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NHS
North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 28 April 2016
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Dr R Sofat	UCLH, Consultant Clinical Pharmacologist	
	Ms K Landeryou	Patient Partner	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Dr A Stuart	NHS Camden, GP Clinical Lead Medicines Management	
	Ms P Taylor	NHS Haringey, Head of Medicines Management	
	Dr R Fox	RNOH, DTC Chair	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr B MacKenna	Islington CCG, Deputy Head of Medicines Management	
	Mr TF Chan	RFH, Deputy Chief Pharmacist	
In attendance:	Mr J Minshull	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFH, Formulary Pharmacist	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Mr A Barron	NCL JFC, Support Pharmacist	
	Ms S Sanghvi	UCLH, Formulary Pharmacist	
	Dr A Shah	UCLH, SpR Clinical Pharmacology	
	Ms H Mehta	NMUH, Formulary Pharmacist	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Dr F Bennett	UCLH, SpR Clinical Pharmacology	
	Ms E Frank	UCLH, NHNN Clinical Lead Pharmacist	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr M Kelsey	WH, Chair DTC	
	Dr C McGuinness	Patient Partner	
	Ms H Taylor	WH, Chief Pharmacist	
	Mr T James	MEH, Chief Pharmacist	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr V Thiagarasah	Enfield CCG, GP	
	Ms W Spicer	RFH, Chief Pharmacist	

2. Meeting observers

Prof MacAllister welcomed Ms E Frank as an observer to the meeting.

3. Minutes of the last meeting

Mr E Hindle requested that the conflicts of interest he declared be correctly attributed to item 8.4, not 8.3 as stated.

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

4. Matters arising

4.1 Asthma Guideline

At the March 2016 meeting, the Committee approved an asthma inhaler choice guideline for use across NCL. It was noted after the meeting that Symbicort® inhalers were included in the guideline despite having been 'not recommended' by the JFC in September 2015 for regular and PRN use. It was highlighted by three of the CCGs that there was already extensive use of Symbicort® within their areas, and to remove it completely would cause confusion for GPs and patients. It was agreed, therefore, to keep Symbicort in the guidelines for regular maintenance inhaler use, but not for the PRN indication as this has not been endorsed by the JFC.

5. Declarations of relevant conflicts of interest

Dr Koepp declared that he has taken part in an advisory board for and chaired a meeting session sponsored by Eisai Ltd (item 7.3). He has received honoraria and educational event sponsorship from UCB Pharma Ltd and has applied to lead a trial of brivaracetam (item 7.4).

Mr Minshull reminded committee members to complete and return the JFC Declaration of Interests forms by 12 May.

6. Local DTC recommendations / minutes

6.1 Approved by DTC

Month	DTC site	Drug	Indication	JFC outcome
Mar-16	UCLH	Mycophenolate	Interstitial lung disease (Connective tissue disease, Hypersensitivity Pneumonitis and Idiopathic Non-specific Interstitial Pneumonia)	Added to NCL Joint Formulary
Mar-16	UCLH	Methotrexate (oral)	Second-line treatment for sarcoidosis (after corticosteroids)	Added to NCL Joint Formulary
Mar-16	RFL	Nivolumab (early-access scheme)	Second and third-line use in treatment of advanced renal cell carcinoma	RFL only
Historical	All	Topical adapalene 0.1% cream	Acne	Added to NCL Joint Formulary

6.2 Under evaluation by DTC

Month	DTC site	Drug	Indication	JFC outcome
Mar-16	RFL	Oxybutynin MR	Hyperhidrosis	Under evaluation at RFL only

The Committee heard from Ms Samuel that RFL had developed a treatment pathway for hyperhidrosis. The RFL were undertaking an evaluation of oxybutynin MR in 30 patients with hyperhidrosis due to the limited published evidence base available. The Committee agreed that the application was applicable to other Acute Trusts across NCL and would also impact primary care prescribing, therefore both the treatment pathway and evaluation should be presented at JFC.

Action: Ms Samuel to submit the hyperhidrosis treatment pathway and evaluation report to JFC

7. New Medicine Reviews

7.1 Anthelios XL SPF 50+ Sun Cream (Applicant: Dr K Taghipour, WH)

The Committee reviewed an application for Anthelios XL SPF 50+ Comfort Cream for protection from UV radiation in abnormal cutaneous photosensitivity resulting from genetic disorders or photodermatoses, including those resulting from radiotherapy and chronic or recurrent herpes simplex labialis.

Anthelios XL SPF 50+ Comfort Cream, Sunsense Ultra Lotion and Uvistat Cream are included on the 'Advisory Committee for Borderline Substances (ACBS)' list. Anthelios XL SPF 50+ Comfort Cream is already on formulary at RFL and makes up approximately 10% of the prescriptions for sunscreen in NCL.

There were no studies comparing the efficacy of Anthelios XL SPF 50+ Comfort Cream to Uvistat or Sensense. Anthelios XL SPF 50+ Comfort Cream is more expensive per mL than the comparators however clinical experience suggests Anthelios XL SPF 50+ Comfort Cream is well tolerated, does not leave a white residue and may offer superior UVA protection than alternatives sunscreens. Anthelios XL SPF 50+ Comfort Cream presents in a small pack size and therefore may be most useful for frequent application to face and the back of hands (areas that are most exposed to the sun) whilst Uvistat may be beneficial for application to larger areas.

The application was in line with recommendations from the 'Advisory Committee for Borderline Substances (ACBS)' therefore the Committee agreed that Anthelios XL SPC 50+ Comfort Cream should be included for this indication on the NCL Joint Formulary.

Decision: Approved
Prescribing: Primary and secondary care
Tariff status: In tariff
Funding: Hospital and primary care budgets
Fact sheet or shared care required: No
Audit required: No

7.2 Testosterone gel for poor libido post menopause or due to premature ovarian insufficiency (Applicant: Prof Conway, UCLH)

The Committee reviewed an application for poor libido due to menopause or premature ovarian insufficiency in women who had no improvement with oestrogen based HRT alone.

Testosterone is recommended as a treatment option for menopausal women with low sexual desire if HRT alone is not effective in the latest NICE guideline for menopause (NG23). Similar recommendations are provided in other national and international guidelines.

The Committee noted that the majority of data supporting testosterone for poor libido was for testosterone patches. The INTIMATE NM1 study was a 24-wk randomised, double-blind, multinational, placebo controlled trial to evaluate the efficacy of testosterone 300mcg/day patch in treating Hypoactive Sexual Desire Disorder in women. Postmenopausal women who underwent natural menopause were included. Exclusion criteria were extensive and bring into question the issue of generalisability of the trial. Patients were randomised 1:1 to testosterone 300mcg/day patch or placebo. In total 377 women were assessed for eligibility and 272 (72%) were randomised; of these only 207 (76%) completed the 24-wk trial, primarily due to adverse effects or withdrawal of consent. Results showed a clinically meaningful increase in the "frequency of sexually satisfying episodes" compared to placebo. Four other trials of very similar design in women without concurrent HRT, or in women with surgical menopause found nearly identical results.

One randomised, double-blind, multinational, placebo controlled cross-over trial evaluated the efficacy of Testogel (transdermal testosterone gel) in treating low libido in naturally menopausal women. Only 77 women were assessed for eligibility and 60 were randomised, 7 dropped out and data for these patients were not included in the results. Results found sex life improved from baseline and psychological wellbeing also improved. Serum testosterone levels increase from <1nmol/L at baseline to >7nmol/L on testosterone.

With regards to safety, there is no long-term data in this population. A Cochrane review included 35 trials with a study durations ranging from 1.5 to 24 months. Significant adverse effects identified were decreased HDL cholesterol levels and an increased incidence of hair growth and acne. There was no significant impact on weight, BMI, cognition or breast density.

The budget impact is expected to be £11,000 per annum assuming 100 patients per annum in NCL with an average treatment duration of 2 years.

The Committee discussed concerns arising from long-term testosterone gel use; predominant adverse effects would include acne, hirsutism and deepening of the voice which women would respond to by withdrawing treatment or lowering the dose. The cardiovascular risk associated with a small reduction in HDL was thought to be minimal.

CCG and GP representatives expressed concern with prescribing testosterone gel in primary care due to absence of robust data and uncertain long-term effects. The Committee agreed that prescribing and monitoring should remain in secondary care.

The Committee were minded that testosterone gel was a replacement for testosterone patches which were withdrawn from the market due to commercial reasons in 2013. In summary, the Committee was satisfied that testosterone gel (at a dose of approximately 1/10th of the adult male dose) was likely to be effective in some women with poor libido and should be included for this indication on the NCL Joint Formulary.

Decision: Restricted to sexual function clinics only (not for GP prescribing)
Prescribing: Secondary care prescribing only
Tariff status: In tariff
Funding: Hospital budgets
Fact sheet or shared care required: NA
Audit required: No

7.3 Eslicarbazepine for partial onset epilepsy (Applicant: Dr M Koepp, UCLH)

The Committee reviewed an application for eslicarbazepine acetate to be as 3rd line adjunctive therapy in adults with partial onset seizures. Eslicarbazepine acetate is a pro-drug of the active metabolite eslicarbazepine (S-li-carbazepine). Oxcarbazepine (already on the formulary) is a pro-drug of the active metabolite S-li-carbazepine and R-li-carbazepine. Therefore the Committee considered the natural comparator for eslicarbazepine to be oxcarbazepine. It was noted that no head-to-head studies of eslicarbazepine and oxcarbazepine had been conducted. Knowledge of efficacy of eslicarbazepine is limited to placebo-controlled trials that excluded patients who were already receiving oxcarbazepine.

In the four placebo-controlled trials considered by the Committee, it was noted that eslicarbazepine 1,200 mg daily was statistically significantly superior to placebo at reducing the standardised seizure frequency, improving responder rate and reducing median relative reduction in seizure frequency. The results for the 800 mg daily dose were significant in two studies (Elger *et al* 2009 and Ben-Menachem *et al* 2010). The Committee was interested to note that placebo response was high in all of these studies, ranging from 13% responder rate in Ben-Menachem *et al* to 23% in Sperling *et al*. The proportion of seizure free days was low where reported (1.2% for placebo and 4.8% for ESL 400 mg, Gil-Nagel *et al*) and seizure freedom was low (5% of ESL 800 mg patients in Ben-Menachem *et al* 2010, compared to 1% of placebo patients).

The results of an in-house meta-analysis of published data were considered, which showed that the odds ratio for achieving 50% response to oxcarbazepine was 7.02 (CI: 4.11, 12.02), whereas the OR for eslicarbazepine was 2.79 (CI: 2.12, 3.66).

From a safety perspective, it was noted by the Committee that eslicarbazepine was included in the December 2012 MHRA safety alert warning of the risk of serious skin reactions. Common adverse events associated with eslicarbazepine include headache, dizziness, nausea and somnolence. Dr Koepp clarified that the discontinuation rate for eslicarbazepine was 14% in pooled analyses.

Dr Koepp explained that, while oxcarbazepine and eslicarbazepine are similar, they are not identical compounds. Eslicarbazepine acetate is converted to S-licarbazepine (not the R isomer), which some consider to be the more effective component, has fewer adverse effects, and crosses the blood brain barrier more efficiently than R-licarbazepine. This might explain both better tolerability and efficacy.

Dr Koepp explained to the Committee that the main advantage of eslicarbazepine over oxcarbazepine is that it requires once daily dosing, whereas the half-life of oxcarbazepine necessitates it be administered thrice daily (though the SPC advises twice daily administration). Dr Koepp acknowledged that seizure freedom rate is very low in the trials for the newer anti-epileptic drugs (AEDs), highlighting that these patients are often debilitated due to their high seizure frequency, therefore reduction in this frequency would be a patient-centred outcome.

On consideration of the evidence, the Committee did not feel that eslicarbazepine was superior to oxcarbazepine. Its advantages over oxcarbazepine were considered to be minor and theoretical and were offset by its greater cost. Therefore it was not approved for use in NCL.

Decision: Not approved

7.4 Brivaracetam for partial onset epilepsy (Applicant: Dr H Angus-Leppan, RFL)

The Committee reviewed an application for brivaracetam (BRV) as a 2nd or 3rd line adjuvant in partial onset seizures. The Committee noted that BRV is a second generation AED similar to levetiracetam (LEV). Both drugs were originally marketed by UCB Pharma, though the patent for LEV ended in 2010. As LEV is a commonly used, generic AED, the Committee was interested to understand whether BRV offered any clinical advantage over that drug. Dr Angus-Leppan explained to the Committee that it is possible to manage 70% of epilepsy patients on old fashioned, cheaper agents. However, 30% of patients remain refractory, suffering from potentially life-threatening seizures, resulting in A&E attendances.

Efficacy of BRV was demonstrated in four placebo-controlled randomised trials. There were no head-to-head studies exclusively comparing BRV to LEV, and none of the studies looked at the effect of their drugs on death rates. In three of the four RCTs, up to 20% of enrolled patients could be taking concomitant LEV. In the fourth study, patients were excluded if they had taken any LEV in the 90 days prior to randomisation.

Rvylin *et al* (2014) demonstrated that, although the median percentage reduction from baseline in focal seizure frequency/week was numerically higher in BRV treated patients (29% to 40%) than placebo treated patients (20%) for LEV-naïve patients and for patients who had discontinued LEV (17% to 36% with BRV, vs. 10% with PBO). For patients receiving concomitant LEV, the response to placebo was higher (17%) than for BRV 50 mg/day (3.2%) and BRV 100 mg/day (4.7%). There were similar findings for the "≥ 50% responder rate". Kwan *et al* (2014) showed similar findings, with percentage reduction from baseline in focal seizures/week of 14.2% vs 15.9% (placebo vs. BRV) in concomitant LEV use, compared to 19.2% vs. 31.5% (placebo vs. BRV). The "≥ 50% responder rate" for LEV patients was lower in those receiving BRV than placebo (13.1% vs. 18.2%).

The seizures can occur multiple times per month. It was proposed that initiation of this drug would be by a Consultant Neurologist specialising in epilepsy to ensure it is prescribed appropriately. Regarding continuity of use, it was proposed that if patients do not respond to an AED that they quickly stop taking it; therefore there is little risk of patients staying on ineffective treatments. Every patient rendered seizure free would be counted as a success.

Dr Koepp added that within the refractory cohort, each patient may need to be trialled on multiple drugs before finding one that is effective, therefore an armamentarium of drugs is required. BRV has subtle mechanistic difference from LEV, such as higher affinity for synaptic protein 2A and no involvement with calcium currents or AMPA-gated currents meaning fewer off-target effects. It was noted by the Committee, however, that the EMEA had specifically addressed this in their assessment and reported that these differences have not yet been demonstrated in clinical practice; therefore it is difficult to know if they are of clinical relevance.

The cohort of patients identified as most appropriate to receive BRV by the applicant were those who cannot take LEV due to psychological disturbance. The Committee found this proposed benefit had yet to be demonstrated within a clinical trial setting. Indeed, the SPC for BRV continues to warn clinicians about the risk of suicidal ideation.

On consideration of the evidence, the Committee were of the opinion that BRV did not offer any clinical advantages over levetiracetam, therefore the drug was not approved for prescribing in NCL.

Decision: Not approved

7.5 Celiprolol for Ehlers-Danlos syndrome (Applicant: Ms T Mastracci, RFL)

The Committee reviewed an application for celiprolol for vascular Ehlers-Danlos syndrome (EDS).

A multinational, prospective randomised, open-label trial (BBEST) investigated the efficacy and tolerability of celiprolol in vascular-EDS (n=53). Patients aged 15 to 65 years with vascular-EDS (using Villefranche diagnostic criteria) were eligible for the study. Patients who were pregnant, at risk of pregnancy, prior β-blocker treatment or had contraindications to celiprolol were excluded. Patients were randomised 1:1 to celiprolol or 'no treatment'. The primary endpoint was a composite of cardiac or arterial events (rupture or dissection, fatal or not) during follow-up. An ambitious treatment effect (50% relative risk reduction) was used to determine the sample size. 87 patients were recruited into the study

and 53 patients were randomised. Median follow-up was 50 months and the study was ended prematurely due to significant differences between the two groups in the whole population after 64 months. Results showed that celiprolol arm was associated with a significant reduction the primary endpoint; 20% experienced an event on celiprolol versus 50% with 'no treatment' (HR = 0.36 [95% CI: 0.15 to 0.88]).

The principal adverse effect reported in the trial was fatigue. No clinical hypotension or bradycardia was reported. All but two patients achieve the full dose of 400mg BD suggesting that celiprolol was well tolerated

The Committee discuss that the mechanism of action of celiprolol in vascular-EDS is unknown. It was hypothesised that celiprolol would decrease brachial systolic blood pressures, pulse pressure and heart rate however the inverse was found to be true. An alternative mechanism of action is via the inhibition of renin secretion (though β1 blockade) which may lower the activation of 'transforming growth factor β', a key factor in the pathogenesis of arterial lesions in other conditions.

The Committee heard from Ms Mastracci that celiprolol was the only drug that has demonstrated benefit in vascular-EDS and patients considered access to this treatment of upmost importance. Celiprolol is on formulary at Guys & St. Thomas's Hospital for proven vascular-EDS.

In camera, the Committee agreed that there were no specific monitoring requirements for celiprolol in vascular-EDS and therefore this treatment would be suitable for prescribing in primary care. Given that patient numbers would be below the threshold for shared care or fact sheet (2 per 100,000) the CCG and GP representatives requested that detailed written individualised treatment plans be shared with GPs.

In summary, the Committee had many reservations about the use of celiprolol, including the absence of a haemodynamic effect and the treatment effect which seemed too good to be true. Nonetheless, these were the best data available there were no other treatments for this indication. The JFC agreed to include celiprolol for this indication on the NCL Joint Formulary.

Decision: Approved
Prescribing: Initiated in secondary care, continued in primary care
Tariff status: In tariff
Funding: Hospital and primary care budgets
Fact sheet or shared care required: No
Audit required: No

8. Dipeptidyl peptidase 4 inhibitor (DPP-4i) to alogliptin switch proposal

Mr Barron presented conclusions drawn from the proposal to switch the majority of DPP-4i ('gliptin') prescribing to alogliptin. The proposal was prompted by a 20% cost savings of alogliptin versus sitaglitpin and linagliptin.

The HbA1c benefits of all the drugs in class were similar. Three of the DPP-4is had cardiovascular outcomes studies versus placebo; alogliptin (EXAMINE study), sitagliptin (TECOS study) and saxagliptin (SAVOR study). Results from these studies found no differences in the composite cardiovascular primary endpoint, however saxagliptin had a significantly greater risk of hospitalisation for heart failure (hHF) versus placebo, alogliptin had a numerical increase and sitagliptin had no increase.

The EMEA and FDA both reviewed the EXAMINE data; EMEA did not raise a concern however the FDA were minded that they could not explain the observed increase in hHF by differences in baseline characteristics. The FDA agreed that there was an unconfirmed reason for concern which should be monitored as other long-term DPP-4i CV studies emerges.

It was discussed that the cardiovascular risk should theoretically reduce with a reduction in HbA1c and this had not been demonstrated; there were three explanations (i) HbA1c is only a weak predictor of cardiovascular risk, (ii) DPP-4i drugs are causing some degree of cardiovascular harm, or (iii) the benefit of lowering HbA1c is not seen in trials with a short follow-up.

The Committee heard that the absolute difference in repeat heart failure in EXAMINE was only 0.6% over a mean follow-up of 17.5 months (3.9% vs 3.3%, HR=1.19 [95% CI: 0.9-1.58]), and therefore the actual importance of this increase may not be significant relative to the perceived risk or the large cost savings. It was noted that any alogliptin switch would need to be a double switch (sitagliptin to alogliptin now and alogliptin to sitagliptin to sitagliptin in 2022 when the patent for sitagliptin expires).

The Committee were minded that it would be inappropriate to recommend a switch in light of the FDA decision and agreed that a change in practice to alogliptin could no longer be supported.

9. Regional Medicines Optimisation Committees - Update

At the last meeting the Committee noted a letter from Dr Keith Ridge (Chief Pharmaceutical Officer) on behalf of NHS England describing the establishment of Regional Medicines Optimisation Committee (RMOCs). A meeting with key senior stakeholders was held on 20th April, which Prof MacAllister attended. The aim of the meeting was to discuss the role and responsibilities of the four RMOCs. The following potential medicines optimisation activities were discussed:

- Assessment of newly licensed medicines (not reviewed by NICE / NHSE)
- Assessments of exceptional funding requests
- Assessment of cost pressure identified through horizon scanning
- Assessment of unlicensed medicines
- Assessment of rarely used medicines
- Translation of national guidance into local pathways
- Implementation of safety and quality agendas
- Patient-facing medicines optimisation schemes
- Quantifying impact of medicines use on patient outcomes

Of the above, the RMOCs have tasked the assessment of newly licensed medicines (not reviewed by NICE / NHSE) as their initial key priority, roughly 45 per year, distributed across the four RMOCs. The outcomes of the assessment will be either 'recommended' or 'not-recommended' and unlike NICE TA recommendations they will not be legally required to be adopted, although a statement of variance will be expected for non-adopted recommendations. In order to facilitate the outcomes of the RMOCs, it was noted at the meeting that Area Prescribing Committee (like the NCL JFC) will be pivotal to their success.

In light of the above the Committee were reassured that the priorities of the NCL JFC remain unchanged albeit a reduction in the number of non-specialist new medicines applications requiring assessment locally. The ToR and work-plan for the NCL JFC and its Sub-Committees also remain unchanged.

10. JFC Work-plan

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

11. Next meeting

Thursday 26th May 2016, Room 6LM1, Stephenson House, 75 Hampstead Rd.

12. Any Other Business

Nil