North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 15th April 2021

Present:	Prof R Sofat	NCL JFC 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)	
	Mr T Dean	Patient Partner	
	Mr G Kitson	WH, Deputy 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)	
	Mr S Semple	MEH, Chief Pharmacist	
	Dr K Tasopoulos	NMUH, DTC Chair	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Dr A Sell	RNOH, DTC Chair	
	Ms K Delargy	BEH, Chief Pharmacist	
	Dr M Kelsey	WH, DTC Chair	
	Mr A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Mr A Stein	NMUH, Deputy Chief Pharmacist	
In attendance:	Ms H Weaver	NHSE, Specialised Commissioning 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 C Obierne	UCLH, Formulary Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr F Master	RFL, Formulary Pharmacist	
	Ms S Amin	UCLH, Formulary Pharmacist	
	Mr S O'Callaghan	UCLH, Formulary Pharmacist	
	Ms SY 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	
	Mr D Abdulla	RFL, Clinical Pharmacist	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor High-Cost Drugs	
	Dr J Costello	RFL, Consultant in emergency medicine	
	Dr E Witt	RFL, Consultant in Emergency Medicine	
	Dr A Sheri	RFL, Consultant Oncologist	
	Dr D Patch	RFL, Consultant Hepatologist	
Apologies:	Dr S Ishaq	WH, Consultant Anaesthetist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Ms S Lever	NCL CCG, Head of Medicines Management (Barnet)	
	Ms S Stern	NMUH, Chief Pharmacist	
	Dr D Burrage	WH, Consultant in Emergency Medicine	

Mr S Richardson	WH, Chief Pharmacist
Ms R Clark	NCL CCG, Head of Medicines Management (Camden)

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 18 March 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
RNOH	Feb 21	Denosumab	Treatment of Aneurysmal Bone Cysts in adults and paediatrics	Decision: RNOH only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
UCLH	Mar 21	Risdiplam	Appeal: MHRA EAMS Type 2 Spinal Muscular Atrophy in Adults	Decision: UCLH only Prescribing: Secondary care Tariff status: N/A Funding: FoC Fact sheet or shared care required: No
UCLH	Mar 21	Tepotinib	FoC†: Advanced/Metastatic Non-Small-Cell-Lung-Cancer with MET exon 14 skipping mutation	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: N/A Funding: FoC Fact sheet or shared care required: No

† The relevant commissioner should be notified in line with NCL Free of Charge scheme guidance.

7.2 Not approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Mar 21	Continuous Subcutaneous Hydrocortisone Pumps	Primary Adrenal Insufficiency	Decision: Not approved

8. New Medicine Reviews

8.1 COVID-19 vaccine Moderna

The Committee was informed that the Moderna vaccine for COVID-19 was approved via Chair's action in early April 2021.

Decision: Added to the NCL joint formulary
Prescribing: Primary and secondary care only
Tariff status: N/A
Funding: N/A
Primary and secondary care Fact sheet or shared care required: No

8.2 Apixaban for splanchnic vein thrombosis (Applicant: Dr Patch, RFL)

The Committee considered an application for apixaban, a Factor Xa inhibitor, for cirrhotic and non-cirrhotic patients with non-malignant splanchnic vein thrombosis (SVT), which includes portal vein thrombosis (PVT), mesenteric vein thrombosis, splenic vein thrombosis and Budd-Chiari syndrome. The objective of treatment is recanalization of vessels to avoid outcomes of chronic vessel occlusion..

There are no RCTs directly comparing apixaban to traditional anticoagulation for SVT however one RCT compares a different DOAC with a similar mechanism of action to apixaban (the Factor Xa inhibitor, rivaroxaban) to warfarin for the treatment of PVT. Hanafy et al. was a one-year, active-comparator, open-label, randomised controlled study to compare the safety and efficacy of rivaroxaban and warfarin for patients with non-neoplastic hepatitis-C related compensated cirrhosis (n=80). Patients were randomised to rivaroxaban 10mg BD or warfarin with a target INR of 2-2.5. The primary endpoint, complete recanalization, was significantly better with rivaroxaban compared to warfarin (85% vs. 45%; [p=0.001]). The other primary endpoint, partial recanalization (50% restoration of lumen), was also significantly better with rivaroxaban (15% vs 0% [p=0.001]). There were no instances of major bleeding in the study; however, gastrointestinal bleeding was lower with rivaroxaban (0 vs. 17). Key limitations of the study were the open-label design, the exclusion of Child-Pugh C patients and patients with raised ALT >3 times the upper limit of normal, the relatively low number of patients used, the lack of detail on randomisation, the lack of a power calculation, the INR being potentially out of range for some patients, and the use of a hepatitis-C population only.

Several observational studies are available, though many of these grouped DOACs together when determining efficacy and safety, which made it difficult to discern the data for apixaban specifically.

In the non-cirrhotic cohort, one retrospective study compared outcomes for patients with PVT treated with 'standard therapy' (warfarin or low molecular weight heparin), DOACs or no anticoagulation. DOACs were found to be more effective than warfarin in achieving complete radiographic resolution of PVT (HR: 2.91 [95% CI 1.87 to 4.52], and this effect was maintained with apixaban. It also reported a significantly lower rate of major bleeding with DOACs compared to warfarin (HR: 0.20 [95% CI 0.05 to 0.86]). Limitations of the study include 6% of DOAC users in this study used apixaban (majority used rivaroxaban), and the groups were unbalanced with the warfarin group having a higher proportion of patients with occlusive and PVT with additional SVT (and therefore potentially easier to achieve complete radiographic remission in the DOAC group).

In the cirrhotic population, there are seven relevant observational studies. Few studies report efficacy data; however one retrospective study comparing DOACs, vitamin K antagonists and low molecular weight heparin in mesenteric vein thrombosis reported similar complete or partial recanalization rates between DOACs and vitamin K antagonists (68.8% and 70.7% respectively). Several studies reported on bleeding risk being at least similar to similar if not better with DOACs compared with traditional anticoagulation. All of these studies were limited by the retrospective design; patients with Child-Pugh C patients receiving anticoagulation were either excluded or reported in very small numbers in studies.

In terms of safety, a meta-analysis of five observational trials reported that there was no difference between DOACs and warfarin in cirrhotic patients in terms of 'all cause' bleeding (RR: 0.72 [95% CI 0.32 to 1.63]) and 'major' bleeding (OR: 0.46 [95% CI 0.10 to 2.09]). In contrast to warfarin, there is lack of a reversal agent for intracranial haemorrhage secondary to with apixaban. There is an increased baseline risk of treatment inefficiency using anticoagulation alone in certain populations (e.g., patients with a JAK2 mutation), which is of particular concern in cirrhotic patients who also have a higher baseline risk of bleeding. There are several MHRA alerts for DOACs (to warn of the risk of bleed, avoidance in antiphospholipid syndromes and to make an appropriate estimate of the renal function of recipients). There is limited evidence to support the use of any anticoagulant, including DOACs, in patients with Child-Pugh C therefore the risks and benefits of treatment in these patients with a high baseline risk of bleeding is largely unknown.

In terms of budget impact, two scenarios were considered. If the whole SVT population is treated with warfarin, apixaban is expected to cost an additional £30,000 per annum (based on a six-month treatment course). However, if the SVT population is treated with low molecular weight heparin (LMWH), apixaban would be expected to save £86,000 per annum (based on a six-month treatment course).

The Committee heard from Dr Patch that throughout the COVID pandemic, patients prescribed warfarin found it difficult to have adequate INR monitoring due to reduced anticoagulation clinic activity. The studies which support the current standard of care (LMWH and warfarin) are based on similarly low-quality evidence, specifically retrospective observational and prospective series data. It is unlikely that further RCTs would be conducted with DOACs compared against traditional anticoagulation. Trials in cardiovascular indications (e.g., prevention of stroke risk amongst those with atrial fibrillation) have demonstrated a lower bleeding rate with apixaban (and most DOACs) compared to warfarin. Although it is correct that the more severely cirrhotic patients will have an increased risk of bleeding, this is due to the increased risk of oesophageal varices. Cirrhotic patients will however also be at higher risk of thrombosis due to a net increase in the proportion of procoagulant factors compared with anticoagulant factors being produced. In terms of the most appropriate comparator; anticoagulant therapy is tailored to the patient therefore some receive a full course of LMWH and some will receive warfarin therefore the true budget impact is expected to be somewhere in between those figures calculated. If apixaban is approved, the choice of anticoagulant would again depend on the clinical scenario.

In camera, the Committee considered the advantage of using a DOAC in terms of reduced ongoing monitoring and the reduced bleeding risk compared to warfarin in cardiac indications. The Committee also considered the potential risks in therapy, including the timing of the OGD for variceal screening if early anticoagulation is indicated, and whether an initial high intensity period of anticoagulation would be required. The Committee also considered this being a relatively new indication for primary care to continue prescribing following initiation, and guidance for the initiation and transfer of prescribing would be useful. However, the Committee understood the need for a treatment option which addresses issues in compliance and monitoring, and agreed that apixaban for SVT may be suitable if a guideline can be created between hepatology and haematology to form a harmonised treatment pathway that can be used across NCL.

In summary, the Committee agreed in principle to add apixaban to the NCL Joint Formulary for treatment of non-malignant splanchnic vein thrombosis in cirrhotic and non-cirrhotic patients, however deferred a final decision until a guideline describing prescribing and monitoring responsibilities was reviewed and approved by the Committee.

Decision: Deferred

8.3 Infliximab for steroid-refractory immunotherapy induced colitis (Applicant: Dr Sheri, RFL)

The Committee considered an application for infliximab, an anti-TNF therapy, for immune checkpoint inhibitor (including ipilimumab) induced steroid-refractory colitis.

There are no RCTs directly comparing infliximab to other therapies for the proposed indication. A literature review identified a recent systematic review and meta-analysis of observational studies.

Ibraheim et al conducted a systematic review and meta-analysis of observational studies to estimate the efficacy of anti-inflammatory therapies for treatment of checkpoint-inhibitor induced enterocolitis; data for patients with steroid-refractory colitis who received infliximab was included (n=333). The primary outcome of interest, pooled analysis of 'response' to therapy, was 81% [95% CI: 73% to 87%]. Key limitations of the study were that the meta-analysis was based on single-arm observational studies therefore it is unknown how well infliximab compares to active comparator, a lack of standardisation of included studies, and the definition of 'response' was based on different efficacy endpoints (ranging from 'symptom improvement' to 'complete remission'). Several other small observational studies were identified which generally reported a treatment effect with infliximab.

In terms of safety, infliximab is a well-established drug used routinely for ulcerative colitis and Crohn's disease. There are certain scenarios where infliximab should not be used (e.g. patients with a perforated bowel), and patients should be screened in advance of use to determine eligibility.

In terms of budget impact, infliximab is expected to cost an additional £6,000 per annum across NCL Trusts, as compared to no treatment. The costs could rise depending on the number of patients requiring a second dose, whether infusions are administered via outpatient clinics, and if use of checkpoint inhibitor immunotherapies are used more widely in the future.

The Committee heard from Dr Sheri that the appearance and histology of colitis seen in the immunotherapy-induced population is variable however the outcome of interest is symptomatic

improvement of colitis. Patients who develop checkpoint inhibitor-induced steroid-refractory colitis will mostly discontinue immunotherapy permanently, however a subgroup will reinitiate treatment and further adverse effects would be managed similarly.

In camera, the Committee acknowledged the high unmet clinical need for this cohort. The quality of evidence was considered low however the Committee took reassurance from the efficacy and safety of infliximab in other inflammatory gastroenterological conditions. The budget impact was low as the gastroenterology community in NCL has adopted best-value infliximab.

In summary, the Committee approved the use of infliximab for steroid-refractory immunotherapy induced colitis. Commissioning arrangements with NCL CCG were to be confirmed.

Decision: Approved pending funding approval
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: To be confirmed, business case already submitted.
Primary and secondary care Fact sheet or shared care required: No

8.4 Appeal: Penthrox® (methoxyflurane) for emergency relief of moderate to severe pain in conscious adult patients with trauma and associated pain (Applicant: Dr Costello, RFL)

The Committee considered an appeal for methoxyflurane for first-line treatment of emergency relief of moderate to severe pain associate with bone fractures and joint dislocations in conscious adult patients in Accident & Emergency. The Committee reviewed methoxyflurane in May 2018 however declined the application because (i) the Committee considered the treatment effect of methoxyflurane in the STOP! Study [a placebo-controlled RCT] to be typical of a weak analgesic and similar to Entonox®, (ii) it was unclear why Entonox® was unsuitable for these individuals, and (iii) due to the potential for prescribing creep.

The RFL team addressed the concerns previously raised:

i) A RCT versus standard analgesic therapy reported the treatment effect of methoxyflurane is equivalent to IV paracetamol for moderate pain and IV morphine for severe pain and provides a faster onset to pain relief

MEDITA, a phase IIIb active-controlled, open-label study to demonstrate non-inferiority of methoxyflurane compared to standard analgesic treatment (SAT) for the treatment of moderate-to-severe acute trauma pain; and superiority of methoxyflurane compared to SAT for the treatment of moderate acute trauma pain (n=270). Adults with fracture, dislocation, crushing or contusion to one limb and a Numerical Rating Score (NRS) ≥4 were included. Patients were randomised to 1 inhaler of methoxyflurane or SAT. Patients with severe pain (NRS≥ 7) received IV morphine, patients with moderate pain (NRS 4–6) received IV paracetamol or IV ketoprofen at investigator discretion. At baseline the mean VAS was 67 mm; approximately two-thirds of patients had moderate pain (NRS 4–6) and one-third had severe pain (NRS≥7). In the SAT group, the majority of patients (88%) with moderate pain received IV paracetamol, 95% of patients with severe pain received IV morphine. The primary endpoint, change in pain intensity measured by a Visual Analogue Scale (VAS) from 0 to 100mm at 3-, 5- and 10-minutes following randomisation, were statistically significantly greater for the overall population (overall change over 10 min: SAT -8.8mm vs methoxyflurane -14.7mm; mean ETD - 5.9mm; 95% CI: -8.8 to -3.1mm). The median time to onset of pain relief was shorter in the methoxyflurane group compared with the SAT group (9 mins vs 15 min). Key limitations include only 45% presented with fracture or dislocation, patients in the severe pain subgroup did not observe the same improvement in pain scores and intrinsic bias associated with open label study design that would affect patient reported pain scores.

ii) Entonox® is not used in RFL ED as it is less convenient in terms of transferring patients to scans, physical limits to the number of cylinders in ED, time taken to locate components before administration, patient compliance and satisfaction with treatment is reportedly poor.

iii) Trusts outside NCL who have approved methoxyflurane spend on average £15-20K per annum. Imperial and GSTT formulary teams have reported that usage of methoxyflurane for fractures or dislocations is consistent year on year. Use in NCL ED will be recorded and quarterly audits are proposed to monitor prescribing creep.

The applicant proposes that the introduction of methoxyflurane will enable faster onset of pain relief and reduce requirements for IV opioids and progression to IV procedural sedation, which requires 3 staff members to carry out a 30-minute procedure in a resuscitation room. This is proposed to reduce patient stay in ED and free up ED staff time. The British Journal of Anaesthesia supports methoxyflurane as an alternative to IV sedation for outpatient procedures. The Committee heard that 2 observational studies reported on the use of methoxyflurane, one versus propofol for shoulder dislocation and the other was a matched cohort study in trauma associated pain, patients were matched based on patient characteristics, including age group, gender, injury type and previous medical history. Use of methoxyflurane resulted in a reduction in the length of stay in ED, ~70minutes faster, in both studies.

In terms of budget impact, methoxyflurane is estimated to cost £80 000 per annum across NCL (£20,000 per annum at each Trust).

The Committee heard from Dr Costello and Dr Witt that methoxyflurane is more convenient to administer than current treatment options which would be beneficial in a busy ED setting for staff and patients. Methoxyflurane may also enable patients to receive analgesia quicker, which is important in the management of pain; audits indicate that patients do not receive analgesia quick enough. Patient satisfaction is also higher with methoxyflurane; patients are often distressed and require encouragement to use Entonox®, treatment is dependent on patient's capability to manage Entonox.

In camera, the Committee felt that the concerns raised previously by the JFC had been addressed by the MEDITA RCT and the real-world, observational studies which indicate methoxyflurane is at least as efficacious as IV paracetamol and IV opioids and may reduce the need for IV procedural sedation. The Committee accepted that Entonox® was not a real-world comparator in ED however there remain some uncertainty as to why. The Committee was assured by usage data from other London Trusts that prescribing creep could be controlled by restricting usage to ED only.

In summary, the Committee were satisfied that methoxyflurane was likely to improve speed of onset of pain relief, reduced progression to IV sedation, free up staffing time and ease of patient movement compared to Entonox® and IV analgesia. The advantages of methoxyflurane are useful when managing acute pain in the context of busy emergency departments.

Action: RFL to report on expenditure and outcomes of the evaluation locally (pain scores and use of rescue analgesia or IV sedation)

Decision: Approved
Prescribing: Secondary care, under supervision of ED consultants and registrars only
Tariff status: In tariff
Funding: Trust
Primary and secondary care Fact sheet or shared care required: No

9. Antihyperglycaemic agents for Type 2 diabetes

Existing NICE guidance for the management of type 2 diabetes (NG28) was published in 2015. Since then, new clinically important evidence on cardiovascular and renal outcomes is available which has been incorporated into American (ADA) and European (EASD) guidelines. NICE plan to revise their guidelines however the publication date is unknown, therefore interim guidance for NCL was considered necessary. This interim guidance will remain until updated NICE guidance is available.

The proposed interim guidance was adapted from recently approved guidance from NWL and is closely aligned with ADA/EASD. The NCL Diabetes Transformation Board have contributed to and approved this work. It complies with NCL formulary choices. Whilst all recommendations in the proposed interim guidance are clinically optimal, the cost-effectiveness of some recommendations have not been confirmed by NICE therefore are subject to change.

The Committee approved the guideline clinically and referred it to NCL CCG MMT for funding considerations.

In terms of GLP-1RAs, the NCL Diabetes Transformation Board positioning for subcutaneous semaglutide, dulaglutide and oral semaglutide was accepted. A decision on whether to update or remove the NCL Fact Sheet for GLP-1RA will be deferred to the NCL Shared Care Group.

Drug: Semaglutide subcutaneous, 0.25 mg to 1 mg pre-filled pens

Decision: Approved for the management of hyperglycaemia only when used in line with NCL guidance
Prescribing: Specialist initiation with GP continuation
Tariff status: In tariff
Funding: Trust and CCGs
Primary and secondary care Fact sheet or shared care required: TBC

Drug: Dulaglutide subcutaneous, 0.75 mg to 4.5 mg autoinjectors
Decision: Approved for the management of hyperglycaemia only when used in line with NCL guidance
Prescribing: Specialist initiation with GP continuation
Tariff status: In tariff
Funding: Trust and CCGs
Primary and secondary care Fact sheet or shared care required: TBC

Drug: Semaglutide oral, 3 mg to 14 mg tablets
Decision: Non-preferred option for the 4th line management of hyperglycaemia in patients *with* BMI > 35 kg/m^2 (>30 kg/m^2 if BAME ethnicity) *and without* cardiovascular-renal disease. See NCL guidance for further information.
Prescribing: Specialist initiation with GP continuation
Tariff status: In tariff
Funding: Trust and CCGs
Primary and secondary care Fact sheet or shared care required: TBC

10. Preferred choice of CGRP inhibitors for migraine (e.g. erenumab)

Three CGRP inhibitors have recently received positive NICE TAs; erenumab, fremanezumab and galcanezumab. Fremanezumab is NICE-approved for chronic migraine only, whereas galcanezumab and erenumab are NICE-approved for both chronic migraine and episodic migraine.

In the absence of within class head-to-head data, the Committee agreed that any claim of differences between the products was hypothesis generating only. As such, the Committee agreed to prefer the product with the lowest acquisition cost. Clinical teams at RFL and UCLH agreed with this position.

For patients already on treatment with a non-preferred CGRP inhibitor from a private clinic, the Committee recommended that a conversation takes place to encourage a switch to the preferred product when NHS treatment commences. However, a switch would not be forced as all three drugs are on formulary in line with their respective NICE TAs.

In summary, patients initiating their first CGRP inhibitor should be initiated on the lowest cost option. NEL proposed to develop a pathway to position the CGRP relative to Botox® (also NICE-approved for migraine) and medicines recommended in the existing NCL migraine pathway.

11. Next meeting

Thursday 20th May 2021

12. AOB

12.1 Flowchart for transitioning patients from Freestyle Libre (FSL) to FSL2 in primary and secondary care

A flowchart to support the safe transition from FSL to FSL2 in both primary and secondary care was presented. The flowchart was approved with minor amendments.