North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 24 November 2016
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Mr T James	MEH, Chief Pharmacist	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Dr V Thiagarasah	Enfield CCG, GP	
	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 Kapoor	UCLH, Consultant Neurologist	
	Dr C McGuinness	Patient Partner	
	Mr TF Chan	RFL, Deputy Chief Pharmacist	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Dr R Sofat	UCLH, DTC Chair	
	Dr H Taylor	WH, Chief Pharmacist	
	Dr M Kelsey	WH, Chair DTC	
In attendance:	Mr J Minshull	NCL JFC, Support Pharmacist	
	Mr A Barron	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms A Fakoya	NEL CSU, Assistant Director Acute Services	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms A Saleemi	Islington CCG, Prescribing Advisor	
	Mr D Ralph	UCLH, Consultant Andrologist	
	Dr O Swayne	UCLH, Neurologist	
	Dr McBride	RFL, Dermatologist	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Prof A Tufail	MEH, DTC Chair	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Ms W Spicer	RFL, Chief Pharmacist	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr P Hyatt	NMUH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr S Shaw	RFL, DTC Chair	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Prof D Robinson	UCLH, Consultant in Respiratory Medicine	

2. Meeting observers

Prof MacAllister welcomed Ms Saleemi (NHS Islington, Pharmacist) as an observer of the meeting and explained the role of Joint Formulary Committee in NCL.

3. Minutes of the last meeting

The minutes should be updated in line with 4.1 'Relvar (fluticasone furoate / vilanterol trifenatate) for asthma' and were otherwise accepted as an accurate record of the meeting.

4. Matters arising

4.1 Relvar® (fluticasone furoate / vilanterol trifenatate) for asthma

Ms Clark asked for clarity on the process followed to add Relvar® inhalers to the formulary at the October 2016 meeting. The Chair reminded the Committee that it had agreed to accept Relvar® on to the formulary because we then knew it was cheaper than the generic ICS/LABA inhalers; this additional information meant that we were able to change our previous decision based on cost minimisation. There was no additional information required, which is why no paperwork was submitted.

The Chair reminded the Committee that it had asked Prof Robinson to liaise with the Responsible Respiratory Prescribing (RRP) group to gain consensus on how Relvar® will be used in NCL; this will be discussed at their February 2017 meeting. In the meantime, prescribing will be restricted to Prof Robinson for patients seen in his specialist clinic.

The Committee agreed to amend the October 2016 minutes to "…the Committee agreed to approve Relvar to support cost minimisation. Prof Robinson should liaise with the Responsible Respiratory Prescribing group to discuss how this will fit into their guidelines. In the interim, this will be restricted to prescribing by Prof Robinson for patients seen in his specialist clinic."

5. Declarations of relevant conflicts of interest

Mr A Barron declared that he has worked with Novartis on sacubitril valsartan (Entresto®); Novartis also manufacture secukinumab which is considered under item 8.1 'Ustekinumab, secukinumab or ixekizumab for Plaque psoriasis following failure of two anti-TNFs (etanercept, adalimumab or infliximab)'. No other conflicts of interest were declared by members of the Committee.

6. Local DTC recommendations / minutes

6.1 Approved by local DTC

DTC site	Month	Drug	Indication	JFC outcome
RFL	Sep-16	Sodium Fluoride	Imaging of skeletal metastases	RFL only
WH	Aug-16	Deferasirox film-coated tablets (**post-trial access only**)	Transfusion related iron-overload in transfusion dependant thalassaemia and sickle cell disease (or non-transfusion dependant iron overload in patients with thalassaemia intermedia)	Added to NCL Joint Formulary

7. New Medicine Reviews

7.1 Phentolamine & aviptadil (Invicorp®) for erectile dysfunction (Applicant: Mr Asif Muneer and Mr Suks Minhas, UCLH)

The Committee discussed an application for Invicorp®, an intracavernosal injection containing 2 mg phentolamine and 25 mcg aviptadil, for the treatment of erectile dysfunction in men who have failed to respond to oral PDE5i (sildenafil and tadalafil) and intracavernosal/urethral alprostadil. This will be started by a specialist urologist. The Chair welcomed Mr Ralph to answer the Committee's questions about the application

The Committee noted that efficacy has been demonstrated in three studies: two placebo-controlled and one which used alprostadil as an active comparator.

Shah *et al* reported the findings from a randomised, open-label, active comparator, cross over-study in 187 men. Patients were initially randomised to receive a single dose of Invicorp® or alprostadil, which was escalated until a grade 3 erection was achieved. Patient-completed diaries were then used to report the response to treatment. The proportion of injections that resulted in a grade 3 erection was similar in

all three treatment arms: 83% alprostadil, 84% Invicorp® ampoule, 85% in the Invicorp® auto-injector arm. It was noted that during the initial dose-finding phase fewer men had responded to Invicorp® (73%) than to alprostadil (83%).

Dinsmore *et al* reported a placebo-controlled study of a similar design, in a group of 236 men. The 82% of patients (n=192) who experienced a grade 3 erection following administration of the active drug were automatically enrolled in the second phase, again excluding anyone who wouldn't respond to the drug and setting participants up to be able to tell the difference between responses to study drug and placebo. A modified intention-to-treat population was used, based on patients who received at least one dose of study drug (and thus excluding anyone unwilling to comply with the injection regimen). 73% of men receiving treatment and 13% receiving placebo achieved a grade 3 erection. 56% of men who had discontinued previous ED treatment due to poor efficacy responded to Invicorp®.

Sandhu *et al* conducted a similar, placebo controlled study, finding that 83.9% of responded to treatment during the active treatment "dose finding phase". After twelve injections or six months (whichever happened first), patients diaries (records of response, duration and adverse events to each dose administered) were reviewed and physical examination, blood tests and ECG were performed. Patients were then entered into the second placebo-controlled phase; a dose increment could be made before entry into the second phase if deemed necessary. 73.7% treated with a low-dose combination of active drugs and 12.9% treated with placebo achieved grade 3 erections (with the lower dose of Invicorp®), compared to 69.1% (active) and 13.7% (placebo) in the higher dose Invicorp®, the committee noted that the lower response to higher Invicorp® doses is likely to be because this group of men were specifically also not responding to the lower dose. Of those patients to have withdrawn from previous therapy due to poor efficacy, 73% responded to Invicorp®.

The Committee noted that the studies all had significant methodological flaws such as screening out non-responders, including limitations to blinding in placebo-controlled studies. For example, a large number of patients (45%) dropped out of treatment in the Shah *et al* study between the screen and treatment phases.

The Committee was interested to note that penile fibrosis (including Peyronie's disease) is potential complications following administration, but noted this is also the case for alprostadil injections which are already on the formulary. Evidence from Shah *et al* indicates that Invicorp® may be associated with less pain than alprostadil injection is.

It was noted by the Committee that injections with Invicorp® will be less convenient than oral treatment with a PDE5i, and compared to treatment with alprostadil because it requires reconstitution before use. Patients will require administration training with the first prescription to ensure correct use. The impact of ongoing monitoring recommended every 3 months in urology clinic was noted.

The treatment pathway specifying where this drug will be used was reviewed and amendments were requested. The Committee noted that it had previously approved tadalafil PRN use in ED as a second line option for patients who experience idiosyncratic reactions to sildenafil. It was discussed that vacuum pumps for use in ED should initially be supplied by the hospital urology clinic and not by the GP.

In summary, the Committee agreed that the Invicorp® combination offers another potential treatment option for men with erectile dysfunction who have not responded to or have not tolerated alprostadil injections. The Committee acknowledged that due to its different mechanism of action, it is feasible that it would be effective where alprostadil had not demonstrated efficacy. Although Invicorp® is not yet subject to SLS prescribing restrictions, the Committee agreed to limit prescribing to those patients who would meet these criteria, as is the case with alprostadil prescribing.

Decision: Approved
Prescribing: Secondary care initiation, primary care continuation (SLS only)
Tariff status: In tariff
Funding: Hospital and GP budgets
Fact sheet or shared care required: No
Audit required: No

7.2 Rotigotine or co-careldopa for Hemispatial neglect (Applicant: Dr O Swayne, UCLH)

The Committee discussed an application for rotigotine or co-careldopa for hemispatial neglect. The Chair welcomed Dr Swayne to answer the Committee's questions about the application.

The inclusion criteria were adult patients with clinical stroke, or other acquired brain injury, causing clinically evident hemispatial neglect which has persisted since admission and was interfering with the progress of neurorehabilitation. The suitability for ongoing treatment would be assessed on an individual patient basis using an 'ABA' evaluation approach (outcomes at time period A1 [before treatment], B [on treatment] and A2 [off treatment]); response would be defined using bedside tests of hemispatial neglect (Star cancellation or Mesulam) and functional task assessment (e.g. dressing or kitchen activities).

Gorgoraptis et al. report a single centre, double-blind, randomized, placebo-controlled trial of rotigotine in 16 patients with left hemispatial neglect. The study was an 'ABA' design whereby all patients received placebo, then rotigotine 4mg/24hr patch, then placebo; however the duration of each period was blinded and randomised across patients. All patients received 20 assessments each testing spatial neglect (with the line bisection test from the BIT, Mesulam cancellation, bells cancellation and a visual search task performed on a computer), spatial working memory, selective and sustained attention, and motor performance. The primary objective was an improvement in neglect and cognitive components, the secondary objectives were improvement on motor performance. At baseline, the majority of patients had ischaemic stroke and the number of days post stroke varied widely from 30 to 1990 days. Results showed rotigotine was associated with a significant improvement in the Mesulam shape cancellation task; differences from baseline in the detection of targets were +12.8% on the left side (p=0.012) with a -0.7% reduction on the right side (p=0.466). There were no significant positive effects on other tests of spatial neglect, or spatial working memory, or motor tasks.

Local experience at NHNN from three patients with hemispatial neglect treated with rotigotine during neurorehabilitation, found all patients showed significant improvements in their 'Star cancellation task' on medication as compared with off medication. Subjective improvements in functional tasks were also observed.

Mukand et al. report a case series of four patients with acute left hemispatial neglect. Neglect was assessed using a modified Behavioural Inattention Test (BIT) before and after one week of co-careldopa 25/100mg three times daily. Results found an increase in the modified BIT scopes for 3 patients one week after co-carbidopa. The case series had no control group so it is unknown whether the improvement was a normal part of the recovery process or a drug-related effect.

With regards to safety, both rotigotine and co-careldopa would be initiated in the specialist setting and patients would be closely monitored for adverse effects. Monthly costs are approximately £149 for rotigotine and £23 for co-careldopa with treatment durations of 3 to 6 months. The application proposes 8 patients on rotigotine and 4 patients on co-careldopa therefore the total annual budget impact would be £7,600 assuming 6 months of treatment per patient.

The Committee heard from Dr Swayne that published literature did not include data on functional gains. Level 1 neurorehabilitation involves full-time treatment for up to three months and experts believe interventions that support patients to fully engage in treatment would have a lasting beneficial effect. Detailed consultation would be required before patients could consent to off-label treatment given uncertain functional benefits and risks of adverse effects. The duration of treatment was uncertain as both drugs would be continued whilst patients are benefiting functionally.

The Committee agreed with the hypothesis that rotigotine and co-careldopa might be beneficial however a clinical trial was needed to confirm the theory. There were concerns that approving this application would jeopardise such a trial as ethics would not permit a placebo group if 'standard of care' at the NHNN became rotigotine or co-careldopa. The Committee suggested an evaluation period (a pilot) would provide data to perform the power calculation necessary to conduct a randomised controlled trial. The risk associated with the pilot period was considered low given the intensity of monitoring and low budget impact.

In camera, the Committee agreed there was insufficient evidence to support the addition of rotigotine or co-careldopa to the NCL Joint Formulary for the proposed indication and furthermore, doing so might jeopardise any future randomised placebo controlled trials. However, an evaluation period to collect functional data was considered worthwhile to inform power calculations for forthcoming trials. Rotigotine and co-careldopa were therefore approved under the Category of Evaluation restricted to the NHNN site for hemispatial neglect that is interfering with progress of neurorehabilitation. This approval was subject to Dr Swayne working with Dr Sofat and JFC support to agree the data-collection form and the duration of the pilot study.

Decision: Approved under evaluation, subject to a pilot study protocol being developed and approved.
Prescribing: Secondary care

Tariff status: In-tariff
Funding: Hospital budgets
Fact sheet or shared care required: No
Audit required: Yes; duration TBC at JFC in January 2017.

Action: Dr Swayne, Dr Sofat and JFC Support to develop a pilot study protocol and data collection form. Funding should be secured from the NHNN Divisional Director. Dr Swayne to submit the pilot data to JFC on completion.

8. Evidence review

8.1 Ustekinumab, secukinumab or ixekizumab for Plaque psoriasis following failure of two anti-TNFs (etanercept, adalimumab or infliximab) or one anti-TNF and one other biologic (e.g. secukinumab or ustekinumab)

The Committee discussed an evidence review for the newer biologics for plaque psoriasis following failure of two prior biologics. The Chair welcomed Dr McBride to answer the Committee's questions about the evaluation.

NICE have positive Technology Appraisals for three anti-TNFs (etanercept, adalimumab or infliximab), ustekinumab (anti IL-23/12) and secukinumab (anti IL-17A); a positive Appraisal Consultation Document has also been published for ixekizumab (anti IL-17A). Patients with psoriasis may discontinue their first biologic due to primary failure (lack of initial efficacy), secondary failure (loss of efficacy with time) or intolerance/side-effects. During the development of NICE CG153 a cost-effectiveness analysis found 2nd line biologics were cost-effective compared to best supportive care. An evaluation of 3rd or 4th line biologics had not been completed by NICE.

There is an absence of randomised controlled studies designed to evaluate the efficacy of 3rd or 4th line biologics. Multiple subgroup analyses were identified that confirmed ustekinumab, secukinumab and ixekizumab were more effective than placebo when used in biologic pre-treated populations. Data from the PSOLAR observational study showed ustekinumab was associated with superior 'drug survival' rates compared to anti-TNFs when used 3rd line; this study was noted to be at high risk of bias. With regards to safety, the adverse effect rate is not thought to be dependent on the degree of biologic pre-treatment.

The Committee heard from Dr McBride that the management of psoriasis had changed over recent years. Historical practice was to switch more frequently whereas best practice is now to support patients on their first biologic for longer (so called 'riding the wave'), potentially with supportive methotrexate, exercise programmes, weight loss (e.g. referral for bariatric surgery) and smoking cessation.

The Committee agreed 3rd line biologics were likely to be cost-effective and recommended patients in NCL should be offered one drug from each therapeutic class. The evidence for 4th line biologics (which may include a 2nd anti-TNF) was less clear therefore the Committee asked Dr McBride to develop a treatment pathway which should consider:

- Place in therapy for biosimilars (infliximab and etanercept, adalimumab expected in 2018)
- Most appropriate therapy for patients failing 3rd line biologic
- Place in therapy for apremilast
- Impact of joint involvement (psoriatic arthritis) on treatment choices

If the proposed pathway positions the newer biologics (ustekinumab, secukinumab, ixekizumab) before established anti-TNFs (etanercept, adalimumab), JFC would need to review the evidence base underpinning this recommendation before the pathway could be agreed.

Action: RFL to lead the development of the psoriasis treatment pathway. The pathway must receive input from all stakeholders in NCL.

9. Guideline

9.1 Methotrexate Shared Care Guideline

The Committee reviewed a Shared Care Guideline for the Prescribing and Monitoring of Methotrexate when used for its licensed indications in moderate/severe active rheumatoid arthritis and for treatment of severe psoriasis in adults. This document has previously been approved by the MON and was presented at JFC for ratification.

The Committee approved the Shared Care Guideline, noting that an update is expected to incorporate the unlicensed indications that were agreed at the August 2016 JFC meeting.

9.2 Lithium Fact Sheet

The Committee reviewed a Fact Sheet to support GPs with the prescribing and monitoring of lithium in bipolar illness and as an adjunctive treatment in resistant depression. This document has previously been approved by the MON and was presented at JFC for ratification.

The Committee approved the Fact Sheet.

Post meeting notes:

Islington CCG provided additional comments on this Fact Sheet subsequent to its approval. These comments were reviewed with the author and the following amendments were made and agreed at the December 2016 MON:

- Reference to renal function monitoring should be consistently referred to as U&Es, creatinine and eGFR
- Calcium monitoring should refer to "corrected calcium" and should be conducted six monthly in line with NICE guidance.

10. Consultation: Proposals for changes to the arrangements for evaluating and funding drugs and other health technologies appraised through NICE's technology appraisal and highly specialised technologies programmes

Mr Barron provided a summary of the proposed amends to the NICE TA and HST programme. The Committee agreed the proposal was inadequately aligned with the Government's Accelerated Access Review and would perversely encouraged the approval of 'me too' drugs. The changes would compound existing difficulties in pragmatically incorporating high cost drugs with NICE TAs into clinical guidelines. Dr McGuinness expressed concern that patient experts were not an essential part of the proposed Fast Track process.

Action: Ms Landeryou to provide patient representative feedback. Mr Barron to update the proforma and submit to NICE on behalf of JFC.

11. Proposal for fibrin sealants to be taken off the PbR exclusion tariff for 2017/18

Mr Purohit informed the Committee that NHS England published a proposal to remove fibrin sealants from the PbR exclusion tariff. The Committee suggested Chief Pharmacists work with their Contracting managers to respond to the NHS England proposal.

12. Next meeting

Thursday 26th January 2017, Room 6LM1, Stephenson House, 75 Hampstead Rd.

13. Any Other Business

Mr Purohit queried whether JFC planned to review the 'not recommended' decision for Collatamp from May 2016 (indication: Osteomyelitis including Brodie abscess). Mr Barron informed the Committee an appeal letter had not been received therefore a review was not scheduled.