North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Monday 18 June 2018
G12 Council Room, South Wing, UCL, Gower Street, London WC1E 6BT

Present:	Dr R MacAllister	NCL JFC Chair	**(Chair)**
	Dr R Urquhart	UCLH, Chief Pharmacist	
	M S Semple	MEH, Interim Chief Pharmacist	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Dr M Dhavale	Enfield CCG, GP Clinical Lead Medicines Management	
	Dr D Hughes	RFL, Consultant Haematologist	
	Mr T Dean	Patient Partner	
	Dr R Sofat	UCLH, DTC Chair	
	Dr M Kelsey	WH, DTC Chair	
	Mr S Richardson	WH, Chief Pharmacist	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Ms W Spicer	RFL, Chief Pharmacist	
	Dr T Rashid	NHS Haringey, GP Clinical Lead Medicines Management	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Dr R Woolfson	RFL, DTC Chair	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
In attendance:	Mr A Barron	NCL JFC, Support Pharmacist	
	Dr P Bodalia	UCLH, Principal Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms S Sanghvi	UCLH, Formulary Pharmacist	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Ms K Shah	UCLH, Clinical Pharmacist	
	Dr D Nair	RFL, Consultant Chemical Pathologist	
	Dr M Shephard	UCLH, Consultant in Oral Medicine	
Apologies:	Mr G Kotey	NMUH, Chief Pharmacist	
	Prof L Smeeth	NCL JFC Vice-Chair	
	Dr A Bansal	Barnet CCG, GP Clinical Lead Medicines Management	
	Dr A Mian	NMUH, Clinical Director for Specialty Medicine	
	Dr A Sell	RNOH, DTC Chair	
	Prof A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms M Bhogal	NMUH, Formulary Pharmacist	
	Dr F Gishen	RFL, Palliative Care Consultant	
	Ms L Reeves	C&I, Chief Pharmacist	
	Ms M Kassam	MEH, Formulary Pharmacist	
	Ms K Davies	NEL CSU, Deputy Director Medicines Management	
	Ms M Bhogal	NMUH, Formulary Pharmacist	

2. Meeting observers

Ms K Shah was welcomed as an observer to the meeting.

3. Minutes of the last meeting

The minutes and abbreviated minutes were accepted as accurate reflections of the May meeting.

4. Matters arising

Dr Johal & Dr Costello (RFL) and Dr Elkhodair (UCLH) plan to jointly appeal the May 2018 decision to not approve methoxyflurane (Penthrox®) for emergency relief of moderate to severe pain in A&E. The applicants asked the Committee to consider adding an Emergency Department physician to the Committee membership; this was discussed under agenda Item 10 'JFC Membership (update)'.

5. JFC Work Plan & outstanding actions

5.1 Outstanding actions

There were no outstanding actions due to conclude this month.

5.2 JFC Work Plan

This item was included for information only. Any questions should be directed to Mr Barron.

6. Declarations of relevant conflicts of interest

There were no declarations of interest from Committee members or applicants.

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
RFL	Nov-11	Icatibant	Treatment of Acute Attacks in Hereditary Angiodema in adults (in line with NHS Commissioning Policy NHSCB/B09/P/b)	Decision: Added to NCL Joint Formulary Prescribing: Secondary care only Tariff status: Excluded Funding: NHSE Fact sheet or shared care required: No

7.2 Not approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	May-18	Imatinib (off-label)	Locally advanced and metastatic chordoma	Not Approved

7.3 In progress

DTC site	Month	Drug	Indication	JFC outcome
RFL	Apr-18	Liothyronine	Primary hypothyroidism (as part of T3 and T4 combination therapy) for patients who remain symptomatic with T4 monotherapy	Await RFL evaluation protocol

8. New Medicine Reviews

8.1 Volanesorsen Early-Access to Medicines Scheme (EAMS) for Familial Chylomicronaemia syndrome (Applicants: Dr D Nair [RFL] & Dr Lunken [UCLH])

The Committee considered two applications to use volanesorsen Early-Access to Medicines Scheme as adjunct to low fat diet for the treatment of adult patients with familial chylomiconemia syndrome (FCS). Volanesorsen is an antisense oligonucleotide that inhibits the expression of ApoC-III, and this leads to an increase in lipoprotein lipase activity.

The APPROACH study, the pivotal placebo-controlled study demonstrating efficacy of volanesorsen for patients with FCS, remained unpublished at the time of review. The MHRA 'Information for health care professional' (effectively an SPC) which was considered by the Committee to be inadequate for decision

making. The Committee agreed to consider the application as FDA papers were available which provided sufficient information to conduct a thorough review of the study quality and the efficacy and safety data.

APPROACH was a randomised, double-blind, placebo-controlled, 52-week, multicentre trial in patients with FCS (n=66). Adults with a history of chylomicronemia and a diagnosis of FCD (Type 1 hyperlipoproteinaemia), fasting TG ≥ 8.48 mmol/L at screening and a history of pancreatitis were recruited. The primary endpoint was the percentage change in fasting triglycerides from baseline to Month 3, as compared to placebo. At 3 months; patients receiving volanesorsen had a reduction in fasting triglyceride level of -77% (95% CI: -97% to -56%) compared to the placebo arm of +18% (95% CI: -4 to +39%); estimated treatment difference was -94% (95% CI: -122% to -67%; p<0.0001). This is similar to the effect of a low fat diet. The absolute change was -19 mmol/L (95% CI: -24 to -15) and +1 mmol/L (95% CI: -3 to +5) for volanesorsen and placebo respectively; estimated treatment difference was -20 mmol/L (95% CI: -26 to -15). The treatment difference remained clinically and statistically significant over 52 weeks although the difference diminished from -94% to -49%. This reduction was primarily a consequence of the ITT analysis and a large number of patients in the volanesorsen arm withdrawing from treatment but returning for assessment over the 52 week period. In terms of patient orientated outcomes; there was a numerical but not statistically significant reduction in incidence of pancreatitis (1 event vs. 4 events; n=66). In a *post-hoc* analysis which combined results from APPROACH and COMPASS the reduction was significant (1 event vs. 9 events; n=179). The FDA reported no difference in abdominal pain between arms. A significant rise in LDL was observed.

By week 52, 42% of patients randomised to volanesorsen had discontinued treatment and 21% had discontinued due to adverse effects. Very common adverse effects include thrombocytopenia, myalgia and injection site reactions. Thrombocytopenia was the most concerning problem caused, and seems to be a class effect of antisense oligonucleotides. Common adverse effects include eosinophilia, immune thrombocytopenia purpura, spontaneous haematoma, haematoma and hypertension. The FDA estimated volanesorsen increased the risk of thrombocytopenia by 2.8-fold, and bleeding by 4-fold. The mechanism for the observed haematological effects is unknown. Uncontrolled hypertension was an exclusion criterion however 1 patient developed hypertensive crisis and 3 developed hypertension with volanesorsen (0 patients on placebo).

A further limitation of the study was poor adherence to the inclusion criteria; 14% of patients had neither confirmatory genetic testing nor abnormal LPL activity.

The Committee heard from Dr Nair that she had no personal experience of using volanesorsen however she has spoken to UK colleagues who had used volanesorsen successfully. Dr Nair has two patients eligible for treatment; both had homozygous FCD which is known to respond poorly to fibrates. The only current treatment option for homozygous FCD is dietary modification to <5% fat which has major compliance challenges. The observed increase in LDL was thought to be either a normalisation of pre-treatment very low LDL levels or a consequence of the reduction in the triglyceride levels resulting in the LDL test being more accurate. The absolute increase in LDL was not considered clinically meaningful as the baseline CV risk for these patients is low. The Committee heard volanesorsen inhibits ApoC-III which is an inhibitor of LPL, therefore it was anticipated that volanesorsen would increase LPL activity. However LPL activity was found to fall, indicating that volanesorsen acts via additional and unknown pathways. The high drop-out rate was considered to limit the usefulness of volanesorsen however Dr Nair suggested it would prevent a few episodes of pancreatitis before monoclonal antibody based therapies become available. The Committee noted the very limited experience informing on use of the medicine (small cohort size, short total duration of exposure) and the unknown mechanism of action and toxicity. Furthermore there were concerns that patients on treatment with volanesorsen may see this as an alternative to dietary modification and it is essential that patients are counselled to understand that volanesorsen is an adjunctive treatment. The Committee heard the company had provided assurances that free-of-charge stock would be provided in the event of a negative funding decision by NICE.

With regards to monitoring, Dr Nair agreed to perform the necessary platelet monitoring for patients in clinic as specified by the MHRA (monitoring every 2 weeks to twice per week).

In camera, the Committee agreed volanesorsen reduced triglyceride levels to a meaningful extent and was likely to reduce the risk of pancreatitis for patients who were able to remain on therapy. The Committee had concerns about the safety profile however took reassurance that the FDA voted to approve the drug (12:8 in favour). The Committee therefore agreed to approve volanesorsen EAMS, as adjunct to low fat diet, for the treatment of adult patients with familial chylomiconemia syndrome subject to the below risk minimising measures being adhered to:

- All patients must have recurrent pancreatitis

- All patients must be ineligible for inclusion into a clinical trial (each patient to be assessed for trials available in either RFL or UCLH); this includes both existing and future trials as appropriate
- Contraindicated in patients with thrombocytopenia (platelet count <140 x 10^9/L) with treatment emergent thrombocytopenia treated and monitored in line with the 'Treatment protocol for healthcare professionals'
- Contraindicated in patients with uncontrolled hypertension (BP >160/100 mmHg)
- Patients agree to maintaining dietary modification
- Patients consent to the drug being withdrawn if free-of-charge stock is unavailable in the event of a decision not to fund volanesorsen nationally
- Patients understand the increased risk of thrombocytopenia and bleeding and consent to platelet monitoring in clinic as described in the MHRA 'Information for prescribers'

Decision: Approved with additional restrictions
Prescribing: Secondary care
Tariff status: NA
Funding: FOC via EAMS
Fact sheet or shared care required: No

8.2 Azithromycin (off-label) for orofacial granulomatosis (Applicant: Dr M Shephard, UCLH)

The Committee considered an application to use azithromycin (off-label) for orofacial manifestations of orofacial granulomatosis which are resistant to topical immunomodulatory medications, intralesional corticosteroids, and dietary modification. The place in therapy is therefore before corticosteroids or immunosuppression (azathioprine, mycophenolate mofetil, thalidomide).

A literature review identified three case-studies which included azithromycin monotherapy for orofacial granulomatosis; 2 were negative and 1 was positive.

Given the lack of evidence for azithromycin in orofacial granulomatosis, it use in paediatric Crohn's disease was reviewed. The AZCRO study found the addition of azithromycin to metronidazole had a numerical impact on response rates (65.7% vs. 44.7% [p=0.07]), as defined as an improvement in the Paediatric Crohn's Disease Activity Index, and a statistically significant impact on remission rates (65.7% vs. 39% [p=0.025]). The Committee noted the recognised role of bacteria in the pathogenesis of Crohn's disease therefore did not consider this paper relevant to orofacial granulomatosis.

The Committee heard from Dr Shephard that the application was in response to evidence heard at a conferences, and that it is used to good effect in Glasgow who have a particular large cohort of patients with orofacial granulomatosis.

The Committee heard that the use of azithromycin for non-infectious causes is expanding but overall use is still very small compared to its use as an anti-infective agent. The use of azithromycin for this indication is therefore not a concern in terms of antimicrobial stewardship. The key reason for concern is if the patient develops a supra-infection whilst using azithromycin then their treating physician would need to avoid using a macrolide as this would be ineffective.

In camera, the Committee considered the available evidence did not support use of azithromycin for orofacial granulomatosis and requested that Dr Shephard request the data presented at the conference for review by this Committee. The option to 'approve under evaluation' was rejected as evaluations are commonly poorly conducted and there is no reason to anticipate UCLH specific data would be different to data from other centres who are already using azithromycin for this indication.

Decision: Deferred

8.3 Hydroxychloroquine (off-label) for severe symptomatic erosive oral lichen planus (Applicant: Dr M Shephard, UCLH)

The Committee considered an application to use hydroxychloroquine (off-label) for symptomatic erosive oral lichen planus refractory to topical treatment (corticosteroids or tacrolimus). The place in therapy is therefore before corticosteroids or immunosuppression (mycophenolate mofetil, azathioprine).

A Cochrane review from 2012 summarised all the randomised-controlled trials for systematic and topical treatments for erosive lichen planus affecting mucosal sites and did not identify any RCTs using systemic treatments. A structured review for JFC did not identify any relevant RCTs.

Two case series (n=10 and n=8) reported the effectiveness of hydroxychloroquine for patient with erosive lichen planus. Patients were assessed against their baseline according to assessment of degree of erythema, erosion, and symptoms; ≤20% improvement, 20-50% improvement, 50-80% improvement and >80% improvement. Combining the studies showed 13 patients achieved >80% improvement, 3 achieved 50-80% improvement, 1 experience 20-50% improvement and 1 got worse. Data from a single arm of a RCT indicate 7 of 10 patients had a complete response. All studies reported relapse of symptoms when the hydroxychloroquine dose was reduced or treatment stopped.

Specialists consider oral lichen planus synonymous with chronic ulcerative stomatitis therefore supportive evidence for this indication was additionally reviewed. One literature review (methods not presented) identified 39 cases of chronic ulcerative stomatitis reported the majority of patients were prescribed hydroxychloroquine and nearly all reported positive outcomes.

Hydroxychloroquine side-effects include abdominal pain, nausea. There is a risk of eye disorders including irreversible retinopathy with changes in pigmentation and visual field defects, corneal changes including oedema and opacities, maculopathies and macular degeneration which warrant ophthalmic examinations whilst on treatment. BSR/BHPR 2017 guidelines state that patients should have baseline formal ophthalmic examination within 1 year of commencing an antimalarial drug. All individuals taking hydroxychloroquine who have additional risk factors for retinal toxicity may be screened annually from the baseline visit or annually after 5 years on treatment.

The number of patients eligible for treatment is anticipated to be 5 to 10 per annum with a total budget impact of approximately £600 per annum.

The Committee heard from Dr Shephard that the application was in response to an early review on an unpublished case series from Guy's Hospital. Oral lichen planus is rare condition which is challenging to treat and the addition of an alternative, not immunosuppressing therapy, would be advantageous.

The Committee agreed the responsibility for arranging the required ophthalmic examination at baseline and annually after 5 years on treatment lay with the initiating consultant; therefore the clinic must set up robust processes to ensure compliance to this requirement is high.

In camera, the Committee agreed the data was limited however was sufficient for a low cost medicine with a favourable risk profile being prescribed for a rare disease. In summary, the Committee agreed to approve the addition of hydroxychloroquine (off-label) for symptomatic erosive oral lichen planus refractory to topical treatment (corticosteroids or tacrolimus) on to the NCL Joint Formulary. The oral medicine clinic is responsible for arranging all ophthalmic examinations.

Decision: Approved
Prescribing: Primary and secondary care
Tariff status: In tariff
Funding: GP and hospital budgets
Fact sheet or shared care required: SCG to review appropriateness of adding this indication to the NCL DMARD fact sheet
Other notes: Recommended dose is 200 – 400 mg once daily. The oral medicine clinic is responsible for arranging all ophthalmic examinations (baseline and annually after 5 years, more intensive monitoring may be recommended for high risk patients by the Consultant ophthalmologist following the baseline visit).

9. JFC Terms of Reference (update)

The Committee reviewed the revised terms of reference and the following actions were agreed:

- A poll should be taken to elicit the Committee's preference for the duration of tenure of the Chair. Consideration should be given as to whether a maximum number of terms is appropriate, and to the frequency of which the tenure should be re-advertised.
- '2. Accountability' – Ms Clark requested the words "Governing Bodies of the Clinical Commissioning Groups" were amended to "the Clinical Commissioning Groups".
- '4. Key Relationships' – Dr Woolfson requested clarification around the process of "consideration and ratification" of DTC minutes so the responsibility of the Committee in this process was explicit
- '4. Key Relationships' – Ms Clark noted that some providers of community services are not included within the membership of JFC. This creates challenges for CCGs if community providers want to prescribe medicines that are not included on the NCL Joint Formulary as they are unable to submit an application. A historical case of JFC reviewing 'Ethinylestradiol 30 micrograms/ Drospirenone 3mg film-coated tablets' subsequent to an application from a Central and North West London NHS

Foundation Trust clinician was noted and the ToR already permits this. It was agreed that Mr Barron and Ms Clark should discuss any specific challenges off-line.

- 'Appendix 1: New medicine submissions flow diagram' Mr Semple requested clarification for the process of identifying whether an application is only relevant to a single Trust (and therefore might appropriately be reviewed by DTC). The established process is for Trusts to complete the DTC/JFC application form, submit to JFC Support for dissemination to Trusts via the Formulary Pharmacists. Trusts are then given two weeks to respond. If no expressions of interest are made, the application may be reviewed by the submitting Trusts' DTC assuming no GP prescribing or CCG commissioning. The Committee agreed the applying Trust could establish cross-sector interest in their application independently of JFC Support.

10. JFC Membership (update)

The Committee reviewed an analysis of applications considered by the JFC between March 2016 and April 2018. The specialisms with the greatest number of applications were neurology, oncology, anti-infective, endocrinology and respiratory. The Committee agreed members would identify suitable candidates for the vacant neurology and respiratory membership positions.

The Committee considered a request to include specialists from Emergency Medicine. The Committee agreed this addition was unnecessary as the current membership includes acute physicians and a trauma anaesthetist. It was further agreed that it is not necessary for every specialism to be represented on the Committee as consultants are routinely invited to JFC to support their application, and therefore provide the perspective of the specialism which will inform the Committee's decision.

11. Applications to remove medicines from the NCL Joint Formulary

JFC Support have received enquiries from members asking how to apply for a drug to be removed from the NCL Joint Formulary; two enquiries relate to the NHSE/NHS Clinical Commissioners 'Items which should not routinely be prescribed in primary care' and one that falls outside the scope of this document.

The Committee heard that removing a drug from the formulary required a greater degree of consultation that adding a drug to the formulary as there was a risk patients may have their treatment plans disrupted and there was a risk the drug could be unintentionally removed for an unintended indication.

The Committee agreed the consultation process should include all CCGs, and the form should be updated to reflect this fact (Section 6). JFC Support was asked to seek advice from NHSE regarding patient consultation when considering decommissioning medicines.

The application form was approved subject to adding the 5 NCL CCGs to Section 6.

12. Freestyle Libre – implementation update (verbal)

The Freestyle Libre implementation group met on 12th June with representatives from adult & paediatric Type 1 diabetes services (NMUH, RFL, UCLH, WH), NEL CSU and CCGs. The group was chaired by Prof Hingorani.

A key outcome from the meeting was a preference to not follow the LPP/LCDN proposal for transfer of care / shared care between specialists and GPs. Two alternative options are being considered:

- All prescribing to remain in secondary care in the long term
- All prescribing to remain in secondary care for 6m, before being transferred to GPs

For this reason, the 'Position statement and Patient FAQ' approved at JFC last month has become inaccurate and will not be uploaded. A second interim FAQ is being drafted which will continue to recommend GPs do not initiate or continue Libre. The Committee heard there had been a sharp increase in the amount of Libre being prescribing in primary care therefore an update Position statement was urgently required.

The implementation group are exploring options for data capture, including Blueteq, and the feasibility of Libre being procured via Pharmacy procurement at each Trust. The implementation group will meet again in July.

13. Next meeting

Monday 16 July 2018, G12 Council Room, South Wing, UCL, Gower St. WC1E 6BT

14. Any other business

Nil