NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 15th November 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
	Ms S Drayan	SD	NMUH Chief Pharmacist
	Mr A Shah	AS	RNOH Chief Pharmacist
	Dr M Kelsey	MK	WH Consultant Microbiologist
	Mr P Gouldstone	PG	NHS Enfield, Head of Medicines Management
	Dr A Tufail	AT	MEH DTC Chair
	Mr T James	TJ	MEH Chief Pharmacist
	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 E Mortty	PT	NHS Haringey, Deputy Head of Medicines Management
	Mr G Irvine	GI	Lay member
	Dr R Fox	RF	RNOH DTC Chair
	Dr C Stavrianakis	WZ	NHS Haringey, CCG
	Dr L Wagman	LW	NHS Barnet, CCG
	Mr TF Chan	TC	BCF Chief Pharmacist
	Mr A Karr	AK	NCL Procurement Chair
	Ms J Cope	JC	GOSH Chief Pharmacist
In Attendance:	Dr A Grosso	AG	UCLP Lead Pharmacist
	Ms B Coleman	BC	WH Deputy Chief Pharmacist
	Mr P Bodalia	PB	RNOH Deputy Chief Pharmacist
	Mr K Thakrar	KT	UCLH Formulary Pharmacist
	Ms C Kwok	CK	UCLP Board Secretary
	Mr K Mole	KM	UCLH Medicines Information Pharmacist
	Dr E Saridogan	ES	Consultant, UCLH
	Dr M Brown	MB	Consultant, RNOH
Apologies:	Dr H Hughes	HH	NCL Medical Director
	Ms P Shah	PS	NCL Pharmacist
	Prof L Smeeth	LS	NCL JFC Vice Chair
	Ms P Taylor	PT	NHS Haringey, Head of Medicines Management
	Dr H Taylor	HT	WH Chief Pharmacist
	Dr E Boleti	EB	RFH Consultant Oncologist
	Dr P Ancliff	PA	GOSH DTC Chair
	Dr A Jolly	AJ	BMJ Health Economics
	Dr N Trevor	NT	BMJ Health Economics
	Dr P Sardana	PS	NHS Enfield, CCG
	Prof A Jones	AJ	UCLH & RFH Consultant Oncologist
	Dr D Bavin	DB	NHS Camden, CCG
	Mr A Dutt	AD	NHS Islington, Head of Medicines Management
	Dr S Bennett	SB	NHS Islington, CCG

1. Members & meeting observers

The chair welcomed the applicants and observers to the meeting.

2. Minutes of the last meeting

These were accepted as accurate except it was noted that Dr Bennett had sent apologies.

3. Matters arising

3.1 Appeals procedure

The NCL JFC appeals procedure was circulated and approved for use.

3.2 Low Molecular Weight Heparin (LMWH) use within NCL

Following on from the October meeting, it was noted significant progress had been made with respect to addressing the various issues with LMWH prescribing. Accordingly, a draft document was circulated detailing the categories of patients that should be treated in the primary or secondary setting and any monitoring requirements associated with LMWHs. This document is currently being considered by secondary care. Once agreed, it will be circulated to primary care stakeholders for further comment before returning to the JFC for final ratification.

4. Response to previous decisions

4.1 Fidaxomicin

An appeal from Dr Mack regarding the Committee's decision to restrict fidaxomicin use to patients with *C.Difficile* infection who have failed to respond to all other medical therapies and for third recurrence was presented. The basis of this appeal was that the Committee's decision was non-evidenced based and not fitting with inclusion and exclusion criteria of the registration studies. Like all other bodies that had considered these data, the Committee had used its judgement in determining how to handle the uncertainty that the trials had generated. Fidaxomicin was merely non-inferior to vancomycin for its primary endpoint and is considerably more expensive. The advantage for fidaxomicin was shown on a secondary endpoint (recurrence rate). Conclusions based on secondary end-point data would ordinarily be considered hypothesis-generating and not policy-defining. Moreover, fidaxomicin has not been tested against a combination of metronidazole and vancomycin. The Committee also considered the model submitted with the original application and the appeal to be flawed with respect to the purported incremental drug cost-per-case saved as it presumed a substantial reduction in bed days. It also factored in additional tariff income activity none of which was evidence-based. For the 32 patients the applicant intended to treat per annum, the use of fidaxomicin might reduce four episodes of recurrence at an incremental drug cost of £160,000 i.e. £40,000 per case. Thus the Committee considered that the original decision was a pragmatic compromise, recognising the limitations of the trial data and the modelling tool. It was agreed that the original decision should stand.

4.2 Fesoterodine

Dr Grosso informed the Committee that Dr Wood will appeal against the fesoterodine decision at the January 2013 meeting.

5. Local DTC recommendations

5.1 Doxycycline MR for rosacea

Doxycycline m/r (Efracea®) was discussed at the BCF DTC and a recommendation not to include it into the formulary was suggested, mainly based on cost-effectiveness in comparison to doxycycline 50mg capsules. The Committee agreed with this decision.

5.2 Actikerall for actinic keratosis

The Committee were informed that the Actikerall application was deferred from the BCF DTC due to a poor quality application.

5.3 Perampanel for partial seizures

Perampanel was discussed at the UCLH DTC. The recommendation was to include it on the formulary for use in patients that have failed all other options, or did not tolerate these options. The Committee agreed with this decision. The UCLH DTC could not recommend its use in children due to an absence of evidence.

5.4 Regadenoson for perfusion imaging

Regadenoson was discussed at the WH DTC and a recommendation to include it onto the formulary for perfusion imaging was suggested. The Committee agreed with this decision.

5.5 Aldesleukin for idiopathic CD4 lymphocytopenia

Aldesleukin was discussed at the RFH DTC and a recommendation to include it onto the formulary for CD4 lymphocytopenia was suggested. The Committee agreed with this decision. Aldesleukin is PbR-excluded however as this condition is exceptionally rare (all [six] current NHS patients currently reside outside of London) it was suggested that a business case would not be required. AG agreed to liaise with PS on this issue outside of the meeting.

5.6 Busulphan IV for pre-transplant conditioning

The busulphan application was deferred at the RFH DTC as the applicant could not attend.

5.7 Enzalutamide for metastatic prostrate cancer

Enzalutamide was discussed at the RFH DTC. The recommendation was to include it on the formulary for metastatic castrate-resistant cancer in patients previously treated with docetaxel, and unable to tolerate or progressing on abiraterone. The Committee agreed with this decision although this will need to be re-reviewed upon license or upon closure of the compassionate use scheme.

6. Members declarations of conflicts of interests

None declared

7. Nominations for presentation of new medicine applications

Ms Shah suggested that it would be a conflict of interest for primary care members of the JFC to verbally present a new medicine application. The Committee disagreed with this view. Dr Grosso reported that he was finding it difficult to secure agreement from members to present at the JFC so it was agreed that non-members, including pharmacists or doctors, could be asked to present applications.

8. New Medicine Applications

8.1 Ulipristal (Esmya®; *HRA Pharma*) for uterine fibroids

Applicant (Trust)	Presented by	Outcome
Dr Saridogan	AG	Approved

The Committee considered ulipristal acetate for the pre-operative treatment of moderate to severe uterine fibroids in women of reproductive age. The current treatment of choice is gonadotropin-releasing hormone analogues such as leuprorelin for about 3 months to reduce fibroid size pre-operatively. Ulipristal acetate is a newly licensed medicine with a steroid-like structure, that acts as a selective progesterone receptor modulator with predominantly inhibitory effects on the progesterone receptor.

The Committee reviewed two randomised controlled phase III trials, however focused on the PEARL II (n = 307) study as it was active-controlled whereas PEARL I was placebo-controlled. The primary endpoint was the proportion of patients with controlled bleeding at week 13 and was obtained in 90% of patients in the ulipristal arm compared to 89% in the comparator leuprorelin arm. The median time to achieve amenorrhea was also reduced for ulipristal [7 days compared to 21 days for leuprorelin]. However, there was a trend suggesting that leuprorelin might be more effective than ulipristal for reducing leiomyoma bulk (36% for ulipristal and 53% for leuprorelin) and reduction in uterine volume (20% versus 47%, respectively).

There were no major safety concerns reported in the trials, however it was noted that the follow-up was limited to a relatively short period of time. Ulipristal resulted in significantly fewer episodes of hot flushes (11% versus 40%). However the Committee raised concerns with regards to the possibility of developing endometrial hyperplasia, dysplasia and carcinoma as a result of ulipristal's mechanism of action. About 60% of women showed histological changes on endometrial biopsy at 3 months, but all resolved after a 6 month drug-free period. The Committee discussed these endometrial changes in detail and were assured that these are not considered as malignant although further long-term safety studies are currently on-going. The Committee were informed that the intended duration of ulipristal is only for three months as licensed.

In terms of convenience, ulipristal is an oral tablet whereas the gonadotropin-releasing hormone analogues are given by subcutaneous or intramuscular injection once a month for about 3 months.

Ulipristal costs about £400 per patient for a three month course in comparison to £150 for leuprorelin. However ulipristal may be cost-saving for commissioners where patients currently attend hospital to receive their injections.

In summary, the Committee were satisfied that ulipristal appears non-inferior in terms of uterine bleeding to the current standard of treatment, leuprorelin. In addition, it has a quicker onset of action, is more convenient and appears to be better tolerated in the short term. The Committee agreed to include it into the NCL Formulary as a second-line treatment in patients who do not tolerate the gonadotropin-releasing hormone analogues [as proposed by the applicant].

8.2 Lidocaine plasters (*Versatis®; Grunenthal*) for neuropathic pain

Applicant (Trust)	Presented by	Outcome
Dr Fernandez	PB	Not approved

The Committee considered lidocaine plaster, a local amide-type anaesthetic that block voltage-sensitive sodium channels on the cell membrane, for neuropathic pain. Lidocaine is used as a surface anaesthetic that is rapidly and extensively absorbed following application to the mucous membrane or damaged skin. Neuropathic pain is very challenging to manage due to the heterogeneity of its aetiologies, symptoms and underlying mechanisms. Currently a number of pharmacological agents are available (licensed and off-label) to manage neuropathic pain and include anti-depressants, anti-epileptics, opioids, and topical treatments.

The Committee reviewed a number of trials studying the efficacy of lidocaine plaster in neuropathic pain. However, most were open-labelled studies and thus open to bias, particularly with respect to subjective outcomes such as pain scores.

The Binder et al trial was a double-blinded and placebo-controlled study [in 265 patients]; however the results were only presented for an enriched population of 71 participants that had responded to lidocaine in the initial phase of the trial. The primary endpoint was defined as a lack of efficacy on two consecutive days leading to withdrawal from treatment, which occurred in 25% (n=9/36) of lidocaine-exposed patients versus 46% (n=16/35) on placebo. The difference between the two groups was not reported as statistically significant ($p = 0.15$).

The Committee were particularly interested in an unpublished study noted in the SMC submission because it was the largest trial of a non-enriched design. This double-blind study in 150 adults randomised patients on a 2:1 ratio between lidocaine plaster and placebo. The end-point was pain intensity measured on a 100mm VAS scale, assessed via a 6-point categorical scale. There was no significant difference between the lidocaine and placebo arms in the mean reduction from baseline in VAS pain intensity (45 versus 47mm). These data were not considered by the MHRA in its deliberations regarding licensing of lidocaine patches.

The Committee were informed that the RNOH would see refractory patients with severe neuropathic pain that would have no other options. However in view of this large unpublished study, the Committee were not convinced that lidocaine plasters represent an evidence-based and cost-effective option. In addition, the Committee were informed that capsaicin patches appear more effective and are less expensive. Capsaicin patches will be assessed at their local DTC in December 2012.

Lidocaine plasters appeared generally well tolerated, with most adverse effects reported at the application site. The majority of the adverse effects were mild to moderate in intensity and resolved spontaneously.

The annual cost of lidocaine plasters is about £4K per patient. All other neuropathic pain medicines are considerably cheaper.

In summary, the Committee were not convinced of the efficacy of lidocaine plasters in neuropathic pain. There were concerns about publication bias; the largest [non-enriched] randomised study showed no difference between lidocaine and placebo. This trial remains unpublished and was not considered by the MHRA. The Committee agreed that lidocaine plasters should not be included into the NCL Formulary. The Committee suggested the RNOH consider setting up a trial for lidocaine plaster use in their large refractory population.

8.3 Rituximab (*mabThera®; Roche*) for idiopathic thrombocytopenia

Applicant (Trust)	Presented by	Outcome
Dr A Rismani	WS	Approved

The Committee considered rituximab for immune thrombocytopenia (ITP), which is characterised by isolated thrombocytopenia often occurring in the absence of identifiable precipitants. The Committee were informed that rituximab would be only be considered in patients who are refractory or relapse after standard first-line treatment options i.e. steroids, immunosuppressants, anti-D and IVIg. Removal of the spleen (reported 60% success rate) is considered for patients unresponsive to medical therapy.

The Committee reviewed a recent meta-analysis by Auger et al which analysed 19 studies and 364 records that assessed rituximab as an effective splenectomy-avoiding option in adult chronic ITP. The ORR was 57% (95% confidence interval [CI]: 48–65), for 368 non-splenectomised patients after rituximab; CR was 41% (95% CI: 0·33–0·51) for 346 patients. The Committee also reviewed a study by Patel et al that assessed the durability of rituximab in adults and children that had responded to initial treatment. The 5-year estimates of persisting response were similar in adults and children (21% and 26%, respectively) and children did not relapse after 2 years from initial treatment whereas some adults did.

The Committee noted that rituximab is now widely used and that its adverse effects, as well as their management, are well documented; most adverse events manifest during the administration of the first dose. However, this improves with subsequent doses and can often be managed with supportive medications.

Rituximab would cost about £840 per patient plus the four associated infusion tariffs. Treatment with rituximab is likely to be much less expensive than the costs of splenectomy and associated support, follow-up and complications (estimated at about £8000 per patient). The Committee noted that rituximab is PbR-excluded and local agreements for this indication are already in place for UCLH and RFH. A suggestion of a pan-NCL business case was raised. The Committee considered this unnecessary seeing that it is already commissioned at the two major centres. AG agreed to liaise with PS outside of the meeting on this issue.

In summary, the Committee were convinced that rituximab appears to maintain a treatment-free response for at least 5 years in about one fifth of adults and a quarter of children treated. The Committee agreed to include rituximab into the NCL Formulary in patients who are refractory or relapsed after standard first-line treatment options pending funding confirmation for all centres in NCL.

8.4 Tigecycline (Wyeth) for bone and joint infections

Applicant (Trust)	Presented by	Outcome
Dr S Warren	MK	Approved

The Committee considered tigecycline, an antimicrobial agent structurally related to the tetracyclines, for the treatment of multi-drug resistant complex bone or soft tissue infections or severe systemic infection. Tigecycline exhibits broad spectrum antimicrobial activity including both gram-positive and gram-negative bacteria, tetracycline-resistant organisms, anaerobes, methicillin-resistant *staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended spectrum beta-lactamase (ESBL) producing enterobacteriaceae.

The Committee noted the absence of any prospective clinical trial data for tigecycline use in bone or soft tissue infections. The evidence is limited to a small retrospective study in six patients, and three animal model studies. However, the Committee acknowledged that there are sufficient data for tigecycline use within its licensed indications of complicated skin and soft tissues and intra abdominal infections, as well as community-acquired and hospital-acquired pneumonia (off-label use).

The Committee discussed results from a meta-analysis by Tasina et al revealing that tigecycline has comparable efficacy when compared to other antimicrobial agents, however is associated with a higher mortality in some unlicensed indications.

The Committee were informed that tigecycline has the potential to be a valuable treatment option in staphylococcal infections with a high level of resistance and / or intolerance or contraindication to various other antimicrobial therapies.

In addition, it was suggested that tigecycline could be used as an out-patient treatment option to prevent hospital admissions.

Tigecycline's adverse effect profile is similar to the tetracyclines and a six week course would cost £2700 per patient.

In summary, the Committee agreed to include tigecycline into the NCL Formulary for the treatment of complex multi-drug resistant bone or soft tissue infections or severe systemic infections. The Committee suggested that treatment should be initiated by microbiology consultants only.

9. Policy

9.1 JFC review of Cancer Drug Fund and NICE Technology Appraisals

The Committee agreed that the JFC should table drugs approved by the Cancer Drug Fund (CDF) and NICE Technology Appraisals (TA). The Committee agreed that it was not a priority of JFC to re-assess these drugs and that they should be implemented locally where appropriate. However, where NICE, for example, list a variety of drugs as an option for the same indication, the JFC agreed to facilitate agreement of a prescribing algorithm.

9.2 Horizon scanning & 2013/2014 financial planning

The Committee agreed that this should form part of JFC activity in the future but did not have the capacity to manage this at present.

9.3 Prescribing guidance and discharge

The Committee reviewed the above appendix to the Medicines Policy. The Committee requested that all hospitals ensure that out-patients are informed whether a medicine is urgent or not when being referred to the GP for prescribing.

9.4 Red-list management

The Committee agreed that the JFC would be the most appropriate forum to ratify the NCL "red-list" of drugs.

9.5 Shared care guideline criteria

The Committee agreed that the JFC would be the most appropriate forum to agree suitability of shared care and ratify shared care guidelines.

10. Date of next meeting

24th January 2013.

11. Any other Business

There was none.