North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 16th September 2021

Present:	Prof R Sofat	NCL JFC Chair	(Chair)
	Dr M Kelsey	WH, DTC Chair	
	Dr K Tasopoulos	NMUH, DTC Chair	
	Ms G Smith	RFL, DTC Chair	
	Mr S Semple	MEH, Chief Pharmacist	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Mr J Harchowal	UCLH, Chief Pharmacist	
	Mr P Gouldstone	NCL CCG, Head of Medicines Management (Enfield)	
	Ms E Mortty	NCL CCG, Deputy Head of Medicines Management (Haringey)	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Ms W Spicer	RFL, Chief Pharmacist	
	Dr A Scourfield	UCLH, Interim DTC Vice Chair	
	Mr S Richardson	WH, Chief Pharmacist	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms R Clark	NCL CCG, Head of Medicines Management (Camden)	
In attendance:	Mr A Barron	UCLH, Principal Pharmacist	
	Mr G Grewal	North London Partners, JFC Support Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms S Amin	UCLH, Formulary Pharmacist	
	Ms H Matthews	UCLH, Formulary Pharmacist	
	Ms C Obeirne	UCLH, Formulary Pharmacist	
	Ms S Y Tan	NEL CSU, Contracting and Commissioning Pharmacist	
	Ms A Fakoya	NEL CSU, Commissioner Support Pharmacist	
	Ms A Sehmi	NMUH, Formulary Pharmacist	
	Ms H Thoong	GOSH, Formulary Pharmacist	
	Dr A Hosin	UCLH, Clinical Pharmacology Registrar	
	Dr M George	UCLH, Consultant Clinical Pharmacologist	
	Ms P McCormick	WH, Lead Pharmacist Finance, Business and Performance	
	Mr S O'Callaghan	UCLH, Medicines Safety Officer	
	Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	
	Dr P Eleftheriou	UCLH, Haematology Consultant	
	Mr A Tailor	UCLH, Haematology Pharmacist	
	Ms K Von Both	UCLH, Paediatric Oncology Pharmacist	
	Ms R Allen	UCLH, Commissioning Pharmacist	
	Dr A Bahra	NHNN, Consultant Neurologist	
	Mr I Quarm	NCL CCG, Prescribing Advisor	
	Dr R Popat	UCLH, Consultant Haematologist	
	Ms R Burgoyne	UCLH, Haematology Pharmacist	
	Dr G Satta	UCLH, Consultant Microbiologist	
Apologies:	Dr B Subel	NCL JFC Vice Chair	
	Mr T Dean	Patient Partner	
	Mr A Dutt	NCL CCG, Head of Medicines Management (Islington)	
	Dr A Sell	RNOH, DTC Chair	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr A Tufail	MEH, DTC Chair	

Mr A Shah	RNOH, Chief Pharmacist
Mr S Tomlin	GOSH, Chief Pharmacist
Ms M Singh	NCL CCG, Head of Medicines Management (Barnet)
Ms S Stern	NMUH, Chief Pharmacist
Dr D Burrage	WH, Consultant in Emergency Medicine

2. Meeting observers

Ms Weaver (NHSE, Specialised Commissioning Pharmacist) was welcomed as an observer of the meeting.

3. Minutes of the last meeting

The minutes and abbreviated minutes of the 19 August 2021 meeting were accepted as accurate reflections of the meeting.

4. Matters arising

Nil

5. JFC Outstanding Items & Work Plan

These items were included for information only. Any questions should be directed to Mr Grewal.

6. Members declarations of conflicts of interest

Nil

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
BEH	May 2021	Buprenorphine long-acting injection	For use in opioid substitution treatment (via substance misuse service)	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No Additional information: For use via substance misuse services at BEH and C&I
RFL	July 2021	Sodium zirconium cyclosilicate (Lokelma®)	Hyperkalaemia in pseudo-hypoaldosteronism Type 1	Decision: RFL only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
RFL	July 2021	VeraSeal	Topical haemostatic agent for supportive use during partial nephrectomy surgery	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
UCLH	July 2021	Obinutuzumab	Immune-mediated thrombotic thrombocytopenic purpura	Decision: UCLH only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

7.2 Decisions pending

DTC site	Month	Drug	Indication	JFC outcome
UCLH	July 2021	Indometacin	Hemicrania Continua & Paroxysmal Hemicrania	Approved pending development of a treatment protocol Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

8. New Medicine Reviews

8.1 Lithium for cluster headache (Applicant: Dr A Bahra, NHNN)

The Committee considered an application for lithium for the prevention of cluster headache not responding to verapamil.

Three relevant trials were identified. Bussone et al (1990) conducted a 23-week, double-blind, double-dummy, crossover study to compare the efficacy and safety of lithium and verapamil for patients with chronic cluster headache (n=30). Following a two-week washout period, patients were randomised to lithium with placebo or verapamil with placebo for 8-weeks; following a further 2-week washout period, subjects were alternated to the other active treatment. The primary endpoint, reduction in headache index score, was significantly better with both medicines after one week of treatment compared with baseline (37% and 50% respectively [p<0.01]). The secondary endpoint, a reduction in analgesic consumption, was similar in both groups after one week of treatment compared with baseline (58%). Key limitations of the study include a 20% dropout rate after the first placebo washout.

Steiner et conducted a placebo-controlled, double-blind study to assess the safety and efficacy of lithium for episodic cluster headache (n=27). Patients were enrolled to matched parallel groups to receive lithium carbonate 800mg/day or placebo. The primary endpoint, cessation of attacks after one week, demonstrated no difference between lithium or placebo groups (15.3% vs 14.2%). The secondary endpoint, subjective assessment of being substantially better after one week, efficacy rates were better with lithium (62% vs.43%). Key limitations of the study include the small sample size and lack of details on randomisation.

Ekbom et al conducted a retrospective study to assess the safety and efficacy of lithium for chronic cluster headache and episodic cluster headache (n=19). All eight patients with chronic cluster headache experienced partial remission of their headaches in the first two weeks of lithium treatment; in the episodic cluster headache cohort, four patients experienced a positive effect which could be attributed to lithium therapy; conversely, the remaining seven patients had only slight or no effect on the headaches. Key limitations of the study were the retrospective design.

In terms of safety, lithium is a well-known medicine with a narrow therapeutic window, which requires a series of baseline tests prior to initiation, and careful titrating and therapeutic drug monitoring during treatment.

In terms of budget impact, lithium is expected to cost up to £14,000 per annum to treat an estimated 100 patients. However, the cohort eligible for treatment is across the UK, and not solely patients within NCL.

The Committee heard from Dr Bahra that cluster headache is a very small proportion of the overall population of migraine sufferers. Whilst episodic cluster headache sometimes resolves spontaneously, chronic cluster headache is difficult to treat with verapamil being the only treatment option available. The only current alternative to those who cannot tolerate verapamil are invasive procedures. Dr Bahra has 20 years' experience in prescribing lithium for chronic cluster headache; in that time, fewer than 100 patients have been initiated on lithium. Response to lithium therapy has generally been effective and well tolerated, though concomitant interacting medicines and deteriorating renal function remains a concern. Only patients who will comply with monitoring requirements are considered for treatment.

In camera, the Committee acknowledged that we are unlikely to see more robust data to support the use of lithium for chronic cluster headache in the future. The Committee queried the feasibility of retaining monitoring responsibilities at NHNN, but this was deemed to be inconvenient for the patient cohort due to their wide geographical spread. The Committee considered the evidence and agreed that the quality of evidence was very low however took assurance from anecdotal reports of benefit, absence evidence of patient harm amongst the selected cohort who agree to comply with monitoring requirements, and the potential to avoid invasive interventions. On balance, the Committee agreed that this established practice could continue.

In summary, the Committee agreed to add lithium to the NCL Joint Formulary for patients who do not respond to verapamil or require add-on therapy for symptomatic relief. The decision of whether a factsheet or shared care protocol would be most suitable was deferred to the NCL Shared Care Group.

Decision: Approved
Prescribing: Specialist initiation; Primary care continuation

Tariff status: In tariff
Funding: Hospital and CCG
Fact sheet or shared care required: Yes – deferred to NCL Shared Care Group

8.2 Tigecycline for severe clostridium difficile infection in patients unable to tolerate oral treatments (Applicant: Dr G Satta, UCLH)

The Committee considered an application for tigecycline, a glycycline antibiotic, for patients with *clostridioides difficile* (*C. difficile*) infection who are unable to tolerate oral therapy with vancomycin or fidaxomicin.

There were no prospective randomised controlled trials investigating the use of tigecycline for the treatment of *C. difficile.* Kechagias et al conducted several retrospective case series, which included four studies with >10 patients versus a comparator arm. The most relevant was by Gergely et al, who conducted a single-centre retrospective analysis in patients with severe *C. difficile* (n=359). 45 patients had been treated with tigecycline monotherapy (either 1st or 2nd line), and was compared to a randomly selected cohort of 45 patients treated with standard therapy of vancomycin and metronidazole. The primary endpoint, rate of clinical cure by the end of treatment, was significantly better with tigecycline compared to standard therapy (75.6% vs. 53.3% [p=0.02]). Key limitations of the study were the retrospective design, unbalanced groups at baseline, no clear criteria for initiating tigecycline, and there lack of standardisation within treatment arms.

In terms of safety, data from tigecycline RCTs for intraabdominal infection found common adverse events to include nausea, vomiting, diarrhoea, adverse effects of the digestive system, secondary infection, hypnatraemia and dyspnoea. An MHRA alert highlighted an increased mortality associated with tigecycline from clinical trials (occurring in 2.3% of patients receiving tigecycline versus 1.5% of those receiving comparator drugs).

In terms of budget impact, tigecycline costs up to four times the cost of oral vancomycin, though is around half the cost of fidaxomicin.

The Committee heard from Dr Satta that the application is limited to rare cases of severe disease and where enteral (oral/NG/PEG) vancomycin or fidaxomicin cannot be given. NICE suggests that when oral therapies are not appropriate, rectal vancomycin is an alternative; however, Dr Satta stated that dosing and administration of rectal vancomycin is difficult in practice due to poor anal sphincter contraction. Tigecycline has limited data but offers a last resort for very severe cases with a poor prognosis (mortality risk of 55%). Its use would be overseen by Trusts' weekly *C. difficile* MDTs which reduces the risk of overprescribing and emerging resistance.

In camera, the Committee agreed there was an unmet clinical need for patients with severe disease who could not tolerate enteral vancomycin or fidaxomicin. Whilst the available evidence was limited, it was unlikely that more robust data would emerge in the future. The Committee considered the poor prognosis of these individuals and were reassured that Microbiology would ensure tigecycline remained a last-line treatment option.

In summary, the Committee agreed to add tigecycline to the NCL Joint Formulary for patients with severe *C. difficile* (with or without IV metronidazole, or PR vancomycin) who are unable to tolerate enteral vancomycin or fidaxomicin.

Decision: Approved
Prescribing: Secondary care
Tariff status: In tariff
Funding: Hospital
Primary and secondary care Fact sheet or shared care required: No

8.3 Free of Charge scheme: Carfilzomib and daratumumab for relapsed multiple myeloma (Applicant: Dr R Popat, UCLH)

The Committee considered a Free of Charge (FOC) scheme for carfilzomib and dexamethasone +/- daratumumab as a treatment option for patients with relapsed or refractory multiple myeloma, who are on at least their fifth line of therapy, if carfilzomib +/- daratumumab has not been used in a previous line of therapy.

The CANDOR study was a multicentre, randomised, open-label, phase 3 study that compared the use of daratumumab, carfilzomib and dexamethasone (DCd) to carfilzomib and dexamethasone (Cd) in patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy. After a median follow up of 17 months, the primary end point, progression free survival, was significantly improved with DCd compared by Cd (HR = 0.63 (95% CI 0.46-0·85; p=0.0027). Median progression free survival was not reached in the DCd compared to 15.8 months with Cd . Overall Response Rate (ORR) was higher with DCd (84% vs. 75%). Overall survival was not available as there were not enough events. Limitations of the study included that it was underpowered, the open-label design, and the short follow up time of 18 months meant conclusions on overall survival couldn't be drawn.

The ENDEAVOR study was a multicentre, randomised, open-label, phase 3 study comparing carfilzomib and dexamethasone (Cd) to bortezomib and dexamethasone (Bd) in patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy. The primary outcome, progression-free survival, was significantly higher with Cd compared to Bd (18.7 months vs 9.4 months; HR = 0.53 [95% CI 0.44 to 0.65]). ORR (defined as partial response or better) was higher with Cd than Bd (77% vs. 63%). Overall survival data was immature at analysis. Limitations of the study included it was open label and there was no overall survival data available.

In terms of safety, common adverse events seen in either CANDOR or ENDEAVOR studies include thrombocytopenia, diarrhoea, respiratory infections/pneumonia, fatigue, anaemia and hypertension. In the CANDOR study, the DCd group had more grade 3 or higher adverse events, adverse events leading to dose reductions and treatment related deaths than in the Cd group. There were five treatment related deaths reported in the DCd group (reasons for death include pneumonia, infection and sepsis, and cardiorespiratory arrest). In the ENDEAVOR study, peripheral neuropathy was significantly higher in the Bd group than in Cd group. Compared to the Bd group, the Cd group demonstrated a higher rate of serious adverse events (48% vs 36%) and dose reductions due to adverse events (23% vs 48%). 5% of patients died in each group but it was unclear if any of these deaths were treatment related. There is an MHRA alert associated with carfilzomib for the risk of potentially fatal cardiac events.

In terms of budget impact, carfilzomib and daratumumab are available free of charge. Additional costs include monitoring, day care administration, cost of aseptic production for carfilzomib and management of any infusion related reactions or adverse effects. There is an estimated total of 15 eligible patients per annum in NCL.

The Committee heard from Dr Popat, who informed the Committee that new data from the ENDEAVOR study demonstrates an overall survival advantage of 7 months with Cd compared to Bd (47.6 vs. 40.0 months; HR = 0.791 [95% CI 0.648 to 0.964]). Dr Popat explained that multiple myeloma is difficult to treat and patients can require ≥5 lines of therapy. He explained that the combination of carfilzomib and dexamethasone +/- daratumumab would ideally be used as early as possible but use would be restricted to the free of charge scheme criteria starting in the 5th line setting.

In camera, the Committee were reassured with the recent overall survival data from the ENDEAVOR study and felt that having this treatment available for ≥5th line therapy was reasonable owing to a lack of other treatment options available.

In summary, the Committee approved the use of carfilzomib and dexamethasone +/- daratumumab for relapsed/refractory multiple myeloma as a treatment option for patients with relapsed/refractory multiple myeloma, who are on at least their fifth line of therapy, if carfilzomib +/- daratumumab has not been used in a previous line of therapy.

Decision: Approved
Prescribing: Secondary care
Tariff status: N/A – Free of charge
Funding: N/A – Free of charge
Primary and secondary care Fact sheet or shared care required: No

8.4 Free of Charge scheme: Voxelotor for the treatment of haemolytic anaemia in patients aged 12 years or older with sickle-cell disease (Applicant: Dr P Eleftheriou, UCLH)

The Committee considered a pre-NICE free-of-charge (FOC) scheme for voxelotor, an allosteric HbS modulator, for patients aged 12-65 years with sickle-cell disease, haemoglobin level ≤10.5 g/dL and are ineligible, intolerant, or refractory to hydroxycarbamide.

The HOPE trial was initially reported as a 24-week, Phase III, placebo-controlled, double-blind study to assess the safety and efficacy of voxelotor for patients with sickle-cell disease aged 12-65 years, with a haemoglobin level of 5.5g/dL to 10.5g/dL and who had suffered 1-10 vaso-occlusive crises in the previous 12 months (n=274). Patients were excluded if they had regular red-cell transfusions, or had a transfusion within 60 days or a vaso-occlusive event within 14 days of consent. Patients were randomised to voxelotor 1500mg, voxelotor 900mg or placebo; the Committee reviewed the evidence for the recommended dose of 1500mg versus placebo. The primary endpoint, haemoglobin response (an increase by at least 1g/dL) from baseline to week 24, was significantly better with voxelotor 1500mg compared to placebo (51% vs. 7% [p<.001]). Secondary outcomes include markers of haemolysis; compared to baseline, there were significant improvements at week 24 in the relative change in indirect bilirubin (-29.1% vs -3.2% [p<0.001]) and the relative change in absolute reticulocyte count (-19.9% vs +4.5% [p<0.001]). There was also a non-significant reduction in the relative change in lactate dehydrogenase from baseline to week 24 (-4.5% vs +3.4%). Key limitations of the study were that the primary outcome of haemoglobin response was arbitrary, patient-oriented and sickle-cell outcomes were not reported, individuals requiring red-cell transfusions were specifically excluded (although are included in this FOC scheme) and finally the study was pharma sponsored.

The Committee reviewed an analysis of 72-week data from the HOPE trial. Compared with baseline, the adjusted mean change in haemoglobin remained improved with voxelotor 1500mg compared with placebo at week 72 (1.0g/dL vs 0.0g/dL [p<0.001]), a result that was statistically significant however the proportion of patients requiring red cell transfusions were the same in both arms (36%), so it was unclear of the clinical significance of this result. There were fewer annualised incidents of anaemic episodes per year with voxelotor 1500mg compared with placebo (0.05 vs 0.15 incidences per year). The annual incidence of vaso-occlusive crises was lower in the voxelotor arm at week 72, the result was not statistically significant (2.4 vs 2.8; IRR = 0.85 [95% CI 0.60 to 1.21]). In terms of quality-of-life data, mean EQ-5D-5L index score and VAS scale scores were similar at baseline; there was no discernible trends that could be gathered from this data.

In terms of safety, voxelotor 1500mg had a similar risk of adverse events compared to placebo (97% vs. 90%). The most common adverse events with voxelotor include headache, diarrhoea, arthralgia and pain. Voxelotor is currently unlicensed in the UK, and may require dose adjustment in hepatic impairment.

In terms of budget impact, voxelotor is currently offered under a FOC scheme. However, if the NICE TA is negative or patients do not fit the criteria under NICE TA approval, the company will only offer FOC stock for an additional 365 days post-NICE TA. In this scenario, the estimated cost is up to £90,000 per patient per annum. The FOC scheme is only open for 50 patients in the UK, and therefore there was interest in registering patients to reserve a place on the scheme. There were two patients known to have been registered thus far, with the potential for additional patients to be added on.

The Committee heard from Dr Eleftheriou that the only treatments currently available for sickle-cell patients are hydroxycarbamide or blood transfusions. Dr Eleftheriou considered the primary outcome of moderate importance to patients. However, the secondary outcomes (markers of haemolysis) are widely recognised as corresponding to complications of haemolytic disease, leading to organ damage and sickle-cell related outcomes such as nephropathy, hypertension or leg ulcers. Dr Eleftheriou stated that it may be too early to interpret quality-of-life and vaso-occlusive crises data. In terms of eligibility, only those patients who remain unstable requiring disease modifying treatment but cannot receive hydroxycarbamide will be eligible for voxelotor.

In camera, the Committee were generally supportive of having an additional therapy available for a cohort of patients with limited treatment options, but were concerned by the limitations in the current data. There was also concern of the potential impact of the FOC scheme (leading to inequity of access once the scheme reaches capacity, and the substantial financial risk if the NICE TA was either negative or excluded patients who had been initiated on voxelotor). The decision to add voxelotor to the NCL Joint Formulary was placed to a vote; 7 voted in favour and 4 voted against the approval of voxelotor. In order to provide reassurance and minimise risk to NCL Trusts, the Committee requested that patients be appropriately consented using the NCL FOC scheme guidance consent form (with support from RFL in reviewing the wording of the consent form). The Committee also agreed that the eligibility criteria should be appropriately robust to ensure only those with an unmet need (i.e., patients with unstable disease despite regular or frequent transfusions) are initiated on voxelotor.

In summary, the Committee agreed to add voxelotor to the NCL Joint Formulary for patients with sickle-cell disease aged 12-65 years, haemoglobin ≤10.5 g/dL and are ineligible, intolerant, or refractory to hydroxycarbamide and their disease state is not stable despite frequent or regular transfusions.

Decision: Approved
Prescribing: Secondary care
Tariff status: N/A – Free of charge
Funding: N/A – Free of charge
Primary and secondary care Fact sheet or shared care required: No
Additional information: Approval subject to Trust finance approval and patient consent onto FOC scheme; RFL supporting NCL to review NCL FOC scheme consent form. Patients are eligible if their disease state is not stable despite being considered for all other available treatments (e.g., hydroxycarbamide, frequent or regular transfusions, etc).

9. Proposal for therapeutic switch from linagliptin to sitagliptin

Linaglitpin and sitagliptin were DPP4 inhibitors prescribed routinely for the treatment of hyperglycaemia in Type 2 diabetes. Sitaglitpin was the first to market and linaglitpin is a 'me too' which offers no advantage in terms of efficacy, safety, convenience or tolerability. NICE consider the DPP4-4i class equivalent and the Committee have rejected applications for linagliptin on two occasions. Despite this, linagliptin represents approximately 20% of the DPP4-i market share. Sitagliptin loses patent protection in March 2022 and generic versions are anticipated, however linagliptin had patient protection until 2026. The price difference between generic sitagliptin and branded linaglitpin is expected to be £900,000 per annum for 4.5 years in North Central London (total £4 million).

The Committee agreed it was appropriate for patients to be transitioned from linaglitpin to sitaglitpin as part of a comprehensive project which ensured patient awareness and agreement. Renal function should be checked as sitaglitpin requires a dose reduction (within product license) for patients with CrCl less than 45 mL/min.

10. Review – Intranasal fentanyl for severe pain in paediatrics

The Committee reviewed the use of intranasal fentanyl for severe pain in paediatric patients administered in the paediatric emergency department in NCL Acute Trusts, replacing intranasal diamorphine (used historically but has recently become unavailable for the foreseeable future). Fentanyl is licensed for intravenous administration but is administered intranasally off-label at NMUH and other UK Trusts (supported by internal Trust guidance). As the addition to the NMUH formulary was historic, the Committee considered a rapid review of the evidence to support the ratification for use at other NCL Acute Trusts.

The Committee reviewed a synthesis of scientific evidence endorsed by the Faculty of Pain Management and a Cochrane review, both of which supported the view of intranasal fentanyl being effective (although it could not definitively state superiority, non-inferiority or equivalence to parenteral morphine). There was some risk of adverse events owing to the route of administration (e.g. throat irritation and epistaxis). The budget impact was expected to be negligible.

The Committee supported the use of intranasal fentanyl in paediatrics in other NCL Trusts to replace intranasal diamorphine, and requested that Trust DTCs consider whether local guidance is required.

Decision: Approved
Prescribing: Secondary care
Tariff status: In tariff
Funding: Trust
Primary and secondary care Fact sheet or shared care required: No
Additional information: Trust DTCs to assess whether local guidance is required

11. Next meeting

Thursday 21st October 2021