North Central London
Joint Formulary Committee

# JOINT FORMULARY COMMITTEE (JFC) – MINUTES

**Minutes from the meeting held on Thursday 27 July 2016**
**Room 6LM1, Stephenson House, 75 Hampstead Rd**

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|---|---|---|---|
| **Present:** | Prof R MacAllister | NCL JFC Chair | **(Chair)** |
| | Dr R Sofat | UCLH, Consultant Clinical Pharmacologist | |
| | Mr P Gouldstone | Enfield CCG, Head of Medicines Management | |
| | Ms E Mortty | Haringey CCG, Deputy Head of Medicines Management | |
| | Mr A Shah | RNOH, Chief Pharmacist | |
| | Dr C McGuinness | Patient Partner | |
| | Ms K Landeryou | Patient Partner | |
| | Mr T James | MEH, Chief Pharmacist | |
| | Mr A Dutt | Islington CCG, Head of Medicines Management | |
| | Dr M Kelsey | WH, Chair DTC | |
| | Dr S Ishaq | WH, Consultant Anaesthetist | |
| | Dr R Fox | RNOH, DTC Chair | |
| | Ms K Delargy | BEH, Deputy Chief Pharmacist | |
| | Dr R Breckenridge | UCLH, DTC Chair | |
| | Ms I Samuel | RFL, Formulary Pharmacist | |
| | Mr I Man | WH, Interim Deputy Chief Pharmacist | |
| | Prof D Robinson | UCLH, Consultant in Respiratory Medicine | |
| | Ms A Fakoya | NEL CSU, Assistant Director Acute Services | |
| **In attendance:** | Mr J Minshull | NCL JFC, Support Pharmacist | |
| | Mr A Barron | NCL JFC, Support Pharmacist | |
| | Mr K Thakrar | UCLH, Formulary Pharmacist | |
| | Ms H Mehta | NMUH, Formulary Pharmacist | |
| | Mr E Hindle | MEH, Formulary Pharmacist | |
| **Apologies:** | Dr V Thiagarasah | Enfield CCG, GP | |
| | Prof L Smeeth | NCL JFC Vice-Chair | |
| | Mr TF Chan | RFL, Deputy Chief Pharmacist | |
| | Mr G Kotey | NMUH, Chief Pharmacist | |
| | Dr R Kapoor | UCLH, Consultant Neurologist | |
| | Dr C Cooper | Islington CCG, GP | |
| | Dr R Urquhart | UCLH, Chief Pharmacist | |
| | Dr A Stuart | Camden CCG, GP Clinical Lead Medicines Management | |
| | Mr C Daff | Barnet CCG, Head of Medicines Management | |
| | Ms W Spicer | RFL, Chief Pharmacist | |
| | Mr G Purohit | RNOH, Deputy Chief Pharmacist | |
| | Ms R Clark | Camden CCG, Head of Medicines Management | |
| | Mr P Bodalia | UCLH, Principal Pharmacist | |
| | Ms P Taylor | Haringey CCG, Head of Medicines Management | |
| | Ms H Taylor | WH, Chief Pharmacist | |
| | Mr B Sandhu | NEL CSU, Assistant Director Acute Services | |
| | Ms L Reeves | C&I, Chief Pharmacist | |

## 3. Minutes of the last meeting

Item 7.1 'Naltrexone for cholestatic itch': update minutes to clarify that the use of naltrexone in cholestatic pruritus of pregnancy had not been discussed as part of the application, therefore the recommendation to use it did not include this indication.

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

## 4. Matters arising

### 4.1 Eslicarbazepine in partial epilepsy (appeal)

At the July 2016 JFC meeting, the Committee did not approve eslicarbazepine for prescribing in partial epilepsy because it felt that eslicarbazepine was not superior to oxcarbazepine, and that any advantage was considered to be minor and theoretical, which would be offset by the greater cost. Prof M Koepp submitted an appeal to the Committee because he believed that the "original decision was based on inaccurate or incomplete information" and "a perverse decision was made based on the evidence considered by the Committee". Specifically, it was felt that the Committee did not give due consideration to the differences in tolerability of the pro-drugs eslicarbazepine acetate and oxcarbazepine.

Prof Koepp explained that an international advisory board of epilepsy specialists has advised that the structural differences between eslicarbazepine and oxcarbazepine resulted in differences in pharmacokinetics. These differences could justify switching patients experiencing adverse effects from oxcarbazepine to eslicarbazepine. He explained that use would be limited to those patients who do not tolerate oxcarbazepine, or those who are unable to comply with oxcarbazepine treatment; 70% of patients would remain on oxcarbazepine. Although there is no evidence to support it, patients who experience nocturnal seizure may benefit most from eslicarbazepine.

Pharmacokinetic data were presented comparing the plasma and CSF levels of oxcarbazepine in patients who received oxcarbazepine and those who received eslicarbazepine, showing that patients treated with oxcarbazepine experience a larger peak in oxcarbazepine levels with a smaller peak in eslicarbazepine treated patients. Prof Koepp proposed that this early peak in oxcarbazepine levels may be the cause of neurological adverse events that are observed with oxcarbazepine. The Committee discussed the differences in the metabolites of eslicarbazepine acetate (the pro drug of eslicarbazepine) and oxcarbazepine.

After dosing with eslicarbazpine acetate the proportions of each metabolite in the plasma expressed as a percentage of the original dose of eslicarbazepine are;

Eslicarbazepine 91%. R-licarbazepine 5% and oxcarbazepine 1%

After dosing with oxcarbazepine, the proportions of each metabolite in the plasma expressed as a percentage of the original dose of oxcarbazepine are;

Eslicarbazepine 81%. R-licarbazepine 16% and oxcarbazepine 3%

It is accepted that each metabolite is equipotent anti-epileptic drugs.

The small differences in the absolute amounts of oxcarbazepine were noted. The Committee were content to accept the European Medicines Agency's Public Assessment Report statement for eslicarbazepine that described the "very close pharmacological relationship of eslicarbazepine acetate with oxcarbazepine" and that "it is highly probable that adverse events, which occur after administration of oxcarbazepine may also occur after administration of [eslicarbazepine]". The Committee was not convinced that this small difference in oxcarbazepine exposure was sufficient to cause the differences in adverse effects that were being described.

Prof Koepp acknowledged that there were no convincing head-to-head data comparing tolerability of eslicarbazepine to oxcarbazepine, and it was unlikely that such trials would ever be undertaken. Indirect comparisons between the existing randomised trails of the two drugs were considered. At face value, there seemed to be more adverse events in the single oxcarbazepine trial than in the three eslicarbazepine trials. However there were also more adverse events in the oxcarbazepine placebo group compared to the eslicarbazepine placebo groups. It seemed implausible that the oxcarbazepine placebo was more toxic than the eslicarbazepine placebo. On close inspection of the comparative trial designs two differences stood out.

Firstly, the oxcarbazepine trial recruited patients on up to **three** other anti-epilpetic drugs whereas each of the three eslicarbazepine studies recruited patients who were only on up to **two** other anti-epilieptic

drugs. This difference in recruitment criteria (patients on polypharmacy recruited to the oxcarbazepine trial) was a plausible explanation for the increased incidence of adverse effects seen in the placebo group. It would also influence the experiences of patients in the oxcarbazepine treated group. It did not escape the JFC that the sponsors of the eslicarbazepine trials would see a marketing advantage wrought by judicious patient selection criteria. Secondly, the oxcarbazepine trial treated one third of patients with a dose of 2400 mg per day. In comparison the eslicarbazepine, trials limited the dose to 1200 mg of this drug per day. This high dose of oxcarbazepine has been noted by eight other epilepsy specialists from NHNN as an explanation for the high incidence of adverse effects seen with oxcarbazepine (Zaccara *et al*. BJCP 2013; 76(5): 827-828).

Therefore the JFC concluded that the apparent increase in adverse effects in the oxcarbazepine trial in comparison to the eslicarbazepine trials was a dose effect (in agreement with the substantial body of opinion from the epilepsy specialists from UCLH) or an effect of concurrent medication, and not best explained by the pharmacology of either drug.

A study comparing adverse event rates in patients who had been switched from oxcarbazepine to eslicarbazepine due to adverse events showed that 58% no longer had adverse events after switching, with 42.3% continuing to experience adverse events. However open label retrospective audits are far down the evidence hierarchy, and these data were rightly not policy-defining. The Committee did not approve eslicarbazepine for the treatment of partial seizures.

## 5. Declarations of relevant conflicts of interest

Mr A Barron declared that he has worked with Novartis on sacubitril valsartan (Entresto®). No other conflicts of interest relevant to the agenda were declared by the Committee members.

Dr Seaton declared he been a guest speaker for Galderma and attended conferences with support for Galderma; both in 2015.

Mr J Hurst declared that he has conducted consultancy work for all four studies that manufacture combination LAMA/LABA inhalers in the UK (Novartis, GSK, Boehringer Ingelheim, AstraZeneca).

## 6. Local DTC recommendations / minutes

### 6.1 Approved by DTC

| DTC site | Month | Drug | Indication | JFC outcome |
|---|---|---|---|---|
| UCLH | June-16 | Eculizumab (Compassionate Use Scheme) | Cold Agglutinin Disease | UCLH only |

### 6.2 Deferred approved by DTC

| DTC site | Month | Drug | Indication | JFC outcome |
|---|---|---|---|---|
| UCLH | June-16 | Dactinomycin | Third line treatment in patients with refractory or relapsed acute myeloid leukaemia (AML), where cytarabine plus clofarabine is not appropriate or not effective | Deferred |

## 7. New Medicine Reviews

### 7.1 Rituximab for autoimmune haemolytic anaemia (Applicant: Dr E Jacob, NMUH)

The Committee reviewed an application for rituximab for the treatment of auto-immune haemolytic anaemia (AIHA). Approximately two thirds of cases are classified as warm type, 30% as cold type, and 5% mixed. The proposal was to use rituximab 2$^{nd}$ line (after prednisolone) in warm and mixed-type AIHA, and 1$^{st}$ line in cold-type. The Committee welcomed Dr Jacob (NMUH) and Dr Scully (UCLH) to answer questions about this application.

The Committee discussed the evidence presented in NICE Evidence Summary: Unlicensed or off-label medicine 39 (Autoimmune haemolytic anaemia: rituximab). It was acknowledged that the evidence base is quite limited, though this would be expected for such a rare condition; the applicants suggested that incidence is less than one in 100,000 patients.

The evidence base in warm-AIHA is composed of an RCT of 64 adults with newly diagnosed, previously untreated disease (Birgens *et al* 2013), and four uncontrolled studies (n=101). In the RCT, patients were randomised to receive prednisolone or prednisolone plus rituximab. Complete response (normalisation

of Hb concentration without further need for immunosuppressive therapy and no biochemical signs of ongoing haemolysis) was seen at 12 months in 75% of the treatment arm, compared to 36% of the placebo arm (p=0.003). Relapse free survival in patients who showed any response to treatment was improved in the rituximab and steroid group compared to the steroid-only group [HR 0.33 (95% CI: 0.12 to 0.88, p=0.02)]. At three years, 70% of rituximab patients who had shown either complete response or partial response were relapse-free, compared to 45% in the steroid group.

The committee noted that this response rate was similar to that seen by in a retrospective analysis of patients who had received rituximab (Maung *et al* 2013), in which 71% of patients had an improvement of Hb, 27% of patients had a complete response to treatment. Fifty percent of patients were relapse free for their follow up (median 30 months, range 3 to 60 months); median time to relapse was 16.5 months. In a further single-arm, prospective study looking at the use of rituximab in idiopathic autoimmune haemolytic anaemia (Bercellini *et al*, 2013), eighteen patients were treated with a low dose of rituximab (100 mg weekly for four weeks) with 1 mg/kg/day prednisolone. 67% of patients achieved a complete response at 6 months. At 36 months, complete response was experienced by 6 of the 7 patients still being followed up. All patients experienced had at least some response to treatment.

The committee noted that response rates in cold-haemagglutinin disease were lower than in warm-type condition, ranging from 4% to 54%. According to a meta-analysis reported, overall response was 57% (95% CI: 47 to 66%) and complete response was 21% (95% CI: 6 to 51%), though it was noted that the meta-analysis was subject to substantial heterogeneity.

In an open label, single arm study of 27 adults, only one patient (4%) showed complete response (absence of anaemia, no signs of haemolysis, disappearance of symptoms, undetectable monoclonal serum protein, and no signs of clonal lymphoproliferation) after the first four-week course of treatment (Berentsen *et al,* 2004). Partial response (stable increase in haemoglobin concentration, along with reduced serum IgM concentration by at least 50%, improved clinical symptoms/transfusion independence) was seen in 13 of the 27 patients (48%). Eight of the 14 patients who had shown any response to treatment then went on to relapse. 48% of patients did not respond at all to the first course of treatment. In a retrospective study of 86 patients, 40 patients received rituximab monotherapy. Complete response was seen in 2 of the 40 patients (5%) receiving monotherapy, and partial response was seen in 21 (53%) of patients who had received monotherapy (Berentsen *et al* 2004).

From a safety perspective, the Committee noted that infusion reactions with rituximab are common, affecting more than 10% of patients. Fatal reactions to rituximab have also been seen in post-marketing surveillance. The applicant has acknowledged that patients will receive pre-medication with hydrocortisone, paracetamol and chlorphenamine to manage injection reactions. The infusion rate will be escalated at a prescribed rate.

Rituximab in this indication is a PbR excluded high cost drug (£6,288 + VAT per course of 4 doses), for commissioning by CCGs, though it isn't routinely commissioned yet. The applicant clarified that she would expect to treat 1 patient per 100,000 population per year (approximately 15 patients in NCL).

In summary, the Committee agreed that there is an evidence base to support the use of rituximab in this indication. The Committee acknowledged that the small number of patients and methodological limitations (particularly in cold-AIHA) reflect the rarity of the disease. As prednisolone is effective and much cheaper than rituximab, it should remain first line in warm-AIHA, with rituximab as a second line treatment. In cold-AIHA, rituximab should be a first-line treatment in this condition.

Decision: Approved
Prescribing: Secondary care only
Tariff status: PbR excluded
Funding: CCG pending service development
Fact sheet or shared care required: No
Audit required: No

### 7.2 Surgiflo with thrombin [haemostatic agent] for complex spinal surgeries (Applicant: Mr A Casey, UCLH & RNOH)

The Committee discussed an application to replace Floseal (5mL, 10mL; 400iU/mL thrombin in bovine gelatin) with Surgiflo (8mL; 250iU/mL thrombin in porcine gelatin) in complex spinal surgeries.

The Committee reviewed evidence from a single centre, non-randomised controlled trial in laminectomy procedures. Patients received Surgiflo or Floseal based on the personal experience of the operating surgeon and on the availability of the product in the operating room; the study is therefore at risk of bias.

In total 149 patients received a thrombin haemostat; 86 cases with Floseal and 63 cases with Surgiflo. Complete haemostasis was achieved in 332±54 seconds for Surgiflo and 335±52 seconds for Floseal. There were no patients with early or delayed haemorrhages of the surgical site and a postoperative CT scan obtained 3 months after the intervention did not show any abnormal signs that could be related to postsurgical haematomas.

The manufacturer of Surgiflo funded a US database analysis to compare outcomes for Surgiflo and Floseal in spinal fusion/refusion surgery between 2010 and June 2012. Baseline data indicated slightly higher mortality risk and surgery severity for Surgiflo than for Floseal. When the differences in baseline risk were accounted for, there were no differences in the risk of adverse effects.

The manufacturer of Floseal funded a separate US database analysis to compare outcomes in spinal fusion/refusion or resection surgery between January 2006 and June. Importantly this study excluded all cases where other haemostatic agents, fibrin sealants, and sealants were used which removed 95% of the patient records and creates concerns about generalisability of the results to NCL. Patients were stratified by surgical severity; major or severe. The adjusted results for major surgeries found no differences in blood loss but a statistically significant increase in transfusions, surgical time and mL of haemostat with Surgiflo vs. Floseal. The adjusted results for severe surgery found no differences with transfusions, blood loss and mL of haemostat but a statistically significant increase in surgical time.

Both products are prepared if needed in theatre. There were differences identified in the methods for preparation which would require theatre staff to be retrained; Ethicon are willing to provide this training. The literature, a data-on-file from Ethicon and the applicant suggest that Surgiflo is quicker to prepare than Floseal however this difference was not thought to be clinically meaningful.

There were small differences noted in the licensing however these were not thought to be clinically meaningful. The evidence base supporting Floseal was considered more established than for Surgiflo, reflecting the differences in time on the market.

Spinal surgeons at UCLH are using Surgiflo in their private practice and found the thickness of Surgiflo to be more consistent than Floseal which can be too runny or granular to use effectively. These reports are contradicted by experiences at other Trusts.

With regards to cost, both Surgiflo and Floseal have offered discounts to their list price. Surgiflo has a simple discount whereas Floseal has both a volume based discount scheme administered through the 'Healthcare Europe Framework' and a separate simple discount scheme. With discounts considered, Surgiflo costs less per pack than Floseal and is expected to be cost-minimising.

When calculating the budget impact, the lower concentration of thrombin with Surgiflo was not considered meaningful. Both published cost-analyses showed trends towards larger volumes (+1mL) of haemostat being required for Surgiflo vs. Floseal however this was accounted for by the greater volume of Surgiflo per pack (+3mL). With discounts considered, Surgiflo is expected to be cost-minimising compared with Floseal.

The disadvantages to having both products on the formulary relate to stock control, space in theatres and both the likelihood of products expiring is increased.

In summary, the Committee were unconvinced of any meaningful differences between the two agents and unimpressed by the low quality of the data. The choice of agent should lie with the individual Trusts who must consider the acquisition costs, which may differ between sites, and the training needs of the theatre staff. Individual Trusts will need to discuss this application with their procurement team responsible for flowable haemostatic agents.

See update in November 2016 minutes

***Action: Mr Barron to circulate costings with NCL Formulary Pharmacists. Mr Barron to confirm with NEL CSU that Surgiflo would be funded by the same mechanism as Floseal and fibrin sealants.***

***Post-meeting note: NCL CSU have agreed Surgiflo will be funded by the same mechanism as Floseal and fibrin sealants.***

Decision: Approved
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: To be confirmed
Fact sheet or shared care required: No
Audit required: No

## 7.3 Ivermectin 1% cream for papulopustular rosacea (Applicant: Dr Seaton, RFL)

The Committee discussed an application for ivermectin 1% cream for papulopustular rosacea.

The Committee reviewed the evidence from, two 12-week, double-blind, parallel-group randomised controlled trials which found ivermectin cream was significantly more effective than vehicle in improving rosacea severity score, achieving treatment success, and reducing inflammatory lesion count.

A third study was a 16-week multinational, randomised, investigator-blinded study to compare the efficacy of ivermectin cream with metronidazole cream. Inclusion criteria were patients with moderate to severe papulopustular rosacea and 15 to 70 facial inflammatory lesions. Patients were randomised 1:1 to once-daily ivermectin 1% cream or twice-daily metronidazole 0.75% cream, applied to the entire face for 16 weeks. The primary endpoint was % change in inflammatory lesion count, from baseline to week 16. Second endpoints were success rate, defined as being 'clear' or 'nearly clear' and the change in DLQI score. A total of 1034 subjects were screened and 962 were randomised. At baseline, the majority, 83.0%, had moderate papulopustular rosacea and 10% of participants had previously used topical metronidazole. After 16 weeks, patients treatment with ivermectin had a larger reduction from baseline in inflammatory lesion counts; 83.0% vs. 73.7% for metronidazole. Ivermectin also had a greater success rate; 84.9% for ivermectin vs. 75.4% for metronidazole, and a larger mean reduction in the DLQI score however the estimated treatment difference is unlikely to be clinically meaningful.

An extension study recruited participant who were 'clear' or 'nearly clear' at week 16, into a 23-week extension phase. The median time to first relapse, was 115 days in the ivermectin group and 85 days in the metronidazole group. Two separate extension studies found the number of patients treated with ivermectin increased from 38.4-40.1% at week 12 to 71.1-76.0% by week 52.

Ivermectin had a similar incidence of adverse effects to metronidazole cream (2.3% vs. 3.7% for ivermectin and metronidazole respectively) and a lower incidence than azelaic acid gel (1.9-2.1% vs. 6.7-5.8% for ivermectin and azelacic acid respectively).

Ivermectin costs £18.29 per 30g tube, which is expected to last 60 days (£9.14 per month) compared to a mean price of £12.88 per month for generic metronidazole 0.75% gel or £6.35 for generic metronidazole cream.

The Committee discussed that the single-blinded nature of the key study introduced ascertainment bias, which could have been avoided using a double-dummy design. The study may also have been inadequately designed to maintain blinding which is particularly relevant for subjective outcomes like those used in the trials. Participant awareness of treatment may also be important because metronidazole is considered the first line topical treatment opinion, although less than 10% of participants in the trial reported previous use of topical metronidazole. It was discussed that ivermectin might avoid a dermatology referral in addition to being cheaper than topical metronidazole.

The Committee was concerned about prescribing creep into erythematotelangiectatic rosacea for which ivermectin has no evidence.

In summary, the Committee agreed to add ivermectin 1% cream for papulopustular rosacea onto the NCL Joint Formulary, as an alternative to topical metronidazole 0.75%. Ivermectin 1% cream should not be restricted to secondary care initiation.

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

## 7.4 & 7.5 Umeclidinium/vilanterol combination inhaler (Anoro Elipta) and aclidinium/formoterol combination inhaler (Duaklir Genuair) for COPD (Applicant: Dr Hurst, WH)

The Committee reviewed two applications for new COPD inhalers containing combinations of a long-acting beta-agonist (LABA) and a long-acting antimuscarinic (LAMA). These were the first applications for this combination of drugs requested to be on the formulary.

The intended patient group is those with COPD who decline or cannot tolerate inhaled corticosteroids (ICS) and have:

(a) FEV1 <50% and persistent breathlessness despite PRN short-acting beta-agonist or short acting antimuscarinic (patients could be in GOLD stage C or D)
(b) FEV1 ≥ 50% predicted who are experiencing exacerbations, or have breathlessness despite maintenance with LAMA, will also be considered for treatment with combination, especially if there isn't a clear need for ICS (patients could be GOLD stage B, C or D)

The Committee welcomed Dr Hurst to speak about these applications on behalf of the Responsible Respiratory Prescribing Group.

The Committee reviewed one "NICE Evidence Summary: New Medicine" documents for each of these inhalers. These evidence summaries considered each inhaler in isolation and did not make an effort to compare them to each other. The NICE Evidence Summaries each showed that the combination inhalers demonstrated a statistically significant improvement in trough $FEV_1$ and dyspnoea scores when compared to mono-treatment.

Evidence from an additional meta-analysis of 14 studies (23,168 patients) was also considered because it attempted to rank five combination inhalers (four of where are available in the UK). This analysis ranked umeclidinium/vilanterol most effective, and aclidinium/formoterol least effective at improving $FEV_1$. All combination inhalers had a significant impact on dyspnoea (TDI) and disease status (SGRQ). Aclidinium/formoterol was the only drug combination that did not affect the ratio of responder patients compared to its individual single components.

There has been concern about the cardiac side effects of long-acting antimuscarinic drugs. The MHRA recommended that individual patient risks of cardiovascular side effects are taken into account when prescribing tiotropium in COPD. Although no other LAMA or LABA has been subject to the same restrictions by the MHRA, there are warnings about CV safety in the individual SPCs. With regards to cardiac adverse events compared to treatment with the mono-components, there was a non-significant (OR 0.59, 95% CI 0.35, 1.02, p=0.057) signal that umeclidinium/vilanterol combination may have a protective effect against cardiovascular side effects, whereas aclidinium/formoterol did not influence the OR of major cardiac event or a serious adverse event compared to individual components (OR 1.28 [95% CI 0.65, 2.51]. Treatment with glycopyrronium/indacaterol combination, on the other hand, led to a significant reduction in cardiac serious adverse events (OR 0.59, 95% CI 0.38 to 0.93). The committee agreed that it is sensible to consider CV safety when prescribing any LAMA.

Both the umeclidinium/vilanterol combination inhaler and the aclidinium/formoterol combination inhaler are black triangle drugs, therefore suspected reactions should be reported to the MHRA. As individual components of these inhalers are new, there is less experience than with the more established COPD treatments (e.g. tiotropium, formoterol, salmeterol).

Dr Hurst explained to the Committee that the management of COPD patients should take into account exacerbation rate and symptoms, as well as impact of drugs on bronchodilation (GOLD A to D grading system). He referred to the recent FLAME study, a large (n=3362), 52-week, randomized, double-blind, double-dummy, non-inferiority study looking at the safety and efficacy of LABA/LAMA combination (indacaterol/glycopyrronium) compared to a combination including inhaled corticosteroids (ICS) and a LABA (fluticasone propionate/salmeterol), which shows that LAMA/LABA combination may be superior to ICS/LABA combination in terms of avoiding COPD exacerbations.

The FLAME study was sponsored by Novartis, who manufacture a combination of indacaterol and glycopyrronium. The primary outcome considered was impact on the annual exacerbation rate. The study included patients with modified Medical Research Council (mMRC) scale symptom score ≥ 2 and at least one COPD exacerbation of any type in the last year. The primary finding from FLAME was that that LAMA/LABA combination had a lower annual exacerbation rate [3.59 (95% CI 3.28 to 3.94)] than the ICS/LABA comparator [4.03 (95% CI 3.68 to 4.41], giving a RR of 0.89 (95% CI 0.83 to 0.96; p=0.003). As the upper limit of the confidence interval was within the 1.15 non-inferiority margin, indacaterol-glycopyrronim was considered to be non-inferior to salmeterol-fluticasone. In the FLAME study, treatment with the LAMA/LABA combination demonstrated superiority to ICS/LABA in a number of secondary end points. For example, LAMA/LABA resulted in a longer time to first exacerbation (71 d [95% CI 60 to 82] vs. 51 d [95% CI 46 to 57]), HR = 0.84 [95% CI 0.78 to 0.91, p<0.001], and LAMA/LABA showed a reduced annual rate of moderate to severe COPD exacerbations [RR=0.83, 95% CI 0.75 to 0.91, p<0.001]. The SGRQ-C score improved in the LAMA/LABA group than in the ICS/LABA group (-1.2 points (12 weeks) and -1.8 points (52 weeks), p<0.01 for both comparisons). The number of patients having a clinically meaningful reduction in SGRQ-C (-4 points) was also greater in the LAMA/LABA group than the

ICS/LABA group at 52 weeks (49.2% vs. 43.7%, OR=1.3, p<0.001). Although the incidence of adverse events was similar between the two treatment groups, the incidence of pneumonia was significantly lower in the LAMA/LABA group than the ICS/LABA group (3.2% vs 4.8%, p=0.02). Although the FLAME study considered only one LAMA/LABA combination, it took the view that the meta-analysis described suggests this could be a class-related effect.

Dr Hurst explained to the Committee that umeclidinium/vilanterol (Anoro Ellipta®) is a dry powder inhaler requiring once daily administration. Aclidinium/formoterol (Duaklir Genuair®) is also a dry powder inhaler, but requires twice daily administration. He explained that there was debate in the COPD community over whether twice daily administration is better for nocturnal symptom control. However, he said there is as yet no convincing evidence that once daily or twice daily administration was more suitable for patients, therefore choice could be individualised to the patient. The Committee heard that the Responsible Respiratory Prescribing Group had reported that Camden and Islington COPD patients in a workshop had found the umeclidinium/vilanterol device easiest to use.

The Committee was not convinced by the argument that using one inhaler as opposed to two inhalers to deliver the required dose of drug would have a significant impact on the patient's experience of their condition, despite Dr Hurst's comment that different inhalers require different techniques. It was acknowledged that using a combination LAMA-LABA inhaler would offer a cost-minimisation compared to using separate inhalers. The annual cost of combination inhalers is £395/patient, compared to between £580 (tiotropium plus formoterol) and £726 (glycopyrronium and indacaterol) per patient per year when separate inhalers are prescribed, thus saving at least £185/patient/year. Further saving could be achieved is there is a reduction in prescribing of ICS/LABA in favour of LAMA/LABA inhalers.

*In camera,* there was a discussion during which the majority of members stated that they did not think there was a need for both inhalers to be added to the formulary; Prof Robinson did not agree with this. The Committee agreed to approve the application for umeclidinium and vilanterol combination only; the application for aclidinium and formoterol was not approved. This decision was reached based on patient preference, this combination may be slightly more effective, and the price is the same as for other combinations. The Committee acknowledged that the cost-minimisation was the only factor that influenced this decision and it will be re-examined should there be a reduction in the price of the individual component inhalers.

Decision: Approved umeclidinium and vilanterol (Anoro Ellipta) combination only
Prescribing: GP and secondary care
Tariff status: In tariff
Funding: CCG and hospital budgets
Fact sheet or shared care required: No
Audit required: No

## 8. Guidelines

### 8.1 Sacubitril valsartan (Entresto®) Fact Sheet

The Committee heard from Mr Barron that a Fact Sheet had been prepared to support GPs in caring for patients initiated and stabilised on sacubitril valsartan by heart failure specialists. The Fact Sheet had been prepared by the NCL/NEL sacubitril valsartan working group and has been circulated to GPs and CCGs in NCL for comments. The Committee approved the Fact Sheet.

### 8.2 GLP-1RA (liraglutide and dulaglutide) Fact Sheet for Type 2 diabetes

The Committee reviewed the Fact Sheet for liraglutide and dulaglutide in Type 2 diabetes. The document has previously been prepared as a Shared Care Guideline however the NCL MON (June '16) requested it was adapted into a FS as there is no regular, ongoing need for monitoring and/or assessment of effectiveness/toxicity by specialists. The Committee approved the Fact Sheet pending comments from Camden CCG.

***Action: Camden CCG to forward comments to Mr Barron***

### 8.3 Rifaximin Shared Care

The Committee reviewed the Shared Care Guidelines for rifaximin in hepatic encephalopathy, in line with NICE TA 337. This document had previously been approved by the NCL MON and was presented at the JFC for ratification.

RFL clarified that rifaximin cannot be initiated in the acute setting as the pivotal study (RFHE3001) recruited patients who were in remission after documented recurrent overt hepatic encephalopathy (2 or more episodes in the 6 months before screening).

The Committee approved the Shared Care Guideline, acknowledging that there is potential for creep of this drug outside its target group, therefore there is a need for formulary pharmacists to stay abreast of how it is being prescribed locally.

## 9. JFC Annual Report

The Committee reviewed the annual report. Prof MacAllister discussed that the secondary care Joint Formulary should be a priority for this financial year. JFC Support should also routinely capture the real-time impact of JFC decisions to evaluate whether actual usage is greater than predicted usage, which may indicate prescribing creep.

The governance line for the Committee needs to be formalised as the footprint for UCL Partners is substantially larger than the JFC footprint. Prof MacAllister proposed to approach the David Sloman, RFL Chief Executive who leads the NCL Sustainability and Transformation Plan (STP) about this issue.

The report should be updated to describe how the JFC will work with the newly established Regional Medicines Optimisation Committees (RMOC).

## 10. Soluble alendronic acid

Soluble alendronic acid (Binosto) is a new formulation of alendronic acid which costs £5.70 per dose compared to £0.19 for tablets and £6.84 for alendronic acid liquid (Rosemont). The Committee heard the soluble formulation was being heavily marketed in NCL. The manufacturer claims soluble alendronic acid lowers gastric pH to a lesser extent than alendronic acid tablets which may reduce the incidence of gastro-oesophageal ulceration. The Committee heard that the primary cause of gastro-oesophageal ulceration is the relaxation of the oesophageal sphincter which is expected to be similar with both products and there was no evidence that soluble alendronic acid had a lower risk of GI adverse effects compared to either alendronic acid tablets or liquid.

The administration requirement for alendronic acid tablet, dispersible tablet and liquid are very similar.

Discussions with specialists at UCLH suggested one liquid or dispersible product would be useful for patients who cannot tolerate the oral tablets, and cannot tolerate, or are unsuitable for IV zolendronic acid and denosumab.

The Committee agreed alendronic acid liquid is likely to be more resistant to prescribing creep than dispersible tablets, therefore alendronic acid liquid should be the preferred choice for patients who cannot tolerate alendronic acid oral tablets, and cannot tolerate, or are unsuitable for IV zolendronic acid and denosumab. Soluble alendronic acid (Binosto) should not be added to the NCL Joint Formulary.

Decision: Not approved

## 11. JFC Work-plan

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

## 12. Next meeting

Thursday 25th August 2016, Room 6LM1, Stephenson House, 75 Hampstead Rd.

## 13. Any Other Business

**NOACs in atrial flutter**

Mr Minshull updated the Committee that the NOAC Stakeholder Group had questioned whether patients with atrial flutter should be treated with NOACs in accordance with the pathways being agreed in NCL. NICE CG 180 states that patients with atrial flutter should be risk assessed using $CHA_2DS_2$-VASc. Of the trials of NOACs in AF, the ARISTOTLE and ENGAGE AF trials include patients with flutter, but the other trials don't mention these patients. Dr Sofat advised the Committee that as atrial flutter patients are included in clinical trials, our advice in NCL should be used to cover this patient cohort. The Committee agreed to this recommendation.

**Section 7.4 & 7.5 updated on 6 October 2016 following discussion at September 2016 meeting.**