersome symptoms which fall below the *minimal clinical importance difference* of these scales.

The Committee also compared the evidence for tolterodine immediate-release versus modified-release. The Committee concluded that there was no evidence for any major significant clinical advantage for using the modified-release preparation (the cost of generic immediate-release tolterodine is currently 50% cheaper than the generic modified-release version).

In summary, festoterodine, an apparent me-too of tolterodine, appears to offer little clinical advantage at the expense of increased xerostomia and budget impact. It was therefore agreed that fesoterodine should not be included into the NCL Formulary. It was also agreed that new patients should only be started on immediate-release generically available anti-muscarinics (i.e. oxybutynin or tolterodine) and questioned the role of using a third-line [branded] preparation which most patients would likely eventually sequence through to due to the lack of efficacy and poor tolerability of all these agents. However, it was agreed that this third-line issue should be tackled at a later date as there is further potential for disinvesting in this area.

7.2 Fidaxomicin *(Dificlir®; Astellas)* for *Clostrdium difficile* infection

Applicant (Trust)	Presented by	Outcome
Dr D Mack	MK	Approved with restrictions

The Committee considered fidaxomicin, a narrow spectrum, macrocytic antibiotic that has a bacteriocidal activity against *Clostridium difficile*, and works by interfering with RNA synthesis within the bacterial cells affecting DNS synthesis and replication. *Clostridium difficile* is a gram positive, spore forming, anaerobic bacterium that can cause infection in susceptible patients during or after exposure to broad-spectrum antibiotics. Some hospital guidelines recommend no additional pharmacological treatment for mild disease

(excepting stopping the causative antibiotics) or metronidazole if diarrhoea continues, and vancomycin for severe infection.

The Committee reviewed the results from two large randomised, double-blinded, Phase III trials that compared fidaxomicin [200mg twice daily] to oral vancomycin [125mg four times a day]. Eligible patients has >3 unformed bowel movements in the 24 hours prior to randomisation and no [or one] previous episode of *Clostridium difficile* infection in the 3 months prior to infection. There was no difference [within the pre-specified margin of non-inferiority [10%]) in the primary endpoint of clinical cure (defined as resolution of diarrhoea for the treatment duration) between the two groups. However, there was a significant difference in the secondary endpoint of recurrence; 15.4% for fidaxomicin compared to 25.3% for vancomycin. The Committee challenged the paradox where a 10% difference was considered clinically non-significant and acceptable as a margin of non-inferiority for the primary endpoint yet a difference within this margin is being used as evidence of superiority for a secondary [and hence hypothesis-generating only] endpoint. With regards to safety, the Committee were assured that fidaxomicin appears generally well tolerated with adverse events primarily affecting the gastro-intestinal tract [such as nausea, vomiting, and constipation]. With regards to cost, the Committee noted that the cost for a 10-day treatment period would be £0.57 for metronidazole; £58 for vancomycin; and £1620 for fidaxomicin. The Committee discussed, at length, the challenges faced with *Clostridium difficile* infections and in particular with regards to directing its use to patients with more severe disease. Although it was noted that due to trial exclusion criteria only five patients receiving fidaxomicin had a reported diagnosis of pseudomembranous colitis and there was no significant difference in recurrence rates between fidaxomicin and vancomycin in patients infected with the aggressive NAP1/BI/027 strain. Moreover, it was agreed that there was no way of predicting which patients may be more likely to experience a recurrence.

The Committee were informed that the Scottish Medicines Consortium have approved the use of fidaxomicin in recurrent cases only, however other NHS hospitals such as Guy's and St Thomas' NHS Foundation Trust have approved it for all toxin-positive cases.

In summary, the Committee agreed that fidaxomicin appears non-inferior to vancomycin for the treatment of *Clostridium difficile* infection, however could not justify its position above vancomycin for the treatment of all patients that are toxin-positive. As a result, the Committee agreed to include fidaxomicin into the NCL Formulary for patients that have multiple recurrent infections (at least three). This decision was based on a majority member vote. The Committee agreed that fidaxomicin could also be used in patients in extremis when all other drugs had failed. Finally, it was agreed that a relapse in any patient whilst on fidaxomicin would not be eligible for further fidaxomicin treatment and that prescribing should be restricted to consultant microbiologist recommendation only.

8. NCL prescribing guidance on discharge

This item was deferred to the next meeting.

9. Red-list management

This item was deferred to the next meeting.

10. Shared care guideline criteria

This item was deferred to the next meeting.

11. Next meeting

Thursday 15th November, UCLP Board Room, 3rd Floor, Tottenham Court Road.

12. Any other business

AG informed the Committee that Barnet CCG have made it a contractual obligation for Trusts to adhere to the recommendations of the NCL JFC.