North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Monday 20 August 2018
Room 6LM1, Stephenson House, 75 Hampstead Rd, NW1 2PL

Present:	Dr R MacAllister	NCL JFC Chair
	Mr C Daff	NHS Barnet, Head of Medicines Management
	Ms P Taylor	Haringey CCG, Head of Medicines Management
	Ms L Reeves	C&I, Chief Pharmacist
	Mr T Dean	Patient Partner
	Dr R Sofat	UCLH, DTC Chair
	Dr F Gishen	RFL, Palliative Care Consultant
	Dr M Kelsey	WH, DTC Chair
	Mr S Semple	MEH, Interim Chief Pharmacist
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management
	Mr S Richardson	WH, Chief Pharmacist
	Ms R Clark	Camden CCG, Head of Medicines Management
	Dr A Sell	RNOH, DTC Chair
	Dr R Woolfson	RFL, DTC Chair
	Dr S Ishaq	WH, Consultant Anaesthetist
	Dr R Urquhart	UCLH, Chief Pharmacist
	Mr A Dutt	Islington CCG, Head of Medicines Management
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor
	Dr T Rashid	NHS Haringey, GP Clinical Lead Medicines Management
In attendance:	Mr A Barron	NCL MEP Lead Pharmacist
	Dr P Bodalia	UCLH, Principal Pharmacist
	Ms M Kassam	NCL JFC, Support Pharmacist
	Mr G Grewal	NCL JFC, Support Pharmacist
	Ms M McErlean	NCL MEP, Pharmacist
	Ms I Samuel	RFL, Formulary Pharmacist
	Ms K Saxby	UCLH, Formulary Pharmacist
	Dr S Ward	RFL, Consultant Intensivist
	Mr S O'Callaghan	UCLH, Formulary Pharmacist
	Dr J Fullerton	UCLH, Clinical Pharmacologist
	Dr JP Carter	UCLH, Academic F2 Clinical Pharmacology
	Dr S Aung	NMUH, Consultant Gynaecologist
	Dr M Shephard	UCLH, Consultant in Oral Medicine
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair
	Dr M Dhavale	Enfield CCG, GP Clinical Lead Medicines Management
	Ms K Delargy	BEH, Deputy Chief Pharmacist
	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
	Ms K Davies	NEL CSU, Deputy Director Medicines Management
	Dr D Hughes	RFL, Consultant Haematologist
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management
	Ms W Spicer	RFL, Chief Pharmacist

2. Meeting observers

Dr MacAllister welcomed Ms McErlean and Dr Carter as observers of the Committee and explained the role of Joint Formulary Committee in NCL.

Dr Bodalia introduced the Committee to two new members of the JFC Support team; Ms Kassam from Moorfields Eye Hospital and Mr Grewal from Croydon Health Services. Mr Barron had been appointed as a project lead for the NCL Medicines Efficiency Programme and would continue to provide support to JFC.

3. Minutes of the last meeting

Ms Samuel agreed to establish whether lidocaine infusion for chronic pain was approved for use at RFL.

Mr Barron agreed to establish whether a meaningful difference existed between the RFL and UCLH definitions of 'high risk PE' (i.e. those patients in whom catheter-directed thrombolysis for pulmonary embolism is contraindicated).

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

Post meeting note: Ms Samuel confirmed the minutes relating to lidocaine infusions for chronic pain should be updated to "Decision: RFL and UCLH only". Mr Barron confirmed there were no meaningful differences between the RFL and UCLH definitions of 'high risk PE'. The minutes and abbreviated minutes were updated to reflect these facts.

4. Matters arising

There were no matters arising from the minutes.

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

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	Jul-18	Regorafenib FOC scheme (whilst Bayer appeal against NICE TA514 decision)	Advanced hepatocellular carcinoma and has previously been treated with sorafenib	Decision: RFL only Prescribing: Secondary care only Tariff status: FOC Funding: Bayer FOC scheme Fact sheet or shared care required: No

8. New Medicine Reviews

8.1 Denosumab (Xgeva®; off-label) for malignant hypercalcaemia (Applicant: Dr A Sheri, RFL; Presented by: Dr J Fullerton, UCLH)

The Committee considered an application to use denosumab (Xgeva®) for patients with hypercalcaemia of malignancy who are either refractory to bisphosphonates or have creatinine clearance < 30mL/min in whom bisphosphonates are contraindicated.

Current management for malignancy hypercalcaemia involves rehydration with intravenous (IV) 0.9% sodium chloride and second-line IV bisphosphonates (typically zolendronic acid) for patients who do not adequately respond. Other treatment options include, calcitonin (short term efficacy only), cinacalcet (if parathyroid hormone driven), glucocorticoids (for lymphomas) or dialysis. Denosumab is unlicensed for hypercalcaemia of malignancy in the UK but was granted Orphan Drug designation by the FDA in 2015. Pharmacological therapy can transiently improve hypercalaemia however sustained maintenance of normocalcaemia requires eradication of the underlying malignancy.

There were no head to head comparisons of bisphosphonates vs. denosumab for this indication. Published experience of denosumab for hypercalcaemia of malignancy refractory to bisphosphonates was limited to 55 patients. The primary supporting evidence was a Phase II, prospective, single-arm trial of adults with cancer and hypercalcaemia refractory to bisphosphonates, defined as corrected serum

calcium levels of ≥ 3.0 mmol/L despite IV bisphosphonate treatment within 7 to 30 day (n = 33). All patients received denosumab 120mg SC on days 1, 8, 15 and 29, and then every 4 weeks thereafter. Results showed 64% reached corrected serum calcium ≤ 2.9mmol/L after a single dose by day 10 and 70% had achieved this outcome by the end of the study. The estimated median response duration was 104 days.

With regards to safety, the most commonly reported AEs were nausea (30%) and dyspnoea (24%). In the general population, hypocalaemia and hypophosphataemia are commonly experienced in addition to nausea, diarrhoea, dysponea, hyperhidrosis and musculoskeletal pain. Denosumab is associated with osteonecrosis of the external auditory canal with steroid use and chemotherapy identified as possible risk factors; patients should be advised to report ear pain, discharge from the ear, or an ear infection during denosumab treatment.

The application was heard in absentia however the applicant had responded to questions identified by Dr Fullerton in advance of the meeting. The Committee heard eligibility for treatment would be driven by serum corrected calcium cut-offs (>3 mmol/L) however the Committee took the view that the patient should have symptomatic hypercalcaemia to justify treatment. The applicant did not intended to use the dosing regimen in the Phase II study due to concerns of hypocalaemia, the proposal was to administer a single dose with a second dose offered if/when serum calcium levels rose again; the Committee agreed with this view. The Phase II paper reported 19% required retreatment due to rising serum calcium levels however the Committee heard multiple retreatments would only be required for those ineligible for systemic anticancer therapy including those requiring palliative care.

Denosumab (Xgeva) is not excluded from tariff and is not recommended for GP prescribing. Any impact on activity was considered to be inconsequential due to the small cohort number.

Oncologists in NCL anticipated approximately 19 patients requiring treatment annually, with a usual maximum of 2 doses per patient. The associated budget impact was therefore estimated to be £10,032. The Committee believed this to be an underestimate with a high risk of prescribing creep therefore asked JFC Support to monitor usage over the next 12 months.

In summary, the Committee agreed denosumab was effective for the proposed indication however should only be offered to patients with rising or symptomatic hypercalcaemia of malignancy. Denosumab (Xgeva) was added to the NCL Joint Formulary for the management of patients with symptomatic hypercalcaemia of malignancy, who are either refractory to bisphosphonates or have creatinine clearance < 30mL/min in whom bisphosphonates are contraindicated. Denosumab for this indication should only be prescribed on the advice of oncology or palliative care consultants.

Decision: Approved with additional restrictions and only on the advice of oncology or palliative care consultants
Prescribing: Secondary Care
Tariff status: In Tariff
Funding: Hospital budgets
Fact sheet or shared care required: No
Additional information: Usual dose is 120 mg STAT with a repeated dose offered for patients with recurring symptomatic hypercalcaemia. Repeated retreatments may be required for those ineligible for treatment of their underlying malignancy, including palliative care.

8.2 Dequalinium chloride 10mg vaginal tablets for treatment of bacterial vaginosis (Applicant: Dr S Aung, NMUH; Presented by: Mr S O'Callaghan, UCLH)

The Committee considered an application to use dequalinium chloride for treatment of bacterial vaginosis (BV).

Weissenbacher et al (n=321) report a phase III, single-blind, randomised, non-inferiority study in women with a diagnosis of BV, comparing dequalinium vaginal tablets 10mg daily for 6 days with clindamycin vaginal 2% cream daily for 7 days. Dequalinium resulted in a clinical cure rate of 81.5% in the per-protocol population, compared with 78.4% for clindamycin cream (treatment difference 3.1% [95% CI: –7% to +13%; p = 0.0004]) at 7 days following treatment, demonstrating non-inferiority within a pre-specified margin of 15%. Cure rates were also similar between groups 25 days after treatment (79.5% with dequalinium vs. 77.6% with clindamycin, 95% CI –8% to 12%), a secondary outcome for the study. There were no other significant or clinically meaningful differences in the secondary outcomes of the study or the reported adverse effects between the two groups.

It was noted that there were a number of limitations to the study including: a relatively wide non-inferiority margin of 15% with no justification provided; differences in formulations risked unblinding investigators and reporter bias; the follow up period was too short (25 days) to draw conclusions on dequalinium's effect on recurrence rates of BV; the primary outcome was based on a disease orientated criteria rather than patient reported improvement in symptoms; and dequalinium was not compared with other first-line treatments for BV such as oral/topical metronidazole.

Based on the current use of clindamycin intravaginal cream across NCL, a switch to dequalinium vaginal tablets could save approximately £4,500 per annum.

The Committee heard from Dr Aung who highlighted that BV is a common condition that affects women who are often reluctant to report symptoms. Dequalinium tablets offered an additional choice to patients for the treatment of BV, noting that intravaginal gels/creams can cause embarrassment during sexual intercourse and clindamycin cream can weaken latex condoms, however it was noted there was no differences in tolerability reported between groups in the above study.

Dequalinium is an antibiotic-sparing antiseptic agent however the Committee heard bacteria can develop resistance to antiseptic agents. The role of bacteria resistance is not well established in BV as re-occurrence was likely caused by failure to re-establish normal vaginal flora. Dequalinium favourably does not mask the diagnosis of gonorrhoea whereas clindamycin cream does.

In camera, the Committee agreed dequalinium was non-inferior to clindamycin cream in terms of efficacy and safety for the management of BV and offered advantages in terms of patient convenience, cost-minimisation and antimicrobial stewardship.

In summary, the Committee agreed to add dequalinium 10mg vaginal tablets to the NCL Joint Formulary for the management of BV as a second-line alternative to clindamycin 2% intravaginal cream in patients who have not tolerated or failed metronidazole treatment. It was agreed to consult with stakeholders within NCL as to whether clindamycin cream should be removed from the formulary

Decision: Approved
Prescribing: Primary and Secondary Care
Tariff status: In Tariff
Funding: GP and hospital budgets
Fact sheet or shared care required: No

Action: Mr Barron to consult with NCL Microbiologists and Gynaecologists on the proposal to remove clindamycin 2% vaginal cream from the NCL Joint Formulary.

8.3 Pilocarpine for the treatment of dry mouth (xerostomia) (Applicant: Dr R McMillan and Dr M Shephard, UCLH; presented by: Mr A Barron, NCL MEP)

The committee considered an application to use pilocarpine for the second-line treatment of xerostomia caused by Sjogren's syndrome or head and neck radiotherapy, for those who have not responded adequately to saliva substitutes.

Sjogren's syndrome

A 12-week, double-blind, randomised controlled study (n=72) compared pilocarpine to artificial saliva for patients with xerostomia and xerophthalmia caused by either primary or secondary Sjogren's syndrome. Patients were randomised to pilocarpine or artificial saliva, each at a dose of 10 drops three times daily (equivalent to pilocarpine 5 mg three times daily). At 12 weeks, both treatment arms had greater salivary flow, though the improvement was greater for pilocarpine. Symptom scores improved with pilocarpine and a greater proportion of patients on pilocarpine had no symptoms compared with artificial saliva (97% vs. 51%). Limitations of the study include the liquid formulation of pilocarpine and the restricted use of artificial saliva spray, which is normally for "PRN" usage.

A systematic review designed to compare pilocarpine to placebo identified relevant randomised controlled trials. The largest was a 12 week, three-arm study to compare 2 different doses of pilocarpine (2.5 mg and 5 mg 6 hourly) to placebo. There was a higher frequency of "global improvement of dry mouth" in the pilocarpine 5 mg group compared with placebo (week 6: 46% vs. 22% respectively; week 12: 61% vs. 31% respectively), though not in the 2.5 mg group. Patients were also more likely report specific improvements in mouth comfort (62% vs. 38%), decreased use of saliva substitute (53% vs. 20%) and ability to speak, sleep & swallow food without sipping water.

Head and neck radiotherapy

A systematic literature review and meta-analysis was undertaken to establish the efficacy of pilocarpine for radiation associated xerostomia and hyposalivation. Two placebo-controlled, randomised controlled studies were identified. Results identified that more patients randomised to pilocarpine achieved the meta-analysis primary outcome of 'reduction in xerostomia' compared to placebo (OR: 2.37 [95% CI: 1.43 to 3.94]).

A limitation of all three placebo-controlled studies (including Sjogren's syndrome and Head and neck radiotherapy) was the use of a VAS score with arbitrary cut offs to categories response; subsequently the effect size and the clinical significance of the 'response' is unknown.

In terms of safety, pilocarpine is contraindicated in patients with clinically significant cardiorenal disease, uncontrolled asthma and other chronic disease at risk for cholinergic agonists. Pilocarpine is associated with many symptomatic side effects including headache, sweating and increased urinary frequency. Based on an assumed cohort of 30 patients per year using a dose of 5 to 10 mg TDS, the budget impact was estimated to be £21,000 per year. The Committee heard pilocarpine is already established therapy at UCLH therefore the real budget impact of a positive recommendation was expected to be negligible.

The committee heard from Dr Shephard that EDH primarily treat patients with Sjogren's disease with objectively proven xerostomia. Patients tolerate saliva substitutes poorly and it is useful to offer an alternative. In terms of adverse effects, some patients using pilocarpine do not report any AEs whereas many report excessive sweating. Patients with intolerable AEs are told to reduce their dosage and, if side effects persist, to discontinue treatment. Pilocarpine is not used for patients who would be compromised by the use of a muscarinic agent (e.g. asthma). Consultants routinely counsel patients on side effects, when to reduce dose and discontinuation of treatment, and will review patients after 3 months to decide whether to continue treatment.

In camera, the committee noted that although pilocarpine is primarily used for Sjogren's syndrome at EDH and this is factored in their overall spend currently, approving the use of pilocarpine for radiation associated xerostomia may see a significant rise in overall spend throughout NCL. RFL also use pilocarpine for Sjogren's associated xerostomia, though this pre-dates the RFL DTC records. The committee agreed it was appropriate to limit the use of pilocarpine to EDH and RFL Rheumatology. It was considered reasonable for GPs to adopt prescribing after 1 month as the medicine is licensed for this indication, they were not expected to make an assessment of efficacy and could contact EDH for advice if required. Shared care or Fact sheet was inappropriate due to low patient numbers. In summary, pilcoparine was added to the NCL Joint Formulary for xerostomia (dry mouth), restricted to EDH and RFL Rheumatology.

Decision: Approved for use in EDH and RFL Rheumatology
Prescribing: Primary and Secondary Care
Tariff status: In Tariff
Funding: GP and hospital budgets
Fact sheet or shared care required: No

8.4 Pentoxifylline (off-label) for oral mucosal inflammatory disease (Applicant: Dr R McMillan and Dr M Shephard, UCLH)

The Committee considered an application to use pentoxifylline for recurrent aphthous stomatitis (RAS); a type of oral mucosal inflammatory disease. The proposed place in therapy was after failure of colchicine and dapsone (approved by JFC in April 2018) and before thalidomide.

A Cochrane review of systemic interventions for RAS concluded that no single treatment was found to be effective. One randomised, double blind, placebo-controlled trial compared the efficacy of pentoxifylline 400mg TDS to placebo. Patients with more than 2 ulcers per month who were not receiving treatment or willing to stop current treatment were eligible. Patients completed a 60 day ulcer diary to assess eligibility and those who remained eligible (n=26) were randomised to pentoxifylline or placebo for 60 days. Patients continued their ulcer diary during treatment and for 60 days after treatment. Results identified no significant differences between any of the outcomes recorded in the ulcer diaries, however all results trended in favour of pentoxifylline. There was no difference in the proportion of ulcer-free days (trial vs baseline) or subjective changes at day 120 (ie. "How do you think your ulcers have been while taking the medication vs 2 months before?"). A key limitation of the study was the lack of a power-calculation to inform the required sample size.

The committee considered the evidence from two open-label, single arm observational studies reporting the effectiveness of pentoxifylline in patients with RAS. The first study (n=24) included patients with a history of RAS > 1 year and failure to respond to topical therapies. Patients were asked to record the

number and duration of ulcers for 2 weeks before starting pentoxifylline 400 mg TDS for 4 weeks. Clinical examination occurred at 6 weeks. Results showed 58.3% had a 'great improvement', 4.2% had a 'slight improvement', 33.3% experienced 'no change' and 4.2% got 'worse'. The committee noted several limitations of this study; objectives were not clearly pre-specified, it was not clear how many ulcers were present at baseline which makes interpretation of the categorised results challenging, the number of outcomes reported were very limited, the time-point for assessment was unclear, treatment duration was short (4 weeks) and follow-up was short.

The second observational study (n=6) included patients with severe RAS. All patients used topical treatments for the 1st month, pentoxifylline 400mg TDS with topical treatment for the 2nd month, and PRN topical treatment for the 3rd month. Patients were asked to self-report the mean number of ulcers per week. Results highlighted a significant reduction in ulcers over 3 months ($p \leq 0.001$); the mean (±SD) ulcer count at Month 1 was 3.05 (±0.37), Month 2 was 1.69 (±0.51) and Month 3 was 0.20 (±0.23. A limitation of the study was the short term use of pentoxifylline which is not known to be a 'cure' for RAS and the lack of external validity with the double-blind study (this study report ulcer number per week reducing to nearly zero after 30 days of treatment however the double-blind study reports only a numerically small reduction in the ulcer number per episode [2.46 to 2.14 ulcers/episode] and number of episodes [4.86 to 4.00 episodes] after 60 days of pentoxifylline treatment).

EDH estimate approximately 15 patients per annum would be eligible for treatment. The catchment area for EDH extends beyond NCL therefore the budget impact was assumed to be £1163 for NCL.

In terms of safety, pentoxifylline is well tolerated with gastrointestinal adverse effects the most commonly reported AE (<5%). By contrast, thalidomide, which would be the next step in the treatment pathway is a relatively toxic intervention (very common AEs include neutropenia, leukopenia, anaemia, lymphopenia, thrombocytopenia, peripheral neuropathy, tremor, dizziness, paraesthesia, dysaesthesia, somnolence).

The Committee heard from Dr Shephard that the objective of treatment with pentoxifylline was to offer another option before considering thalidomide. Treatment would be initiated by a specialist and continued by the GP.

In camera, the Committee took the view that the randomised controlled trial was too small to identify a treatment effect and the quality of the open-label studies was too poor to inform decision making. The committee acknowledged that the place of pentoxifylline therapy was before the initiation of thalidomide, and that the potential adverse effects of pentoxifylline were favourable compared with thalidomide however in view of the effect that effective treatments were already available; the addition of non-evidence based pentoxifylline would inappropriately extend the treatment pathway for this condition.

Decision: Not approved

9. Ulipristal (Esmya®) for uterine fibroids

Following concerns about ulipristal induced hepatotoxicity in February 2018, the MHRA wrote to health professionals advising treatment should not be initiated in new users or those between treatment courses and liver function monitoring should be carried out in current or recent users of ulipristal acetate (Esyma®). In response, JFC removed the NCL shared care guideline, removed ulipristal from the NCL Joint Formulary and with support from Mr Fakokunde [NMUH] and Mr Saridogan [UCLH], issued an Interim Position Statement to advise on the appropriate monitoring of current or recent users.

Latest available data shows only 4 prescriptions for Esyma were dispensed in the community (May 2018; OpenPrescribing) and none were dispensed by Trusts (July 2018; DEFINE).

In August 2018 the MHRA issued updated advice to permit prescribing of ulipristal however amended the licensing authorisation so more than one treatment course is now authorised only in women who are not eligible for surgery, liver function monitoring is to be carried out in all women and treatment is to be initiated and supervised by a specialist.

The Committee agreed that changes to the licensing were substantial and a new application was required before Esyma could be prescribed in NCL. The Interim Position Statement should be removed from the NCL website as all patients would now be off treatment. In summary, ulipristal (Esmya®) for uterine fibroids remained non-formulary.

10. JFC Terms of Reference (Update)

The Terms of Reference (ToR) had been updated in response to comments received at the June 2018 meeting and discussions pertaining to the tenure of Chair at the July 2018 meeting. The Committee approved the revised ToR which would be uploaded to the NCL website.

11. **Next meeting**

Monday 17th September 2018, Location TBC

12. **Any other business**

Dr Kelsey discussed a recent article published by Science magazine reporting that fraudulent papers relating to bone density had been published and incorporated into several meta-analyses. The Committee asked JFC Support to establish whether any of these papers had influenced JFC decisions.