North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 17th June 2021

Present:	Dr K Tasopoulos	NMUH, DTC Chair	(Chair)
	Mr P Gouldstone	NCL CCG, Head of Medicines Management (Enfield)	
	Ms G Smith	RFL, DTC Chair	
	Mr A Dutt	NCL CCG, Head of Medicines Management (Islington)	
	Dr M Kelsey	WH, DTC Chair	
	Mr S Richardson	WH, Chief Pharmacist	
	Ms W Spicer	RFL, Chief Pharmacist	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms P Taylor	NCL CCG, Head of Medicines Management (Haringey)	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Ms R Clark	NCL CCG, Head of Medicines Management (Camden)	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
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 H Weaver	NHSE, Specialised Commissioning Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms S Amin	UCLH, Formulary Pharmacist	
	Ms S Y Tan	NEL CSU, Contracting and Commissioning Pharmacist	
	Ms A Sehmi	NMUH, Formulary Pharmacist	
	Ms H Thoong	GOSH, Formulary Pharmacist	
	Mr D Sergian	MEH, Formulary Pharmacist	
	Dr S Balestrini	NHNN, Consultant Neurologist	
	Prof S Sisodiya	NHNN, Professor of Neurology	
	Dr R Roylance	UCLH, Consultant Oncologist	
	Dr N Chopra	RFL, Consultant Oncologist	
	Dr E Boleti	RFL, Consultant Oncologist	
Apologies:	Dr A Sell	RNOH, DTC Chair	
	Mr S Semple	MEH, Chief Pharmacist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Ms S Stern	NMUH, Chief Pharmacist	
	Dr D Burrage	WH, Consultant in Emergency Medicine	
	Prof R Sofat	NCL JFC Chair	
	Mr T Dean	Patient Partner	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Ms M Singh	NCL CCG, Head of Medicines Management (Barnet)	

2. Meeting observers

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

3. Minutes of the last meeting

The minutes and abbreviated minutes of the 20 May 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 Ms Kassam.

6. Members declarations of conflicts of interest

Nil

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	May 2021	Lenvatinib	FoC†: Symptomatic metastatic adenoid cystic carcinoma of the head, neck and lungs	Decision: UCLH only Prescribing: Secondary care Tariff status: N/A Funding: FoC Fact sheet or shared care required: No
UCLH	May 2021	Avapritinib	FoC†: KIT-D816V mutated advanced systemic mastocytosis	Decision: UCLH only Prescribing: Secondary care Tariff status: N/A Funding: FoC Fact sheet or shared care required: No
UCLH	May 2021	Salbutamol liquid	Congenital myasthenic syndromes (existing patients)	Decision: UCLH only Prescribing: Secondary care Tariff status: In tariff Funding: Hospital Fact sheet or shared care required: No
RFL	Aug 2019	Cefazolin	Second or third line treatment of gram positive infections in non-dialysis patients who are penicillin allergic or where other antimicrobials are not suitable	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: In tariff Funding: Hospital Fact sheet or shared care required: No

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

7.2 Approved under evaluation

DTC site	Month	Drug	Indication	JFC outcome
WH	March 2021	Phospho-Soda	Part of bowel cleansing protocol for Colon Capsule Endoscopy	Decision: UCLH and WH only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

8. New Medicine Reviews

8.1 FoC: Selpercatinib for previously treated NSCLC, Non-medullary Thyroid cancer and medullary thyroid cancer (Applicant: Dr N Chopra and Dr E Boleti, RFL)

The Committee considered a pre-NICE free-of-charge (FOC) scheme for selpercatinib, a RET-receptor tyrosine kinase inhibitor, for previously treated patients with RET-fusion positive non-small cell lung cancer (NSCLC), RET-mutant medullary thyroid cancer (MTC) or RET-fusion positive thyroid cancer.

LIBRETTO-001 is an ongoing, Phase I/II, single-arm, open-label study to assess the safety and efficacy of selpercatinib for patients aged 12 or over with solid tumours, an ECOG status of 0-2 and RET alteration (n=531). The primary endpoint was objective response as assessed by independent review. In previously-treated NSCLC patients (n=105), objective response was 64% [95% CI 54% to 73%]; in previously-treated MTC (n=55), objective response was 69% [95% CI 55% to 81%]; in previously-treated thyroid cancer (n=19), objective response was 79% [95% CI 54% to 94%]. Key limitations of the study were the single-arm open-label design, the absence of overall survival, the cohorts used mostly made up of patients with an ECOG status of 0 or 1, and that the thyroid cancer cohort was considered exploratory (and therefore no power calculation was performed for this group).

In terms of safety, common grade 3 and 4 adverse events from LIBRETTO-001 include hypertension, increase in liver transaminases, hyponatraemia, lymphopaenia, diarrhoea and tumour lysis. The manufacturers documents also list other adverse events (e.g., QT prolongation, bleeding problems) and interacts with acid suppression therapies. It requires frequent monitoring (e.g., LFTs, blood pressure).

In terms of budget impact, selpercatinib is offered free of charge for use within all three indications.

The Committee heard from Dr Chopra and Dr Boleti that it is desirable to target mutations in order to deliver optimal efficacy with limited toxicity. All patients would have received NICE approved therapies before selpercatinib (e.g. platinum-based chemotherapy or immunotherapy in NSCLC patients), though no specific RET inhibitors are available within NICE pathways. Despite LIBRETTO-001 being an early phase study, results from the study are promising whilst expected adverse effects are predictable based on the historic use of other tyrosine kinase inhibitors. The FOC scheme will not affect Phase III studies as the focus of those studies is the treatment naïve cohort.

In camera, the Committee agreed that comparative data with patient orientated outcomes (survival and QoL) would be preferrable for decision making. However, the case for early acceptance was strengthened by the availability of Phase II data demonstrating an objective response, and by tyrosine kinase inhibitors having similar adverse effect profiles [therefore concerns around the limited safety data for selpercatinib were reduced]. It was noted that recent applications for novel targeted therapies available under FOC schemes, with similar Phase I/II level of evidence, were approved by the Committee. The Committee acknowledged that there were no ongoing RCTs available for this cohort, so the only access to targeted treatment for this cohort is via the FOC scheme.

The Committee discussed an increasing trend of applications for targeted anti-cancer medicines which lacked data to demonstrate an improvement in patient orientated outcomes. This was driven by Pharma making medicines available via FOC schemes in advance of Phase III data. Regulators are approving medicines without Phase III data; for example, selpercatinib already has a conditional marketing authorisation (CMA) from the EMA. The EMA website provides information on what criteria must be met for a CMA to be offered. The Committee agreed that the RAG rating used for the majority of applications did not apply for targeted anti-cancer FOC medicine schemes. It requested that JFC Support develop and consult on criteria for accepting anti-cancer therapies in the future, and suggested that the EMA criteria for CMA was a sensible starting point. This would ensure JFC was not out of line with regulators.

In summary, the Committee agreed to add selpercatinib to the NCL Joint Formulary for previously treated RET-fusion positive NSCLC, RET-mutant MTC or RET-fusion positive thyroid cancer.

Decision: Approved (conditional on the provision of a free of charge scheme agreement and funding statement, and notification of the relevant commissioner)
Prescribing: Secondary care
Tariff status: N/A
Funding: FOC
Primary and secondary care Fact sheet or shared care required: N/A

8.2 Ibandronate for early stage breast cancer in post-menopausal women with medium to high risk of relapse to reduce bone recurrence and cancer mortality (Applicant: Dr Roylance, UCLH)

The Committee considered an application for oral ibandronic acid, a bisphosphonate, for early stage breast cancer in post-menopausal women with moderate or high risk of relapse who are not receiving adjuvant intravenous chemotherapy. Treatment is proposed to be initiated by specialists and continued in primary care.

In NCL, zolendronic acid IV infusion is the first line adjuvant therapy for post-menopausal women with breast cancer; oral ibandronic acid is available for patients who cannot received IV zoledronic acid (hospital only prescribing). NICE guidance on early and locally advanced breast cancer (NG101) 2018 recommends zoledronic acid or sodium clodronate for postmenopausal women with node-negative invasive breast cancer and a high risk of recurrence. At the time of NICE publication, these bisphosphonates had greatest supportive data, the head-to-head bisphosphonate trial comparing ibandonrate to zoledronic acid (S0307) was in abstract form.

S0307 was a Phase IIIa, active-comparator controlled study, unblinded study to compare the efficacy and safety of oral ibandronate, oral clodronate and intravenous zoledronic acid, in early-stage breast cancer (n=6,097). Patients were randomised to one of three bisphosphonate treatments for 3 years: intravenous zoledronic acid (monthly for 6 months, then every 3 months); oral clodronate (1600mg daily); or oral ibandronate (50mg daily). The primary outcome, disease-free survival (DFS) at 5 years, was similar across treatment arms (clodronate 87.6%; ibandronate 87.4%; zolendronic acid 88.3% [p=0.49*]). A secondary outcome was overall survival (OS) at five years was also similar across treatment arms (zoledronic acid 92.6%; clodronate 92.4%; ibandronate 92.9% [p=0.50*]). Key limitations of the study were; the study may have been underpowered due to a lower than expected event rate & too few patients in the ibandronate arm, it is unclear how many of the cohort match the proposal i.e. post-menopausal and medium to high risk of relapse (50% were node-negative, but tumour size and menopausal status is unknown), the study used a higher frequency of zoledronic acid infusions than clinical practice and lack of long-term data.
*The p-value tests for a statistically significant difference among the three arms

In terms of safety, severe or life-threatening adverse events were reported more frequently with ibandronate (clodronate 8.3%; ibandronate 10.5%; zoledronic acid: 8.8%). Osteonecrosis of the jaw was reported more frequently with with zoledronic acid (clodronate 0.36%; ibandronate 0.77%; zoledronic acid 1.26%).

In terms of budget impact, ibandronate is expected to save up to £400,000 over 3-year treatment course across NCL, compared to 6 monthly zoledronic acid, due to a reduction in outpatient activity. This does not account for increase in primary care activity for prescribing and monitoring of renal function and calcium levels).

The Committee heard from Dr Roylance there is a cohort of patients who do not need to attend hospital regularly for adjuvant IV chemotherapy, and these patients would benefit from oral bisphosphonate therapy. The oral formulation may also be a preferred route for some patients. Currently these patients would receive 6 monthly intravenous zoledronic acid, therefore this proposal will reduce outpatient attendance.

In camera, the Committee acknowledged there were several points in favour of the application - the publication of a Phase 3 study reporting no difference between DFS and OS at 5 years between IV zoledronic acid, oral sodium clodronate and oral ibandronic acid, the well-established safety profile of bisphosphonate, reduction in outpatient attendance and the convenience an oral option would offer for patients who do not need to regularly need to attend hospital.

In summary, the Committee agreed to add ibandronic acid to the NCL Joint Formulary for early stage breast cancer in post-menopausal women with medium to high risk of relapse who are not receiving intravenous chemotherapy to prevent bone recurrence and reduce cancer mortality. The Committee deferred to the NCL Shared Care Group to identify and resolve any prescribing interface issues (i.e. standardised GP letter from specialists vs. formal shared care).

Decision: Approved clinically. Deferred to NCL Shared Care Group to support with safe prescribing in primary care.

8.3 Stiripentol for initiation in adults with Dravet syndrome (Applicant: Dr S Balestrini/Prof S Sisodiya, NHNN)

The Committee considered an application for stiripentol, an anti-seizure medication, for initiation in adult patients with confirmed diagnosis of Dravet syndrome; the proposal is for the initial six-months provided by NHNN, with continuation in primary care under a shared care protocol. Stiripentol is currently available

within NCL for paediatrics with Dravet syndrome, and continuation into adulthood as long they continue to derive benefit from treatment. Initiation in adults was considered off-label treatment.

There are no RCTs in which stiripentol was specifically initiated in adult patients with Dravet syndrome. The available evidence was found in audit and open-label data, in which certain patients were aged 18 or over at the point of initiation.

Sisodiya and Balestrini conducted an observational clinical audit of patients with Dravet syndrome who were initiated on stiripentol. Out of 32 patients, eight were initiated from the age of 18 onwards. Four patients went on to have stiripentol discontinued within the initial six months of prescribing due to either a lack of efficacy or adverse events. The remaining four patients successfully continued treatment after tolerating treatment with either a reduction of generalised tonic-clonic seizure frequency by ≥50% or reduction in status epilepticus episodes. Chiron et al conducted a retrospective observational study in which seven patients (out of a total of 40 patients with Dravet syndrome) initiated stiripentol at a median age of 18.6 years; the number of seizures experienced in the month prior to the patient's appointment in adulthood was lower than the appointment in the last visit before the age of 21 (median of 18 seizures versus 4 seizures).

Inoue et al conducted two open-label studies in Dravet syndrome patients who received stiripentol. In the 2009 study, eight patients out of a total of 23 were included in a group of 'elder' patients. At a dose of 50mg/kg, four patients in this group achieved ≥50% reduction in seizures (of which three were aged 18 or over). In the 2014 study, four patients out of a total of 27 were aged between 19-30 years. Three out of these four patients achieved ≥50% reduction in seizures (and one became seizure free). Key limitations of all studies were the single-arm design, lack of comparator and no trials being focused on initiation in the adult population.

In terms of safety, stiripentol is associated with adverse events and has led to discontinuations (e.g. anorexia, somnolence etc). However, stiripentol is already in use in paediatric patients and continued into adulthood, therefore clinicians have experience in its use. A shared care guideline is currently employed in NCL to transfer patients who continue treatment into adulthood at NHNN to primary care.

In terms of budget impact, initiating stiripentol for adults is expected to cost an additional £42,000 per annum at NHNN (4 patients per annum, 6 months' supply). In primary care, the ongoing cost of stiripentol is expected to be £20,000 per patient per annum; as Dravet syndrome is a rare condition and NHNN reviews patients across the UK, this cost is held by the patients' respective CCG and is not expected to be retained within NCL.

The Committee heard from Dr Balestrini that genetic sequencing has helped to diagnose Dravet syndrome over the years, which has led to diagnosis in adult patients who previously went undiagnosed. Both the diagnosis of Dravet syndrome and the syndrome itself are the same, regardless of the age of the patient. Therefore, there is currently an unwarranted variation in adult patients who cannot access an effective treatment. Both NHNN and GOSH have seen the effectiveness of stiripentol in their respective populations.

In camera, the Committee agreed that provided the pathophysiology of Dravet syndrome was the same for children as for adults, it would be inequitable to deny treatment based on age alone. The Committee was satisfied that the syndrome remained unchanged in adulthood, , and therefore considered stiripentol to be an appropriate treatment of refractory seizures in Dravet syndrome patients. Stiripentol should only be initiated in adulthood where there is agreement for primary care continuation (via shared care) once efficacy and tolerability has been established by the NHNN consultants.

In summary, the Committee agreed to add stiripentol to the NCL Joint Formulary for initiation in adult patients with refractory seizures due to Dravet syndrome.

Decision: Approved clinically. Deferred to (i) NCL CCG for funding consideration and (ii) NCL Shared Care Group to amend current NCL shared care guideline.

8.4 Inhaled budesonide for COVID-19

The Committee reviewed a DHSC position statement for inhaled budesonide dry powder inhaler, an inhaled corticosteroid, for the treatment of COVID-19 in adult patients in the community setting. The position statement states that routine use is not recommended, but may be considered on a case-by-case basis.

This was discussed at JFC to provide clarity as to whether budesonide should be added to the NCL Joint Formulary, and if so, which patients would stand to benefit from therapy.

The PRINCIPLE trial was an adaptive platform, controlled, open-label study to assess the safety and efficacy of inhaled budesonide for patients aged 65 or over (or aged 50 or over with a comorbidity) with COVID-19. Patients were randomised to inhaled budesonide 800micrograms twice daily alongside SoC (n=751) or SoC alone (n=1,028). The first co-primary endpoint, time to self-reported recovery, was significantly shorter with inhaled budesonide compared to SoC alone (11 days vs. 14 days [probability of superiority = 0.999]). In the second co-primary endpoint, rate of hospitalisation or death at 28 days, was not significantly better with inhaled budesonide vs SoC alone as it did not meet the pre-determined probability of superiority threshold of 0.975 (8.5% vs. 10.3% [probability of superiority = 0.928]). Key limitations of the study include that the trial terminated early, and as such, did not reach the required number of participants in each arm for the outcome of 'hospitalisation or death at 28 days'.

Another trial discussed was the STOIC trial – a phase II, controlled, open-label study to assess the safety and efficacy of inhaled budesonide for patients aged 18 or over with COVID-19. Patients were randomised to inhaled budesonide 800micrograms twice daily alongside SoC (n=70) or SoC alone (n=69). The primary endpoint, the number of patients with COVID-19 related urgent care visit, ED assessment or hospitalisation, was significantly lower with inhaled budesonide compared to SoC alone (1 vs. 10 [p=0.004]). Key limitations of the study include the relatively small cohort, and that this trial also terminated early before full recruitment, and as such, also did not reach the required number of participants in each arm as described in the power calculation.

In terms of safety, inhaled budesonide is used widely for asthma and COPD, and therefore adverse events are well known and manageable. In terms of budget impact, inhaled budesonide is expected to cost an additional £142.50 for every 10 patients treated; the true budget impact could not be estimated due to the fluctuating number of patients suffering from COVID-19 since the introduction of vaccines and the delta variant.

The Committee recognised that the current situation has changed significantly since the introduction of the DHSC alert. An application has not been submitted to the JFC from a clinician to support the use of inhaled budesonide. The Committee could not identify a meaningful benefit, or a particular subgroup who were likely to benefit from treatment, and therefore inhaled budesonide was not added onto the Joint Formulary; however, the Committee would reconsider this position if more evidence became available in the future.

In summary, based on the evidence available and lack of information on which subgroups may benefit from treatment, the Committee could not recommend the use of inhaled budesonide for COVID-19.

Decision: Not approved

8.5 NCL Inflammatory Bowel Disease pathway

8.6 Anti-TNF for moderate Crohn's disease

NICE TA187 (published in 2010) recommends the use of infliximab and adalimumab for severe Crohn's disease only, in line with their respective marketing authorisations at the time of review. The NICE appraisal Committee noted that trials included people with moderate to severe Crohn's disease and the results of the trials suggested that response to treatment did not differ between moderate and severe disease. More recently, both drugs received marketing authorisation for moderate Crohn's disease and are now used commonly for this indication in NCL.

Subsequent NICE TAs for ustekinumab and vedolizumab recommend their use in moderate disease following use of anti-TNF (TA456 & TA352 respectively). The Committee agreed to add adalimumab and infliximab to the NCL Joint Formulary for moderate Crohn's disease to (i) comply with TA456/TA352 requirements and (ii) to encourage the use of adalimumab and infliximab which are thought to be the mostcost-effective first-line biologics.

Drug: Adalimumab and infliximab for moderate Crohn's disease
Decision: Approved
Prescribing: Secondary care only
Tariff status: In tariff
Funding: CCG

Primary and secondary care Fact sheet or shared care required: No

8.7 High-cost drug pathway for moderately to severely active CD

The pathway was approved clinically and referred to NCL Commissioners for funding consideration.

8.8 High-cost drug pathway for moderately to severely active UC

The pathway was approved clinically and referred to NCL Commissioners for funding consideration.

8.9 Changes to reporting of antimicrobial susceptibility results

EUCAST (the European Committee on Antimicrobial Susceptibility) have provided new recommendations on Antimicrobial Susceptibility Result Definitions. These are mandatory requirements that labs must adopt by 21st June 2021. The most significant change is the re-definition of the 'I' category. If an antibiotic susceptibility result was previously reported as 'I – Intermediate', the clinical tendency was to avoid using this antibiotic agent. However, a result now reported as 'I – Susceptible, increased exposure' indicates a high likelihood of success if the antibiotic is given at a higher dose, increased frequency or at a higher concentration at the site of infection. The changes are necessary due to increased levels of antibiotic resistance to standard dosing regimens and recognition that, for some organisms, low-level resistance can be overcome by increasing the dosage of some antibiotics.

HSL lab have produced and circulated 2 documents. The first document 'New High Dose Antibiotic Susceptibility Category' contains supportive information on the changes for clinicians. The second 'Standard and High Dose Antibiotic Dosing Regimens' contains the dosing recommendations for when 'I - susceptible, increased exposure' or 'S – susceptible using standard dose' are reported; these recommendations have been agreed upon by the NCL antimicrobial stewardship group. The documents do not provide recommendations in renal impairment, extremes of weight or paediatrics, there is a separate workstream for paediatrics.

The Committee agreed for the HSL documents to be hosted on the MON website, and GP communication to be hosted on the NCL CCG website. It was requested for the document to highlight where recommended doses are outside of the license/SPC.

8.10 Review of NCL JFC application form

JFC support have worked with NCL formulary pharmacist to review the NCL new medicines application form. The form was updated to make the unmet need, proposed treatment pathway, goals of treatment and changes to patient numbers/activity associated with the proposal clearer. The updated application form will be circulated to JFC members virtually for comment and approved via Chair's action.

9. Next meeting

Thursday 15th July 2021