North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 25 May 2017
Conference Hall, St Pancras Hospital Conference Centre, 4 St Pancras Way, London, NW1 0PE

Present:	Dr R Sofat	UCLH, DTC Chair	**(Chair)**
	Ms W Spicer	RFL, Chief Pharmacist	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Mr T James	MEH, Chief Pharmacist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Ms H Mehta	NMUH, Formulary Pharmacist	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Mr S Richardson	WH, Chief Pharmacist	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
In attendance:	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Mr J Minshull	NCL JFC, Support Pharmacist	
	Dr A Smaje	UCLH, Clinical Pharmacology SHO	
	Mr A Barron	NCL JFC, Support Pharmacist	
	Dr J Fullerton	UCLH, Clinical Pharmacology SpR	
	Dr N Zarate-Lopez	UCLH, Gastroenterologist	
Apologies:	Dr R MacAllister	NCL JFC Chair	
	Prof L Smeeth	NCL JFC Vice-Chair	
	Ms K Landeryou	Patient Partner	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Dr V Thiagarasah	Enfield CCG, GP Clinical Lead Medicines Management	
	Dr A Bensal	Barnet CCG, GP Clinical Lead Medicines Management	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr E Boleti	RFL, Consultant Medical Oncologist	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr P Hyatt	NMUH, DTC Chair	
	Dr S Shaw	RFL, DTC Chair	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Prof D Robinson	UCLH, Consultant in Respiratory Medicine	
	Prof A Tufail	MEH, DTC Chair	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms M Kassam	MEH, Formulary Pharmacist	
	Dr R Fox	RNOH, DTC Chair	
	Dr M Kelsey	WH, Chair DTC	

2. Meeting observers

Dr J Fullerton and Dr A Smaje were welcomed as observers to the meeting.

3. Minutes of the last meeting

The minutes were accepted as accurate.

4. Matters arising

Mr Minshull informed that Committee that bevacizumab for pre-operative adjunct to diabetic vitrectomy was incorrectly recorded as under evaluation in the April JFC minutes. This will be corrected to state that it has been ratified for use at MEH only (not under evaluation).

5. Declarations of relevant conflicts of interest

There were no declarations of interest.

6. Local DTC recommendations / minutes

6.1 Approved by local DTC

DTC site	Month	Drug	Indication	JFC outcome
RFL	Oct-16	Iron(III) isomaltoside (Monofer)	Intravenous iron of choice for patients who require rapid iron administration due to capacity issues or certain pathways e.g. pre-op (replaces ferric carboxymaltose [Ferinject])	Added to NCL Joint Formulary – individual Trust to make local decisions on parenteral iron
RFL	Apr-17	Riociguat	Pulmonary Arterial Hypertension, in line with the NHSE Commissioning Policy (16055/P)	RFL only
RFL	Apr-17	ProHance	Contrast enhancement in MR imaging	Added to NCL Joint Formulary
RFL	Apr-17	Atezolimumab EAMS	Advanced or metastatic bladder cancer that has progressed following platinum based chemotherapy	Added to NCL Joint Formulary[†]
UCLH	Mar-17	Pneumovax II and Menitorix	Test vaccination to diagnose or exclude antibody deficiency including CVID and SAD	UCLH only
UCLH	Mar-17	Venetoclax (compassionate access scheme)	Chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor. CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor	UCLH only
UCLH	Mar-17	Ruxolitinib	Steroid refractory acute graft versus host disease (GVHD)	Added to NCL Joint Formulary – subject to IFR/compassionate access

[†] Atezolimumab EAMS has now closed to recruitment.

6.2 Deferred by local DTC

DTC site	Month	Drug	Indication	JFC outcome
RFL	Apr-17	Obeticholic acid EAMS	Primary biliary cholangitis	Deferred

7. New Medicine Reviews

7.1 Lidocaine 2% and adrenaline 1:200,000 epidural 'top-up' for emergency caesarean section (Applicant: Dr S Makinde, WH)

The Committee reviewed an application for the use of lidocaine 2% plus adrenaline 1:200,000 (Fast Mix) when converting labour epidural analgesia to surgical anaesthesia for an emergency C-section. The Committee was informed that this is already used in practice at UCLH as part of a strategy of 'Saving Mothers Lives'. In June 2013, the JFC had ratified a WH DTC decision to use lidocaine 2% and adrenaline *with sodium bicarbonate 8.4%* for the same indication. Since the approval, the preservative free formulation of sodium bicarbonate 8.4% has been discontinuation and therefore no longer suitable to include in the mixture. The Committee noted that the additional benefit from the sodium bicarbonate was unclear, although it was included within some mixtures within the evidence review which had shown to reduce the onset time.

The Committee considered the evidence from a meta-analysis of eleven RCTs (n=779 participants) (Hillyard *et al*, 2011). A specific sub-group of this analysis included the intervention lidocaine 2% *plus* adrenaline 1:200,000 (+/- fentanyl), which resulted in a faster onset of surgical block compared to the other local anaesthetic choices (MD – 1.66 minutes, 95% CI -2.4 to -0.91 minutes, p <0.0001). When a trial accounting for a marked heterogeneity was removed from the analysis, the time to onset of block was improved further (MD -4.51 minutes, 95% CI -5.89 to -3.13 minutes, p<0.00001). Although safety and quality were poorly reported, there was no difference between top-up mixtures in rate of vomiting, cardiovascular outcomes, hypotension, Apgar score or cord gases.

The Committee also considered audit results from UCLH following implementation of lidocaine + adrenaline Fast Mix compared with a historic dataset (four year average pre-implementation) where 0.5% bupivacaine was used. The outcomes associated with Fast Mix were: reduction in onset time to achieve surgical anaesthesia; faster onset of regional block (avoiding need for general anaesthesia which carries greater risk); and 22% reduction in general anaesthesia for emergency caesarean section.

Dr Ishaq explained that the rationale behind this application was safety, with the applicant wanting to switch from using four 5 mL lidocaine vials to using one 20 mL vial to prepare the top-up anaesthesia in order to reduce the risk of incorrect preparation, and reduce the preparation time. It was noted that this was associated with a negligible cost difference and in place at UCLH.

In summary, the Committee approved the use of a combination of lidocaine 2% and adrenaline 1:200,000 for epidural 'top-up' for emergency caesarean section.

Decision: Approved
Prescribing: Secondary care only
Tariff status: In tariff
Funding: Hospital budgets
Fact sheet or shared care required: No
Audit required: No

7.2 Calcipotriol and betamethasone cutaneous foam (Enstilar®) for psoriasis [APPEAL] (Applicant: Dr S Wolfman, Barnet GP)

The Committee heard an appeal for calcipotriol and betamethasone cutaneous foam (Enstilar®) for trunk and limb psoriasis, in line with the ToR.

The Committee rejected an application for Enstilar in February 2017 due to the following concerns:

- Single-blinded study with subjective primary outcomes
- Inadequate explanation as to how two excipients created such a large treatment effect
- Concerns over the power calculation (not referenced, assumed a large treatment effect)
- Concerns over combination products increasing likelihood of patients applying prolonged courses of topic corticosteroids
- Positive budget impact

The Phase II and Phase III studies were both investigator-blinded with subjects blinded to whether the product was active or vehicle; the trial design therefore did not minimise the risk of bias in favour of a foam formulation. The Committee stated a preference for a double-blind, double-vehicle trial design. When considering vehicle gel/ointment vs. vehicle foam; the Phase II data showed preference towards

the ointment, whereas Phase III data showed preference to foam. The risk of bias in favour of the foam formulation therefore could not be excluded.

The manufacturer claim Enstilar is superior to Dovobet because the excipients create a supersaturated environment, which optimises drug absorption. An expert in topical drug delivery was consulted to review the Enstilar pre-clinical paper published in an open-access journal without an impact factor (Lind et. al 2016). The expert confirmed supersaturation was a recognised method to increase topical drug absorption however it was unclear whether DME and butane (the two additional excipients) created the required protective supersaturate environment. The pre-clinical study did not include the appropriate tests to prove supersaturation, however the study did prove, albeit with some methodological weaknesses, that higher concentrations of active agents were identified in the skin when using Enstilar, compared with Dovobet ointment. The expert stated it was more likely that the rapid evaporation of DME and butane results in 'dose dumping' (not supersaturation) which forces a higher concentration of drug into the skin was the mechanism of enhanced drug absorption. The higher drug concentrations were confirmed in a Phase I study which found Enstilar was more potent than Dovobet ointment, whilst remaining a Class III corticosteroid.

The manufacturer provided references to support the power calculations used in the Phase III study. The Committee heard Dovobet **ointment** was the true comparator therefore a decision to change from ointment (Phase II study) to gel (Phase III study) was cause for concern. There were no published non-inferiority studies of Dovobet gel vs. Dovobet ointment therefore the Committee assumed Dovobet gel (the newer formulation) was unable to demonstrate non-inferiority and subsequently the relative treatment effect of Enstilar would be exaggerated in the Phase III study. The Committee discussed the power calculation in the Phase III study; by using an absolute treatment effect of 18.3% the study had a smaller sample size than if the Phase II results were used (11.6%), this created the possibility the Phase III study was underpowered, returning a false-positive result. The decision on whether the Phase III study is underpowered requires a judgement call on whether Dovobet gel is inferior to Dovobet ointment (and it was correct to use 18.3%) or not (and if 11.6% should have been used). Moreover it is well known that a first trial of any drug often overestimates real treatment effects

The Committee had concerns over patients using prolonged courses of topical corticosteroids and it was agreed the applicant should support NCL to develop a treatment pathway, which promoted the use of separate corticosteroids and Vitamin D analogues as 1st line therapy.

The Committee reviewed the gram/week usage of Enstilar in the Phase III study and found higher use was observed during the initial few weeks before returning to the same level as Dovobet; an identical pattern was observed for foam vehicle suggesting that the higher usage was associated with the novelty of the product, rather than a requirement for higher doses. The budget impact estimate was consequentially lowered.

In summary, the Committee agreed the quality of evidence was low and there was a high risk of bias in favour of Enstilar. The Committee accepted the pre-clinical data indicating higher drug absorption (although not the proposed mechanism), which explained the higher steroid potency observed in the Phase I study and a proportion of the treatment effect in the Phase II and III studies. When considering the limited experience with Enstilar, the comparatively unknown adverse effect profile, and the likelihood of Enstilar being more potent that Dovobet, the Committee agreed that Enstilar should be added to the NCL Joint Formulary for trunk and limb psoriasis as third-line therapy after failure of 1st line separate corticosteroid + vitamin d analogue and 2nd line Dovobet ointment. The approval was conditional on an NCL Primary Care Psoriasis formulary being developed and generic calciprotriol/betamethasone ointment remaining similarly priced to Dovobet ointment (Drug Tariff Category C).

Decision: Approved
Prescribing: Primary and secondary care
Tariff status: In tariff
Funding: GP and hospital budgets
Fact sheet or shared care required: No (although Primary Care guidance on psoriasis is requested)
Audit required: No

7.3 Linaclotide for moderate to severe irritable bowel syndrome with constipation (IBS-C) [APPEAL] (Applicant: Dr N Zarate-Lopez. UCLH)

The Committee heard an appeal for the use of linaclotide in the management of irritable bowel syndrome with constipation. The Chair welcomed Dr Zarate-Lopez to propose and answer questions about this appeal. Mr Minshull reminded the Committee that when the evidence for this medicine was reviewed in March 2014, it was acknowledged that it appeared to be more effective than placebo at increasing the number of bowel movements and at reducing pain than placebo, but had not approved the drug due to the following reasons, which were discussed at this meeting:

1. No studies have compared linaclotide to existing treatments. Dr Zarate-Lopez acknowledged that no new clinical trials had been conducted comparing linaclotide in a head to head manner with other treatments.
2. The trial population differed from the refractory population detailed in the application. Dr Zarate-Lopez explained that patients included in the clinical trials did reflect the group of patients that linaclotide would be used in, as the trials allowed patients on stable laxative regimens to continue receiving these during the linaclotide trial.
3. Many of the patient's symptoms are psychogenic in nature, therefore the unknown long-term risks are a concern. Dr Zarate-Lopez explained that both antidepressants (off-label) and psychologist input are options for the management of IBS. These would be considered where thought to be appropriate for the individual patient. Off-label antidepressant would be considered following use of linaclotide because patients are unhappy to take antidepressants for what they perceive to be an unrelated condition.
4. Diarrhoea occurs in 19.8% of patients (compared to 3% placebo). The Committee heard that the proportion of patients discontinuing treatment due to diarrhoea (5%) or reporting severe diarrhoea (2%) were much lower.

The Committee acknowledged that although linaclotide in included within NICE Clinical Guideline 61, it is referenced as a "weak recommendation" where optimal or maximal tolerated doses of previous laxatives from different classes have not helped, and where constipation has been a problem for at least 12 months. The Committee acknowledged that NICE had considered the same clinical trial evidence as the JFC in March 2014.

Agreeing criteria to determine success or failure of linaclotide, should it be approved, was identified as an important step. Dr Zarate-Lopez agreed that maintaining careful selection of patients eligible to receive this treatment would prevent indication creep. Linaclotide would be considered when two laxatives (from different classes) and an antispasmodic (at optimal doses) have failed to alleviate the symptoms. Dr Zarate-Lopez explained that both increase in bowel motions and a reduction in pain were important patient-related outcomes considered in the clinical trials. The Committee noted that the European Medicines Agency end-point considered in March 2014 was a composite of reduced abdominal pain and increased complete spontaneous bowel motion, which linaclotide demonstrated with statistically superior efficacy to placebo. In its critique of the linaclotide data, NICE reported that reduction in pain was not clinically significant. Considering this, Dr Zarate-Lopez agreed that linaclotide should not be considered in patients who have relief of pain without improvement in complete spontaneous bowel motions.

The Committee questioned whether initiating linaclotide in primary care would lead to a reduction in the need for referral to specialist gastroenterology services, or a reduction in use of psychological therapies. It was acknowledged that there was no evidence that this would be the case, as some patients with severe symptoms will still require psychological input.

As the Committee was unable to reach a unanimous decision if or how to approve linaclotide, a vote was taken:

Approved for primary and secondary care initiation	Zero
Approved for secondary care initiation and continuation in primary care with a Fact Sheet	Six (including Chair's casting vote)
Approved under evaluation	Five
Rejected	Two

In summary, the Committee approved linaclotide for the management of IBS-C in adults where two optimally dosed laxatives (from different classes) and an antispasmodic fail to relieve symptoms. Initiation should be by a Gastroenterologist and reviewed at 4 weeks. Prescribing should be transferred to GPs for ongoing prescribing if found to be effective. The Committee acknowledged that the evidence base was weak, but welcomed the potential to offer this difficult to manage cohort an additional treatment option. A Fact Sheet should be developed to support GPs with monitoring of ongoing efficacy and to support discontinuation where necessary.

Decision: Approved
Prescribing: Initiation in secondary care, continuation in primary (supported by GP Fact Sheet)
Tariff status: In tariff
Funding: GP and hospital budgets
Fact sheet or shared care required: Yes
Audit required: No

8. Bisphosphonate treatment duration in women [for approval]

Mr Minshull noted that he had received a number of comments before the JFC meeting, which he is working through. The Committee agreed that the document can be approved via Chair's action following satisfactory resolution of these comments.

9. Low clinical value list

Mr Minshull presented a paper on Low Value Prescription Items, which have been identified by NHS England and NHS Clinical Commissioners as an opportunity to save £128million across England. The specific areas identified for review were co-proxamol, omega-3 fatty acids, lidocaine plasters, rubefacients, liothyronine, daily tadalafil, doxazosin MR, fentanyl immediate release preparations, gluten free food, and travel vaccines. The Committee acknowledged the importance of Joint Formulary Committee endorsing each of the clinical areas as a clinically effective opportunity for cost-avoidance. Ms Clarke informed that Committee that additional areas are likely to be identified for review by NHS England, including use of dosulepin and complimentary medicines.

The Committee agreed that each of these clinical areas represents a valuable opportunity to reduce inefficient prescribing in NCL. It was agreed that there is a mix of primary and secondary care initiated prescribing, therefore implementation may need collaboration across the sectors.

Action: JM to present this paper at NCL Medicines Optimisation Committee to agree an implementation plan for each clinical area identified.

10. Midazolam Fact Sheet

The Committee approved the Fact sheet.

11. JFC Work plan

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

12. Next meeting

Thursday 29 June 2017, G12 Council Room, South Wing, UCL, Gower St. WC1E 6BT

13. Any Other Business

Nil