North Central London
Joint Formulary Committee

# JOINT FORMULARY COMMITTEE (JFC) – MINUTES

**Minutes from the meeting held on Thursday 31st March 2016**
**Room 6LM1, Stephenson House, 75 Hampstead Rd**

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|---|---|---|---|
| **Present:** | Prof R MacAllister | NCL JFC Chair | **(Chair)** |
| | Ms R Clark | Camden CCG, Head of Medicines Management | |
| | Dr R Urquhart | UCLH, Chief Pharmacist | |
| | Mr T James | MEH, Chief Pharmacist | |
| | Mr A Dutt | Islington CCG, Head of Medicines Management | |
| | Dr R Sofat | UCLH, Consultant Clinical Pharmacologist | |
| | Dr C Cooper | Islington CCG, GP | |
| | Dr C McGuinness | Patient Partner | |
| | Ms K Landeryou | Patient Partner | |
| | Mr I Man | WH, Deputy Chief Pharmacist | |
| | Prof D Robinson | UCLH, Consultant Respiratory Physician | |
| | Ms E Mortty | Haringey CCG, Deputy Head of Medicines Management | |
| | Mr P Gouldstone | Enfield CCG, Head of Medicines Management | |
| | Dr V Thiagarasah | Enfield CCG, GP | |
| | Ms W Spicer | RFH, 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 E Hindle | MEH, Formulary Pharmacist | |
| | Dr H Amer | UCLH, SpR Clinical Pharmacology | |
| | Mr J Paszkiewicz | NEL CSU, Senior Prescribing Advisor | |
| | Ms A Fakoya | NEL CSU, Senior Prescribing Advisor | |
| | Mrs P Chambers | UCLH, Cancer Pharmacist | |
| **Apologies:** | Prof L Smeeth | NCL JFC Vice-Chair | |
| | Mr A Shah | RNOH, Chief Pharmacist | |
| | Dr A Stuart | NHS Camden, GP Clinical Lead Medicines Management | |
| | Dr R Kapoor | UCLH, Consultant Neurologist | |
| | Ms P Taylor | NHS Haringey, Head of Medicines Management | |
| | Dr R Fox | RNOH, DTC Chair | |
| | Mr B Sandhu | NEL CSU, Assistant Director Acute Services | |
| | Mr C Daff | NHS Barnet, Head of Medicines Management | |

## 2. Meeting observers

Prof MacAllister welcomed Ms A Fakoya as an observer to the meeting.

## 3. Minutes of the last meeting

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

## 4. Matters arising

### 4.1 Levonorgestrel 13.5 mg intrauterine system for contraception (Jaydess®)

At the February 2016 meeting, the Committee was unable to approve the addition of Jaydess to the formulary due to lack of information about the perceived advantage of the device over the Mirena® intra-uterine contraception system. It has since come to light that the Whittington Hospital already has Jaydess® available for prescribing by the Sexual Health Clinic. Mr Minshull presented further clarification on three points which had been sought from Dr Jo Power, Consultant in Sexual and Reproductive Health at CNWL, who put the application forward.

The Committee had identified that the Mirena® device available on the UK market is smaller than that used in the trials comparing it to Jaydess®. This raised the possibility that there might not be any practical advantage associated with Jaydess®. Dr Power explained that there is a small cohort of patients for whom fitting the Mirena® intrauterine device is associated with unacceptable pain. For experienced operators, this is likely to be less than 1% of patients. Other methods are also employed to make the fitting less uncomfortable, such as use of a topical anaesthetic.

The reporting of reduced pain and discomfort associated with placement of Jaydess® and its translation to long-term benefit was raised by the Committee. Dr Power agreed that this may be a theoretical benefit, but did not think it would be a reason for choosing Jaydess® over Mirena® as there is no definite evidence that these devices are associated with any reduction in in-use pain/discomfort. The reduced dose of steroid may confer some benefit in terms of adverse effects (e.g. acne, breast tenderness), but again this is not conclusively proven in the data and therefore would not be a definite reason for choosing Jaydess® over Mirena®. However, it might be an issue for women who have experienced adverse effects from an intrauterine device in the past.

Although avoiding amenorrhoea was raised as a potential reason for choosing Jaydess® over Mirena®, Dr Power again did not think this would form the main cohort of patients as there are other contraceptive methods available (e.g. combined oral contraceptive, patches, ring, barrier method and IUD).

The JFC took the view that the only indication for the Jaydess® device was in women who had failed an insertion attempt using Mirena®.

Decision: Approved for use 2nd line following unsuccessful fitting of Mirena® device
Prescribing: Sexual Health Clinic only
Tariff status: In tariff
Funding: Sexual Health Clinic budget
Fact sheet or shared care required: No
Audit required: No

### 4.2 Dulaglutide for Type 2 Diabetes

The Committee discussed a letter from Dr Cohen that commented on the Committee's decision making for dulaglutide (28th January 2016). The letter raised the following issues:

- Draft minutes were not circulated to the applicant prior to publication on the JFC website
- It was not clear from the minutes that the final decision was held in-camera
- Dulaglutide should not be the only GLP-1RA used over the 6 month evaluation period
- It is not possible to switch all patients prescribed a GLP-1RA to dulaglutide due to capacity constraints within the service.

The Committee agreed that minutes should state which parts of the discussion were closed to the applicant e.g. "In-camera, the Committee agreed…". It was also agreed that an early draft of the minutes could be sent to the applicant; this would allow at least two weeks for the applicant to respond to any potential inaccuracies before the minutes are ratified at the next meeting and published on the JFC website.

The Committee discussed whether it was desirable for only one GLP-1RA to be included on the formulary. The applicant requested that liraglutide remains on formulary because: (i) patients may prefer to inject

daily; (ii) patients may have a skin reaction to either agent to may prefer an alternative; (iii) liraglutide may produce greater weight loss than dulaglutide as it passes blood-brain barrier; and (iv) early results from liraglutide CV appears promising. The patient partners agreed that patient choice regarding the dosing frequency was important. The Committee disagreed that there was likely to be any differences in prevalence of skin reaction (only 0.3% developed an injection site reaction with dulaglutide vs 0.7% with liraglutide). The Committee also disagreed that liraglutide should be preferred in patients with a high body weight; liraglutide 1.2mg is the only dose commissioned in NCL and dulaglutide was found to have clinically similar weight reducing benefits to liraglutide 1.8mg in AWARD 6 (estimated treatment difference +0.71Kg from baseline of 94Kg) and is expected to be superior to liraglutide 1.2mg (treatment difference between liraglutide 1.8mg and 1.2mg in LEAD4 was +1.0Kg). The Committee agreed that cardiovascular risk was an important consideration with the GLP-1RA class due to the observed increase in heart rate which may be a herald for cardiovascular problems. A recent meta-analysis of dulaglutide clinical trials signals this risk with HR=2.02 (95% CI: 0.41 to 9.88) verses placebo for hospitalisation of heart failure. It was noted that both liraglutide and dulaglutide increase heart rate (+2.4 and +3.1 respectively) therefore both were likely to be associated with this risk.

The Committee acknowledged that a GLP-1RA switch could only take place with support from prescribers. Given this and the small sums of money that would be saved by a GLP-1RA switch, it was agreed that liraglutide 1.2mg and dulaglutide should have equal weight on the NCL formulary. The Committee clarified that liraglutide 1.8mg is not recommended for use. It was requested that the 6-month evaluation period takes place, and assuming experience with dulaglutide is positive, exenatide 2mg MR would be removed from the NCL Joint Formulary. Lixisenatide and exenatide BD would remain non-formulary.

## 5. Declarations of relevant conflicts of interest

Mr E Hindle declared he had consulted for Santen UK Limited (item 8.4).

Committee members were reminded to complete and return the JFC Declaration of Interests forms circulated with the agenda.

## 6. Local DTC recommendations / minutes

### 6.1 Approved by DTC

| Month | DTC site | Drug | Indication | JFC outcome |
|---|---|---|---|---|
| UCLH | Feb-16 | Palbociclib (compassionate use) | ER +ve, HER2-ve metastatic breast cancer whose tumours have progressed on at least 4 lines of standard of care therapy and who are ineligible for ongoing palbociclib trials | Added to NCL Joint Formulary |
| RFH | Feb-16 | FOLFIRI | 2nd line for high grade neuroendocrine tumour | RFH only |
| RFH | Feb-16 | Tenofovir alafenamide (TAF) as F/TAF, R/F/TAF and E/C/F/TAF (compassionate use) | HIV triple combination treatment for patients with CKI stage 3-5, patients with HIV and hepatitis co-infection | Added to NCL Joint Formulary |
| RFH | Feb-16 | Ketoconazole | First line in pre-treatment prior to surgery (4-6 weeks prior to surgery) or second line post-surgery in patients with persistent Cushing syndrome (long term treatment) | RFH only |
| RFH | Dec-15 | Cobicistat | Second line protease inhibitor booster for HIV for confirmed ritonavir intolerance | Added to NCL Joint Formulary |

### 6.2 Not approved by DTC

| Month | DTC site | Drug | Indication | JFC outcome |
|---|---|---|---|---|
| UCLH | Nov-15 | Teduglutide | Short bowel syndrome in adults (reducing TPN requirement) | Not Approved |

### 6.3 Under evaluation by DTC

| Month | DTC site | Drug | Indication | JFC outcome |
|---|---|---|---|---|
| UCLH | Feb-16 | Paracetamol IV | Second line option after ibuprofen for closure of the patent ductus arteriosus (PDA) | Under evaluation across NCL |

***Action: Ms S Sanghvi to circulate the UCLH paracetamol IV evaluation form to RFH and NMUH. All centres were required to collect the same data for a single NCL wide evaluation in 12 months.***

## 7. New Medicine Reviews

### 7.1 Palonosetron for chemotherapy induced nausea and vomiting

The Committee reviewed an application for palonosetron (a long acting 5-HT3 antagonist) to be used to avoid chemotherapy induced nausea and vomiting (CINV). This would be prior to chemotherapy with moderate risk of causing emesis and prior to chemotherapy with anthracyclines and cyclophosphamide regimens in breast cancer treatment.

The Committee noted that as palonosetron has such a long half-life (approximately 40 h, extending to 100 h in 10% of patients).

The Committee considered evidence from three non-inferiority studies that compared single doses palonosetron to other 5-HT3 receptor antagonists (ondansetron or dolasetron; single doses) in patients receiving moderately or highly emetogenic chemotherapy. Further evidence of the superiority of palonosetron over older 5-HT3 agonists is demonstrated in a meta-analysis.

For primary efficacy end point, complete response (CR) was measured as no emetic episodes and no need for rescue medication during the 24 h following administration. In each of these three studies, palonosetron 0.25 mg demonstrated non-inferiority to the reference 5-HT3 receptor antagonist at 24 h using the ITT population. In PALO-99-03, 81% of palonosetron 0.25 mg patients experienced complete response at 24 h, compared to 68.6% of ondansetron 32 mg treated patients (difference in CR palonosetron – ondansetron 97.5% CI: 1.8% to 22.8%). In PALO-99-04, 63% of palonosetron 0.25 mg patients experienced complete response at 24 h, compared to 52.9% in the dolasetron 100 mg group (difference in CR palonosetron – dolasetron 97.5% CI: -1.7% to 21.9%). In PALO-99-05, 59.2% of the palonosetron 0.25 mg population had CR at 24 h compared to 57% of the ondansetron 32 mg population (difference in CR palonosetron – ondansetron 97.5% CI: -8.8% to 13.1%).

A meta-analysis of parallel group and cross-over trials of adults receiving moderately or highly emetogenic chemotherapy (Jin *et al,* 2012; 9 trials, 3,463) compared the 5-HT3 receptor antagonists for two outcomes: CR (no emetic episodes and no rescue medication during acute, delayed and overall time periods) and complete control (CC: no emetic episode, no need for rescue medication and no more than mild nausea during determined time periods). Palonosetron 0.25 mg IV was more effective at achieving complete response than the first generation 5-HT3 receptor antagonists [RR of CR at day one = 1.11, 95% CI: 1.05 to 1.17; from days 2 to 5 RR=1.26, 95% CI: 1.16 to 1.36; overall 5 day period RR=1.23, 95% CI: 1.13 to 1.34). Palonosetron was statistically significantly more likely to achieve CC than a first generation 5-HT3 receptor antagonist at days 2 to 5 (RR=1.27, 95% CI: 1.10 to 1.47) and for the overall five-day period (RR=1.23, 95% CI: 1.03 to 1.47). There was no statistically significant difference between palonosetron and first generation 5-HT3 receptor antagonists risk of headache and constipation (the most common adverse events).

The JFC were unsurprised by these data, given the long half-life of palonosetron: ondansetron, by comparison, has a terminal half-life of 3 h. There were concerns that palonosetron might accumulate with repeat (and mistaken) dosing. The Committee heard from Ms Chambers, who advised that prescribing will be via ChemoCare, but there was concern that the drug could still be added to EPMA, which means there is a risk of prescribing and administration by people not familiar with the drug.

As there will be approximately 1,000 cycles per annum in NCL eligible for administration of a dose of palonosetron, there is an additional cost burden of £44,500 compared to ondansetron IV 8 mg, however this may be reduced when generic preparations become available (LPP expects 5 to become available by June 2016).

In camera, the Committee agreed that palonosetron did not offer any clinical advantage over correctly (repeat) dosed ondansetron, and use would expose patients to the risk of accumulation from inadvertent re-administration of palonosetron. Therefore, the Committee did not see a role for palonosetron and agreed that it should not be included on the NCL Joint Formulary.

Decision: Not approved

## 7.2 Palonosetron and netupitant for chemotherapy induced nausea and vomiting

The Committee reviewed an application for a combination capsule of netupitant and palonosetron for the prophylaxis of acute nausea and vomiting with single-day high risk chemotherapy. It was proposed that netupitant/palonosetron would replace ondansetron 12mg IV and three days of aprepitant.

The Committee noted that Phase III studies had not investigated the efficacy of netupitant/palonosetron compared to aprepitant/ondansetron.

One Phase III, double-blind, double-dummy, multinational randomised controlled trial compared oral netupitant/palonosetron to oral palonosetron. Adults who had not previously received chemotherapy and were due to receive their first course of highly emetogenic chemotherapy were eligible. Patients were randomised 1:1 to receive either netupitant/palonosetron plus 12mg dexamethasone or palonosetron 500 microgram plus 20 mg dexamethasone on day 1 of chemotherapy. The primary outcome was a complete response during the delayed phase (24-120hrs) of cycle 1. A key secondary outcome was complete response during the acute (0-24hrs) phase of cycle 1. Results found netupitant/palonosetron achieved a significantly higher proportion of delayed complete response than palonosetron (76.9% vs 69.5%, OR=1.48 [95% CI: 1.16-1.87]). A small but significantly higher proportion of patients also achieved a complete response in the acute phase (88.4% vs 85.0%, OR=1.37 [95% CI: 1.00-1.84]).

One exploratory Phase II study with a similar design to the Phase III study included treatment arms for both netupitant/palonosetron and aprepitant/ondansetron. Although the study was not powered to identify differences between the arms, the study reported similar results for both arms. A complete response during the delayed phase was achieved in 90.4% and 88.8% of patients treated with netupitant/palonosetron and aprepitant/ondansetron respectively, a complete response during the acute phase was achieved in 98.5% and 94.8% respectively.

A Phase III study compared the safety of netupitant/palonosetron and aprepitant/ondansetron. Results found treatment emergent adverse effects were generally similar. Numerically more patients had 'any treatment emergent AE during cycle 1' with netupitant/palonosetron however numerically fewer patients had 'any treatment emergent AE during multiple cycles'.

The list price of netupitant/palonosetron is £69.00 however the manufacturer was expected to submit a confidential contract price through LPP. Aprepitant is due to come off patent in 2018 and ondansetron is already generic. In addition to drug cost considerations, considerable staff costs would be required to change chemotherapy regimens from aprepitant/ondansetron to netupitant/palonosetron and then back again in 2018 when aprepitant becomes generic.

The Committee heard from Mrs Chambers that netupitant/palonosetron and aprepitant/ondansetron were likely to be equivalent in their efficacy and safety profiles, and the application was prompted by the potential for a small reduction drug costs associated with netupitant/palonosetron. Netupitant/palonosetron has a longer half-life than aprepitant (120hr vs 9-13hrs) and is therefore associated with a reduced tablet burden.

In-camera, the Committee agreed that netupitant/palonosetron offered no clinical advantage over aprepitant/ondansetron and was likely to be available at a similar price. Considerable staff costs would be required to update all single-day high risk chemotherapy regimens from aprepitant/ondansetron and to reverse this work in 2018. Considering these additional costs, the Committee agreed that netupitant/palonosetron was not cost-effective and should not be included on the NCL Joint Formulary.

Decision: Not approved

## 7.3 Olanzapine for chemotherapy induced nausea and vomiting

The Committee reviewed an application for olanzapine for breakthrough chemotherapy induced nausea and vomiting (off-label) when parenteral cyclizine, levomepromazine and prochlorperazine were unavailable due to national drug shortages.

A double-blind, multi-centre randomised controlled trial compared the efficacy and safety of olanzapine to metoclopramide as rescue therapy for breakthrough chemotherapy induced nausea and vomiting. Adults scheduled to receive highly emetogenic chemotherapy were eligible. Patients were randomised 1:1 to either olanzapine 10mg OD for 3 days or metoclopramide 10mg TDS for 3 days. All patients received prophylactic fosaprepitant, palonosetron and dexamethasone. Only those patients who experienced breakthrough nausea and vomiting used the double-blinded rescue therapy and were followed up for 72 hours. The primary outcome was the proportion of patients who achieve no emesis in

the 72-hour observation period. Results found the percentage of patients with breakthrough nausea and vomiting who then experienced 'no emesis' in the observation period was significantly higher with olanzapine compared to metoclopramide; 70% vs 31% respectively ($p<0.01$). The proportion of patients who experience 'no nausea' was also higher (68% vs 23%, $p<0.01$).

The Committee heard from Mrs Chambers that olanzapine was an alternative to established antiemetics during periods of national stock shortages. Recently parenteral cyclizine, haloperidol and levomepromazine were unavailable simultaneously.

In camera, the Committee agreed that olanzapine was likely to have similar efficacy to prochlorperazine and levomepromazine, therefore should only be used when the licensed alternatives were unavailable due to national supply shortages.

Decision: Approved when prochlorperazine, levomepromazine and cyclizine are unavailable
Prescribing: Hospital only
Tariff status: In tariff
Funding: Hospital budget
Fact sheet or shared care required: N/A
Audit required: No

## 8. Guidelines

### 8.1 Chemotherapy induced nausea and vomiting guideline

The Committee reviewed the chemotherapy induced nausea and vomiting guideline. It was requested that the reference to fosaprepitant be removed from the guideline. The guideline would also require updating to reflect the Committee's decisions regarding palonosetron (item 7.1) and netupitant/palonosetron (item 7.2).

### 8.2 Asthma guideline

Mr Minshull presented an Adult Asthma Inhaler Choice guideline that has been developed in collaboration with the Responsible Respiratory Prescribing Group (RRP) and in consultation with all stakeholders in North Central London. The guideline aims to direct prescribers to cost-effective inhaler choices at each step of the BTS Asthma Guidelines, for use when initiating a new inhaler or increasing/decreasing the treatment step. Clinical efficacy of individual inhalers has been determined either by previous evidence reviews presented at JFC, or according to their inhaled corticosteroid (ICS) equivalency to beclomethasone dipropionate.

Mr Minshull informed the Committee that there was no reference to inhalers containing fluticasone propionate and salmeterol (e.g. Sirduipla® or Seretide®). This combination was omitted after it was identified that the Flutiform® suite of inhalers would provide MDI fluticasone plus LABA. It was commented that Seretide® 250 microgram Evohaler is a high spend areas for CCGs, therefore future work looking at how to manage this spend (e.g. through use of Sirdupla® MDI) could be beneficial.

There was discussion about the inclusion of DuoResp® Spiromax® and Symbicort® Turbohaler, as both deliver budesonide together with formoterol fumarate through a dry powder inhaler, with the DuoResp® device costing up to 22% less than the Symbicort® according to NHS list price. Prof Robinson informed the Committee that the manufacturers of the originator product are likely to offer a discount to CCGs in recognition of this. Mr Dutt explained that CCGs follow London Procurement Partnership recommendations that formulary decisions should be based on a clinical decision as rebates can be withdrawn without notice. Following the meeting, it was noted that, as no application for Symbicort® has yet been received, and previous evaluation of Symbicort® by the Committee saw its rejection, Symbicort® should not be part of this guideline until this application has been received.

A major concern of the RRP was that it is harmful to switch patients from one inhaler device to another without appropriate training, therefore this guideline has added in Fostair® 200/6 (both MDI and DPI) and the 100/6 DPI to prevent the need to switch devices when "stepping up" a patient with worsening asthma control.

A question was raised about the INCA device which is proposed to be used by the Severe Asthma Service along with Seretide® Accuhalers. Prof Robinson explained to the Committee that use of the INCA device is used as standard care to listen to how the patient uses their inhaler. Although it is only available within specialist centres, it is not being used as part of a clinical trial.

The Committee approved the guidelines.

***Actions: CCGs to submit application for Seretide® Evohaler to Sirdupla® MDI switch if required.***

### 8.3 Diabetic Macular Oedema (DMO) Pathway

Mr Hindle presented the Committee with an updated Diabetic Macular Oedema pathway. The update included Ozurdex® (dexamethasone intravitreal implant) and Iluvien® (fluocinolone intravitreal implant) in line with NICE TAs. The Committee approved the guideline.

### 8.4 Ciclosporin eye preparations fact sheet

Mr Hindle presented the Committee with an updated ciclosporin fact sheet. The update identified the indications covered by NICE TA369 and those that were off-label. The Committee discussed whether the fact sheet should specify which lubricants should have failed before ciclosporin is initiated. On balance the Committee was minded that a pathway written into the fact sheet was unnecessary because MEH had already provided a dry eye pathway for GPs, who are unlikely to refer patients to MEH before trying all appropriate lubricants. As ciclosporin is only initiated by the Corneal Service inappropriate use was considered to be unlikely. The Committee approved the guideline without further amendments.

### 9. Shared Care and Fact Sheet Decision Process

Mr Minshull presented an update to the current process for approval. The document had been updated to include a flow diagram to support the process by which the Committee decides whether a factsheet or shared care guideline was required. The revised process was approved.

### 10. JFC Workplan

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

### 11. Letter from Chief Pharmaceutical Officer: Establishing Regional Medicines Optimisation Committees (9th Feb 2016)

The Committee were not aware of any further updates to this letter.

### 12. Next meeting

Thursday 28 April 2016, Room 6LM1, Stephenson House, 75 Hampstead Rd.

### 13. Any Other Business

Mr Minshull informed the Committee that he had met with Dr Hurel (Endocrinologist, UCLH) and work was now underway to develop NCL recommendations on the use of liothyronine.

Mr Barron informed the Committee of a Direct Healthcare Professional Communication from Gilead (Ref: 1101-16-208) that recommended idelalisib is not initiated as a first-line treatment in chronic lymphocytic leukaemia (CLL) patients with 17p deletion or TP53 mutation. In July 2015 the Committee approved a compassionate access scheme for idelalisib for this indication. Mr Barron had confirmed with the original applicants that idelalisib was no longer used for that indication. The Committee agreed to remove idelalisib from the NCL Joint Formulary for this indication.

Ms Amer informed the Committee that a positive NICE TA for sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction was expected to be published in April 2016. The MHRA approved sacubitril valsartan under the Early Access to Medicines Scheme and subsequently routine commissioning needed to be in place 30 days' post NICE. Sacubitril valsartan requires specialist initiation however continued prescriptions should take place in primary care. UCLH, Barts Health and RFH were expected to be working together on an NCL wide treatment pathway and it was requested that JFC was a stake holder in this work. Ms Amer provided the Committee with an early draft for comment; comments would be returned via Mr Barron.