North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 25 August 2016
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Dr R Sofat	UCLH, Consultant Clinical Pharmacologist	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Dr C McGuinness	Patient Partner	
	Ms K Landeryou	Patient Partner	
	Mr T James	MEH, Chief Pharmacist	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr M Kelsey	WH, Chair DTC	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Dr R Breckenridge	UCLH, DTC Chair	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr I Man	WH, Interim Deputy Chief Pharmacist	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
In attendance:	Mr J Minshull	NCL JFC, Support Pharmacist	
	Mr A Barron	NCL JFC, Support Pharmacist	
	Mr K Thakrar	UCLH, Formulary Pharmacist	
	Ms H Mehta	NMUH, Formulary Pharmacist	
	Ms A Fakoya	NEL CSU, Assistant Director Acute Services	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Ms S Sanghvi	UCLH, Formulary Pharmacist	
Apologies:	Dr V Thiagarasah	Enfield CCG, GP	
	Prof L Smeeth	NCL JFC Vice-Chair	
	Mr TF Chan	RFL, Deputy Chief Pharmacist	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Dr C Cooper	Islington CCG, GP	
	Ms W Spicer	RFL, Chief Pharmacist	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Ms H Taylor	WH, Chief Pharmacist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Dr R Fox	RNOH, DTC Chair	
	Prof D Robinson	UCLH, Consultant in Respiratory Medicine	
	Mr E Hindle	MEH, Formulary Pharmacist	

3. Minutes of the last meeting

Item '6.1 Local DTC recommendations': the minutes should reflect that eculizumab (compassionate use scheme) for Cold Agglutinin Disease was restricted to UCLH only.

Item '7.2 Surgiflo with thrombin [haemostatic agent] for complex spinal surgeries': the minutes should reflect that Surgiflo will be funded by the same mechanism as Floseal and fibrin sealants.

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

4. Matters arising

4.1 GLP-1RA (liraglutide and dulaglutide) Factsheet for Type 2 Diabetes

Comments were received from Camden CCG. Mr Dutt, in the capacity of NCL MON Chairperson, confirmed the agreed amendments have been approved. The final GLP-1RA (liraglutide and dulaglutide) Factsheet is available on the NCL JFC website and the original liraglutide shared care guideline had been removed.

5. Declarations of relevant conflicts of interest

No conflicts of interest relevant to the agenda were declared by the Committee members.

6. Local DTC recommendations / minutes

6.1 Pegylated granulocyte colony stimulating factor (pegfilgrastim [Neulasta] or lipegfilgrastim [Lonquex]) for prevention of febrile neutropenia

The Committee requested a secondary review of an application considered by the WH DTC where pegylated-GCSF was approved for patients who are unable to receive daily GCSF injection and for patients with a history of severe neutropenia despite prophylactic GCSF. The basis of this request was to ensure equality of prescribing and access, as other Acute Trusts within NCL removed pegylated-GCSF from their Formulary a number of years ago in line with a cost-effectiveness review supporting the use of biosimilar daily GCSF.

The Committee considered pegylated-GCSF for two distinct patient cohorts; those who can receive daily GCSF but cannot self-inject, and those who are not candidates for daily GCSF (e.g. severely needle phobic). International guidelines (ASCO and EORTC) give equal recommendations to GCSF and pegylated-GCSF therefore equivalence can be assumed.

Across NCL, for patients who can receive daily GCSF but cannot self-inject, current practice is to arrange 5 district nurse visits per cycle. Using PSSRU costs for district nurses, the overall costs for daily GCSF + district nurse administration is almost identical to that for pegylated-GSCF administered via a district nurse (£2,007 vs. £1,973 per course). Daily GCSF is reimbursed by NHS England, district nurses are paid for by community providers and pegylated-GCSF are in-tariff. Acute Trusts therefore bear no cost for daily GCSF administered by district nurses; WH however is the exception within NCL as they also provide community services hence savings from reduced district nurse home visits could be used to offset the budget pressure from pegylated-GCSF. From a service level perspective the Committee agreed that WH should have access to pegylated-GCSF for this population. The Committee did not recommend that other Trusts adopt pegylated-GCSF for these patients as arranging daily GCSF + district nurses would be cheaper with similar therapeutic outcomes.

For patients who are not candidates for daily GCSF, pegylated-GCSF is considered the only viable option. This population is expected to be extremely small and may include patients with severe needle phobia or non-compliance to self/district nurse administration. The Committee agreed this was appropriate for all Acute Trusts.

The Committee considered the use of pegylated-GCSF for patients with a history of severe neutropenia following use of prophylactic GCSF. A literature search did not identify any studies that compared daily GCSF to pegylated-GCSF in preventing neutropenia in patients with a history of prolonged neutropenia. A recommendation to use pegylated-GCSF over biosimilar daily GCSF in patients with a history of prolonged neutropenia is not included within London Cancer or ASCO/EORTC guidelines. Other cancer centres in NCL preferentially commence biosimilar daily GCSF 3 days before predicted individualised nadir (the time at which absolute neutrophil count is at its lowest point) and continue treatment for 10 days. The cost of pegylated-GCSF is twice as much as biosimilar daily GCSF; furthermore biosimilar daily GCSF is reimbursed by NHS England whereas pegylated-GCSF is in-tariff. In the absence of any supportive published data, the Committee were unconvinced of the value of pegylated-GCSF for this specific indication. Dr Kelsey (WH DTC Chair) agreed that the WH DTC would reconsider the evidence for this population.

The Committee noted a consensus amongst the members present that the Acute Trusts would like pegylated-GSCF to be available for truly exceptional patients, such as patients with complex comorbidities including glycogen storage disease type 1b which predispose them to being neutropenic. As these would be outside of the scope of any guideline it was agreed that this should be considered via each Trust's 'One-off' application process.

In summary, pegylated-GSCF can be considered as an alternative to GCSF + district nurse administration at WH only for patients who can receive daily GCSF but cannot self-inject. Pegylated-GSCF is recommended for patients who are not candidates for daily GCSF, at all Trusts. WH DTC is to re-review their recommendation to use pegylated-GSCF for patients with a history of severe neutropenia. On a related note, as part of the horizon scanning process the Committee are aware that a biosimilar pegfilgrastim preparation (Ristempa) has been approved by the EMA with another product (LA-EP2006) expected to be launched during Q4 of 2016/17. The JFC will add this to their work plan with a view to review the evidence underpinning the EMEA application when the price is known.

6.2 Endoclot (polysaccharide haemostatic system) for non-variceal bleeding in the upper gastrointestinal tract

Endoclot was approved under evaluation by NMUH DTC in March 2015 and the decision was ratified by the JFC in June 2015 pending approval of a local treatment pathway. The JFC Support Pharmacists revisited this decision and found that Endoclot is not a drug, nor is it a device for which a drug is the logical comparator, therefore the decision relating to Endoclot is outside of the remit of the JFC. The Committee agreed to remove Endoclot from the JFC Work Plan and the NCL JFC website.

6.3 Approved by DTC

DTC site	Month	Drug	Indication	JFC outcome
RFL	Jun-16	Rezolsta	HIV Infection	Added to NCL Joint Formulary
RFL	Jun-16	Evotaz	HIV infection	Added to NCL Joint Formulary
RFL	Jun-16	Tenofovir alafenamide	HIV infection for patients with osteoporosis	Added to NCL Joint Formulary
RFL	Jul-16	Ajmaline (unlicensed)	Diagnosis of Brugada syndrome	Added to NCL Joint Formulary
RFL	Jul-16	Infliximab	Steroid-refractory ipilimumab-induced Colitis	RFL only
UCLH	Jul-16	Ubiquinone	Primary mitochondrial deficiency in patients with confirmed mitochondrial defect or defined respiratory chain deficiency	UCLH only
WH	May-16	Pegylated GCSF	Prevention of febrile neutropenia	See agenda item 6.1

6.4 Deferred by DTC

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Jul-16	Ubiquinone	Secondary mitochondrial deficiency	Deferred

7. New Medicine Reviews

7.1 Alitretinoin for pityriasis rubra pilaris (Applicant: Dr S McBride, RFL)

The Committee discussed an application for alitretinoin for pityriasis rubra pilaris (PRP), after topical treatment and first-line retinoid (acitretin/isotretinoin) have failed to produce an adequate response.

Evidence was limited to one case series and four case reports which reflect the rarity of PRP and the positioning of therapy. The case series describes a retrospective analysis of 5 patients. All were treated orally with alitretinoin 30 mg/day. Prior to initiation of alitretinoin, all patients had failed previous topical treatments, 4 had failed corticosteroids however only one had failed previous acitretin. Four patients showed a clinical response after 4–8 weeks and in these patients, PASI score was reduced by a mean of 71% (baseline level was not reported) after 4–8 weeks. In patient 5 the existing PRP lesions showed only slight reduction after 13-week treatment with acitretin 30 mg/day. When medication was switched to alitretinoin 30mg/day a rapid progression and occurrence of new PRP skin lesions were observed within 3

weeks. Therapy was subsequently changed back to acitretin but in a higher dosage (75 mg/day) leading to a clear but slow improvement of skin symptoms over 15 weeks.

Other supportive case reports include 1 patient who failed acitretin, 1 patient who failed corticosteroids & methotrexate, 1 patient who failed corticosteroids, acitretin, ciclosporin & adalimumab and 1 patient who failed corticosteroids & acitretin.

Alitretinoin adverse effects include dry skin and mucous membranes, hyperlipidemia, transaminase elevations, and visual or bone changes. Very commonly causes headache and commonly causes anaemia, thyroid dysfunction, depression, dizziness, flushing, hypertension, tinnitus, arthralgia and fatigue. The incidence of adverse effects is higher with the 30mg dose which is important as the majority of PRP case reports used the 30mg dose. Alitretinoin is teratogenic therefore contraindicated in pregnant women and women of childbearing age should be on the Pregnancy Prevention Programme.

Alitretinoin is excluded from tariff therefore funding will need to be sought via IFRs. Each course costs £2,962 and repeated courses may be required.

The Committee discussed whether alitretinoin would be effective in people who have failed other retinoids, irrespective of the subtle differences in the pharmacology or the small number of case reports. It was unknown whether there was evidence of alitretinoin efficacy in retinoid failure in other diseases. The proposed positioning for alitretinoin in the application was before methotrexate, however methotrexate had a slightly stronger evidence base, is considerably cheaper and has a different adverse effect profile. There were no insurmountable safety concerns for using methotrexate as Dermatologists commonly prescribe methotrexate for the management of psoriasis. The Committee agreed patients should not be denied methotrexate based on the current quality of evidence for alitretinoin.

In summary, alitretinoin was approved under evaluation at RFL only for patients with PRP who have not achieved an adequate response with topical agents or acitretin/isotretinoin, and who *either* fail to improve with methotrexate *or* have a contra-indication to methotrexate. Results from the audit should be brought back to JFC in September 2017.

Decision: Approved under evaluation
Prescribing: Secondary care only
Tariff status: PbR excluded
Funding: IFR
Fact sheet or shared care required: No
Audit required: Yes

7.2 Fosfomycin IV for Micro approved indications (Applicant: Prof P Wilson, UCLH)

The Committee discussed an application for IV fosfomycin for the treatment of infections, or suspected infections caused by multi-drug resistant Gram negative organisms, including ESBLs.

Fosfomycin has a broad spectrum of activity and the oral formulation is already on the NCL Joint Formulary for treating ESBL UTIs.

Data from a structured literature review evaluated bacterial susceptibility rates to fosfomycin against multidrug-resistance and extensively drug-resistant infections. Papers published between 2010 and 2015 were included to capture the contemporary use of fosfomycin and any increase in resistance. Results found very high susceptibility rates for ESBL producing *Klebsiella pneumoniae* and *E. coli,* however a significant trend of decreasing susceptibility over time was identified. Good susceptibility rates were found for CROs (carbapenem resistant organisms) including *Klebsiella pneumonia* and *Pseudomonas aeruginosa*.

A prospective study reported outcomes of patients with fosfomycin-susceptible, extensively drug-resistant and pan drug-resistant infections across 11 ICU centres in Greece. In total, 68 patients received fosfomycin and 48 were included in the effectiveness analysis. Bacteraemia and ventilator-associated pneumonia were the main infections. All infections were CROs, with 41 cases of *Klebsiella pneumonia* and 17 cases of *Pseudomonas aeruginosa*. Fosfomycin was administered intravenously at a median dose of 24 g/day for a median of 14 days, mainly in combination with colistin or tigecycline. Clinical outcome at day 14 was 'successful' in 54.2% of patients, whilst 'failure', 'indeterminate outcome' and 'superinfection' were documented in 33.3%, 6.3% and 6.3%, respectively. Bacterial eradication was observed in 56.3% of cases. Fosfomycin resistance developed in three cases. By Day 28, 37.5% had died.

A second prospective study of 11 patients with fosfomycin-susceptible Klebsiella pneumonia CROs in a Greek ICU found good bacteriological and clinical outcome of infection for all patients.

With regards to adverse effects, reversible hypokalaemia is mostly commonly observed. Due to the high sodium content within each vial, a low sodium diet is recommended in addition to regular monitoring of serum electrolyte levels and water balance during therapy. A 5 day course of IV fosfomycin costs £540-£1,080 compared to £300-£600 for IV temocillin which can also treat ESBLs.

The Committee heard from Prof Wilson that the number of CROs identified have increased at an alarming rate, driven predominantly by the large increase in carbapenem use. Meropenem sparing agents such as fosfomycin IV and temocillin would be appropriate where meropenem cannot be used due to resistance, or where meropenem use was undesirable. An increase in resistance to fosfomcyin will be expected as usage increases, however the Microbiology team would be actively restricting their recommendation for fosfomycin IV in order to minimise the occurrence of this. The treatment course is likely to be 5 days, which is shorter than courses typically used in Greece. Lower doses of fosfomycin IV in combination with other agents would be used in critically ill patients in order to minimise the sodium load. Higher doses might be considered in younger patients who are more likely to clear the sodium.

In camera, the Committee agreed to add fosfomycin IV to the NCL Joint Formulary with usage restricted to Microbiology approval only.

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

7.3 EVRA transdermal patch for menstrual disturbances (Applicant: Dr E Yasmin, UCLH)

The Committee discussed an application for EVRA transdermal patch (norelgestromin and ethylestradiol) for the control of menstrual disturbances in adolescents in whom the combined oral contraceptive is appropriate, however cannot take oral medicines, for example patients with physical and learning difficulties, or tube feeding.

For patients in whom pharmacological treatment is indicated, first-line treatment in otherwise healthy adult women is typically with a levonorgestrel intrauterine device (e.g. Mirena®). The disadvantage of an intrauterine device is irregular bleeding that may last more than 6 months. As an alternative, combined contraceptives can be considered which are also more effective at regulating the menstrual cycle and reducing dysmenorrhea, however are less effective at reducing blood loss. For patients in whom combined hormonal contraceptives are indicated, the majority will take the combined oral contraceptive. Patients with physical or learning disabilities and women who use enteral feeding tubes may be unable to take medicines orally.

Two head-to-head studies of EVRA vs. two different combined oral contraceptives found similar percentages of subjects in each treatment groups reporting breakthrough bleeding or spotting at Cycle 3. Similar observations were made at each of the other cycles and there were no statistically significant differences between the treatment groups, confirming that overall bleeding patterns seen with EVRA are similar to those seen with marketed oral contraceptives.

EVRA had an overall increased risk of breast symptoms (breast discomfort, breast engorgement, and breast pain) and application site reactions compared to oral contraceptives. The EPAR states that the relative risk for VTE for EVRA vs. levonorgestrel is between 1.0 to 2.0; similar to combined oral contraceptives (COCs) containing gestodene/desogestrel/drospirenone which have a relative risks of 1.5 to 2.0 vs. levonorgestrel.

It was clarified that the population who are tube fed were being considered due to the lack of liquid preparations available, rather than their inability to absorb drugs from the GI tract. The Committee note guidance from the Royal Pharmaceutical Society, that preparations containing hormones should not be crushed due to the risks associated with powder aerosolisation. The EVRA patch can be applied to the buttocks, abdomen, upper outer arms or upper back therefore application sites can be found where patients with learning difficulties cannot inadvertently remove the patch.

The Committee agreed that the simplicity of transdermal administration for patients with learning difficulties was non-trivial and was supportive of this application. The principle concern was related to prescribing creep outside the proposed indication therefore JFC Support Staff would monitor usage over the next year.

In summary, EVRA was approved for the control of menstrual disturbances in adolescents and women in whom the combined oral contraceptive is appropriate, however cannot take oral medicines, for example patients with physical and learning difficulties, or tube feeding.

Decision: Approved
Prescribing: GP and secondary care
Tariff status: In tariff
Funding: CCG and hospital budgets
Fact sheet or shared care required: No
Audit required: No

8. Guidelines

Nil

9. Liothyronine for primary hypothyroidism (PrescQIPP)

Mr Minshull presented a PrescQIPP prescribing bulletin and summary about the use of oral liothyronine in hypothyroidism. PrescQIPP is a community interest company that provides prescribing advice to NHS organisations, including the CCGs in NCL.

PrescQIPP has recommended that levothyroxine (T4) should be the main agent when treating primary hypothyroidism, and that all people receiving liothyronine (T3) for this indication either alone or in combination with levothyroxine should be reviewed with a view to switching them to T4 treatment alone. The JFC discussed the recent, significant increase in the cost of treatment with liothyronine, which has highlighted the importance of reviewing this group of patients. Liothyronine makes up a small proportion of prescriptions when compared to levothyroxine (0.3% of items in NCL), yet accounts for 24% of the spend on these two drugs in primary care.

The JFC acknowledged that it was likely that most patients were already being treated in line with the recommendations of the PrescQIPP document which were based around the British Thyroid Association (BTA) advice. The BTA states that T4 treatment should be used in the majority of patients for primary hypothyroidism, and that for these patients the combination of T4/T3 therapy should not be routinely used as there is insufficient evidence to show it is superior to T4 monotherapy, and monotherapy with T3 or thyroid extracts is not backed up by convincing evidence. There is still a small, but significant group of patients receiving liothyronine, either alone or in combination with levothyroxine. There was discussion about the use of treatment with liothyronine in addition to levothyroxine where thyroid stimulating hormone had returned to normal with levothyroxine therapy; the Committee believed that any additional benefit from adding liothyronine to the therapy of patients with normal TSH was likely to arise from making patients hyperthyroid, which would expose the patient to associated side effects such as osteoporosis and arrhythmias. It was agreed that these patients were clearly representing a challenge to prescribers, and it would likely be very difficult to get them to switch over to levothyroxine.

Feedback had been gathered from stakeholders before the meeting, who emphasised that liothyronine was not being used routinely in hypothyroidism and that many patients on T3 for primary hypothyroidism are keen to continue. The JFC also noted that some patients with thyroid cancer still require liothyronine, however the Committee agreed that this was not part of the indication under review.

The Committee agreed to remove oral liothyronine from secondary and primary care formularies for use in primary hypothyroidism in new patients. GPs can use the PrescQIPP prescribing support document to help with switching established patients with primary hypothyroidism from liothyronine to levothyroxine.

10. Methotrexate for off-label indications for Shared Care

At the June 2016 meeting, Mr Thakrar was asked to prepare a document listing the off-label indications of methotrexate that the Acute Trusts believe are suitable for prescribing and supply in primary care and thus proposed under shared care. Mr Thakrar presented a paper which detailed all of the proposed indications, together with the grade and strength of published evidence. It was noted that the use of methotrexate was supported with high quality evidence (Sackett et al, 1989, levels 1-2) for all indication with the exception of ulcerative colitis where RCT data failed to demonstrate a statistically significant difference compared with placebo, however its use is supported by expert opinion and national guidelines.

Based on this review, the JFC agreed that methotrexate shared care can be progressed for all indications listed except for ulcerative colitis.

11. Regional Medicines Optimisation Committee: Proposals for Establishment

Mr Bodalia presented the NHS England consultation document for Regional Medicines Optimisation Committees: Proposals for Establishment. The Committee was informed that we will be submitting a JFC response to this consultation, which all members are welcome to contribute to. All contributions should be sent to John Minshull by 31 August 2016.

12. JFC Work-plan

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

13. Next meeting

Thursday 29th September 2016, Room 6LM1, Stephenson House, 75 Hampstead Rd.

14. Any Other Business

Nil