North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 20th August 2020

Present:	Dr R Sofat	NCL JFC Chair	(Chair)
	Dr P Taylor	NCL JFC Vice Chair	
	Dr M Kelsey	WH, DTC Chair	
	Mr P Gouldstone	NCL CCG, Head of Medicines Management (Enfield)	
	Mr A Dutt	NCL CCG, Head of Medicines Management Islington)	
	Ms P Taylor	NCL CCG, Head of Medicines Management (Haringey)	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Mr T Dean	Patient Partner	
	Ms K Delargy	BEH, Deputy Chief Pharmacist*	
	Ms G Smith	RFL, DTC Chair	
	Dr K Tasopoulos	NMUH, DTC Chair	
In attendance:	Dr P Bodalia	UCLH, Principal Pharmacist	
	Mr A Barron	North London Partners, MEP Project Lead	
	Mr G Grewal	North London Partners, JFC Support Pharmacist	
	Ms M Kassam	North London Partners, JFC Support Pharmacist	
	Ms S Amin	UCLH, Formulary Pharmacist	
	Mr S O'Callaghan	UCLH, Formulary Pharmacist	
	Ms SY Tan	NEL CSU, Contracting and Commissioning Pharmacist	
	Ms H Thoong	GOSH, Formulary Pharmacist	
	Mr J Flor	WH, Formulary Pharmacist	
	Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr F Master	RFL, Formulary Pharmacist	
	Ms A Fakoya	NEL, Senior Prescribing Advisor High Cost Drugs	
	Mr D Abdulla	NMUH, Formulary Pharmacist	
	Mr B O'Farrell	RFL, Lead Pharmacist Intensive Care & Theatres	
	Ms R Stennett	NCL Nutrition Group, Co-Chair	
	Ms M Lanzman	RFL, Lead Pharmacist Microbiology	
	Ms P Panesar	UCLH, Lead Pharmacist Microbiology	
	Dr I Balakrishnan	RFL, Consultant Microbiologist	
	Dr N Stone	UCLH, Consultant in Infectious Diseases	
	Prof P Wilson	UCLH, Consultant Microbiologist	
	Ms K Smith	RFL, Consultant Oncologist	
	Dr S Needleman	RFL, Consultant Oncologist	
	Dr J Kimpton	UCL, NIHR Academic Clinical Fellow in Clinical Pharmacology	
Apologies:	Mr S Tomlin	GOSH, Chief Pharmacist	
	Ms R Clark	NCL CCG, Head of Medicines Management (Camden)	
	Dr D Burrage	WH, Consultant in Emergency Medicine	
	Ms S Lever	NCL CCG, Pharmaceutical advisor (Barnet)	
	Dr A Bansal	NCL CCG, GP Clinical Lead Medicines Management (Barnet)	
	Mr A Shah	RNOH, Chief Pharmacist	
	Mr A Tufail	MEH, DTC Chair	

Ms W Spicer	RFL, Chief Pharmacist
Mr S Semple	MEH, Chief Pharmacist
Dr A Sell	RNOH, DTC Chair
Mr S Richardson	WH, Chief Pharmacist
Dr R Urquhart	UCLH, Chief Pharmacist

**Deputising for Committee member*

2. Meeting observers

Ms Weaver (NHSE, Specialised Commissioning Pharmacist) and Dr Kimpton (UCL, NIHR Academic Clinical Fellow in Clinical Pharmacology) were welcomed as observers of the meeting.

3. Minutes of the last meeting

The minutes of the 16 July 2020 meeting were accepted as an accurate reflection of the meeting.

4. Matters arising

4.1 Sorafenib for FLT3-positive relapsed or refractory acute myeloid leukaemia in patients aged 13 or over

In June 2020, the Committee approved a FoC scheme for sorafenib in FLT3-positive relapsed or refractory AML in circumstances where gilteritinib is not accessible. In August 2020 NICE published TA642; gilteritinib for 'FLT3-positive relapsed or refractory AML in adults', which is available via the CDF. The NHS England policy 'Commissioning Medicines for Children in Specialised Services' means TA642 applies to post-pubescent children.

As a consequence, the Committee revised their recommendation for sorafenib FoC to 'adults and post-pubescent children bridging to HSCT with FLT3-positive acute myeloid leukaemia (AML)'.

The original sorafenib FoC included use in children from the age of 13. As it is feasible for a child ≥13 to not be post-pubescent, the Committee issued a second recommendation for sorafenib FoC to '≥13 years pre-pubescent children with relapsed or refractory AML'.

5. Proposed changes to the Committee structure

JFC Chair, Vice Chair, Secretariat and Patient Representative met to review JFC processes. Several amendments were recommended for adoption which would be reviewed in 3 months. The Committee approved the proposal.

6. JFC Outstanding Items & Work Plan

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

7. Members declarations of conflicts of interest

Nil

8. Local DTC recommendations / minutes

8.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	July 2020	Meglumine antimoniate	Management of susceptible leishmania species	Decision: UCLH only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
UCLH	July 2020	Selpercatinib	Pre-NICE FoC scheme: treatment for paediatrics with RET fusion positive/RET mutated medullary thyroid cancer	Decision: UCLH only Prescribing: Secondary care Tariff status: N/A Funding: FoC Fact sheet or shared care required: No

UCLH	July 2020	Memantine	Management of parkinson's disease dementia when cholinesterase inhibitors are not suitable	Decision: Added to NCL joint formulary Prescribing: Primary and Secondary care Tariff status: In tariff Funding: Trust/CCG Fact sheet or shared care required: No
UCLH	April 2011 + November 2017	Levosimenden	Patients not responding to (or intolerant of) conventional inotropes if they have a reasonable expectation of survival and one of the below: • Acute decompensation of severe chronic heart failure (NYHA III/IV) • Low cardiac output syndrome • Takotsubo cardiomyopathy	Decision: Added to NCL joint formulary Prescribing: Secondary care only Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
WH	July 2020	Terizidone	Treatment of TB - alternative to cycloserine when there are supply issues and shortages	Decision: Added to NCL joint formulary Prescribing: Secondary care only Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
WH	July 2020	Levofloxacin	Treatment of TB - alternative to moxifloxacin when there are supply issues and shortages, or in patients with liver impairment	Decision: Added to NCL joint formulary Prescribing: Secondary care only Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

8.2 Decision deferred

DTC site	Month	Drug	Indication	JFC outcome
N/A (NICE approved)	Feb 2020	Hydrogen peroxide 1% cream	Treatment of non-bullous impetigo	Decision: Deferred Additional information: JFC Support to determine from NCL Dermatologists whether hydrogen peroxide 1% cream is recommended for use in inflammatory skin conditions
WH	Sept 2019	Chloroprocaine	Short-acting spinal anaesthesia in day case procedures	Decision: Deferred Additional information: JFC Support to co-ordinate an NCL local anaesthetics pathway to clarify the place in therapy for bupivacaine, chloroprocaine and prilocaine

9. New Medicine Reviews

9.1 Oestrogen patches for metastatic castrate-resistant prostate cancer (Applicant: Dr K Smith and Dr S Needleman, RFL)

The Committee considered an application for oestrogen patches, a proposed treatment to suppress gonadotropin secretion and reduce testosterone production, for metastatic castrate-resistant prostate cancer in men who have failed or progressed on available novel hormonal therapies, chemotherapeutic options and low-dose steroids (or those who are not suitable for therapy).

Stein et al was a Phase II, single-arm open-label study to assess the efficacy and safety of oestrogen patches for patients with castrate and chemotherapy resistant prostate cancer (n=22). The study was terminated early due to futility as the pre-specified requirement for 20% of patients to respond (as defined by a decline in PSA from baseline by ≥50% or normalisation) was not met. In total only 2 patients responded (9%) however a further 7 patients (41%) experienced some decrease in PSA. Key limitations of the study were the lack of a comparator, low number of patients and early termination of the study.

Smith et al was a phase II, single-arm open-label, dose-escalation study to assess the safety and efficacy of transdermal oestradiol in castrate and steroid-resistant prostate cancer in patients who had declined or felt to be inappropriate for chemotherapy (n=41). The primary endpoint, PSA response (defined as >50% reduction of PSA maintained for one month), was reached by five participants (12%). Key limitations of the study were the lack of comparator and the low numbers of patients.

In terms of safety, many of the well-known risks with transdermal oestrogen (e.g. VTE or breast cancer) relate to women using long-term transdermal HRT and do not apply to men with prostate cancer. The Committee heard that transdermal oestrogen for transgender women was thought to be safe, however data is limited.

In terms of budget impact, oestrogen patches are expected to cost up to £4,589 per annum for patients who would otherwise have best supportive care.

The Committee heard from Dr Smith and Dr Needleman that the treatment pathway is not straight forward as many patients are frail and unsuitable for NICE recommended therapies. The only alternative therapy at the proposed stage of oestrogen patches is best supportive care or low-dose steroids (the latter known to cause adverse effects that may reduce the patient's quality of life). Whilst it was acknowledged that the evidence for oestrogen patches is not as strong as most recommended therapies, the evidence for the comparator (low-dose steroids) was taken from observational studies and arguably less robust than the phase II trials presented. However, the phase II trials were also noted to not show a benefit. In their clinical practice, oestrogen patches have shown to be well tolerated, and is used in other London Trusts for the same indication. Moreover, there was no evidence on the QoL data for topical oestrogen in this cohort and that it was not known how well the surrogate outcome 'PSA from baseline by ≥50% or normalisation' maps to patient orientated outcomes for patients with advanced disease.

In camera, the Committee discussed the lack of robust evidence of efficacy and safety in the proposed setting. Based on this, the Committee could not recommend the use of transdermal oestrogen. However, the Committee agreed that it was plausible in some people who are not suitable to receive available novel hormonal therapies, chemotherapeutic options or low-dose steroids that transdermal oestrogens may be beneficial. Without RCT evidence to support this hypothesis, the Committee agreed it was not appropriate to recommend the use of transdermal oestrogen outside of a clinical trial setting, the results of which would allow for firmer guidance in the future.

In summary, based on the lack of convincing evidence for efficacy and safety the Committee could not recommend the use of transdermal oestrogen outside of the context of a clinical trial.

Decision: Not approved

9.2 Isavuconazole for fungal infections (Applicant: Dr N Stone, UCLH)

The Committee considered an application for isavuconazole, a triazole antifungal that blocks the synthesis of ergosterol, for the treatment of proven or probable invasive aspergilosis or mucomycosis when other agents are not appropriate due to inefficacy, contraindications, adverse effects, resistance or drug-drug interactions that cannot otherwise be managed.

SECURE was a Phase III, active-comparator, non-inferiority study to compare the efficacy and safety of isavuconazole to voriconazole for the primary treatment of adults with a proven, probable, or possible invasive fungal disease caused by the Aspergillus species or other filamentous fungi. The primary endpoint was all-cause mortality, the percentage of patients who died from any cause, from first dose of study drug to day 42 in the ITT population (n=516). Non-inferiority was demonstrated if the upper bound of the 95% confidence interval for the treatment difference was less than 10%. Results demonstrated that isavuconazole was non-inferior to voriconazole in terms of all-cause mortality; 19% in the isavuconazole group compared to 20% in the voriconazole group (adjusted treatment difference: -1.0% [95% CI: -7.8% to 5.7%]). Key limitations of the study included a high rate of discontinuation (54.3% and 53.5% in the

isavuconazole and voriconazole arms respectively) and the evidence does not show the response in patients whose treatment had failed prior antifungal therapy, which is the proposed cohort.

There was no comparative data for isavuconazole compared to other systemic antifunagals for the treatment of mucomycosis (e.g. amphotericin B). The best available data is from VITAL, a Phase III, open-label, single-arm study assessing the efficacy and safety of isavuconazole in adults requiring primary therapy or therapy where refractory/intolerant to current treatment for invasive fungal disease (n=146). The primary endpoint was the percentage of patients with 'data review committee-assessed overall response (complete or partial response)' at Day 42. There was no sample-size calculation or statistical testing of hypotheses. Data for the whole population are not available. In the subgroup with mucomycosis (n=37) at Day 42, 0% had a complete response and 11% had a partial response. At 'end of treatment' (up to 180 days) 14% had a complete response and 17% had a partial response (overall response of 31%). All-cause mortality at day 84 was 43%. This compares favourably with AmBizygo trial, a single arm study assessing the efficacy of liposomal amphotericin B (10mg/kg/day) for the treatment of mucormycosis, which reported a mortality rate of 38% at day 84. Key limitations of the study include the small sample size in the mITT-Mucorales population, of which only 16 were refractory or intolerant to previous therapy and a lack of statistical testing.

In terms of safety, the EPAR considered the safety profile of isavuconazole to be in accordance with that expected of a triazole antifungal and to compare favourably with that of voriconazole. Isavuconazole is administered once-daily, does not require therapeutic drug monitoring, does not require liver and renal function monitoring and is not dose-adjusted in people with renal or mild-to-moderate hepatic impairment. Intravenous isavuconazole can be used in patients with moderate to severe renal impairment whereas intravenous voriconazole cannot.

Isavuconazole is a high cost antifungal; as such NHSE will commission isavuconazole for licensed indications when used in accordance with Trust guidelines. Blueteq prior approval is required to ensure trusts are prescribing isavuconazole only when it is clinically appropriate to do so and there is no other alternative. NHSE require that the number of patients treated and proportion given for SPC indications within policy are monitored.

The Committee heard from Dr Stone that there are limited treatment options for invasive aspergillosis or mucomycosis, furthermore a select number of patients cannot tolerate currently available antifungal treatments, isavuconazole would be an appropriate alternative in this setting. QT prolongation is a problem with azoles, isavuconazole shortens the QT interval and may be beneficial in a select group of patients. Due to cost, isavuconazole is not used as first-line therapy.

In camera, the Committee were supportive for the use of isavuconazole for the treatment of proven or probable invasive aspergilosis or mucomycosis where other antifungals are not appropriate.

Decision: Approved, conditional on individual Trusts updating their antifungal guidelines.
Prescribing: Secondary care
Tariff status: Excluded from tariff
Funding: NHSE
Primary and secondary care Fact sheet or shared care required: No

Action: Ms Weaver to confirm if NHSE will commission isavuconazole for children

9.3 Cefiderocol for gram negative infections (Applicant: Dr I Balakrishnan, RFL)

The Committee considered an application for cefiderocol, a cephalosporin, for treatment of multi-drug resistant pathogens with proven susceptibility to cefiderocol with no other suitable treatment options (including ceftazidime + avibactam, ceftolozane + tazobactam and meropenem + vaborbactam), typically class B β-lactamase-producing (aka metaloenzyme producing) pathogens. At the time of JFC review, cefiderocol has been approved by the EMA, but remains unauthorised/ unlicensed in the UK, with access only via a 'compassionate use' scheme (not free-of-charge) through a third-party company.

In terms of efficacy for the proposed indication, there were no relevant *in vivo* studies. Data from *in vitro* studies show cefiderocol to be effective in a broad range of multi-drug resistant gram-negative bacteria, including the metallo-β-lactamases, where the only alternative effective agents were colistin and tigecycline.

There were three studies which informed the product license. APEKS-cUTI, a Phase II study, found cefiderocol to be non-inferior to imipenem/cilastatin for the outcome 'microbiological and clinical response' in carbapenem sensitive UTIs (n=448). CREDIBLE-CR, a Phase III, open-label, active-comparator controlled study found cefiderocol to have similar 'clinical cure' and 'microbiological eradication' rates to 'best available treatment' (1 to 3 antibiotics) in adults with severe infections caused by carbapenem-resistant gram-negative pathogens (n=152). Of importance, mortality rates at 28-days were numerically higher with cefiderocol (27.5% vs. 21.1%) with the difference particularly pronounced in the subgroup with pneumonia (32.5% vs. 15.8%). A third study, APEKS-NP, compared cefiderocol or meropenem in adults with documented HAP/VAP/HCAP and found all-cause mortality rates did not differ between the two agents. Two paediatric safety and efficacy studies were identified (NCT04215991 and NCT04335539) however neither have completed.

In terms of safety, with the exception of the unexplained imbalance in mortality rate observed in CREDIBLE-CR, the safety profile of cefiderocol is similar to other cephalosporines.

In terms of budget impact, cefiderocol is expected to cost £142,452 per annum across NCL.

The Committee heard from Dr Balakrishnan that cefiderocol is solely for the treatment of class B producing organisms, where frequently there are few treatment options available. Colistin and tigecycline may be treatment options in this setting but are less favourable compared to newer agents owing to are nephrotoxic/neurotoxic side effects (colistin) or concerns over excess mortality (tigecycline).

In camera, the Committee acknowledged concerns expressed by EMA around a signal for increased mortality for individuals with carbapenem-resistant pathogens treated with cefiderocol; this is partially addressed by the proposed positioning where there are no alternative agents although there was no clear agreement as to whether colistin or tigecycline should be used prior to cefiderocol. It was noted that *in vitro* testing would be required to guide treatment. The Committee requested clarification from NCL consultant microbiologists on the preference between the antibiotics on formulary for the treatment of gram negative resistant infections, to identify the most appropriate antibiotic where more than one antibiotic may be effective.

In summary, the Committee were supportive of the addition of cefiderocol to the NCL Joint Formulary following clarification on treatment preference.

Decision: Deferred

Action: JFC support and NCL Consultant Microbiologists to produce a summary of the options available for the treatment of resistant gram negative infections which indicates a hierarchy of preference between available antibiotics. This hierarchy should include colistin and tigecycline.

9.4 Meropenem/vaborbactam for gram negative infections (Applicant: Dr I Balakrishnan, RFL)

The Committee considered an application for meropenem/vaborbactam, a carbapenem and a beta lactamase inhibitor, for treatment of infections due to proven or suspected multi-drug resistant aerobic, gram negative pathogens that have susceptibility to meropenem/vaborbactam and other agents cannot be used due to intolerability, contraindication, allergy or interactions; these would usually be KPC producing pathogens.

In terms of efficacy for the proposed indication, there were no relevant *in vivo* studies. Data from *in vitro* studies show the inhibitory spectrum of vaborbactam includes class A carbapenemases (such as KPC) and Class C carbapenemases. Alternative effective agents on formulary include ceftazidime-avibactam, tigecycline and colistin.

There were two studies which informed the product license. Tango I, a Phase III, found meropenem/vaborbactam to be non-inferior to piperacillin/tazobactam for a variety of FDA and EMA measures of overall success in adults with complicated urinary tract infection (n=550). TANGO II, a Phase III open-label, active-controlled study. TANGO II, a Phase III, open-label, active-comparator controlled study found meropenem/vaborbactam has numerically lower rates of all-cause mortality (22.2% vs. 44.4% [95% CI: −59.9% to 15.5%]) but lower rates of 'overall success' at the test of cure visit in the cUTI subgroup (33.3% vs. 50% [95% CI: not reported]) compared to 'best available treatment' in adults with severe infections caused by confirmed or suspected carbapenem resistant carbapenem resistant Enterobacteriaceae (n=47).

The safety profile of meropenem is well-established with mostly mild adverse effects. In TANGO II, meropenem/vaborbactam was associated with fewer treatment emergent adverse events (84.0% vs. 92.0%) and fewer severe treatment emergent adverse events (14.0% vs. 28.0%) compared to 'best available treatment'.

In terms of budget impact, meropenem/vaborbactam is expected to cost up to £25,000 per annum.

The Committee heard from Dr Balakrishnan that meropenem vaborbactam is preferred for the treatment infections caused by resistant KPC producing organisms. Current options include ceftazidime/avibactam, comparatively meropenem/vaborbactam and is less expensive, has fewer concerns with resistance patterns and has a narrower spectrum of activity. Usage is expected to be low as these are rare infections most commonly seen in patients travelling to areas with high resistance patterns.

In camera, the Committee requested clarification on the preference between the antibiotics on formulary for the treatment of gram negative resistant infections, to identify the most appropriate antibiotic where more than one antibiotic may be effective.

In summary, the Committee were supportive of the addition of meropenem/vaborbactam to the NCL Joint Fformulary following clarification on treatment preference.

Decision: Deferred

Action: JFC support and NCL consultant microbiologists to produce a summary of the options available for the treatment of resistant gram negative infections which indicates a hierarchy of preference between available antibiotics. This hierarchy should include colistin and tigecycline.

10. RFL evaluation of nebulised iloprost in COVID-ARDS patients

Mr O'Farrell presented the results of the RFL evaluation of nebulised iloprost (n=10). The final analysis of the evaluation shows equipoise in practice. The data will be submitted into the national COVID research portal to inform future clinical trials.

11. Biosimilar rituximab (Truxima®) to biosimilar rituximab (Rixathon®) switch

The Committee heard that Rixathon was now the 'best value biological' for rituximab. Two large Trusts outside of London have already switched. Trial data on 'switching' for rituximab is limited; two studies are available for 'originator to biosimilar' in the context of rheumatoid arthritis however there is no trial data in haematology. The Committee were satisfied that the switching data for 'originator to biosimilar' could be extrapolated to 'biosimilar to biosimilar' and to non-rheumatoid arthritis indications. It was noted that the switch was not mandated by relevant commissioners however it is associated with a significant cost-saving to the NHS. The Committee approved the proposal to switch to Rixathon.

12. NCL JFC Position Statement Calogen

The position statement was approved.

13. Addition of Aymes ActaSolve® Smoothie to the NCL ONS Formulary

The addition of Aymes ActaSolve® Smoothie to the NCL ONS formulary was approved

14. Next meeting: Thursday 17th September

15. Any other business

Nil