North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Monday 18 March 2019
LG01, 222 Euston Road, London, NW1 2DA

Present:	Dr R MacAllister	NCL JFC Chair	**(Chair)**
	Dr R Woolfson	RFL, DTC Chair	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Dr M Kelsey	WH, DTC Chair	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Dr R Sofat	UCLH, DTC Chair	
	Mr S Semple	MEH, Chief Pharmacist	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Ms W Spicer	RFL, Chief Pharmacist	
	Dr K Tasopoulos	NMUH, DTC Chair	
	Mr S Richardson	WH, Chief Pharmacist	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Ms K Davies	NEL CSU, Deputy Director Medicines Management	
	Ms I Shaban	Islington, Deputy Head of Medicines Management	
	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	
	Dr S Yardley	CNWL, Consultant in palliative medicine [observer]	
	Dr M Samaan	UCLH, Specialist Registrar in Colorectal Medicine	
	Dr T Hillman	UCLH, Respiratory Consultant	
	Dr J Goldring	RFL, Respiratory Consultant	
	Dr S Cherian	UCLH, Respiratory Consultant	
	Dr Y Madani	UCLH, Respiratory SpR	
Apologies:	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	
	Dr A Sell	RNOH, DTC Chair	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Mr T Dean	Patient Partner	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Mr S Tomlin	GOSH, Chief Pharmacist	

2. Meeting observers

The Chair welcomed Dr Yardley (CNWL, Consultant in palliative medicine) as an observer of the meeting.

3. Minutes of the last meeting

The Committee agreed the following amendments:

- Approval of "methylphenidate" in NCL was amended to "methylphenidate MR" – brands approved include Equasym XL®, Medikinet XL® and Concerta XL®. In the case of Concerta XL®, four branded-generic products exist which feature the same dose and release profile as the originator. Concerta XL® will be included under work being undertaken at the Medicines Optimisation Committee on branded generic products to determine the most appropriate cost-effective product to use in NCL.
- Dexamethasone for second line treatment of asthma exacerbation was amended to recognise prescribing in primary care only occurs when initiated at WH
- Approval of Kyleena® was amended to note it was approved for first-line use
- Opicapone decision was amended to state it is initiated by neurologists at NHNN and RFL (i.e. initiated by departments able to offer advanced therapies) before continuation in primary care

The minutes were otherwise accepted as an accurate reflection of the meeting.

4. Matters arising

4.1 Sodium clodronate for adjuvant breast cancer

The committee considered written correspondence from Dr Newby outlining that NICE, CCO and ASCO recommend oral clodronate or IV zolendronic acid, rather than oral ibrandronate as there is less evidence to support its use. NICE/CCO/ASCO each identified the interim report abstract of the Phase III trial (NCT00127205) which indicated non-inferiority between oral clodronate, oral ibandronate and IV zolendronic acid however did not incorporate the findings into their guidelines due to the lack of a full publication.

The Committee agreed that where there was uncertainty about the risks and benefits of a new medicine, it was appropriate to delay decision making until the full results are published. In this case however the available evidence supported the *a priori* assumption of a class effect. The Committee upheld their previous decision to recommend ibandronic acid for adjuvant breast cancer as a second line oral alternative to IV zolendronic acid.

4.2 Diclofenac sodium injection (AKIS®) for acute peri-operative pain - feedback

In February, the Committee deferred a decision on diclofenac injections (AKIS®) until it was known how IV Voltarol® is administered in practice, whether this practice is safe and the budget impact assessment was updated.

JFC Support identified very low use of sodium bicarbonate 8.4% vials in NCL and received confirmation from WH, UCLH and RFL that IV Voltarol® was routinely added directly to a bag of Hartmann's (NMUH tending to use IM Voltarol rather than IV, which is given undiluted). In terms of establishing the safety of this off-label use, the Committee heard diclofenac is stable in pH 6.8-8.3 and the addition of Voltarol® to Hartmann's results in pH 6.5-7.5, therefore it was theoretically deemed stable. The Committee agreed IV Voltarol diluted in Hartmann's was clinically appropriate.

A representative of UCLH and LPP has spoken to the CMU and it has been agreed that AKIS® will have a national product code for contracting at the next available CMU tender (date is currently unknown). The Pharmaceutical Market Support Group (PMSG) advised that cost savings around buffer use, cannula and IV bag costs will be considered to determine if there is a true cost saving. The Committee agreed that since buffer usage is low in NCL, the contract price would need to favour AKIS® compared to IV Voltarol® diluted in Hartmann's. This decision will be deferred until the CMU national product code has been finalised.

Decision: Deferred (until after CMU work has completed)

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

No additional declarations to those noted in the drug application

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Feb-19	Tocilizumab	Supportive care of cytokine storm related to CAR-T cells	Decision: UCLH only Prescribing: Secondary care only Tariff status: Not routinely commissioned Funding: Trust Fact sheet or shared care required: No
UCLH	Feb-19	Lidocaine 1% injection preservative-free	Neonatal seizures	Decision: UCLH only Prescribing: Secondary care only Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

7.2 Not approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Feb -19	Tacrolimus	Chronic Histiocytic Intervillosities	Decision: Not approved

8. New Medicine Reviews

8.1 APPEAL: Intrapleural fibrinolytics (alteplase + dornase alfa) in complex pleural infection (Applicant: Dr Hillman, UCLH)

In June 2015 UCLH's UMC considered an application for the use of intrapleural alteplase and dornase alpha (t-PA + DNase) for the management of parapenumonic effusions in patients who are not clinically responding to conventional methods after 48 hours and are unsuitable for surgery. The application was based on evidence from the MIST2 trial, a study powered to demonstrate a difference in the change in pleural opacity between t-PA + DNase and placebo; important clinical outcomes (e.g. surgical rates and mortality) were secondary endpoints. A follow-up study, MIST3, was planned which was thought to be powered to detect an improvement in important clinical outcomes. UMC concluded that t-PA + DNase was relatively expensive, that a conclusive case had not been made owing to reliance on secondary endpoints and therefore encouraged the applicant to enrol patients in the MIST3 clinical trial.

The Committee considered an appeal against this decision, based on new observational data and an update to the MIST3 trial design.

The Committee reviewed the observational data; studies were generally small and did not include comparator groups. Studies did not consistently report resolution rates or outpatient chest drain rates however treatment success was mainly defined as survival and avoidance of surgery at discharge. Treatment success ranged from 67-93% and surgical referral rates post-treatment were 2-24%; this variability reflected differences between studies for the thresholds to begin intrapleural treatment, the thresholds for surgical intervention, dose, frequency and duration of treatment. Chest pain and intrapleural haemorrhage, sometimes necessitating RBC transfusion, were the most commonly reported adverse effects. Dr Hillman highlighted a multi-national observational series by Piccolo et al. 2014, which was considered previously at UMC in 2015, which reported a treatment success rate of 92.3%.

The Committee heard from Dr Hillman and Dr Goldring that treatment options for patients who are not fit for surgery were limited and there was a high unmet need for these individuals. Surgery itself is high cost (£5,500 per patient), high risk and associated with a long post-operation recovery period therefore there was a clinical rationale for avoiding surgery where possible. Approximately 30% of patients with parapenumonic effusions undergo surgery at UCLH and RFL and it was hoped t-PA + DNase would significantly reduce this number. The applicants confirmed t-PA + DNase is available in Oxford, Imperial, GSST and Cambridge hospital; but not in the Royal Brompton.

The Committee highlighted concern about the risks associated with intrapleural drug administration; Dr Hillman explained that nurses routinely flush and drain the chest tube with normal saline in a sterile fashion multiple times a day and are therefore experienced with this technique; however nurses do not

have experience with intrapleural administration of medication or monitoring of these treatments. Monitoring by an ST3 level doctor was proposed to be feasible if 12-hour administrations are arranged at appropriate times.

Dr Hillman explained that MIST3 is now designed to compare t-PA + DNase to surgery. The lack of a placebo arm reflects that t-PA + DNase is now considered standard of care for parapenumonic effusions. MIST3 will be undertaken in a limited number of centres and if feasible more sites will be included; recruitment has not yet begun. Neither RFL nor UCLH are eligible to be a centre for MIST3.

In camera, the Committee agreed the randomised controlled trial data for t-PA + DNase from MIST2 was inconclusive and that MIST3 was not designed to resolve this uncertainty. It was noted that prior to 2005, clinicians considered t-PA to be effective in avoiding surgery; the MIST1 trial subsequently proved this view to be inaccurate and led to a change in practice. It therefore seemed reasonable to be cautious before accepting that t-PA + DNase is now the care standard. However, observational data appeared to suggest treatment with t-PA + DNase was associated with surgical rates lower than at RFL or UCLH. The surgical rates at these two hospitals appeared to be static.

Balancing the need for non-surgical options, the decision uncertainty and the absence of forthcoming RCT data, the Committee agreed to approve t-PA + DNase under evaluation across NCL, subject to the following criteria being met at each site:

- Dr Hillman and Dr Goldring to develop an NCL protocol detailing inclusion criteria, stopping criteria, referral to surgery criteria, administration procedure and monitoring requirements. Staffing responsibilities should be explicitly stated and the Committee recommended that treatment should be led by a consultant rather than an ST3 grade doctor.
- Each site taking part in the evaluation should:
    - Use the NCL protocol (minor localisation permitted if required)
    - Submit baseline data for the number of patients with parapenumonic effusions who respond to IV antibiotics, those who require surgery and mortality
    - Commit to collecting this outcome for the next 12 months by providing an named responsible individual
    - Obtain DTC clinical approval to ensure all safety measures and funding approval is in place

Provided the following criteria are met, the Committee approved under evaluation t-PA + DNase for patients with ongoing sepsis in association with a persistent pleural collection, who have not responded to 12-24 hours of antibiotics and simple tube drainage, or there is radiological evidence (either on ultrasound and/or CT) that the effusion is unlikely to drain due to multiple loculation; rather than referring for surgical intervention.

Decision: Approved under evaluation (12 month)
Prescribing: Secondary care, consultant only
Tariff status: In tariff
Funding: Trust
Fact sheet or shared care required: No
Notes: The majority of trials use dornase alfa (DNase) 5 mg and alteplase (t-PA) 10 mg administered intrapleurally twice daily for up to 3 days. Administration was followed by clamping of the drain to permit the study drug to remain in the pleural space for 1 hour. One study used dornase alfa (DNase) 5 mg and alteplase (t-PA) 5 mg twice daily.

8.2 Budesonide multimatrix tablets (Cortiment®) for the induction of remission in mild to moderate ulcerative colitis (Dr S Bloom & Dr M Samaan, UCLH)

The Committee considered an application for the use of budesonide multimatrix tablets (Cortiment®) for the induction of remission in mild to moderate ulcerative colitis (UC) where treatment with mesalazine is not sufficient and patients have an intolerance or contraindication to prednisolone.

A Cochrane review from 2015 confirmed Cortiment® increased the probability of remission compared with placebo (RR 2.25; 95% CI 1.50 to 3.39); the treatment effect was found to be larger for combined left-sided ulcerative colitis and proctosigmoiditis (RR 2.98; 95% CI 1.56 to 5.67) but no statistical difference was found for extensive disease (RR 2.41; 95% CI 0.61 – 9.56). In terms of relevant comparative data, there were no studies comparing Cortiment® directly with oral prednisolone, however indirect comparisons indicate that Cortiment® is likely to be much less effective.

The results of ACTH stimulation tests by Rubin et al were presented which demonstrated a reduction in serum cortisol levels below the lower reference range after 8 weeks of use (22.3 µg/dl versus 15.6 µg/dl) demonstrating systemic absorption of Cortiment®. The budget impact of Cortiment® as a second-line therapy for 30 patients at UCLH was calculated as £5,000, with further patients anticipated to access this treatment across the region.

The Committee heard from Dr Samaan that oral prednisolone is the standard of care for patients with mild to moderate ulcerative colitis who have failed to respond to mesalazine, however many patients, particularly in their 20s and 30s, experience side effects (insomnia, weight gain, acne and mood disturbance). As a result of this there is a need for the availability of an alternative oral steroid preparation which is associated with a reduced risk of steroid-related adverse effects (the current alternative is a rectal preparation). Dr Samaan explained there was a potential inequity in the management of patients with UC and Crohn's disease as patients with Crohn's disease have access to modified release budesonide formulations (Entocort® or Budenofalk®) whereas patients with UC do not. It was confirmed by Dr Samann that Cortiment® less effective than oral prednisolone 40mg daily and therefore would not be offered to patients with severe UC. Following this point, the Committee queried whether a lower oral prednisolone dose could be prescribed to reduce the risk of adverse effects. Dr Samaan explained that the evidence-based dose for oral prednisolone is 40mg daily and clinicians would not habitually deviate from this recommendation.

In camera, the Committee reflected on an application for an identical cohort (see April 2015 minutes) for beclomethasone dipropionate (Clipper®). At this time, the Committee heard from the applicant that the modified-release formulation would reduce the risk of steroid-related adverse effects however a subsequently published RCT directly comparing Clipper® to oral prednisolone did not demonstrate such a reduction despite numerically lower remission rates and statistically lower change in CAI total scores. The supportive case for Cortiment® was considered weaker than that for Clipper® owing to the lack of relevant comparative data.

The Committee considered whether having modified-release budesonide available for Crohn's disease but not for UC created an inequity. The Committee was unable to comment on the appropriateness of the inclusion of Entocort® or Budenofalk® onto Trust formularies as the decisions predated JFC however the majority of members did not agree a claim of inequity could be made for different clinical indications. The Committee considered oral prednisolone to be the most appropriate comparator product and not rectal steroid preparations, as oral prednisolone is the product being replaced in therapy and used in all forms of UC that Cortiment® would be used to treat.

In summary, the Committee agreed that Cortiment® is less effective and more expensive than oral prednisolone. There are no direct or indirect evidence available to suggest Cortiment® would be associated with a lower risk of steroid-related adverse effects compared with an equi-effective dose of prednisolone. The decision to include Cortiment® onto the NCL Joint Formulary was placed to a vote; 2 voted in favour and 7 voted against the approval of Cortiment®.

Decision: Not Approved

8.3 Carboplatin and paclitaxel: Advanced squamous cell carcinoma of anus– first line therapy (Dr Goldstein, RFL)

The Committee considered an application *in absentia* for the use of carboplatin and paclitaxel for the first-line management of advanced squamous cell anal carcinoma without radiotherapy, treatment in this setting is palliative. The 2018 NCCN American guidelines recommend this combination with/without radiotherapy as one option for the first-line treatment of metastatic anal cancer.

The Committee considered an abstract of an ongoing, Phase II, international, multicentre, randomised, open-label clinical trial assessing the first line treatment of inoperable, locally recurrent or metastatic, squamous cell carcinoma of the anus (InterAACT trial). Eligible patients were randomised 1:1 to receive cisplatin and 5-fluroruracil (CDDP-5FU; current standard of care in NCL) or carboplatin and paclitaxel (CP). The CP regimen demonstrated a similar response rate to CDDP-5FU, with a trend to longer OS and median PFS, but less toxicity (reported serious adverse events: 62% vs. 36% p=0.016 in the CP and CDDP-5FU arm respectively). Quality of life was not reported in the abstract.

RFL and UCLH both participated in the ongoing InterAACT trial however the trial is not recruiting new patients and is estimated to complete in 2023. It is unlikely that a Phase III trial will be carried out, particularly in the immediate future.

The budget impact of switching chemotherapy regimens from CDDP-5FU would incur an additional £1000 to £1500 across NCL per annum, including VAT and production costs.

Anal carcinoma is a rare cancer and subsequently the available evidence to guide management was limited; typically small, single-centre, retrospective studies. The Committee therefore accepted the interim analysis abstract of a UK based RCT as sufficient for decision making and agreed to add carboplatin and paclitaxel for the treatment of patients with advance squamous cell carcinoma of the anus on to the NCL Joint Formulary.

Decision: Approved (first-line)
Prescribing: Secondary care
Tariff status: Local tariff
Funding: NHSE
Fact sheet or shared care required: No
Notes: Carboplatin AUC5 day 1 of 28 day cycles + paclitaxel 80 mg/m^2 on day 1, day 8 and day 15 of 28 day cycles. 6 cycles (each cycle 28 days).

9. Denosumab for the treatment of osteoporosis in renal impairment

NCL MOC identified an inconsistency in the prescribing of denosumab (Prolia®) between men and women with renal impairment and requested that JFC provide an evidence-based view.

Women with renal impairment currently have treatment continued in primary care in line with recommendations in the NCL Fact Sheet (although NICE TA204, which underpins the fact sheet, did not specifically assess renal impairment). By contrast, in October 2017, JFC agreed men with renal impairment (<35ml/min), should be treated in secondary care due to the risk of significant hypocalcaemia.

The Committee considered whether the baseline risk of hypocalcaemia was different between men and women with renal insufficiency and reviewed data from Dave et al (n=291), Krahenbule et al and Hyunh et al (n=151) which confirmed a correlation between renal impairment and hypocalcaemia but did not identity a clear association between gender and hypocalcaemia. One study did report an increased risk (OR = 5.19) however there was a lack of control of confounding variables, such as the dose, indication, and vitamin D or calcium supplementation.

Given the limited published evidence, consultants in NCL were engaged to seek their views – they agreed that gender would not affect the risk of hypocalcaemia, but were divided on whether treatment is best suited to primary care or secondary care.

The Committee agreed men and women with renal impairment should be treated in the same setting and given the lack of recall ability in primary care, prescribing and administration of denosumab in the secondary care setting was likely to be the safer option. The costs associated with funding outpatient activity to provide this care was not considered.

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

10. Annual report

The Committee were asked to provide feedback by Friday 29th March. If no substantive comments were received, the annual report would approved by Chair's action.

11. Melatonin Fact sheet

The melatonin fact sheet was presented to the Committee for ratification; the document was approved.

12. Update: ADHD Shared Care document

The ADHD shared care document was presented to the Committee for ratification; one minor amendment was noted prior to the meeting to add the names of branded-generic Concerta XL® to the document. Pending this minor amendment, the document was approved for use.

13. Update: Omega-3 fatty acid compound position statement

The omega-3 fatty acid compound position statement has been updated to reflect the JFC recommendations for the review of omega-3 fatty acid and the management of hypertriglyceridaemia. The document was approved.

14. **Update: NCL managing common infections in primary care**

The NCL managing common infections in primary care has been updated to incorporate recent NICE guidance. The guideline was approved.

15. **Inflammatory Bowel Disease (Crohn's and Ulcerative colitis) high-cost drug pathways – withdrawal of clinician support**

The Committee heard clinicians had withdrawn their support for these pathways owing to the restricted number of mechanisms of actions available for use. As concerns relate to commissioning, rather than uncertainty around the available evidence-base, Karen Davis agreed for NEL CSU to adopt the project from JFC Support. A meeting with key clinicians, JFC Support and NEL CSU had been arranged.

16. **UCLH UMC off-label review**

UCLH are conducting a review of existing off-label uses of medicines at the Trust to identify high-risk practice and ensure appropriate governance and safety processes are in place. The initial data gathering identified over 500 entries, from which the highest risk entries have been prioritised. The formulary team have developed a risk assessment tool which evaluates safety, evidence and governance and assigns a RAG rating on this basis. This will allow pragmatic, evidence-based decision making across the significant number of entries.

JFC approved the use of the risk assessment tool for decision making under this process and agreed to support the review and ratification of decisions made by UMC.

17. **Next meeting**

Monday 15th April 2019, 4.30 – 6.30pm, Venue: LG01, 222 Euston Road, London, NW1 2DA

18. **Any other business**

Nil