North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 23 February 2017
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Ms K Landeryou	Patient Partner	
	Dr R Fox	RNOH, DTC Chair	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Mr T James	MEH, Chief Pharmacist	
	Dr R Sofat	UCLH, DTC Chair	
	Dr M Kelsey	WH, Chair DTC	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr S Richardson	WH, Chief Pharmacist	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr V Thiagarasah	Enfield CCG, GP	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
In attendance:	Mr A Barron	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms H Mehta	NMUH, Formulary Pharmacist	
	Dr H Amer	UCLH, SpR Clinical Pharmacology	
	Dr A Shah	UCLH, SpR Clinical Pharmacology	
	Ms M Kassam	MEH, Formulary Pharmacist	
	Mr C Corfield	NWL, Head of Medicines Management	
	Dr L Restrick	WH, Consultant in Respiratory Medicine	
	Dr S Wolfman	GP, Barnet	
	Dr R Wakeel	RFL, Consultant Dermatologist	
	Mr R Hamid	UCLH, Consultant Urologist	
	Mr S Chitale	WH, Consultant Urologist	
	Ms L Smedts	Erasmus student, Netherlands	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr P Hyatt	NMUH, DTC Chair	
	Dr S Shaw	RFL, DTC Chair	
	Ms W Spicer	RFL, Chief Pharmacist	
	Prof D Robinson	UCLH, Consultant in Respiratory Medicine	
	Prof A Tufail	MEH, DTC Chair	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Mr J Minshull	NCL JFC, Support Pharmacist	
	Ms A Fakoya	NEL CSU, Assistant Director Acute Services	

2. Meeting observers

Prof MacAllister informed the Committee that Dr McGuiness (Patient Partner) has stepped down from the Committee owing to other commitments. The Committee thanked Dr McGuiness for her valued contributions. Mr Corfield (NWL CCG Lead) and Ms Smedts (Erasmus student, Netherlands) were welcomed as observers of the meeting.

3. Minutes of the last meeting

These were accepted as accurate.

3.1 Actions from the last meeting

Item 6.1 'Local DTC recommendations approved by DTC': Ms Samuel informed the Committee that NHSE had published the clinical commission policy (16055/P) in January 2017 concluding that riociguat will NOT be routinely commissioned for PAH.

Item 6.2 'Local DTC recommendations approved under evaluation by DTC': Mr Barron had requested a set of outcomes for RFL to collect as part of their evaluation of ketoconazole in metastatic hormone refractory prostate cancer (third-line and beyond); these included QoL (e.g. EORTC QLQ-C30), pain score VAS, PSA, adverse events and suspected drug-related adverse events.

Item 7.1 'Vernakalant for new-onset atrial fibrillation': The vernakalant data collection form had been approved by Prof MacAllister and the RFL DTC.

Item 7.3 'Ropivacaine for total hip replacement (THR) and total knee replacement (TKR)': UCLH Medicines Information Department has established there was no data confirming compatibility of ropivacaine, ketorolac and epinephrine. However, all were found to be stable in sodium chloride 0.9% and had similar pH ranges therefore compatibility was likely. Furthermore, three studies had used the combination without reporting complications.

Item 9 'JFC Conduct Survey': As a recommendation from the survey, JFC Support prepared a PowerPoint® presentation for Item 7.3 'Enstilar (calcipotriol and betamethasone) cutaneous foam for psoriasis'.

The actions under Item 7.2 'Thyrotopin alfa for patients requiring ablation' and Item 8.2 'Bisphosphonates holiday' were deferred to the next JFC meeting.

4. Matters arising

4.1 APPEAL: Relvar Ellipta (fluticasone furoate and vilanterol) in COPD

This item was considered alongside Item 7.1 'Incruse Ellipta for COPD' and 7.2 'Tiotropium (Braltus®) for COPD'. The Chair welcomed Dr Restrick to answer the Committee's questions about the appeal.

The JFC originally considered an application for Relvar Ellipta inhaler in April 2014, when the Committee noted that this inhaler demonstrated non-inferiority in COPD to existing combination inhalers. At the time, the Committee did not approve Relvar Ellipta for use in NCL for a number of reasons, including the likelihood that that the generic inhaler market would introduce price competition.

The Committee heard from Dr Restrick that the multi-disciplinary Respiratory Responsible Prescribing Group (RRP) in Camden, Islington and Haringey had been established for 15 years to rationalise treatment of COPD. This group had recently updated their COPD guidance. The RRP consider there to be an opportunity cost for time spent discussing inhaler choice with patients and subsequently there was an incentive to minimise the choice of inhalers available on the Formulary. A focus for the RRP over the last two years was to identify the devices patients prefer. The RRP's longstanding philosophy that a pressurised meters dose inhaler (pMDI) with a spacer is the default choice but this does not give patient a range of choices. Patients in 'Breathe Easy' and 'Pulmonary Rehabilitation' groups have stated a preference for Ellipta device because it is easy to use and has a visible counter.

To minimise time wasted on re-training patients on their inhaler choice, the RRP request the Ellipta device is available for Step 2 (umeclidionium), Step 3 (umeclidinium + vilanterol) and Step 4 (fluticasone furoate + vilanterol) COPD inhaler therapy. The Ellipta device can be used at an inspiratory flow rate of 30L/min.

There are unlikely to be clinically meaningful differences between devices so the RRP choice was based on patient preference; the RRP currently have no mandate over Barnet and Enfield, therefore clinicians in this area may opt to select different devices. Limited data suggests optimal use of the Respimat device is independent of inspiratory effort, however the RRP did not request this device as it was rejected as an option by the patient groups.

Relvar Ellipta has recently had a price decrease, making it less expensive than other ICS/LAMA inhalers (Seretide MDI and Sirdupla MDI). As the price of Relvar has fallen further than generic salmeterol +

fluticasone propionate, the Committee agreed to add Relvar Ellipta to the NCL Joint Formulary to minimise the opportunity cost from switching devices and to support drug-cost minimisation.

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

5. Declarations of relevant conflicts of interest

There were no declarations of interest.

6. Local DTC recommendations / minutes

6.1 Approved by local DTC

This item was deferred to the next meeting.

7. New Medicine Reviews

7.1 Incruse Ellipta (umeclidinium) for COPD (Applicant: Dr L Restrick, WH)

This item was considered alongside Item 4.1 'APPEAL: Relvar Ellipta in COPD' and 7.2 'Tiotropium (Braltus®) for COPD'.

The key clinical evidence considered by the Committee was presented in a NICE Evidence Summary for umeclidinium inhaler in COPD (January 2015). Effectiveness of umeclidinium was demonstrated in two RCTs, both of which used change in FEV_1 as the primary outcome and neither of which compared treatment with the established LAMA (tiotropium). In the first study (Trivedi *et al* 2014), umeclidinium 55 micrograms daily was associated with an improved FEV_1 at day 85 of 120 mL compared to baseline, which was 127 mL better than placebo FEV_1 at day 85 (95% CI 0.052 to 0.202, p<0.001). St George's Respiratory Questionnaire (SGRQ) score was also statistically significantly improved with umeclidinium compared to placebo (difference -7.9, 95% CI: -12.2 to -3.6; p<0.001). Transition Dyspnoea Index (TDI) did not change.

Donohue *et al* (2013) saw patients randomised to umeclidinium/vilanterol, umeclidinium, vilanterol or placebo. At day 169, umeclidinium therapy led to an improvement in FEV_1 of 119 mL compared to baseline; vilanterol monotherapy saw FEV_1 improved by 76 mL; and placebo saw FEV_1 improve by 4 mL. Umeclidinium was therefore associated with an improvement over placebo at day 169 of 115 mL (95% CI: 0.076 to 0.155; p<0.001). TDI was associated with an improvement of 1 point compared to placebo (95% CI 0.5 to 1.5; P<0.001) and SGRQ improved by -4.69 points (95% CI -7.07 to -2.31; p<0.001).

The Committee discussed findings from a network meta-analysis (Ismaila *et al* 2015) that compared the efficacy of the four LAMA drugs on the market for treatment of COPD. This study was supported by GSK (manufacturers of umeclidinium). Seventeen on the twenty-four included studies measured change in FEV_1 at 12 weeks (n=11,935), with all LAMAs reporting a mean change compared to placebo greater than the 100 mL considered to be the minimally clinically relevant difference. Umeclidinium demonstrated the largest improvement (137 mL), followed by glycopyrronium (117 mL) and tiotropium (114 mL). The authors attempted to compare to umeclidinium to tiotropium, estimating an FEV_1 improvement of +22.6 mL favouring umeclidinium (not statistically significant and unlikely to be clinically meaningful). SGRQ and TDI were both improved at 24 weeks with any LAMA therapy compared to placebo, with the exception that improvement in TDI was not clinically meaningful at 24 weeks for tiotropium therapy. The Committee concluded that this meta-analysis demonstrated that all LAMAs have very similar effects; therefore it is difficult to determine that one is superior to another.

As with tiotropium, umeclidinium use may lead to cardiac arrhythmias, atrial fibrillation and tachycardia; therefore it should be used with caution in this patient group.

The Committee noted that the umeclidinium inhaler offered a cost saving of £6/patient/month when compared to the originator LAMA inhaler (Spiriva® Handihaler), yet was slightly more expensive (+£1.70/patient/month) than the bioequivalent tiotropium device (Braltus® Zonda) [see item 7.2]. As LAMA therapy is a key part of COPD treatment, there are potentially large cost-savings to be achieved from careful selection of LAMA therapy.

In the closed session, the Committee discussed the reason for adding Incruse Ellipta was to minimise the number of devices, rather than an inherent advantage of the molecule itself. It was unclear whether any inhalers could be removed from the NCL Joint Formulary however it was noted that Barnet and Enfield

were not part of the RRP and some clinicians in these areas believed more devices leads to better choice and subsequently improved outcomes. The Committee would have been more sympathetic to this view 15 years ago when dry powder inhalers were limited to Diskhalers and Accuhalers, however devices are now much improved and a large range of choices was not considered clinically necessary. The Committee agreed to add Incruse Ellipta to the NCL Joint Formulary for COPD to support patient preference and streamline the number of devices on the formulary.

Action: Mr Minshull to consolidate all the inhalers on formulary for COPD in NCL and bring to March JFC.

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

7.2 Tiotropium Zonda Inhaler (Braltus®) for COPD (Applicant: Mr P Gouldstone, Enfield CCG)

This item was considered alongside Item 4.1 'APPEAL: Relvar Ellipta in COPD' and 7.1 'Incruse Ellipta (umeclidinium) for COPD'.

The Committee considered an application for Braltus® Zonda inhaler (tiotropium bromide) for treatment of patients with COPD. This device and drug combination was recently approved by the MHRA as bioequivalent to Spiriva® Handihaler® (tiotropium bromide). Braltus® was developed following the patent expiry for Spiriva® Handihaler®, therefore represents a "generic" alternative to the originator product. Bioequivalence was accepted by MHRA based on the findings of three pharmacokinetic studies and two inhalation characteristic studies.

The Committee considered the risk of dosing errors; Braltus is labelled as 10mcg 'delivered dose' where Spiriva is labelled as 18mcg 'pre-meter dose' and both deliver the same dose. The risk of clinicians trying to match 'mcg for mcg' was thought to be very low because the unit dose of 1 capsule would prevent this.

Transitioning established Spiriva Handihaler patients to Braltus would save approximately £140,000 per quarter in NCL. The Committee heard from Dr Restrick that the RRP generally consider switching to be bad for patient care and unlikely to be cost-effective due to time required to re-train patients which was estimated to be 30 minutes per patient. However in the case of Braltus, patient feedback was that they preferred the Zonda device to the Handihaler because it has a longer mouthpiece, a new inhaler is provided each month and the capsules are clear allowing patients to visualise successful inhaler technique. The RRP propose to use Braltus for all new patients, and if it is successful, it may become a self-fulfilling easy switch because patients will request this device thereby reducing the time taken to perform the switch. The Committee heard the Camden MMT, which includes practice nurses and GPs, thought switch counselling would take less than 30 minutes and could be built into a patient's COPD review.

In camera, the Committee agreed the overall saving to the health economy was large and there was no evidence to suggest this switch would destabilise patients given that the active ingredient is the same and the devices are very similar. The Committee agreed to add Braltus to the NCL Joint Formulary for COPD to support patient preference and drug-cost minimisation.

Action: Mr Minshull to identify how to obtain placebo Braltus devices to be used to train patients on the Braltus device. Mr Minshull to consolidate all the inhalers on formulary for COPD in NCL and bring to March JFC.

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

7.3 Enstilar (calcipotriol and betamethasone) cutaneous foam for psoriasis (Applicant: Dr S Wolfman, Barnet and Dr R Wakeel, WH)

The Committee discussed an application to use Enstilar (calcipotriol/betamethasone cutaneous foam) as second-line therapy for patients who require a combination therapy and have adherence issues with

separate mono-component therapies. The Chair welcomed Dr Wolfman and Dr Wakeel to answer the Committee's questions about the application.

PSO-ABLE was a prospective, investigator-blinded, 12-week, randomised controlled trial. Adult patients with mild-to-severe psoriasis limited to the trunk and limbs were included. Patients were randomised to Enstilar, Dovobet gel or vehicles. Results found a significantly larger proportion of Enstilar-treated patients achieved treatment success at week 4, compared with Dovobet-treated patients at week 8 (38.3% vs. 22.5%; odds ratio [OR] 2.55, [95% CI: 1.46 to 4.46]). Results for mean change in mPASI score and the proportion of patients achieving mPASI-75 were correspondingly superior with Enstilar at week 4 than Dovobet at week 8. By week 12, a greater proportion of Enstilar-treated patients had achieved treatment success, compared with Dovobet (44.1% vs. 34.3%, p=unknown).

Koo et al. conducted a prospective, investigator-blinded, 4-week, randomised controlled trial. Study design was otherwise similar to PSO-ABLE with patients randomised to Enstilar, Dobovet ointment or vehicles. Results at week 4, showed significantly more patients using Enstilar achieved treatment success (54.6% versus 43.0%; p = 0.025); mean mPASI was significantly different between Enstilar and Dovobet (mean difference -0.6; p = 0.005) and subsequently a greater proportion of patients using Enstilar achieved mPASI75 although the difference was not statistically significant (PASI75: 50.4 versus 40.7%; OR 1.7 [95% CI = 1.0 to 2.7; p=0.052]).

With regards to safety, PSO-ABLE reported one serious AE related to Enstilar treatment (exacerbation of psoriasis after 69 days of treatment) which was not reported with Dovobet gel. ADRs were reported in 14 patients (7.6%) with Enstilar and 7 (3.7%) with Dovobet gel. The Koo et al. study did not report any serious AEs considered related to Enstilar or Dovobet ointment, however this was smaller and shorter in design. ADRs were reported in 1 patient (0.7%) with Enstilar, and 4 (3.0%) with Dovobet ointment.

With regards to convenience, a numerically greater proportion of patients receiving Enstilar than Dovobet gel favoured their study treatment over previous treatments. These findings were at high risk of bias as the participants were un-blinded to their study treatment.

Drugs costs per gram for Enstilar were identical to Dovobet ointment (the most appropriate comparator) and similar to Dovobet gel. All three combination products were significantly more expensive than applying calcipotriol and betamethasone separately. There was uncertainty regarding the amount of product used per patient; PSO-ABLE reported higher Enstilar use (236g vs. 193g over the duration of the 12 week trial) which may have contributed to the higher reported success rates with Enstilar. Despite this, the applicant and Leo Pharma estimate lower average Enstilar use for the 4 week licensed duration (117g vs. 137g for Dovobet ointment). Consequentially the budget impact in NCL was uncertain.

The Committee heard from Dr Stuart and Dr Wakeel that it was difficult to undertake a double-blind trial comparing a foam to an ointment or gel; using a double-blind double-vehicle study would lead to misleading results due to the effect size of the vehicle. The JFC considered this to be a tractable issue in the design of these trials. The applicants claimed that Enstilar foam is a super-saturated vehicle which includes penetrating enhancers to allow the active drugs to penetrate more quickly and improve the bioavailability to the skin; however the only additional excipients listed in the Enstilar SPC were propellants (butane and dimethyl ether) therefore this claim could not be confirmed.

In camera, the Committee were divided over the benefits of a once-daily preparation, and whether the doubling of costs between separates and combined products could be justified. There were concerns that combination products increase the likelihood of patients applying prolonged courses of topical corticosteroids, compared with separates, which would increase the risk of rebound psoriasis. The risk could be greater with Enstilar due to the larger doses used in PSO-ABLE. The Committee considered the quality of evidence; both studies were single-blinded and used subjective outcomes, the Koo et al. study did not include a power calculation and was therefore considered hypothesis generating only. The PSO-ABLE used the wrong comparator (gel not ointment) and its design was based on a sample size calculation that proposed an absolute treatment effect of 28% which was difficult to justify on scientific or statistical grounds.

The Committee voted on whether to approve Enstilar for addition to the NCL Joint Formulary; 6 voted in favour, 12 against. In summary the Committee was not satisfied that the trials were adequately designed and was unconvinced of the need for an additional once-daily combination preparation. Separate mono-component therapies should be encouraged to improve skin hydration, minimise the risk topical corticosteroids being continued for extended periods of time and reduce treatment costs.

Decision: Not approved

7.4 Hyacyst (sodium hyaluronate intravesical instillation) in interstitial cystitis (Applicant: Mr S Chitale, WH) and Parsons Solution for interstitial cystitis (Applicant: Mr R Hamid, UCLH)

The Committee considered a new application to use Hyacyst (sodium hyaluronate) intravesical instillation to manage the symptoms of interstitial cystitis / painful bladder syndrome. This application was triggered by the Committee following the October 2016 application for Parsons Solution (a mixture of heparin, lidocaine and sodium bicarbonate) for the same indication. The Committee considered whether there was need for either or both of these interventions.

In October 2016, the Committee decided not to approve Parsons Solution (a mixture of heparin, sodium bicarbonate and lidocaine) due to the poor quality data and uncertainty over where this intervention fits in with other treatment options. The RFL advised the Committee that they are interested in using Hyacyst as it is less expensive than Cystistat (also hyaluronic acid), which they are currently using.

The Committee noted that interstitial cystitis (also known as Painful Bladder Syndrome (PBS)) is a chronic urogenital syndrome associated with pain, urinary frequency and urgency, in the absence of any other pathological cause (e.g. stones of infection). Intravesical instillations are considered a third-line treatment option following non-pharmacological intervention (first-line) and oral therapy (second-line).

There is a lack of controlled-trial evidence to support use of hyaluronic acid instillations. The evidence base is limited to three unpublished RCTs with negative findings; two open-label RCTs comparing different hyaluronic acid regimens; one controlled study comparing hyaluronic acid to heparin; and a number of uncontrolled case-series. Established evidence-based guidelines are cautious in recommending intravesical hyaluronic acid as an option due to the existence of the three unpublished RCTs, which failed to demonstrate symptomatic benefit of hyaluronic acid. Guidelines are equally cautious when recommending intravesical heparin (alone or in combination with lidocaine and sodium bicarbonate). Despite the lack of high quality published evidence, the applicant reported that in his experience approximately 40% of patients respond to treatment with Hyacyst; only those patients that demonstrate a response from the first cycle of treatment would be eligible to receive further courses.

The Committee acknowledged that the management of patients with interstitial cystitis is limited by a lack of useful treatment options available. The next treatment steps are Botox, pain management in conjunction with anaesthetics; <5% will go on to have cystectomy.

In summary, due to the three unpublished, large, RCTs demonstrating that Hyacyst is not an effective intervention, the Committee agreed that Hyacyst should not be included on the NCL Joint Formulary.

In considering Parsons Solution, the Committee had not much further to add from its previous assessment. Acute bladder pain relief was a likely benefit because the mixture includes lidocaine. The Committee could only see a role for this agent in the short-term management of acute flares, but did not think there was sufficient evidence to make claims about the long-term benefits of the medicine. Based on the lack of substantial data, the Committee confirmed its prior decision not to support the use of Parsons Solution. It was clear to the JFC that a review of the treatment pathway for pelvic pain and bladder pain across NCL was necessary. The Committee did not find that the evidence sufficiently supported a sustained treatment effect from either of these interventions. The Committee felt that treatment of this complicated syndrome requires multidisciplinary team input to address the psychological and medical needs of the patients and therefore should form part of the evaluation criteria.

In the interim the JFC could see a minor role for the administration of a local anaesthetic intravesically to diagnose and manage flares of bladder pain, and perhaps avoid the surgical removal of the bladder. This decision should be reviewed as part of a wider review of treatment pathway for these patients.

Hyacyst
Decision: Not approved

Parsons solution
Decision: Interim approval (restricted for specialist urology use only pending service review)
Prescribing: Secondary care
Tariff status: In tariff
Funding: Hospital budget
Fact sheet or shared care required: No
Audit required: Yes

Action: Prof MacAllister to discuss with the Whittington Hospital Directory of Strategy the need for a multidisciplinary approach for the management of lower urinary tract symptoms.

8. Guidelines

8.1 MEH Ocular lubricants guideline

This item was deferred to the next meeting.

9. Magnesium aspartate for replacement

This item was deferred to the next meeting.

10. NCL JFC - New Drug Application Form (update)

The New Drug Application Form was updated to enhance the description of the status quo, encourage pan-NCL consultation prior to submission to JFC and support the declaration of conflicts of interest. Ms Landeryou commented that the new form was an improvement from a Patient Partner's perspective as it newly included important questions such as how patients would be treated if the application was not approved and advantages for the patient over existing therapies/interventions. The Committee approved the updated form.

11. JFC Work plan

This item was deferred to the next meeting.

12. Next meeting

Thursday 30th March 2017, Room 6LM1, Stephenson House, 75 Hampstead Rd.

13. Any Other Business

The Committee requested JFC Support Pharmacists continue to present drug evaluations using PowerPoint® to support the verbal presentation.