North Central London
Medicines Optimisation Network

Joint Formulary Committee (JFC): Minutes

Minutes from the meeting held on 20th October 2022

		Present	Apologies
Prof A Hingorani	NCL JFC Chair	✓	
Dr B Subel	NCL JFC Vice Chair	✓	
Ms W Spicer	RFL, Chief Pharmacist	✓	
Ms G Smith	RFL, DTC Chair		✓
Dr A Scourfield	UCLH, DTC Chair	✓	
Mr J Harchowal	UCLH, Chief Pharmacist		✓
Dr R Urquhart	UCLH, Divisional Clinical Director	✓	
Dr K Tasopoulos	NMUH, DTC Chair	✓	
Ms S Stern	NMUH, Chief Pharmacist		✓
Dr M Kelsey	WH, DTC Chair	✓	
Mr S Richardson	WH, Chief Pharmacist	✓	
Dr S Ishaq	WH, Consultant Anaesthetist		✓
Dr A Worth	GOSH, DTC Chair		✓
Mr S Semple	NCL ICS, Interim Chief Pharmacist; GOSH, Interim Chief Pharmacist		✓
Mr A Sell	RNOH, DTC Chair		✓
Mr A Shah	RNOH, Chief Pharmacist		✓
Prof A Tufail	MEH, DTC Chair		✓
Ms N Phul	MEH, Chief Pharmacist		✓
Ms K Delargy	BEH, Chief Pharmacist	✓	
Ms L Reeves	C&I, Chief Pharmacist		✓
Dr L Waters	CNWL, Consultant Physician in HIV	✓	
Ms R Clark	NCL ICB, Head of Medicines Management (Camden)	✓	
Mr P Gouldstone	NCL ICB, Head of Medicines Management (Enfield)	✓	
Ms E Mortty	NCL ICB, Interim Head of Medicines Management (Haringey)	✓	
Ms M Singh	NCL ICB, Head of Medicines Management (Barnet)	✓	
Mr A Dutt	NCL ICB, Head of Medicines Management (Islington)	✓	
Dr D Roberts	NCL ICB, Clinical Director (Islington)	✓	
Mr T Dean	Patient partner		✓
Ms S Amin	IPMO Programme Team, JFC Principal Pharmacist		✓
Mr G Grewal	IPMO Programme Team, JFC Support Pharmacist	✓	
Ms I Samuel	RFL, Formulary Pharmacist	✓	
Mr H Shahbakhti	RFL, Formulary Pharmacist		✓
Mr A Barron	UCLH, Principal Pharmacist	✓	
Mr S O'Callaghan	UCLH, Formulary Pharmacist	✓	
Ms A Sehmi	NMUH, Formulary Pharmacist	✓	
Ms H Thoong	GOSH, Formulary Pharmacist	✓	
Mr D Sergian	MEH, Formulary Pharmacist	✓	
Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	✓	
Ms A Fakoya	NCL ICB, Contracts & Commissioning Pharmacist	✓	
Dr A Hosin	UCLH, Clinical Pharmacology Registrar	✓	
Dr A Drebes	RFL, Consultant Haematologist	✓	

Prof D Williams	UCLH, Consultant Obstetrician	✓	
Ms A Hussain	UCLH, Specialist Pharmacist	✓	
Ms D Waterton	WH, Medicines management nurse	✓	
Ms EY Cheung	NCL ICB, Deputy Head of Medicines Management (Camden)	✓	
Ms H Umer	NHSE, Specialised Commissioning Pharmacist	✓	
Ms K Mistry	RNOH, Formulary Pharmacist	✓	
Dr G Pollara	UCLH, Consultant in Infectious Disease	✓	
Ms D Cunningham	RFL, Specialist Pharmacist	✓	
Mr G Purohit	RNOH, Formulary Pharmacist	✓	
Dr R Maclean	UCLH, Clinical Pharmacology Registrar	✓	
Prof A Salama	RFL, Consultant Nephrologist	✓	
Ms J Bloom	MEH, Associated Chief Pharmacist	✓	
Ms M Thacker	RFL, Clinical Lead Pharmacist	✓	
Ms R McGaw	RFL, Specialist Pharmacist	✓	
Dr V Talaulikar	UCLH, Consultant Reproductive Medicine	✓	
Ms M Lanzman	RFL, Specialist Pharmacist	✓	

2. Meeting observers and members

Prof Hingorani welcomed members, applicants and observers to the meeting (see above). Dr Alex Sell (RNOH, DTC Chair) was noted to have stepped down from the Committee membership and was thanked for his valuable contributions to the Committee meetings.

3. Members' declaration of interests

Declarations of interests register was included for information. No interests relevant to the agenda were declared, and no further declarations were raised by members or attendees.

4. Minutes of the last meeting

The Committee agreed to amend Section 14 ("*Updated high-cost drug pathways for inflammatory bowel disease*") to reflect the discussion on high-cost drugs used in paediatric IBD (particularly those approaching their 18th birthday). Minutes and abbreviated minutes were otherwise accepted as an accurate reflection of the September 2022 meeting.

5. Matters arising

5.1 Potassium permanganate

The Committee discussed the decision to remove potassium permanganate from formulary at the September 2022 JFC meeting, with individual DTCs to review and consider the use of potassium permanganate in exceptional circumstances only. Following the JFC decision, JFC Support were informed of a small number of patients currently receiving potassium permanganate on repeat lists in primary care, and hence a post-meeting note was added to encourage primary care clinicians to review these patients to determine if treatment is still required. Work is underway at RFL and UCLH to consider whether it will be in use in exceptional circumstances and appropriate restrictions.

6. Review of action tracker

Action tracker included for information.

6.1 Hyperemesis pathway

Deferred to November 2022 meeting.

7. JFC Outstanding Items & Work Plan

These items were included for information only. Any questions should be directed to Ms Amin.

8. Local DTC recommendations / minutes

8.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Jul 2022	FOC Scheme: Teclistimab†	Relapsed refractory multiple myeloma	**Decision:** Added to the NCL Joint Formulary **Prescribing:** Secondary care **Tariff status:** N/A – Free of charge **Funding:** N/A – Free of charge **Factsheet or shared care required:** N/A
UCLH	Jul 2022	Intraoperative lidocaine	Prevention of emergence cough	**Decision:** UCLH only **Prescribing:** Secondary care **Tariff status:** In tariff **Funding:** Trust **Factsheet or shared care required:** N/A **Additional information:** Approved clinically; subject to development of a local protocol
UCLH	Jul 2022	Tocilizumab*	Giant cell arteritis – access beyond a 12-month course	**Decision:** UCLH only **Prescribing:** Secondary care **Tariff status:** Not routinely commissioned **Funding:** Trust **Factsheet or shared care required:** N/A **Additional information:** Approved clinically; deferred to High-Cost Drugs Panel for internal funding consideration
UCLH	Aug 2022	Obinutuzumab*	Systemic Lupus Erythematosus	**Decision:** UCLH only **Prescribing:** Secondary care **Tariff status:** Not routinely commissioned **Funding:** Trust **Factsheet or shared care required:** N/A **Additional information:** Deferred to Divisional mangers and the High-Cost Drugs Panel for internal funding consideration
UCLH	Aug 2022	Hyperthermic Intraperitoneal Cisplatin	Ovarian cancer	**Decision:** UCLH only **Prescribing:** Secondary care **Tariff status:** Not routinely commissioned **Funding:** Trust **Factsheet or shared care required:** N/A **Additional information:** Approved conditionally; subject to further implementation considerations

† The relevant commissioner should be notified in line with NCL Free of Charge scheme guidance. Approval is conditional on the provision of a free of charge scheme agreement and funding statement. * Subject to funding consideration.

8.2 Not approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Jul 2022	FOC Scheme: Zanidatamab †	HER2+ metastatic gastro-oesophageal, colorectal and biliary tract cancers	**Decision:** Not approved

8.3 Prucalopride to aid colon capsule endoscopy

The Committee considered the use of prucalopride, a prokinetic agent, at a dose of 1mg (or 2mg in patients with treatment dependent chronic constipation or those with a history of poor bowel cleansing for colonoscopy) for the off-label indication to aid colon capsule endoscopy (CCE) in line with a recent update to NHSE guidance. UCLH implemented the original NHSE guideline for CCE and added prucalopride to their

formulary in line with the recent update though not formally recorded in minutes; RFL are currently seeking to add prucalopride to the Joint Formulary for local implementation.

Evidence supporting the NHSE guideline comes from a nested cohort study by Deding et al based on a larger RCT (Care For Colon, 2015). The study compared a cohort of patients who used a standard bowel preparation regimen versus a bowel preparation regimen containing a dose of 2mg prucalopride. The primary outcome, CCE completion rate (taken as the time the haemorrhoidal plexus was visualised by the capsule), was higher in the prucalopride group compared with control (74.9% vs 56.7%). Other improvements were found in favour of prucalopride, including the prevalence ratio for complete CCE (1.32 [95% CI 1.15 to 1.53]) and bowel preparation quality rated as "fair", "good" or "excellent" (75.9% vs 57.1%). Limitations include the nested-cohort design, the lack of an active comparator (e.g., metoclopramide) and lack of information supporting the 1mg prucalopride dose.

The Committee agreed that whilst there were limitations in the study design, the evidence provided did demonstrate an improvement in successful CCE completion rates with prucalopride and is the best evidence available for the use of any prokinetic agent for CCE procedures.

In summary, the Committee agreed to add prucalopride guidance to the NCL Joint Formulary for to aid successful CCE in line with NHSE.

Decision: Added to the NCL Joint Formulary
Prescribing: Secondary care only
Tariff status: In tariff
Funding: Trust
Fact sheet or shared care required: N/A

9. New Medicine Reviews

9.1 Uromune for prophylaxis of recurrent and severe urinary tract infections

The Committee considered an application for Uromune, an unlicensed vaccine composed of equal amounts of *E. Coli, K. pneumoniae, P. vulgaris and E. faecalis*, to be administered as 2 sprays sublingually daily for three months, for the prophylactic management of patients with recurrent and severe urinary tract infections (UTIs). Recurrent UTIs are defined as at least 2 treated UTIs in the past 6 months or at least 3 treated UTIs in the past 12 months. Severe UTIs are defined as patients who may otherwise need IV antibiotics or have limited treatment options available to them (due to the presence of highly multi-resistant organisms in their urine cultures).

The Committee were informed that EAU guidelines mentioned the use of immunoactive prophylaxis with Uro-Vaxom, an oral vaccine consisting of *E. coli* only. Uro-Vaxom is currently approved for UTI prophylaxis on the South-East London formulary with strict initiation criteria. Uromune is the preferred vaccine due to broader antimicrobial coverage compared to Uro-Vaxom.

Lorenzo-Gomez et al (2022; n=229) conducted a phase 3, double-blind, randomised, placebo-controlled study to compare the safety and efficacy of Uromune to placebo in women with recurrent UTIs (at least 5 episodes per year). Patients were randomised to 2 sprays of Uromune daily for 3 months or a matched placebo. The primary endpoint, the median number of UTIs per participant during the 9-month evaluation period (after 3-months of the intervention), was significantly lower with Uromune compared with placebo (0 UTIs vs 3 UTIs; $p<0.001$). Other important outcomes were the percentage of participants UTI-free during the 9-month evaluation period. This was greater in the Uromune arm compared to placebo (58% vs 25%). Key limitations of the study are that the year-long study limits long-term efficacy and safety data, the patient population only included women and that baseline UTI data was collected retrospectively and therefore may not be reflective of the number of UTI episodes.

In the absence of further RCTs, four additional studies were presented. Sevilla et al (2019; n=794) and Yang et al (2018; n=77) each reported prospective, single-arm, observational studies in patients with uncomplicated recurrent UTIs. The primary endpoint, percentage of patients UTI-free, was 44.1% (after 3-months of treatment) and 79% (during the 12-month follow-up period), respectively. Lorenzo-Gomez et al reported two retrospective reviews in 2015 (n=669) and 2013 (n=319) in women with recurrent UTIs. These reviews compared efficacy of Uromune with continuous antibiotic prophylaxis. The percentage of patients UTI-free in the Uromune arm was reported to be significantly greater compared to the continuous antibiotic prophylaxis

arm (81% vs 3% [p<0.0001] during the prophylactic period in the 2015 review and 34.6% vs 0% [p<0.0001] during the 15-month follow-up period in the 2013 review).

In terms of safety, Uromune was reported to have a low risk of serious adverse effects from the published studies, all of which resolved. However, as the vaccine is still unlicensed, the long-term safety profile has not been established.

In terms of budget impact, Uromune is expected to cost approximately £31,000 per annum compared to prophylactic antibiotics (nitrofurantoin or trimethoprim) which may cost up to approximately £5000 based on an estimated 95 patients across NCL. The Committee was informed that an additional community care clinic at the Whittington Hospital sees many patients with UTIs and therefore costs may increase significantly if utilised by this clinic. However, the cost of hospitalisations, IV antibiotics and OPAT services for patients with severe recurrent UTIs may be reduced if Uromune is effective (although this could not be quantified).

The Committee heard from Professor Salama and Dr Pollara who clarified that prophylactic antibiotics are not the preferred comparator and Uromune is intended to be used ahead of antibiotic prophylaxis due to high antimicrobial resistance encountered. The number-needed-to-treat (NNT) to prevent one UTI episode is 3.2 for Uromune, which can help reduce costs associated with prolonged hospitalisations requiring IV antibiotics for severe recurrent UTIs. The RCT by Lorenzo et al also reported on quality of life which demonstrated improvements with Uromune. Repeated doses are not currently under consideration for this cohort and a new application will be brought to the Committee if felt necessary as the duration of efficacy is currently unknown.

In camera, the Committee discussed the uncertainties in durability of therapy. Concerns were expressed about the mechanism of action being poorly understood and resulting in a need for this vaccine to be administered as a daily dose for 3 months. The Committee acknowledged that the data is limited but the potential for benefit is quite large.

In summary, based on the limited safety and efficacy data available and concerns regarding duration of treatment effect, the Committee considered conditional approval under an 18-month evaluation period. The criteria agreed is for the use of Uromune where:

- Uromune is initiated in specialist clinics that have requested to use it
- It is initiated in patients with recurrent (i.e., at least 2 treated UTIs in the past 6 months and at least 3 treated UTIs in the past year) and severe (i.e., patients that require hospitalisation with IV antibiotics for treatment of acute episodes or patients with difficult-to-treat UTIs due to the presence of multi-resistant organisms in urine cultures) UTIs
- Patients have tried non-antibiotic prophylactic treatment options where suitable.
- MDT approval needed

The approval was made conditional on the applicants returning to the Committee with a flowchart to demonstrate patient selection criteria, a data collection form, agreed outcomes to be collected, a statistical analysis plan, and an agreement on a maximum number of patients allowed enrolment onto the evaluation and sites which will have it available. This documentation should be presented back to the Committee before full approval could be provided. Outcome data was requested to be collected and presented back to the Committee in 18 months.

Decision: Deferred

9.2 Bijuve (bio-identical estradiol/ natural progesterone) for HRT

The Committee considered an application for Bijuve (estradiol 1mg and body-identical progesterone 100mg), an oral HRT given once daily for the licensed indication of continuous combined hormonal replacement therapy in postmenopausal women with an intact uterus and with at least 12 months since last menses to reduce symptoms of oestrogen deficiency. The application outlined two places in therapy where Bijuve would address an unmet clinical need:

(i) To replace low-dose oral combination HRT which contain an oestrogen and progestin (e.g., Kliovance® 1mg/500mcg) with a claim of a superior safety profile; and

(ii) To replace low-dose oestrogen (oral or transdermal) plus oral body-identical progesterone (Utrogestan®), with claims of superior convenience (from use of a combined product over two

separate products) and improved concordance (due to difficulty in escalating progesterone doses to accompany increases in transdermal oestrogen)

To support the first claim of unmet need, the Committee considered evidence from several observational studies. The E3N breast cancer study (Fournier et al, 2008) found a lower risk of breast cancer for oestrogen with progesterone (RR = 1.00 [95% CI 0.83 to 1.22]) compared with oestrogen and other progestogens (RR = 1.69 [95% CI 1.50 to 1.91]), though with overlapping confidence intervals. The CPRD breast cancer study (Abenhaim et al., 2022) found no difference in the association between breast cancer risk with micronized progesterone (OR 0.99 [95% CI 0.55 to 1.79]) and an increased risk with synthetic progestins (OR = 1.28 [95% CI 1.22 to 1.35]), though again with overlapping confidence intervals. The results from two other studies found that progesterone was associated with an increased risk of endometrial cancer (E3N endometrial cancer; HR 1.80 [95% 1.38 to 2.34] though no association with dydrogesterone or other progestins) and an increased association with breast cancer (Breast Cancer IPD meta-analysis; RR = 2.05 [1.38 to 3.06]).

To support the second place in therapy, evidence was provided from the REPLENISH trial to demonstrate efficacy. Lobo et al was a 12-month, phase III, placebo-controlled, double-blind study to compare the efficacy and safety of Bijuve and placebo for women 40-65 years with an intact uterus and vasomotor symptoms (n=1,845). Patients were randomised to Bijuve at a dose range between 0.25mg/50mg to 1mg/100mg or placebo. Of the total population, 726 patients were eligible for the modified intention-to-treat population sub-study investigating the effect of vasomotor symptoms. The first co-primary outcome, frequency of vasomotor symptoms in terms of number of events, was significantly lower with Bijuve given at the licensed dose compared with placebo at week 4 (40.6 vs 35.1) and week 12 (55.1 vs 40.2). The second co-primary outcome, severity of vasomotor symptoms as per a symptom severity score, was significantly lower with Bijuve given at the licensed dose compared with placebo at week 4 (0.48 vs 0.34) and week 12 (1.12 vs 0.56). Key limitations of the study were the relatively short duration, the discontinuation rate (30%) and the lack of an active comparator (particularly compared against a combination of two separate components).

In terms of safety, the study by Lobo et al had safety outcomes reported from 415 participants; this found Bijuve was associated with an increased risk in breast tenderness (10.4%), headache (3.4%) and nausea (2.2%) amongst others (though as it was not an active comparator trial, this was not compared to other treatments).

In terms of budget impact, switching all patients on low-dose continuous combined oral HRT (e.g., Kliovance®) to Bijuve would cost an additional £26,500. A conservative estimate of switching 20% of patients currently utilising an oral estradiol and Utrogestan to Bijuve would cost an additional £15,800. Finally, a conservative estimate of switching 20% of patients currently utilising a transdermal estradiol and Utrogestan to Bijuve would save up to £30,400. Taken in totality, the overall impact was estimated to be £11,000, although this figure was highly dependent on the number of patients switched and their current therapeutic options.

The Committee heard from Dr Talaulikar that an increasing number of women are requesting body-identical HRT due to media publications and perceived improved safety. There are no current combination tablets which includes a body-identical version of oestrogen and progesterone, though Bijuve addresses the need for this. Patients who use a separate oral or transdermal oestrogen cannot appropriately up-titrate their progesterone which is resulting in vasomotor symptoms due to oestrogen overdose.

In camera, the Committee discussed the observational data and how the difference in effect attenuates the larger the samples size becomes. In terms of claim 1, the Committee did not agree that the observational data was adequate to support a claim of superior safety profile. In terms of claim 2, the Committee was not convinced that the data was adequate to demonstrate that Bijuve had more adherence and concordance as compared with known comparators. Additionally, the Committee recognised that the substantial offset on the budget impact was associated with a preference of Bijuve compared with transdermal oestrogen and a micronized progesterone; however, patients receiving transdermal oestrogen with an oral micronized progesterone tend to specifically require a transdermal oestrogen, and therefore this cost offset would be unlikely to happen. The Committee also discussed the risk of prescribing 'creep' and acknowledged that this would be an item which could potentially be prescribed outside the restricted indication.

In summary, based on the evidence available (lack of robust evidence of superior efficacy or safety) and the potential budget impact which could become more significant if costs are not offset with potential for prescribing 'creep' the Committee could not recommend the use of Bijuve for continuous combined HRT.

Decision: Not approved

9.3 Rapid reviews for DMARDs used for autoimmune hepatitis

This item was deferred to the November 2022 meeting.

10. Tecovirimat for monkeypox prescribing information document

The Committee was presented with a prescribing information for the use of tecovirimat for monkeypox. The document was developed by the antimicrobial lead pharmacists from several UK HCID centres, including RFL. It had been locally adapted to help inform NCL centres how they can procure tecovirimat and when supply is considered clinically urgent. The Committee agreed that the document contained useful information pertinent to NCL centres and agreed that it should be hosted on the NCL MON website.

11. Guideline: Adult asthma inhaler choice

The Committee was presented with an update to the adult asthma inhaler choice guideline. Key changes include updated pathways which advocates the use of inhaled corticosteroids in asthmatic patients to avoid over-reliance on short-acting beta agonists, information on the carbon footprint of inhalers, guidance for primary care clinicians to optimise therapies and example clinical scenarios. The Committee were supportive and approved the guideline; the approval was conditional on the outcome of the NCL consultation, and the guideline would require chair's action if any further amends were made.

12. Licensed metolazone 5mg tablets

The Committee discussed the availability of licensed metolazone 5mg tablets. Metolazone was previously licensed in the UK under the brand name Metenix®, though licensing expired in 2012. Since then, metolazone has been imported as either Metenix® or Zaroxolyn®. The newly licensed formulation, Xaqua®, is now available in the UK and reports suggest it has twice the bioavailability compared with other metolazone brands. JFC reviewed the data available for Xaqua® due to the possible risks associated with switching patients who are already established on unlicensed formulations.

A study from the MHRA product assessment report was considered. The study compared Xaqua® with Metenix® (n=22). Participants were given a single 5mg tablet under fasted conditions. C_{max} and $AUC_{0\text{-}inf}$ values were on average 2.54 and 1.93 times higher with Xaqua® compared with Metenix®; there was no data comparing Xaqua® with other brands of metolazone and there was no information on clinical outcomes.

In terms of risk, the Committee were informed that whilst 5mg of Metenix® could be considered bioequivalent to half a tablet of Xaqua®, there was no information on an appropriate bioequivalent dose of Xaqua® if using 2.5mg of Metenix®, nor was there any data for other brands of metolazone. Xaqua® does not contain a substance banned in the UK (red dye no.33) which is used in imported versions of metolazone, and there is less risk associated with use of a licensed product over unlicensed products.

JFC Support spoke with local cardiology and renal specialist services at RFL which should have capacity to review NCL patients should they require a switch from unlicensed metolazone to Xaqua®; an initial cohort of 11 patients were identified in NCL primary care as taking unlicensed metolazone 5mg tablets. JFC Support has also contacted the manufacturer, who has advised that a high quantity of stock is available. They have also advised that switching from one brand of metolazone to another would require careful monitoring and dose adjustments may be necessary individualised to the patient. The potential budget impact from using Xaqua® 2.5mg instead of unlicensed metolazone 5mg was around £100 per patient per annum.

The Committee acknowledged that notwithstanding the increase in bioavailability, there remains an unknown clinical risk in terms of diuretic effect if switching therapies. The Committee felt it would be appropriate to use Xaqua® in new patients, although patients already established on unlicensed metolazone would require a review to re-titrate their therapy safely. The Committee agreed that criteria for starting or switching to Xaqua should be created and presented back at the next meeting.

13. Next meeting

Thursday 17th November 2022

14. Any other business

Membership

The Committee welcomed Jatinder Harchowal as the interim Chief Pharmacist for NCL, and Stuart Richardson and Mandeep Butt will be supporting. The Committee acknowledged that the first Integrated Medicines Optimisation Committee (IMOC) meeting will be held on 1st November 2022 and that the Committee will be updated on the relationship to the JFC following this meeting.