North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 15 April 2019
LG01, 222 Euston Road, London, NW1 2DA

Present:	Dr R Sofat	UCLH, DTC Chair (acting JFC chair)	**(chair)**
	Dr R MacAllister	NCL JFC Chair	**(via telephone)**
	Dr R Woolfson	RFL, DTC Chair	
	Dr M Kelsey	WH, DTC Chair	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Dr K Tasopoulos	NMUH, DTC Chair	
	Mr S Richardson	WH, Chief Pharmacist	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Dr A Sell	RNOH, DTC Chair	
	Prof D Hughes	RFL, Consultant Haematologist	
In attendance:	Mr A Barron	NCL MEP, Lead Pharmacist	
	Ms M Kassam	NCL JFC, Support Pharmacist	
	Mr G Grewal	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms H Mehta	NMUH, Formulary Pharmacist	
	Dr P Bodalia	UCLH, Principal Pharmacist	
	Ms S Sanghavi	UCLH, Formulary Pharmacist	
	Mr F Master	RFL, Formulary Pharmacist	
	Ms F Shivji	NEL CSU, Commissioning & Contacts Support pharmacist	
	Mr A Fakokunde	NMUH, Consultant Obstetrician and Gynaecologist	
	Dr S Bhatti	Barnet CCH, GPsI	
	Dr S Miller	NHNN, Consultant Neurologist	
	Dr M Cohen	RFL, Consultant Endocrinologist	
	Dr E Karra	RFL, Consultant Endocrinologist	
	Dr S Bloom	UCLH, Consultant Gastroenterologist	
Apologies:	Ms K Davies	NEL CSU, Deputy Director Medicines Management	
	Ms W Spicer	RFL, Chief Pharmacist	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Prof L Smeeth	NCL JFC Vice-Chair	
	Ms L Reeves	C&I, Chief Pharmacist	
	Dr M Dhavale	Enfield CCG, GP Clinical Lead Medicines Management	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr A Bansal	Barnet CCG, GP Clinical Lead Medicines Management	
	Prof A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr T Rashid	NHS Haringey, GP Clinical Lead Medicines Management	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Mr T Dean	Patient Partner	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Dr S Yardley	CNWL, Consultant in palliative medicine [observer]	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Mr S Semple	MEH, Chief Pharmacist	

2. Meeting observers

Nil

3. Minutes of the last meeting

The minutes were accepted as an accurate reflection of the meeting

4. Matters arising

4.1 Removal of Jaydess® (levonorgesterel 13.5 mg intrauterine system) from the NCL Joint Formulary

In February 2019 the Committee removed Jaydess for contraception from the NCL Joint Formulary. This decision followed the approval of Kyleena® (levonorgesterel 19.5 mg intrauterine system) due to absence of a demonstrable benefit of Jaydess over Kyleena, and with a view to rationalise the number of levonorgesterel intrauterine devices available in NCL. CNWL appealed against this decision as they identified a small cohort of patients who may benefit from the lower levonorgestrel release rate with Jaydess (patients averse to using hormone contraceptives or those who experience adverse effects with Kyleena).

The Committee considered the evidence to support a claim of improved tolerance with Jaydess. A Phase III head-to-head study reported no difference in discontinuation due to adverse effects between the products (21.9% and 19.1% for Jaydess and Kyleena respectively) however there was a statistically significant difference in the number of ovarian cysts reported (7.7% vs. 13.8% for Jaydess and Kyleena respectively, $p<0.01$). There were no other differences identified and there was no clear trend towards one device reporting a lower rate of adverse events.

Ovarian cysts are a known adverse effect of all licensed levonorgestrel intrauterine systems, including Jaydess and the difference identified could be the play of chance from unadjusted multiple testing. The Committee did not agree Jaydess was better tolerated than Kyleena however acknowledged that the proposed cohort is for <50 women per year and budget impact would be minimal. The Committee agreed to approve the appeal and review usage of Jaydess in twelve months.

Decision: Approved second line
Prescribing: Restricted to sexual health clinics.
Tariff status: In tariff
Funding: CCG/Trust
Fact sheet or shared care required: No
Additional information: Usage to be reviewed by JFC in 12 months to confirm a reduction in use in NCL is < 50 women per year.

5. JFC Work Plan & outstanding actions

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

6. Declarations of relevant conflicts of interest

Dr M Cohen (Item 8.3) declared extensive conflicts of interests with all diabetes companies. Dr E Karra (Item 8.3) declared funding to attend a sponsored workshop from Novo Nordisk who manufactures semaglutide. No other conflicts of interest were declared by applicants or Committee members.

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
RFL	Jan-19	Triclabendazole	Human Fascioliasis Infection	Decision: Added to NCL Joint Formulary Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
RFL	Jan-19	Pepto Bismol® (bismuth subsalicylate) tablets + liquid	Eradication of H.Pylori (after first-line treatment and previous exposure to levofloxacin)	Decision: Added to NCL Joint Formulary Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

RFL	Jan-19	Sirolimus	Low flow venous malformations	Decision: Approved for RFL only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

8. New Medicine Reviews

8.1 APPEAL: Ulipristal acetate for moderate to severe symptoms of uterine fibroids (Applicant: Mr A Fakokunde, NMUH)

In February 2018, following an MHRA alert highlighting the risk of serious liver injury with ulipristal acetate (Esmya®), JfC removed the drug from the NCL Joint Formulary and suspended the shared care document. In August 2018, the MHRA issued updated advice on the safe use of ulipristal, which included intensive liver monitoring and a change in the licensed indications. At the time, the Committee agreed the changes to the licensing were substantial and a new application would be required before Esyma could be prescribed in NCL.

The Committee considered an application to reinstate ulipristal for two indications (i) a single course used pre-operatively in women of reproductive age and (ii) up to four intermittent courses used in women of reproductive age who are ineligible for surgery.

The Committee reviewed the EMA report on the incidence of serious liver injury associated with ulipristal. Pharmacokinetic studies demonstrated increased liver exposure in cholestasis. In Phase II and III studies, no patients fitted Hy's Law criteria (AST/ALT ≥ three times the upper limit of normal and bilirubin ≥ two times the upper limit of normal) though there were several reported adverse liver events. A pharmacovigilance database search found a total of 34 serious liver injuries reported – eight found a role for Esmya, and four led to liver transplant. The four cases of liver transplant occurred in women aged 45 years or over; the EMA concluded that a causal role of ulipristal was possible or probable in two transplant cases, but there was insufficient information in the other two cases. Four other cases of serious liver injury were reported, and a causal role of ulipristal was supported by drug de-escalation resulting in symptom improvement and reduction of raised LFTs.

The EMA recommended a series of risk reducing measures:

- Contraindication in patients with an underlying hepatic disorder
- Restricted to women in whom surgery is not a viable option (Intermittent courses only)
- The initiation & supervision restricted to physicians experienced in diagnosis & treatment of uterine fibroids
- Monthly LFT monitoring for the first two cycles (as well as pre- and post- course LFT monitoring for all courses)
- Additional patient information.

The Committee heard from Mr Fakokunde that uterine fibroids were more common amongst women of African origin and subsequently the prevalence of uterine fibroids is high in NCL. Prior to its withdrawal, ulipristal was frequently used owing to the long-term reduction in fibroid size which aids in reducing associated pressure symptoms. Contrary to the application, some women remain on ulipristal beyond 4 courses.

Mr Fakokunde outlined plans for virtual clinic LFT monitoring prior to a new prescription being furnished to avoid potential incidents. The application includes a proposed shared care pathway for intermittent use of Esmya® up to four courses, with transfer to primary care following the first two courses.

In camera, the Committee queried the causal role of ulipristal in liver injury due to the relatively quick onset of symptoms in two liver transplant cases, and the uncertainties surrounding other cases. The use of potential alternatives was discussed, such as leuprorelin which was non-inferior to ulipristal in control of bleeding though limited to six months use due to adverse effects. The Committee were confident that the drug could safely be used if careful application of suggested risk minimisation measures were implemented. To comply with the EMA recommendation to restrict initiation and supervision of ulipristal to clinicians experienced in the diagnosis and treatment of uterine fibroids, the Committee determined that all prescribing and monitoring should be retained in secondary care. In summary, ulipristal should be reinstated for both modified indications (i) a single course used pre-operatively in women of reproductive age and (ii) up to four intermittent courses used in women of reproductive age who are ineligible for surgery.

Decision: Approved
Prescribing: Secondary care, named consultant only
Tariff status: In tariff
Funding: Trust
Fact sheet or shared care required: No

8.2 Candesartan for the prophylaxis of chronic and episodic migraine (Applicant: Dr S Bhatti, Barnet CCG)

The Committee reviewed an application for the use of candesartan for the prophylaxis of chronic and episodic migraine after failure of propranolol, topiramate and amitriptyline.

Evidence on the clinical effectiveness of candesartan was based on two randomised, double-blind, placebo controlled, crossover studies. Both studies demonstrated superiority over placebo in terms of number of headache days. The active comparator study found candesartan to be non-inferior to propranolol (0.04 days/four weeks, p=0.88) for moderate to severe headaches lasting ≥4 hours or being treated with the patient's usual medication. The secondary outcomes of headache days, migraine days, headache hours and headache severity index were also significantly reduced compared to placebo and non-inferior to propranolol. Both studies were small, short-duration, cross-over studies and funded by AstraZeneca. In addition, the trial population was not fully reflective of the proposed cohort as patients were excluded based on the number of prophylactic treatments previously used, if they had a high number of migraine or headache days.

The Committee noted that guidance from SIGN 155 recommends the use of propranolol and topiramate for the prevention of migraine, amitriptyline should "be considered" whereas candesartan and sodium valproate "can be considered" for the prevention of episodic or chronic migraine. The NICE clinical guideline 150 did not include candesartan within the scope of their guideline.

The Committee heard from Dr Bhatti that safe, established, cost-effective, patient centred strategies are sought after for the management of migraine as it is a condition that confers great co-morbidities e.g. depression, and significantly impacts patient quality of life. Candesartan is a suitable option for the management of patients in primary care. Dr Miller informed the Committee it may be preferable to offer candesartan earlier in the prophylaxis of migraine pathway, owing to improved tolerability, however this was hampered by the limited evidence base. Dr Miller proposed for candesartan to be used as monotherapy, the aim of treatment is for a reduction in in use of acute medications and a 30-50% reduction in acute symptoms. If not effective after three months of treatment candesartan should be stopped; if effective then treatment should be reviewed in six to twelve months with a view to stopping treatment as prophyalxis is not intended to be long-term.

In camera, the Committee concluded that the evidence base for candesartan was limited, however demonstrated a small improvement in migraine-related outcomes compared with placebo. It was queried whether the improvement was clinically relevant, however the order of improvement observed was similar to current prophylaxis options available. Given that further trials are unlikely to be conducted coupled with the low cost of favourable side-effect profile of candesartan it was approved for use. The Committee highlighted that angiotensin II receptor antagonists should be used with due vigilance and with appropriate safety precautions in women of child bearing age as this class of medicines should be avoided in pregnancy.

Decision: Approved
Prescribing: Primary and secondary care initiation
Tariff status: In tariff
Funding: CCG/Trust
Fact sheet or shared care required: No
Additional information: Treatment in primary care should follow the NCL protocol for the management of headaches in primary care. Starting dose is 4 mg BD, increase weekly by 4 mg daily up to 8 mg BD; review at 3 months.

8.3 Semaglutide for type 2 diabetes (Applicant: Dr E Karra, RFL)

The Committee reviewed an application for the use of semaglutide as an alternative to liraglutide and dulaglutide (glucagon-like peptide-1 receptor agonists [GLP-1RA]) for the management of type 2 diabetes after failure of triple oral antidiabetic drug (OAD) therapy (see NCL Factsheet for full place in therapy).

SUSTAIN 7 was an open-label, active-controlled, four-armed trial to compare (pairwise) the efficacy and safety of semaglutide vs. dulaglutide (n=1,201). For a comparison of dulaglutide 1.5 mg weekly and semaglutide 1.0 mg weekly; semaglutide was associated with a greater reduction in HbA1c (-0.41% [95% CI: -0.57 to -0.25]), and body weight (-3.55Kg [95% CI: -4.32 to -2.78]). Generalisability of this study to NCL was limited by the study population being patients failing on metformin monotherapy rather than triple OAD therapy.

SUSTAIN 6 was a long-term, cardiovascular study of semaglutide as an add-on to standard of care in patients with diabetes and established, or at high risk of, cardiovascular disease (n=3,297). Results showed a reduction in time to first occurrence of a 3-point Major Adverse Cardiovascular Event (MACE) in patients treated with semaglutide (HR = 0.74 [95% CI: 0.58 to 0.95]). A limitation of the study was the high baseline cardiovascular risk which limits the generalisability to the general diabetic population.

In terms of safety; semaglutide had a similar risk of hypoglycaemia to dulaglutide however had a higher risk of discontinuation due to adverse effects, mainly caused by differences in gastrointestinal adverse effects. The SUSTAIN 6 also had a higher risk of diabetic retinopathy particular amongst patients taking insulin who had a history of diabetic retinopathy at baseline. The Committee heard from Dr Karra and Dr Cohen that any rapid drop in blood glucose precipitates diabetic retinopathy therefore patients with poor control at baseline would be prepared for GLP-1RA therapy by up-titrating basal insulin before initiating GLP-1RA and withdrawing insulin. Dr Cohen suggested that this risk had not been identified for other GLP-1RAs because studies involving these drugs excluded patients with diabetic retinopathy; *in camera,* the Committee found this statement to be inaccurate for both liraglutide and dulaglutide cardiovascular safety studies.

The Committee reviewed an NCL cost-analysis which showed a doubling of GLP-1RA spend over 5 years which could not be fully explained by changing guidance or diabetes prevalence. Results from the DOVE tool for Barnet CCG revealed rapidly rising costs and declining outcomes for patients with type 2 diabetes; this concerning finding should be escalated to the STP Health and Care Cabinet. Dr Karra highlighted this pattern was not observed for Camden CCG which adopted value based commissioning.

NICE have yet to incorporate data form the various cardiovascular safety studies and recommend GLP-1RAs late in the treatment pathway owing to their high cost. This contrasts with the American Diabetes Association (ADA) which now recommends GLP1-RAs as a second line treatment option for patients with established cardiovascular disease. Dr Karra discussed a desire to move towards ADA recommendations.

Dr Cohen requested that semaglutide be the 1st choice GLP-1RA, dulaglutide be 2nd choice for those who preferred an 'autoinjector' device (e.g. needle phobia) and liraglutide be 3rd choice for those preferring daily injections.

In camera, the Committee agreed it is unknown whether ADA recommendations are cost-effective therefore it is essential UK practice does not veer towards ADA recommendations before NICE recommends such an approach. Semaglutide is superior to dulaglutide in terms of weight loss and HbA1c and is similarly convenient in terms of weekly administration; the differences in device were not considered sufficiently beneficial to justify retaining dulaglutide on the NCL Joint Formulary. In summary, subject to the NCL Fact Sheet and 'Antihyperglycaemic agents for Type 2 diabetes' guideline being updated, semaglutide should be added to the NCL Joint Formulary and dulaglutide should be removed.

Decision: Approved subject to NCL GLP-1RA Fact Sheet for GPs and NCL 'Antihyperglycaemic agents for Type 2 diabetes' guideline are updated to include semaglutide – Trusts should not make semaglutide available until this work is complete.
Prescribing: Specialist initiation and GP continuation
Tariff status: In tariff
Funding: CCG/Trust
Fact sheet or shared care required: Yes

8.4 Tofacitinib for ulcerative colitis, after failure or contraindication to anti-TNF

The Committee reviewed an application for the use of tofacitinib for ulcerative colitis, after failure or contraindication to anti-TNF. This provisional place in therapy was agreed by the IBD pathways working group; it supported clinicians gaining real-world experience of tofacitinib in patients who are not eligible for trials and encouraged the use of more cost-effective anti-TNFs earlier in the pathway.

There were no studies specifically assessing the efficacy of tofacitinib in patients pre-treated with anti-TNF however a post-hoc analysis of the licensing studies was available. In terms of remission; the placebo

adjusted estimated treatment difference (ETD) for tofacitinib was +12.6% for anti-TNF naïve patients, +11.3% for 1 prior anti-TNF, and +9.2% for ≥2 prior anti-TNF. For maintenance of remission, the placebo adjusted ETD was +30.7% for anti-TNF naïve patients using 5 mg BD dose, +33.2% for anti-TNF naïve patients using 10 mg BD dose, +12.9% for anti-TNF pre-treated patients using 5 mg BD dose and +25.3% for anti-TNF pre-treated patients using 10 mg BD dose. The Committee concluded that tofacitinib was superior to placebo for remission and maintenance however the 10 mg BD dose appeared more effective at maintaining remission for anti-TNF pre-treated patients. In terms of comparative data for anti-TNF exposed patients, the Evidence Review Group reviewed a network meta-analysis submitted as part of the TA for tofacitinib and concluded that tofacitinib had the largest treatment effect however vedolizumab and tofacitinib were both superior to placebo.

In terms of safety, an ongoing post-marketing 5 year study to assess risks of cardiovascular events, cancer, and opportunistic infections in rheumatoid arthritis found an increased occurrence of pulmonary embolism and death in patients treated with tofacitinib 10 mg BD compared to patients treated with tofacitinib 5 mg BD or an anti-TNF. The absolute risks involved are unknown.

The Committee heard from Dr Bloom that it is challenging to compare baseline risks for patients recruited into the 5-year RA study (>50 years old and at least one CDV risk factor) to with patients with ulcerative colitis. Patients with ulcerative colitis are typically younger without CVD risk factors however IBD patients have a 3-fold increase in their risk of VTE and PE compared to the general population. Gastroenterologists are aware of the increased risk of PE and death with the 10 mg BD dose and would preferentially use the 5 mg maintenance where possible.

Dr Bloom informed the Committee that there was little evidence to support the ordering of different modes of actions for the treatment of ulcerative colitis however a national IBD registry has been set up to provide an evidence base.

In camera, the Committee agreed tofacitinib is effective after failure of anti-TNF and supported its addition onto the IBD pathway. The Committee agreed with the intention to preferentially use 5 mg BD maintenance dose whenever possible to minimise the risk of PE and death.

8.5 Proposal to remove eflornithine (Vaniqa®) from the NCL joint formulary

This item was deferred to the May 2019 JfC meeting.

9. Cannabis and Cannabis-Related Products Position Statement and Patient Information

Minor amendments to the current position statement and patient information document were presented to the Committee for information. This includes the restriction of adult patients enrolling on to the cannabidiol oral solution early access programme to Dravet Syndrome patients with a mutation in the SCN1A gene only; this is due to a limited allocation set by the manufacturer and will support clinicians targeting the use of cannabidiol at those most likely to benefit.

10. High-cost drug pathways for inflammatory bowel disease

The Committee reviewed two pathways for inflammatory bowel disease; one for moderately to severely active ulcerative colitis and one for active Crohn's disease.

There were no objections to the clinical content of either pathway and were subsequently approved, subject to funding approval.

The ulcerative colitis pathway was given a 6 month review date. During this time the pathway would be updated to incorporate tofacitinib into the flow diagram.

Action: NEL CSU to write a costing statement for review by NCL CCGs

11. Next meeting

Monday 20th May 2019, 4.30 – 6.30pm, Venue: LG01, 222 Euston Road, London, NW1 2DA

12. Any other business

Nil