UCLPartners
Academic Health Science Partnership

NHS
North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 28th May 2015
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Dr D Bavin	Camden CCG, GP	
	Dr E Boleti	RFH, Consultant Oncologist	
	Dr R Breckenridge	UCLH, DTC Chair	
	Mr TF Chan	BCF, Chief Pharmacist	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Mr A Dutt	NHS Islington, Head of Medicines Management	
	Dr R Fox	RNOH, DTC Chair	
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management	
	Mr T James	MEH, Chief Pharmacist	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Ms L Reeves	C&I Mental Health Trust, Chief Pharmacist	
	Mr A Shah	RNOH, Chief Pharmacist	
	Ms N Shah	NHS Camden, Head of Medicines Management	
	Dr R Sofat	UCLH, Consultant Clinical Pharmacologist	
	Ms W Spicer	RFH, Chief Pharmacist	
	Ms P Taylor	NHS Haringey, Head of Medicines Management	
	Dr R Urquhart	UCLH, Chief Pharmacist	
In attendance:	Dr H Amer	UCLH, Specialist Registrar	
	Mr A Barron	NCL JFC, Support Pharmacist	
	Dr F Bennett	UCLH, Specialist Registrar	
	Mr P Bodalia	NCL JFC, Lead Pharmacist	
	Dr E Khan	UCLH, Rheumatologist	
	Mrs H Mehta	NMUH, Formulary Pharmacist	
	Ms S Sanghvi	UCLH, Formulary Pharmacist	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Ms S Drayan	NMUH, Chief Pharmacist	
	Mr E Hindle	MEH, Formulary Pharmacist	
	Mr A Karr	NCL Procurement Consortia Chair	
	Dr M Kelsey	Whittington, DTC Chair	
	Mr J Paszkiewicz	NEL CSU, Prescribing Advisor	
	Ms I Samuel	RFH, Formulary Pharmacist	
	Dr A Stewart	Camden CCG, Clinical Lead Medicines Management	
	Dr H Taylor	Whittington, Chief Pharmacist	

2. Meeting observers

Prof MacAllister welcomed the applicants and observers to the meeting.

3. Minutes of the last meeting

These were accepted as accurate.

4. Matters arising

"NICE FAQ: Demonstration compliance with TA and HST guidance": The Committee were informed by Mr Shah that the London Chief Pharmacist Group have similar concerns to those raised by the JFC. Further to these discussions, Prof MacAllister informed the Committee that as per BMJ article (10.1136/bmj.h2813, published 22nd May 2015) NICE are setting up an 'Office of Market Access' which is designed to help pharmaceutical companies speed up adoption of new drugs to the NHS which is likely to also include *me too* drugs.

The Committee suggested that the concerns of similar networks around London should be sought and that a unified response to the NICE FAQ document should be sent.

Action: Mr Bodalia to contact London networks and draft a letter to NICE in response to the FAQ

5. Declarations of relevant conflicts of interest

None were declared.

6. Guideline: Vitamin D (transfer from secondary to primary care)

The Committee reviewed a new guideline titled "UCLH Osteoporosis Service Guideline on the Management of Vitamin D Deficiency in Adults" which was designed to supplement the Camden CCG Vitamin D Primary Care Guidance document with regards to management of patients following secondary care referral and transfer back to primary care.

The Committee noted that the scope of the guideline is limited to patients being transferred from secondary care with low bone mineral density; the title of the guideline should be updated to reflect this. The Committee heard that there is a wider population of patients with a low vitamin D for which CCGs have their own guidelines. These guidelines recommend dietary and lifestyle recommendations in addition to recommending that patients buy their own vitamin D supplementation.

The Committee requested that a reference for "National Safe Regular Sun Exposure" be provided for inclusion in Primary care documentation. The Committee also suggested that a reference should be added to justify the use of ongoing vitamin D supplementation. Ms Shah advised that the guideline should refer to the latest version of the Camden CCG Vitamin D Primary Care Guidance (2015).

It was noted that paediatric patients are frequently asked to take vitamin D supplementation daily, which is challenging and requires an oral syringe. This contrasts with adult patients who are more commonly prescribed a weekly dose. Dr Khan was of the opinion that children could take a weekly dose, but the JFC concluded that children should remain outside the scope of his practice and this guideline.

Lastly, the Committee identified a discrepancy in the guideline: "> 50 nmol/L reassure and maintenance vitamin D 800 – 1600 iU" however "50 – 200 nmol/L no supplementation required." The committee noted that someone in the general population could have a vitamin D level >50 nmol/L without requiring supplementation and therefore requested that this statement be amended.

The Committee agreed that the document should incorporate the above comments and be brought back to the next meeting for further discussion.

Action: Dr Khan to update the vitamin D guideline for the next meeting

7. New Medicine Reviews

7.1 Melatonin for sleep disorders (Applicant: Dr Quinlivan (NHNN/GOSH); Presentation: Dr F Bennett)

The Committee reviewed an application for the use of melatonin for sleep disorders due to visual impairment.

The Committee considered a Cochrane Collaboration systematic review which aimed to assess the effects of melatonin for non-respiratory sleep disorders in visually impaired children. 127 studies were highlighted as part of the initial search strategy. None of the trials met the inclusion criteria therefore no conclusions could be drawn.

The Committee heard that a number of small studies investigating the use of melatonin in adults have been published which were consistent in showing ~30 minute improvement in TST, however, they were outside of the scope of the above systematic review.

The Committee reviewed a recent study (sponsored by the HTA) where subjects were randomised to receive immediate-release melatonin or placebo in doses of 0.5mg to 12mg for a period of 12 weeks. A total of 275 patients were screened and 146 (53%) patients were randomised. Of the 146 patients randomised, 110 contributed data for the primary endpoint. The primary objective was to determine whether melatonin was beneficial compared with placebo in improving total sleep time (TST), calculated using sleep diaries at 12 weeks. A key secondary outcome was sleep-onset latency (SOL, time taken to fall asleep). Study subjects were aged between 3 and 15 years, with a minimum 5-month history of impaired sleep. The mean difference in TST (adjusted for baseline mean TST) was +22.43 minutes (95% CI 0.52 to 44.34 minutes) in the melatonin group, however, this was less than the *a priori* minimum clinically important difference of 60 minutes. The mean difference in SOL (adjusted for baseline mean SOL) was -37.49 minutes in the melatonin group. The change in 12 week score for sleep quality was small and therefore not clinically or statistically significant.

The Committee was informed that the short term adverse events of melatonin include rash, hypothermia and headache however the cBNF warns that little is known about its long-term effects in children. There is uncertainty as to the effect on other circadian rhythms including endocrine or reproductive hormone secretion. As such the need to continue melatonin therapy should be reviewed every 6 months. Furthermore, the cBNF notes variability in clinical effect of each unlicensed immediate-release melatonin preparation which poses concerns in continuity of supply particularly in the event of manufacturing issues resulting in shortages.

The Committee heard that several points for clarification had been raised with Dr Quinlivan, however no response has been received. This includes further clarification on monitoring, stopping criteria and the role of melatonin relative to other agents such as hypnotics and sedatives.

The Committee heard that modified-release melatonin is the only licensed preparation within the UK (also the cheapest formulation) but is only licensed for adult patients > 55 years old with primary insomnia. Based on the above study, the annual cost for use of an unlicensed immediate-release preparation could range from £600 to £3,000 per patient per annum depending on the dose prescribed and the product available.

On reflection of the above discussion, the Committee agreed that a number of outstanding points required addressing before a final decision could be made on whether melatonin should be included on the NCL JFC Formulary for sleep disorders. The Committee suggested that Dr Quinlivan be re-invited to the next meeting.

Action: Mr Bodalia to re-invite Dr Quinlivan to attend the JFC meeting

7.2 Secukinumab (Cosentyx®) for Plaque Psoriasis (Applicant: RFH/UCLH; Presentation: Mr P Bodalia)

The Committee reviewed an application for secukinumab for adult patients with moderate to severe psoriasis who were candidates for systemic biologic therapy according to NICE criteria. The place in therapy is for patients who have failed, or have contra-indications to the existing biological agents available for psoriasis (adalimumab, etanercept and ustekinumab).

The Committee heard that NICE recommends use of the Psoriasis Area and Severity Index (PASI) to assess the severity of psoriasis in specialist settings. The PASI has a range from 0 to 72 where mild disease is PASI ≤10 and moderate to severe disease is PASI >10. NICE also use DLQI as a dermatology quality of life index which ranges from 0 (no effect on life) to 30 (extremely large effect on quality of life).

NICE Clinical Guidance 153 recommends the use of biological agents (etanercept, adalimumab, ustekinumab) in patients with a PASI score ≥10 and DLQI ≥ 10 (for infliximab PASI of ≥ 20 or more and a DLQI > 18) who have failed to respond or are intolerant to standard systemic therapies. NICE stipulates that if the individual fails to respond adequately to a first biological drug (primary failure) or the psoriasis initially responds adequately but subsequently loses this response (secondary failure), or does not tolerate the treatment or has any contraindication, a switch to an alternative biologic can be considered. Adequate response is defined as either a 75% reduction in the PASI (PASI 75) or a 50% reduction in the PASI (PASI 50) and a 5-point reduction in the DLQI.

The Committee were informed that secukinumab (subcutaneous injection) is a first-in-class fully humanised monoclonal antibody acting against interleukin-17A offering an alternative mode of action to existing biologic treatments. The evidence reviewed came from two phase III, active-controlled, RCTs (FIXTURE and CLEAR).

The FIXTURE study (n=1306) was a multicentre, double blind RCT with patients randomly assigned to secukinumab 300mg, secukinumab 150mg, etanercept or placebo. The inclusion criteria were patients' ≥18 years with mild-to-severe plaque psoriasis (PASI ≥12, Investigator's Global Assessment (IGA) 3-4 and ≥10% involvement of body surface area) and poorly controlled with topical treatments, phototherapy and/or systemic therapies. Patients received secukinumab 300mg or 150mg by subcutaneous injection once a week for 5 weeks then every 4 weeks until week 48. Patients assigned to etanercept received 50mg twice a week until week 12 then weekly until week 51. The primary endpoint was to show superiority of secukinumab over placebo at week 12 with respect to the proportion of patients who had a reduction of ≥ 75% PASI score. The PASI 75 response rates were 77.1%, 67%, 44% and 4.9% for secukinumab 300mg, secukinumab 150mg, etanercept and placebo, respectively at week 12 (statistically significant superiority for secukinumab against etanercept and placebo). The 12-week PASI 100 response was 24.1% for secukinumab 300mg compared to 4.3% in etanercept group and 0% in placebo group.

The CLEAR study (n=679, abstract only) was a multicentre, double-blind RCT in moderate-to-severe plaque psoriasis where secukinumab 300mg compared to ustekinumab. The primary endpoint was the proportion of patients achieving PASI 90 response at week 16. Secukinumab met the primary endpoint of showing superiority to ustekinumab (79.0% vs. 57.6%, $p<0.0001$). Secondary endpoints include completely clear skin (PASI 100) at week 16 that was achieved in 44.3% of the patients compared to 28.4% with ustekinumab ($p<0.0001$).

The Committee reviewed the incidence of adverse events associated with secukinumab and found that it was similar to etanercept, up to week 52. The most common adverse events were upper respiratory tract infections, candida infections, headache and diarrhoea and were mild or moderate in severity. The Committee heard that two other drugs acting against interleukin-17A are in development with one reporting outcomes similar to those reported for secukinumab, and as such considered the treatment effect to be genuine.

The list price of secukinumab is currently unknown, but the manufacturer (Novartis) have agreed to supply secukinumab free-of-charge under an early access scheme (EAS) pre-NICE and for 90 days post-NICE. The EAS also commits Novartis to supply secukinumab indefinitely (free-of-charge) for patients who are started and NICE subsequently rejects secukinumab. It was discussed that the NICE eligibility criteria for secukinumab may be different to NICE CG153 biologic eligibility criteria; in this event, the manufacturer must continue to supply the drug for patients initiated on secukinumab.*

The Committee approved the use of secukinumab for patients who have failed, or have contra-indications to the existing biological agents available for psoriasis (adalimumab, etanercept and ustekinumab) if the manufacturer agrees to continue FOC supply in patients who meet NICE CG153 criteria (known) but do not meet NICE secukinumab eligibility criteria (currently unknown). The Committee therefore agreed to include secukinumab on the NCL Joint Formulary.

**Post meeting: On 29th May, NICE published a FAD recommending secukinumab in line with NICE CG153 as part of a patent access scheme therefore no further action is required*

7.3 Bemfola for IVF therapy (Applicant: UCLH/NMUH; Presentation: Mr P Bodalia)

The Committee reviewed an application for the use of Bemfola® (recombinant human FSH; rhFSH; biosimilar follitropin alfa) as part of assisted reproductive technologies (IVF).

The Committee were informed that NICE Clinical Guideline 156 recommends the use of either urinary or recombinant gonadotrophins, making no distinction between the two in relation to efficacy or safety. A recent Cochrane review also found that there was no difference in live birth rate, severe ovarian hyperstimulation syndrome (OHSS), or any of the other outcomes reported between rhFSH and urinary gonadotrophins. rhFSH is available as Gonal-F® and a new biosimilar called Bemfola® with identical licensing. The Reproductive Medicines Unit at UCLH (the largest area of use within NCL) uses Menopur (a urinary gonadotrophin) which contains the two hormones FSH and LH.

The Committee reviewed the supportive evidence for Bemfola which consisted of a single, phase-III assessor-blinded RCT (n=372). Participants were women aged 20-38 years old undergoing stimulation of multi-follicular development for superovulation for assisted reproductive therapy (ART). The women were randomised to receive either Bemfola or Gonal-F in a 2:1 ratio. The primary efficacy endpoint was the number of oocytes retrieved. The predefined equivalence margin was set at a maximal mean difference of ±2.9 retrieved oocytes. Analysis of results using the per-protocol population consisted of 220 patients in the Bemfola arm and 113 patients in the Gonal-F arm. The mean (±SD) number of oocytes retrieved was 10.8 (±5.11) for Bemfola and 10.6 (±6.06) for Gonal-F; thereby demonstrating a treatment difference of 0.27 (p=0.0003) and thus clinical equivalence. Similar results were reported for the intention-to-treat (ITT) population (10.7 ± 5.62 vs. 10.4 ± 6.14, respectively). There was a non-statistically significant increase in the incidence of OHSS.

Although the clinical trial data for Bemfola submitted for regulatory approval was in women undergoing ART only, the Committee noted that the EMA found that on the basis of data demonstrating equivalence of Bemfola to Gonal-F, they allowed for extrapolation to all the licensed indications for Gonal-F.

With regards to convenience and patient safety, the Committee were informed that Menopur is available in a pack which contains vials (containing powder) requiring reconstitution with saline and drawing up via a needle and syringe. Bemfola is a pre-filled pen and is therefore more convenient for patients with a lower risk of needle stick injury. It was noted that if Bemfola was already approved for this indication at GSTT and KCH. Given the short cycle length, it is anticipated that patients would not be switched from Menopur to Bemfola and therefore would be for new patients only.

The Committee heard that the contract price for Bemfola was roughly 25% less than Menopur. Following a discussion with the RMU team, it is anticipated that Bemfola could be used in approximately two-thirds of their patients which would release a saving in the region of £60,000. The remaining patients who have severe LH deficiency will require Menopur (FSH and LH). Further savings (circa £60,000) may be possible if provision via the Homecare route is considered suitable. The Committee noted that this was an in-tariff drug therefore savings would be realised by the hospitals.

In summary, the Committee approved the use of Bemfola as part of IVF therapy in patients who do not require LH (where Menopur would be clinically suitable). The Committee therefore agreed to include Bemfola on the NCL Joint Formulary.

7.4 Rituximab for ANCA-related vasculitis (Applicant: Prof M Ehrenstein; Presentation: Ms S Sanghvi)

The Committee reviewed an application for the use of rituximab for the induction and maintenance treatment of severe ANCA-vasculitis (all types; Wegener's, microscopic polyangitis [MPA] and eosinophilic granulomatosis with polyangitis [EGPA]). The Committee heard that the submission is taken from an NHS England Clinical Commissioning Policy statement which updates and supersedes prior NICE guidance. The Committee heard that differences relate to (i) rituximab positioning for induction, (ii) rituximab induction dose, (iii) the types of ANCA-vasculitis included, and (iv) the use of rituximab for maintenance therapy.

NICE recommends the use of rituximab for the treatment of ANCA-associated vasculitis (Wegener's and MPA), if specific criteria are met:

- The disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months; OR
- Cyclophosphamide is contraindicated (as defined in the summary of product characteristics) or not tolerated; OR
- The person has not completed their family and treatment with cyclophosphamide may materially affect their fertility; OR
- Further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose (25g); OR
- The person has had uroepithelial malignancy.

The Committee were informed that the maximum cumulative cyclophosphamide dose (25g) is equivalent to two induction course of IV cyclophosphamide which therefore positions routine use of rituximab at the time of second relapse. The Committee reviewed the RAVE trial (relapsing patients) which found that rituximab is more effective than cyclophosphamide. As cyclophosphamide toxicity is likely to increase before a threshold of 25g is reached the Committee appreciated the clinical and cost-effective justification for using rituximab at first relapse, before a threshold of 25g cyclophosphamide is reached.

The Committee understood that NICE is restricted to assess drugs within their Marketing Authorisation at their licensed doses, i.e. rituximab dose of 4 weekly infusions of 375mg/m^2. In England currently, routine clinical practice is to use two 1g infusions two weeks apart. This regimen results in a lower total dose of rituximab delivered over a shorter period of time and is therefore more convenient for patients. The clinical consensus is that both protocols appear equally effective. If the lower dose schedule is employed, there is a significant NHS cost saving in terms of reduced NHS activity (50%) and reduced drug costs (40%) compared to the higher licensed dose.

The Committee noted that NICE only appraised rituximab for the two most common types of ANCA associated vasculitis (Wegener's and MPA). Although the third subtype, EGPA, is much rarer (10% of all cases), it shares similar clinical features and identical treatment strategies to the other two conditions. Despite the absence of large trials of rituximab for EGPA because of its rarity, case series data suggest similar efficacy to that seen in the other two subtypes.

The Committee also noted that maintenance treatment with rituximab was outside the scope of the NICE guidance. Due to the pivotal importance of preventing relapse, there is a subgroup of patients for whom maintenance rituximab is required. Evidence to support maintenance therapy was provided by the MAINRITSAN trial which compared rituximab to azathioprine to maintain ANCA-associated vasculitis remission in a largely new-onset GPA/MPA patient cohort. Following remission with cyclophosphamide, patients were randomly assigned to receive two 500mg rituximab infusions at six months, then every 6 months for a total of 5 infusions (2500mg) over 18 months, or azathioprine for 22 months at an initial dose of 2mg/kg/day. The primary endpoint was the major relapse rate at 28 months. This study demonstrated that rituximab was superior to azathioprine to maintain ANCA-associated vasculitis remission at mean duration of follow-up 34.3 months. Six out of 56 (10.7%) rituximab patients and 24/53 (45.3%) azathioprine patients had at least one major relapse. The risk of major relapse remained lower in the rituximab arm compared to the azathioprine arm (hazard ratio 0.18, 95% CI 0.09 to 0.42, p <0.0001).

The Committee discussed the current contractual arrangements that each hospital within NCL currently has with NHSE, i.e. that all are currently on the 'deferred tariff option', and on that basis were unclear whether or not hospitals on such tariff are eligible to access drugs within newly published NHS England Clinical Commissioning Policies. Ms Spicer confirmed that the RFH have an arrangement for their site.

The Committee approved the use of rituximab in line with the criteria for commissioning within NHS England Clinical Commissioning Policy A13/P/a for Trusts that are eligible to access the policy.
Action: Mr Bodalia to clarify whether NHS England will fund this policy under the emergency contract.

7.5 Sildenafil and bosentan for digital ulceration in systemic sclerosis (Applicant: Prof M Ehrenstein; Presentation: Ms S Sanghvi)

The Committee reviewed an application for the use of sildenafil and bosentan for digital ulceration (DU) in systemic sclerosis (SSc). The Committee heard that the submission is taken from an NHS England Clinical Commissioning Policy statement.

The Committee reviewed the evidence for bosentan for the reduction of DU in SSc. The RAPIDS-1 included 122 patients treated for 16 weeks with either bosentan or placebo and showed a 48% reduction in the formation of new ulcers during this period. Patients with DU at the start of the trial were more at risk of developing ulcers, but a 50% reduction in new ulcer formation was also demonstrated in this subgroup. A significant improvement in hand function was demonstrated in the bosentan-treated patients. In the subsequent RAPIDS-2 study, all SSc patients (n=188) had active DU at commencement of the trial and were followed for 24 weeks. Bosentan treatment was associated with a 30% reduction in new ulcer formation compared with placebo although no effect on DU healing was found. Post hoc analysis suggested that patients with more severe DU disease obtained the most benefit as cases with very high number of new ulcers were only seen in the placebo treated cases and there was more benefit in patients with 3 or 4 ulcers at study onset. Also, in RAPIDS-1, those who had an active ulcer at start of the study benefitted more than those with just a history of previous DU. The results of the above randomised, placebo-controlled studies are borne out in observational studies for up to 3 years.

The Committee noted the results of a meta-analysis which found that PDE-5 inhibitors resulted in significant DU healing (RR 3.28, [95% confidence interval (95% CI) 1.32, 8.13], p=0.01), bosentan significantly reduced mean number of new DUs (standardised mean difference (SMD) -0.34, [95% CI -0.57, -0.11],p=0.004) and IV iloprost significantly prevented new DU formation (SMD -0.77, [95% CI -1.46, -0.08], p=0.03).

The Committee acknowledged that NHS England would fund both sildenafil and bosentan if used in line with the UK Scleroderma Study Group (UKSSG) pathway and that the majority of patients with DU in SSc will be treated at the Royal Free Hospital.

As with the above application the Committee were unsure if Trusts on the 'deferred tariff option' would be eligible to access this however Ms Spicer confirmed that the RFH have an arrangement for their site.

The Committee approved the use of sildenafil and bosentan in line with the criteria for commissioning within NHS England Clinical Commissioning Policy A13/P/e for Trusts that are eligible to access the policy.
Action: Mr Bodalia to clarify whether NHS England will fund this policy under the emergency contract.

8. Local DTC recommendations / minutes

RFH

- Tirofiban for use in place of abciximab as the GPI of choice for MI pts undergoing PPCI –approved on clinical grounds,
- Bedaquiline for multi/ extensively drug- resistant TB when there are no other suitable options to form a treatment regimen, due to resistance or intolerance. Review in 18 months' time, approved on clinical grounds,
- Octreotide LAR formulation (in place of the standard SC formulation) for chylous ascites. Approved on clinical grounds for single case,
- Ambrisentan for CTEPH in single patient on compassionate access basis, following clinical trial cessation. Approved on clinical grounds and review when NHSE clinical commissioning policy is available in future.

UCLH

- FOLFIRI for 2nd or 3rd line treatment for inoperable gastro-oesophageal adenocarcinoma
- FOLFOXIRI for 1st line treatment for unresectable metastatic colorectal cancer

9. Next meeting

Thursday 25th June, Room 6LM1, Stephenson House, 75 Hampstead Rd.

10. Any Other Business

Nil