North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Monday 21 May 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	
	Ms L Reeves	C&I, 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 A Mian	NMUH, Clinical Director for Specialty Medicine	
	Mr T Dean	Patient Partner	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Ms W Spicer	RFL, Chief Pharmacist	
	Ms K Davies	NEL CSU, Deputy Director Medicines Management	
	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 M Kassam	MEH, Formulary Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms S Sanghvi	UCLH, Formulary Pharmacist	
	Mr S O'Callaghan	UCLH, Formulary Pharmacist	
	Ms M Bhogal	NMUH, Formulary Pharmacist	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Dr H Payne	UCLH, Consultant Oncologist	
	Dr V Talaulikar	UCLH, Consultant Obstetrician & Gynaecologist	
	Dr N Johal	RFL, Consultant in Emergency Medicine	
	Dr S Elkhodair	UCLH, Consultant in Emergency 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	
	M S Semple	MEH, Interim Chief Pharmacist	
	Dr A Sell	RNOH, DTC Chair	
	Prof A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr D Hughes	RFL, Consultant Haematologist	
	Dr T Rashid	NHS Haringey, GP Clinical Lead Medicines Management	
	Dr R Woolfson	RFL, DTC Chair	
	Dr F Gishen	RFL, Palliative Care Consultant	
	Dr M Kelsey	WH, DTC Chair	
	Mr S Richardson	WH, Chief Pharmacist	
	Dr R Sofat	UCLH, DTC Chair	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	

2. **Meeting observers**

There were no meeting observers.

3. **Minutes of the last meeting**

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

4. **Matters arising**

There were no matters arising from the minutes.

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. Dr Payne declared she had received payments from Janssen-Cilag Ltd (relevant to agenda item 8.2).

7. **Local DTC recommendations / minutes**

7.1 **Approved**

DTC site	Month	Drug	Indication	JFC outcome
GOSH	Feb-12	Rituximab (off-label)	Second line treatment for anti-NMDAR autoimmune encephalitis (all ages) in line with NHSE Commissioning Policy (170039P)	Decision: Added to NCL Joint Formulary Prescribing: Secondary care only Tariff status: Excluded Funding: NHSE Fact sheet or shared care required: No
RFL	Jan-17	Peginterferon alfa-2a (treatment duration over 48 weeks)	Hepatitis B and D co-infection	Decision: RFL only† Prescribing: Secondary care only Tariff status: Excluded Funding: IFR to NHSE Fact sheet or shared care required: No
RFL	Mar-18	Pegvisomant	Third line option for acromegaly when surgery and other conventional treatments are not suitable in line with NHSE Commissioning Policy (16050/P)	Decision: Added to NCL Joint Formulary Prescribing: Secondary care only Tariff status: Excluded Funding: NHSE Fact sheet or shared care required: No
UCLH	Mar-18	Octreotide (off-label)	Chyle Leak Post Head and Neck Surgery	Decision: UCLH only Prescribing: Secondary care only Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No Other notes: Recommended dose is 50-100mcg TDS s/c

† This is considered a very rare scenario with 1 patient every 3 years maximum.

8. **New Medicine Reviews**

8.1 **Methoxyflurane (Penthrox®) for emergency relief of moderate to severe pain in A&E (Applicants: Dr N Johal & Dr Costello + Dr S Elkhodair & Dr Nabarro [RFL + UCLH])**

The Committee considered an application to use Penthrox® (methoxyflurane inhalator) for the emergency relief of moderate to severe pain in A&E.

STOP! (n=298) was a randomised, double-blind, placebo-controlled study of the efficacy and safety of Penthrox for the treatment of acute pain across multiple sites in the UK. Patients were eligible if their pain due to minor trauma on presentation was scored ≥4 to ≤7 on a 10-point visual analogue scale

(moderate pain). Rescue medication was available immediately on request at any time in either arm, although the authors do not describe what this constituted. The primary outcome was change in pain intensity as measured using the visual analogue scale (VAS) from baseline to 5, 10, 15 and 20 min after the start of drug inhalation. Baseline VAS was 64mm in both groups. Results showed the estimated mean change in VAS pain from baseline to 5, 10, 15 and 20 minutes was significantly greater for the methoxyflurane group than for the placebo group (-23.1, -28.9, -34.0 and -35.0mm vs -11.3, -14.8, -15.5 and -19.0mm respectively). Overall the treatment effect was estimated to be -15.1mm (95% CI: -19.2 to 11.0, p<0.0001). The median time to pain relief was shorter than that for the placebo group, 4 min (95% CI: 2.0 to 5.0) vs 10 min (95% CI: 5.0 to 12.0). The use of rescue medication (as requested by the patient) in the placebo group was significantly higher than in the methoxyflurane group (16.8% vs 1.3% for placebo and methoxyflurane respectively). Penthrox has been used in Australia for 40 years and the adverse effect profile indicates that methoxyflurane is relatively benign.

The Committee discussed the ethical justification of a placebo-controlled trial for patients in pain secondary to fractures, burns, dislocations or contusions; however were satisfied that the device provided pain relief which was similar in magnitude to currently available Entonox (50% nitrous oxide and 50% oxygen), a view that was supported by a low quality indirect comparison.

The budget impact is difficult to estimate as the number of eligible patients is largely unknown; other Trusts in London spend between £500 and £1,000 per month on Penthrox, therefore the budget impact across the 4 A&E departments in NCL is expected to be £24,000 to £48,000 per annum.

The Committee heard from clinical experts, Dr Johal, Dr Costello and Dr Elkhodair, who all had experience of using the device whilst working abroad, that Penthrox is associated with a high level of patient satisfaction, due to the rapid 'time to administration' and the patient controlled nature of the device. Experience at the Royal London is that it reduces the time to discharge for patients presenting with a dislocated shoulder; the Committee were told that Penthrox allows a discharge within 15 minutes compared to intravenous morphine or propofol which requires a recovery time of 4-6 hours. It was unclear how it compared with Entonox in this scenario. Penthrox may also be useful for patients who await intravenous analgesic or sedative; for example if a patient requires joint immobilisation, however use this is outside the indication being considered. Anecdotal reports indicated both Penthrox and Entonox were at risk of being misused, although this may be more likely with Entonox. The time required to locate the various parts to administer Entonox (face mask, tube, cylinder) was a disadvantage of this therapy, in addition to being contraindicated in people with pneumothorax or an air embolism. However, not all Emergency Departments have experience these issues with Entonox. Penthrox does not have these disadvantages although is contraindicated in patients with significant renal impairment, respiratory depression or cardiovascular instability.

In camera, the Committee agreed Penthrox might be therapeutically suitable for patients presenting with dislocated shoulder. However its treatment effect in the STOP! study was typical of a weak analgesic (like paracetamol) and some members of the Committee were sceptical that it would be potent enough for shoulder dislocation. It was also unclear why Entonox was unsuitable for these individuals. There were concerns about the risk of 'prescribing creep' in the Emergency Department, leading to inappropriate and costly use (as has happened with IV paracetamol). The Committee considered the proposed RFL pilot but agreed there was no clear benefit to the proposal; the treatment effect of Penthrox is known from available data, a pilot of 50 patients would be unlikely to yield meaningful results given the lack of a comparator arm (particularly if split across multiple indications) and furthermore, the busy environment of an A&E department was unlikely to be conducive a high quality audit in the absence of dedicated research staff. The Committee took the view that the value of a pilot would be to confirm prescribing was limited to the approved indications however this offered no reassurance that use would not increase after the review date. UCLH had successfully implemented an A&E pilot in the past, with the key objective to control use of a specific medicine; however this involved putting the drug into the CD register/cupboard – an approach which would be inappropriate for Penthrox. In summary, the analgesic benefit of Penthox was considered small, with a similar treatment effect to Entonox therefore the likely budget impact of £24,000 per annum was unjustified.

Decision: Not approved

8.2 Apalutamide (unlicensed; patient-access scheme) for non-metastatic castration resistant prostate cancer (Applicant: Dr H Payne, UCLH)

The Committee considered an application to use apalutamide for non-metastatic Castration Resistant Prostate Cancer (nmCRPC) under a patient-access scheme funded by Janssen-Cilag.

The SPARTAN study (n= 1207), a Phase III, double-blind, placebo-controlled study evaluated the efficacy and safety of apalutamide in nmCRPC. Apalutamide was shown to be superior to placebo in terms of the primary endpoint, metastasis-free survival, with a median improvement of 24.3 months (HR 0.28 [95% CI: 0.23 to 0.35]. There were also improvements in more clinically meaningful secondary endpoints; time to symptomatic progression (HR 0.45 [95% CI: 0.31 to 0.64]) and a non-significant but favourable effect on overall survival (HR 0.70 [95% CI: 0.47 to 1.04] – data immature). There was no difference in patient reported quality of life between groups (FACT-P, EQ-5D-3L). The incidences of severe and non-severe adverse effects were higher with apalutamide than placebo.

The Committee heard from Dr Payne that an exploratory end point of second progression free survival (time from randomization to disease progression during the first subsequent treatment for metastatic CRPC or death) was improved in the apalutamide group (HR 0.49 [95% CI: 0.36 to 0.66]) which suggests the introduction of apalutamide at the nmCRPC stage may delay time to further disease progression or subsequent treatment further down the treatment pathway.

The Committee enquired why apalutamide (an unlicensed medication) should be considered when licensed enzalutamide is available. Dr Payne explained that enzalutamide is not licensed or approved by NICE for the indication of nmCRPC whereas apalutamide was currently available free-of-charge for this indication. Dr Payne confirmed enzalutamide would not be offered to patients who progress on apalutamide as both drugs have the same mechanism of action. Janssen-Cilag has confirmed all patients enrolled in the patient-access scheme would continue to receive free-of-charge apalutamide until disease progression or death. The scheme would remain open until product licensing; expected April 2019.

In camera, the Committee considered the relatively small (non-significant) benefit on overall survival and the potentially high list price of apalutamide (as assumed to be similarly priced to enzalutamide). In these circumstances it is feasible that apalutamide would not be considered cost-effective by NICE and the Committee considered whether approving this scheme would create difficulties in the long term if NICE did not recommend the medicine. It was proposed NHSE should be asked to comment on whether they supported the application. On balance, the Committee agreed the benefits of the scheme outweighed the hypothetical future risks. In summary, the Committee approved apalutamide for non-metastatic prostate cancer (nmCRPC) while it remained available under a manufacturer funded patient-access scheme.

Decision: Approved
Prescribing: Secondary care only
Tariff status: Funded by manufacturer via patient access scheme
Funding: Funded by manufacturer via patient access scheme
Fact sheet or shared care required: No

Post meeting note: NHSE confirmed verbally that patient-access schemes were not considered problematic provided they were not co-administered with other NHSE commissioned high-cost therapies.

8.3 Progesterone (Utrogestan®) for hormone replacement therapy (HRT) (Applicant: Dr M Davies + Dr V Talaulikar (UCLH))

The Committee considered an application to use Utrogestan® (micronised progesterone) for the management of menopausal symptoms or low bone mass in women with premature ovarian insufficiency or natural menopause, specifically, progestogenic opposition as part of oestrogen + progesterone HRT.

The Committee considered the risk benefit of Utrogestan compared to progestins (synthetic progestogens) in terms of efficacy, namely prevention of uterine hyperplasia, and safety, namely breast cancer risk and venous thromboembolism (VTE) risk. The current first-line progestins are norethisterone and dydrogesterone.

In terms of efficacy, the Committee heard data from short-term randomised controlled trials (PEPI trial and REPLENISH trial) identified no increased risk of uterine hyperplasia with Utrogestan compared with progestins, however this contrasts with findings from larger, longer-term, cohort studies. The E3N study identified that, compared with never use of HRT, use of estrogen + micronized progesterone was associated with an increased risk of endometrial malignancy whereas use of estrogen + dydrogesterone was not. The EPIC study identified that, compared with never use of HRT, use of estrogen + micronized progesterone was associated with an increased risk of endometrial malignancy whereas use of estrogen + 'progesterone derivative' was not. The Committee hypothesised the reduced efficacy may be due to reduced compliance in estradiol/Utrogestan users because there are two separate components to their HRT. The Committee heard from Dr Talaulikar that this risk did not apply in his clinical practice as

sequential combined HRT is used only short term (max 3 years) before the patient progresses to continuous combined HRT which does not have the same compliance challenges.

When considering breast cancer risk, there were no head-to-head studies comparing Utrogestan to different progestins. The Committee reviewed data from E3N, a case-controlled cohort study, which reported the risk of breast cancer risk varying according to the type of progestogen: compared with never-users, the relative risk was 1.00 (95% CI: 0.83 to 1.22) for oestrogen plus Utrogestan, 1.16 (95% CI: 0.94 to 1.43) for oestrogen plus dydrogesterone and 1.69 (95% CI: 1.50 to 1.91) for oestrogen combined with other progestogens (primarily norethisterone and medroxyprogesterone).

When considering VTE risk, there were no relevant head-to-head studies. The E3N study found no significant increase in risk of VTE with progesterone, pregnane derivatives [inc. dydrogesterone and medroxyprogesterone acetate] or nortestosterone derivatives [inc. norethisterone], when compared with 'never users' however there was an increased risk with norpregnane derivatives [inc. nomegestrol].

The Committee heard NICE does not make any recommendation for one progestogen over another, furthermore NICE produced two 'recommendations for research' and Dr Davies (UCLH) has written a grant application for a trial to satisfy these research recommendations (cohort: premature ovarian insufficiency). Dr Talaulikar commented that NIHR funding could not be guaranteed as women's health is commonly not a priority for funding.

In terms of incremental cost, Utrogestan would cost an additional £16.30 per patient per annum using sequential combined HRT and an additional £29.96 per patient using continuous combined HRT. It is estimated 4,890 women use HRT in NCL therefore Utrogestan could cost an additional £120,000 per annum.

The Committee heard from Dr Talaulikar that the primary reason for applying for Utogestran is the associated reduction in minor adverse effect compared with progestins; these include bloating, fluid retention and mood lowering. The additional benefits in terms of the potential reduction in breast cancer risk also beneficial; Dr Talaulikar acknowledged the limitations of the data however took the view that Utrogestan was better than progestins as a group. The primary concern for women suffering the symptoms of menopause is the risk of breast cancer; some women choose to delay starting HRT due to these concerns leaving them symptomatic. There is therefore an incentive to approve a medicine that may reduce the risk. Dr Talaulikar confirmed that Utrogestan, and HRT more generally, would be appropriate for GPs to initiate.

In camera, the Committee agreed the substantial budget impact warranted a high degree of decision certainly in order to approve Utrogestan. The Committee was unable to accept anecdotal evidence of improved tolerability. The Committee considered that when relying on observational data, the absolute treatment effect between proposed and current practice needs to be very large before being considered unequivocal. In the case of Utrogestan and dydrogesterone, the differences in risk were small and at risk of confounding, and were therefore considered hypothesis generating. The Committee fully supported Dr Davies's bid for NIHR funding for a randomised-controlled trial to provide the necessary data to inform this decision. If NICE and NIHR considered a trial to be ethically justifiable then the choice between Utrogestan and dydrogesterone/norethisterone is at equipoise. In summary, the Committee considered the observational data hypothesis generating and therefore a claim of superiority between Utrogestan and dydrogesterone/norethisterone was unproven. The incremental cost associated with Utrogestan was therefore considered unjustified.

Decision: Not approved

9. Evidence to support the interchangeability of generic glatiramer (Brabio®) with the branded version (Copaxone®) for the treatment of relapsing forms of multiple sclerosis

The Committee reviewed the Specialist Pharmacy Service review of Brabio, a hybrid generic medicine of glatiramer. The Committee agreed with the SPS conclusion that there is robust evidence from a well-conducted clinical trial which supports the case for switching patients from branded to generic glatiramer as a means of reducing costs without compromising safety of effectiveness.

Dr Bodalia informed the Committee that UCLH Neurology Department supported the switch and were preparing to transition existing patients to Brabio. The Committee supported the view that the best value version of glatiramer should be prescribed, the total cost includes drug acquisition and homecare drug delivery costs.

Decision: Approved

Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: NHSE
Fact sheet or shared care required: No

10. **Guideline for approval: NEL/NCL Ozurdex® (dexamethasone intravitreal implant) in Non-infectious Uveitis Pathway**

The Committee reviewed the Ozurdex pathway for non-infectious uveitis which had been developed jointly by MEH and NCL Commissioners. NEL CSU commented that the recommendation to repeat the dose "4-6 monthly" was inconstant with the NICE TA and SPC which both specified "6 monthly". Ms Kassam explained that the recommendation to consider re-dosing from 4 months was consistent with the evidence-base as patients can lose response from this time point. Ms Kassam and NEL CSU agreed to resolve this query off-line and resubmit a revised version to the Committee.

11. **Position statement and Patient FAQ for FreeStyle Libre 'flash glucose monitor'**

The Committee approved the revised position statement which consistent with the LPP/LDCN advice for the implementation of Freestyle Libre across London, subject to a single amendment "Patients will receive their first supply from their diabetes specialist team with prescribing responsibility transferred to GPs *if the diabetes specialist team feel this is appropriate and the GP is in agreement*".

Post-meeting note: Uploading the revised position statement and Patient FAQ will be delayed until the NCL Freestyle Libre implementation group agree responsibilities for prescribing.

12. **Next meeting**

Monday 18 June 2018, G12 Council Room, South Wing, UCL, Gower St. WC1E 6BT

Post-meeting note: Room change to Haldane Room, Wilkins Building, UCL, Gower Street, London, WC1E 6BT

13. **Any other business**

Nil