North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Monday 16 October 2018
LG01, 222 Euston Road

Present:	Dr R MacAllister	NCL JFC Chair	**(Chair)**
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Dr R Sofat	UCLH, DTC Chair	
	Dr M Kelsey	WH, DTC Chair	
	Mr S Semple	MEH, Interim Chief Pharmacist	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Dr A Sell	RNOH, DTC Chair	
	Ms W Spicer	RFL, Chief Pharmacist	
In attendance:	Mr A Barron	NCL MEP, Lead Pharmacist	
	Dr P Bodalia	UCLH, Principal Pharmacist	
	Ms M Kassam	NCL JFC, Support Pharmacist	
	Mr G Grewal	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms S Sanghvi	UCLH, Formulary Pharmacist	
	Dr D Hughes	RFL, Consultant Haematologist	
	Ms H Mehta	NMUH, Formulary Pharmacist	
	Ms F Shivji	NEL CSU, Observer	
	Ms K Saxby	Formulary Pharmacist, UCLH	
	Dr H Longhurst	UCLH, Consultant immunologist	
	Dr M Dziadzio	UCLH, Consultant immunologist	
	Dr J Fullerton	UCLH, Clinical Pharmacologist	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Dr M Dhavale	Enfield CCG, GP Clinical Lead Medicines Management	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr A Bansal	Barnet CCG, GP Clinical Lead Medicines Management	
	Prof A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr T Rashid	NHS Haringey, GP Clinical Lead Medicines Management	
	Mr TF Chan	RFL, Deputy Chief Pharmacist	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr F Gishen	RFL, Palliative Care Consultant	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Mr T Dean	Patient Partner	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Mr S Richardson	WH, Chief Pharmacist	
	Dr D Hughes	RFL, Consultant Haematologist	
	Ms K Davies	NEL CSU, Deputy Director Medicines Management	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Dr R Woolfson	RFL, DTC Chair	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	

2. Meeting observers

Dr MacAllister welcomed Ms Al-Hayali (MEH, formulary pharmacist) to the Committee and Ms Shivji (NEL CSU) as an observer of the meeting and explained the role of the JFC.

Dr MacAllister informed the Committee that Dr Gishen (RFL) has stepped down from the JFC. *In absentia*, the Chair thanked Dr Gishen for her contribution to the Committee.

3. Minutes of the last meeting

The minutes were corrected to indicate that Caplacizumab (compassionate access) is applicable to UCLH only; and mFolfirinox does not require inpatient admission for the administration of chemotherapy as this will be administered in an outpatient setting.

Following September's meeting the Committee clarified where use of anakinra for sHLH is required in advance of NHSE funding approval, individual Trusts should develop local protocols (to include place in therapy [relative to steroids and IVIG], dosing range, route of administration, duration of treatment and stopping criteria) which would support clinical staff and be used to estimate the budget impact for internal funding consideration. September's minutes were amended to reflect this decision.

4. Matters arising

Nil.

5. JFC Work Plan & outstanding actions

These items were included for information only. Any questions should be directed to Ms Kassam.

6. Declarations of relevant conflicts of interest

Dr Longhurst declared remuneration over the last 12 months from Shire, Pharming Group N.V. and CSL Behring UK Limited due to professional services associated with the development of C1 esterase inhibitors.

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Sep-18	Glycerol phenylbuterate liquid	Urea cycle disorders for patients who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.	Decision: UCLH only Prescribing: Secondary care Tariff status: Excluded from tariff Funding: NHS England Fact sheet or shared care required: No
RFL	Aug-18	Selexipag	Pulmonary Hypertension for compassionate use and in patients from Wales and Northern Ireland for whom the drug is funded following positive recommendations from AWMSG and SMC respectively.	Decision: RFL only Prescribing: Secondary care Tariff status: N/A Funding: FOC Fact sheet or shared care required: No
RFL	Aug-18	Telotristat (FOC scheme)	Carcinoid syndrome diarrhoea for patients who are non-responsive to somatostatin analogues.	Decision: RFL only Prescribing: Secondary care Tariff status: N/A Funding: FOC Fact sheet or shared care required: No
RFL	Aug-18	Anakinra and Tocilizumab	Adult onset Stills disease in line with NHSE Commissioning Policy 170056P	Decision: Added to NCL Joint Formulary Prescribing: Secondary care Tariff status: Not routinely funded Funding: NHSE Fact sheet or shared care required: No

NMUH	Jun-18	Forceval soluble tablets	Prophylaxis of refeeding syndrome	Decision: Added to NCL Joint Formulary Prescribing: Secondary care only Tariff status: in tariff Funding: Trust Fact sheet or shared care required: No
NMUH	Jun-18	Ketovite tablets	Prophylaxis of refeeding syndrome	Removed from formulary in NMUH
NMUH	Jun-18	Ketovite liquid	Prophylaxis of refeeding syndrome	Removed from formulary in NMUH

7.2 Not approved

UCLH	Sep-18	Rivaroxaban	Thromboprophylaxis during neo-adjuvant chemotherapy prior to elective interval debulking surgery or stage III & IV primary epithelial ovarian cancer	Not Approved

8. New Medicine Reviews

8.1 Cinryze®, *Shire* (plasma derived C1 esterase inhibitor) and Ruconest®, *Pharming Group N.V* (recombinant C1 esterase inhibitor) for hereditary angioedema (Applicant: Dr S Seneviratne, RFL)

The Committee reviewed an application for plasma derived and recombinant C1 esterase inhibitors (C1-INH) for the treatment of hereditary angioedema (HAE). HAE is a rare genetic condition caused by a mutation in SERPING1 gene leading to C1-INH deficiency due to inadequate or non-functioning C1-INH, a blood protein that regulates proteases in the complement, fibrinolytic and contact systems. Uncontrolled complement cascade activation, bradykinin cascade activation and kallikreins activation leads to increased vascular permeability; the fluid leak from the intravascular compartment into the subcutaneous or submucosal space manifests as an acute episode of angioedema which can be life threatening if not treated. Multiple regions can be affected, such as GI tract, facial tissues, upper airways and limbs. Laryngeal attacks can be life threatening due to obstruction of upper airway. HAE is classified into 3 types; type 1 which is characterised by abnormal C1-INH levels, type 2 which is characterised by abnormal C1-INH function and type 3 which is very rare and caused by a mutation in factor XII. Acquired angioedema is treated clinically as HAE and presents with low C1-INH level due to an underlying disease.

The Committee heard that management of HAE includes treatment of acute attacks, short–term procedural prophylaxis and long-term prophylaxis to minimise severity and frequency of attacks. C1-INH products are licensed for the treatment of acute attacks of HAE, but only Cinryze® is licensed for prophylaxis. Berinert® and Cinryze are plasma derived C1-INH whereas Ruconest® is recombinant C1-INH; hence Ruconest has less risk of supply problems and transmission of blood borne products.

The Committee noted that Berinert is on the Formulary at RFL and UCLH; this decision was based on cost and convenience. The NHS framework agreement identified Cinryze as the best value C1-INH but due to issues with supply no new patients should be started on Cinryze. The next best value product is Ruconest which following clinical considerations may be appropriate.

Cinryze and Ruconest are proposed to be used for treatment of HAE for acute attacks in line with the license (this will be NHSE commissioned). Cinryze is also licensed for long-term prophylaxis of HAE attacks; it is proposed to be used for long-term prophylaxis as per the NHSE commissioning eligibility criteria for HAE types 1 and 2. Ruconest is not licensed for prophylaxis, however due to supply issues with Cinryze, Ruconest will be the next cost-effective long-term prophylaxis option.

The Committee reviewed 1 RCT for the treatment of acute HAE and 1 RCT for prophylaxis of HAE. LEVP 2005-1/A is a randomised, double-blind, placebo-controlled, parallel group design trial evaluating Cinrzye for the treatment of acute attacks. 71 subjects with acute HAE attacks were randomised (36 Cinryze, 35 placebo). The study demonstrated that treatment with Cinryze within 4 hours after the onset of an HAE attack resulted in a greater than two-fold decrease in the time to beginning of unequivocal relief of the defining symptom of the HAE attack compared to placebo (median 2 hours for Cinryze vs. greater than 4 hours for placebo, p=0.048). Treatment with Cinryze also resulted in a greater than two-fold decrease in the time to complete resolution of the HAE attack compared to placebo (median 12.3 hours vs. 31.6 hours, p=0.001). The percentage of subjects with beginning of unequivocal relief of the defining symptom within 4 hours after dosing was 60% for Cinryze and 42% for placebo (p=0.062).

Study LEVP 2005-1/B used a randomised, double-blind, placebo-controlled, crossover design; 22 subjects were evaluable for efficacy (randomised and treated in both crossover periods). The study demonstrated that prophylaxis with Cinryze resulted in a greater than two-fold reduction in the number of HAE attacks compared to placebo (mean 6.3 attacks for Cinryze vs. 12.8 attacks for placebo, p<0.0001). Angioedema attacks were also less severe during prophylactic Cinryze therapy compared to placebo (mean severity score 1.3 vs. 1.9 or a 32% reduction, p=0.0008) and of shorter duration (mean 2.1 days vs. 3.4 days or a 38% reduction, p=0.0004). The total number of days of swelling during prophylactic Cinryze therapy was reduced compared to placebo (mean 10.1 days vs. 29.6 days or a 66% reduction, p<0.0001). In addition, fewer open-label Cinryze infusions were required for treatment of HAE attacks during therapy with Cinryze compared to placebo (mean 4.7 infusions vs. 15.4 infusions or 70% reduction, p<0.0001).

The Committee evaluated the evidence base for Ruconest for prophylaxis and acute treatment of HAE. Several RCTs support a statistically significant reduction in time to beginning of relief of symptom during acute HAE attacks with Ruconest vs. placebo. The largest RCT conducted by Riedl 2014 included patients older than 13 years of age experiencing an acute angioedema attack (43 Ruconest, 31 saline). Time to beginning of relief of symptoms was significantly shorter in patients treated with Ruconest compared with patients treated with saline (90 vs. 152 min; p=0.031). The primary evidence for HAE prophylaxis is a multicentre, randomised, double-blind, placebo-controlled, cross-over trial conducted by Riedl 2017. 32 patients older than 13 years of age with a history of ≥4 HAE attacks per month for at least 3 months were randomised 1:1:1:1:1:1 to receive one of six treatment sequences for 4 weeks with a 1-week washout between cross-over. The treatment arms were as follows: Ruconest twice weekly, Ruconest once weekly, placebo once weekly, and placebo twice weekly. Mean number of HAE attacks per 4 weeks was significantly reduced with Ruconest twice weekly and once weekly, mean differences of −4.4 attacks (P < 0.0001) and −2.8 attacks (P = 0.0004) respectively vs. placebo (7.2 attacks).

In terms of safety, the only common adverse reaction observed following Cinryze infusion in the clinical studies was rash. None of the rashes were categorised as serious, and none led to discontinuation of treatment. Adverse effects reported from limited studies on long-term prophylaxis included headache, nasopharyngitis, dry mouth, dizziness, hypotension and anxiety.

The Committee heard that C1-INHs are commissioned by NHS England for the treatment of acute HAE attacks. Long-term prophylaxis with Cinryze is commissioned by NHS England. Ruconest on the other hand is not NHSE commissioned for long-term prophylaxis, although due to the shortage of Cinryze NHSE have stated Ruconest may be used for prophylaxis. Based on the NHS Framework agreement for C1-INH, Cinryze was identified as the best value product and Ruconest as next best value. There will be approximately 30 patients, with an average of 2 attacks per annum, managed with C1-INH for treatment of acute HAE attacks at the RFL; there are currently 9 known patients at UCLH. UCLH is hosting a new HAE clinic therefore patient numbers are expected to increase. The average number of attacks that patients experience is 1-4 per annum but this can vary from none to 100 per year.

Dr Longhurst (UCLH) expressed the need for all three C1-INH to be available on the NCL Joint Formulary in context of the new UCLH HAE clinic and in light of current supply issues and shortages limiting access to plasma-derived C1-INHs. The applicants proposed that the most cost-effective product will be selected, in line with NHSE commissioning policy and subject to supply constraints. Anecdotally, despite Ruconests' shorter half-life it appears equivalent to plasma derived C1-INH and is well tolerated. The Committee heard that long-term prophylaxis with intravenous C1-INH requires titrating doses over a period of time which requires patients to be taught to cannulate themselves.

In camera, the Committee recognised the necessity for the C1-INH for treatment and prophylaxis of HAE however expressed concerns over governance processes in approving three C1-INHs for the same indications and was unclear if this would be cost minimising. The Committee requested a protocol to clarify the selection hierarchy between the three proposed products. Concerns around switching between C1-INHs were raised and it was requested to include suitability and process of switching between C1-INHs (e.g. dose conversion) within the protocol. Additionally, the Committee requested an outline of the HAE treatment and prophylaxis proposal to be submitted to NHSE for confirmation that the most clinically and cost-effective C1-INH have been selected (in-line with commissioned criteria), which would also ensure

NHSE funding. Lastly, it was raised that C1-INH are blood products and as such the procurement process, specifically pharmacy involvement, is yet to be decided.

Action: Applicant to create and submit a protocol outlining selection hierarchy between the three proposed C1-INH and the place in therapy, to include HAE treatment and prophylaxis options. This will be submitted to NHSE for confirmation of process and funding.

Decision: Approved across NCL pending NHSE confirmation and protocol
Prescribing: Secondary care only
Tariff status: Not routinely funded
Funding: NHSE
Fact sheet or shared care required: No

8.2 **Danazol and Oxandrolone for prophylaxis of C1 esterase inhibitor deficiency and other bradykinin-mediated angioedema (Applicant: Dr H Longhurst, UCLH)**

The Committee considered an application for danazol and oxandrolone for long-term prophylaxis of C1 esterase inhibitor (C1-INH) deficiency and bradykinin medicated angioedema. Both danazol and oxandrolone are on the Formulary at RFL since 2002 for the long-term prophylaxis of HAE, minutes for which are not available.

The Committee heard that there are 4 main conditions associated with angioedema symptoms with different underlying mechanisms. Idiopathic angioedema is one such condition; this is mediated by bradykinins hence not responsive to antihistamines. HAE and acquired angioedema are also included, and mediated by C1-INH deficiency.

The Committee noted that NHSE have not issued guidance on oral prophylaxis of HAE however commissioning policies for C1-INH consider androgens or antifibrinolytics first line, as do international consensus guidelines. Danazol was proposed as first line long-term prophylaxis of C1-INH deficiency and other bradykinin-mediated angioedemas, also including HAE type 3. Oxandrolone was proposed as a second line option for patients intolerant or contraindicated to danazol, as per international HAE guidelines and NHSE clinical guidance on alternative options for oral prophylaxis of HAE when danazol and stanozolol are not available.

The Committee evaluated efficacy findings from an RCT and observational studies of long-term danazol prophylaxis in patients with HAE. Findings showed danazol reduced the severity and frequency of HAE attacks and resulted in improvement of clinical symptoms. In some studies nearly all patients were able to find an effective dose of danazol that completely prevented HAE attacks. The cumulative percentage of patients without HAE attacks increased with increasing dosage of danazol. An RCT by Gelfand et al. (1976) reported a double-blind, randomised, crossover study in 9 patients whom experienced HAE attacks at least once per month. Patients were treated with alternating courses of danazol 200mg or placebo three times daily. Each treatment course was terminated when an attack occurred, or after 28 days of no attack – in total, 9 patients completed 93 courses. The primary outcome was the rate of attacks. Attacks of HAE occurred in 93.6% of placebo courses vs 2.2% of danazol courses ($p < 0.001$).

The Committee acknowledged that due to the lack of availability of stanozolol, patients intolerant to danazol are recommended by NHSE to use other attenuated androgens such as oxandrolone. This recommendation is based on case reports and expert opinion. The Committee considered a case report by Barakat and Castaldo (1999) which reported the successful use of oxandrolone for HAE prophylaxis in a 14 year old girl experiencing weight gain and elevated testosterone attributed to 8 years of danazol therapy. Over a period of 12 months treatment with oxandrolone treatment, at an average dose of 8.5mg/day, the frequency and severity of attacks was reported as remarkably reduced and disease control improved, whilst testosterone level reduced. Similar significant reductions in severity and frequency of attacks were reported by Church (2004) in a previously treatment naïve, 6 year old boy treated with oxandrolone 0.1mg/kg daily for 20 months, however early virilisation and an advanced bone age were observed.

The Committee discussed that the side effect profile for both is extensive, and intensive monitoring will be necessary. The prevalence and severity of adverse effects associated with danazol appear to increase with dosage strength and duration of therapy. A safety and efficacy assessment of 69 HAE patients on long-term danazol prophylaxis (between 1 and 6 years) was conducted by Hosea et al. (1980); initially reported side effects included weight gain (38% of patients) and menstrual irregularities (amenorrhea, 16%; menometrorrhagia, 34%). More recently, the European Register of HAE collected adverse events from 366 HAE patients on long-term prophylaxis therapy with either danazol (n=312) or stanozolol (n=54). Mean treatment time with either agent was 8.8 years. Side effects were reported in 207 patients (57%), 149 women and 58 men. The most frequent side effects were weight gain, menstrual irregularities, hypertension, acne, virilisation, depression, headache, and myalgia; hepatocellular adenomas developed in 3 patients. The Committee were informed that the proposed monitoring for danazol and oxandrolone is 6 monthly liver function tests, full blood count and cholesterol levels. A liver ultrasound (for adenoma) will be conducted every 2 years.

The Committee discussed the additional cost impact based on 10 patients per year attending the new HAE clinic in UCLH will amount to between £900 to £1,800 for danazol and between £10,000 to £20,000 for oxandrolone.

The Committee heard from Dr Longhurst that a monthly HAE clinic is opening at UCLH which will require the use of oxandrolone and danazol as first line prophylaxis of HAE. Long-term prophylaxis with these agents avoids the use of expensive and invasive C1-INH. Dr Longhurst explained that danazol used at high doses often results in side effects and although there is little evidence available, particularly for oxandrolone, anecdotally oxandrolone seems well-tolerated. Dr Longhurst described the proposed use of long-term oral prophylactic agents for HAE; danazol and tranexamic acid would be used first-line if attacks are more frequent than once per month. The evidence base for tranexamic acid is weak, and does not offer sufficient prophylaxis. Danazol and oxandrolone are not usually used in children until post-puberty. The applicants proposed that following initiation and dose stabilisation, danazol may continue to be supplied in primary care; however oxandrolone would need to remain within secondary care as it requires import from overseas. The monitoring outlined above was proposed to be the responsibility of the HAE clinic; however the Committee raised concerns that the supply of danazol and monitoring would be disjointed. Dr Longhurst explained that patients only attend the clinic 1-2 times per year, so supply poses a logistical issue (note: these are schedule 4 controlled drugs); and the clinic is contactable via email for queries.

In camera, the Committee agreed that these are established treatments, with the precedent for long-term HAE prophylaxis for both oxandrolone and danazol having been set by RFL. The Committee acknowledged that should monitoring and supply of oxandrolone be retained in secondary care whilst the supply of danazol be undertaken in primary care this may lead to inconsistency; the current process for supply of these treatments following initiation at RFL will be explored and fed-back to the JFC Secretariat. The current process for supply of these treatments following initiation at RFL will be explored and fed-back to the JFC Secretariat.

Action: The Committee questioned if long-term prophylaxis of HAE is necessary in children and what would be used; JFC Secretariat to contact the applicant to clarify.

RFL supply process for oxandrolone and danazol to be explored and fed-back to committee.

Decision: Approved
Prescribing: oxandrolone - secondary care; danazol - TBC
Tariff status: in tariff
Funding: TBC
Fact sheet or shared care required: No

8.3 Budesonide rectal foam (Budenofalk®) for active ulcerative colitis limited to the rectum and sigmoid colon (Applicant: Dr C Murray, RFL)

The Committee considered an application *in absentia* for Budesonide rectal foam (Budenofalk®) for active ulcerative proctitis (UP) or ulcerative proctosigmoiditis (UPS). This application was noted as being cost-saving, with Budenofalk® as second-line therapy replacing Predfoam® which is a costlier treatment.

Evidence for Budenofalk's efficacy comes from placebo-controlled and active-controlled studies. Sandborn et al (n=546) performed 2 identical, randomised, double-blind multi-centre trials. One trial was conducted in USA, and the second in Russia. Participants were aged 18 and over and suffered from UP or UPS at least 5cm but not farther than 40cm from the anal verge. Participants were excluded if they had a history of other bowel disorders, a positive stool test for bacterial pathogens or adrenal insufficiency. Participants were stratified, and each group was given either budesonide rectal foam or placebo twice daily for 2 weeks followed by once daily for a further 4 weeks. In the primary efficacy outcome, significantly more patients in the budesonide group were found to be in remission at week 6 in comparison with the placebo group (in each study and as an average across both studies). Further significant improvements were found in the secondary efficacy outcomes; significantly more patients received a Mayo rectal bleeding sub-score of 0 at week 6, and significantly more patients received a Mayo endoscopy sub-score of ≤1 at week 6 (in each individual study and as an average across both studies). Lastly, significantly more patients were found to have a Mayo rectal bleeding sub-score of 0 at various assessment points in each study. Strengths of the study lay in its analysis of the intention to treat population, the secondary analysis of patients who had concomitant (5-ASA) 5-aminosalicylic acid treatment (which also showed significance of Budesonide rectal foam) and the analysis demonstrating significance of budesonide rectal foam in various patient demographics. Weaknesses of the study came from disproportionate ethnicities used in the sample population (due to the studies being conducted in centres in the USA and Russia only) and the lack of information of power and sample size calculations.

Bar-Meir et al (n=251) conducted a randomised, active-control, open-label, parallel group, international, multi-centre trial. They used participants aged 18-70 with UP or UPS. They utilised a scoring system known as the disease activity index (DAI), and included patients with a score of 4 or more. Participant were excluded if their diagnosis was within the last two weeks; if the participant had a positive stool test for bacterial pathogens; any participants with lesions near the sigmoid colon; and those participants taking specific concomitant medications such as corticosteroids within a month of the study start date (though concomitant 5-ASA use was allowed). Randomisation was stratified and participants had either budesonide rectal foam or hydrocortisone rectal foam once a night for eight weeks. Remission rates in the budesonide group were found to be non-inferior to the hydrocortisone group in the per-protocol (55% vs 51%) and intention-to-treat (53% vs 52%) populations. Mean DAI score reductions were also non-inferior; budesonide group DAI score went from 7.2 (± 1.9) to 3.6 (± 3.1); hydrocortisone group DAI score went from 7 (± 2) to 3.9 (± 3.4). The time taken for participants to have fewer than 4 daily bowel movements was also shown to be non-inferior, with 7 days taken for budesonide users and 9 days taken for hydrocortisone users. Strengths of the study were the demonstration of power & sample size calculations. Weaknesses of the study include the use of a non-inferiority design; its primary analysis of the per-protocol population; the definition of "remission" was questionable as participants with a DAI of equal to or less than 3 were considered as "in remission", though it is arguable that full remission would be a DAI of 0. Additionally the study was pharma funded which is liable to the introduction of bias.

In terms of safety, the most common adverse events in studies were decreased blood cortisol concentrations, adrenal insufficiency, headache and nausea. However, the side effect profile will be very similar to the other rectal corticosteroids which are used extensively in the treatment of ulcerative colitis. The budget implications to NCL is favourable, with an estimated £100,000 cost saving in primary care and an estimated £40,000 cost saving in secondary care from replacing Predfoam® with Budenofalk®. Prescribing in the acute setting will be initiated in secondary care for 2 weeks, with the specialist detailing the full course of treatment in the clinic letter to the GP, who will continue prescribing for the duration of treatment.

In summary, the Committee agreed on the use of Budenofalk® for ulcerative proctitis and ulcerative proctosigmoiditis as second line following the use of prednisolone retention enema, replacing Predfoam® in the pathway.

Decision: Approved
Prescribing: Primary and Secondary care
Tariff status: In tariff
Funding: Hospital/CCG funded
Fact sheet or shared care required: No

8.4 **Omega-3 fatty acid ethyl esters (Omacor®, *Mylan*) for inherited hypertriglyceridaemia (Applicant: Dr D Nair, RFL)**

The Committee considered an application *in absentia* for omega-3 fatty acid ethyl esters for the treatment of inherited hypertriglyceridaemia (type 3 hyperlipidaemia, lipoprotein lipase deficiency or in presence of raised chylomicrons and VLDL), if triglyceride (TG) levels are ≥10mmol/L despite addressing secondary causes, uptake of lifestyle changes and pharmacological therapy (statins and fibrates).

The Committee heard that NHSE, NICE, SIGN and SMC recommend against the use of omega-3 fatty acids, however the scope for each recommendation was limited to cardiovascular outcomes, rather than triglycerides or pancreatitis. PrescQIPP did consider the use of omega-3 for hypertriglyceridaemia and recommended patients are reviewed with consideration given to switching to a statin or fibrate and advised to increase their dietary intake of omega-3; PrescQIPP did not provide advice for patients included within the scope of this application. Anecdotally NHSE are considering black-listing Omega 3 fatty acids.

The American Heart Association (AHA), National Lipid Association (NLA), Endocrine Society (ES), and the ESC (European Society of Cardiology) with EAS (European Atherosclerosis Society) have developed guidelines for the management of hypertriglyceridemia; all recommend omega-3 as a treatment option. Whilst the AHA and the ESC/EAS do not recommend a target for TG reduction, the ES and NLA recommends a goal for TG reduction of <11.3 mmol/L and <5.65 mmol/L respectively.

The TG level above which acute pancreatitis may occur is not clear. Multiple guidelines suggest a serum TG level >11.3 mmol/l increases the risk of pancreatitis however one study suggests an increased risk >5.6 mmol/L. The most relevant evidence is a retrospective prevalence study of 129 patients with inherited hypertriglyceridaemia and TG >11.3mmol/L; results suggested 20.2% of the population presented with at least one attack of acute pancreatitis and of these, 85% had TG >33.9 mmol/L.

The Committee heard that no randomised control trials have evaluated the efficacy of omega-3 fatty acid ethyl esters in the reduction in risk of pancreatitis in patients with inherited hypertriglyceridaemia or severe TG level (>10mmol/L).

Several case series have reported reductions in TG levels in patients with inherited hypertriglyceridaemia (type 3 and type 4) with reductions from ranging from 43-56%. Sample sizes were small, each trial used different dosing and omega-3 preparations and the absence of a control arm makes interpretation challenging given the daily variation of TG in response to diet.

The Committee considered three randomised, double blind, placebo controlled trials which evaluated the efficacy of omega-3 fatty acids in reducing hypertriglyceridaemia >5.65 mmol/L. The largest double blind, randomised, placebo-controlled trial of omega-3 fatty acid ethyl esters analysed 42 subjects for 16 weeks with a mean baseline TG of 9.91 mmol/L (range: 5.65–22.3 mmol/L). Triglycerides reduced by 45% in the omega-3 (Omacor) arm vs. a 16% increase in the placebo arm, LDL increased (omega-3 (Omacor) arm: +32% vs. placebo: -5%) and HDL increased (Omega-3 (Omacor) arm: +13% vs. placebo: no change). The Committee noted that gastrointestinal adverse effects were common with omega-3.

In terms of patients numbers; RFL anticipate approximately 60 patients would require treatment, UCLH also treat patients with inherited hypertriglyceridaemia although were unable to provide patient numbers. Data from ePACT2 identified 643 patients per year within NCL suggesting that a large proportion of patients were inappropriately receiving treatment; total NCL in primary care was £203,000.

The applicant proposed all prescribing to be retained in secondary care however the Committee rejected this proposal as it was illogical to assign a food supplement 'hospital only'.

The Committee considered the appropriate place in therapy, supporting the view the omega-3 fatty acids had no place in the primary or secondary prevention of cardiovascular events. Given the lack of high-quality evidence to (i) define a TG threshold at which the risk of pancreatitis in a patient with inherited hypertriglyceridaemia may occur, and (ii) a lack of robust evidence to support the a claim that omega-3 fatty acids reduces the risk pancreatitis [there is evidence that omega-3 fatty acids lowers TG and lowering TGs *may* reduce the risk of pancreatitis], the Committee were unable to recommend the use of omega-3 fatty acids for the <u>primary prevention</u> of pancreatitis. The Committee agreed to retain omega-3 fatty acids on the NCL Joint Formulary for the <u>secondary prevention</u> of pancreatitis if TG levels are ≥10mmol/L despite addressing secondary causes, uptake of lifestyle changes and pharmacological therapy (statins and fibrates)

Decision: Approved with additional restrictions: Omega-3 fatty acids ethyl ester for secondary prevention of pancreatitis for the treatment of inherited hypertriglyceridaemia (type 3 hyperlipidaemia, lipoprotein lipase deficiency or in presence of raised chylomicrons and VLDL), if TG levels are ≥10mmol/L despite addressing secondary causes, uptake of lifestyle changes and pharmacological therapy. To be initiated in lipid clinics only.

Prescribing: Primary and secondary care
Tariff status: In tariff
Funding: CCG and hospital funding
Fact sheet or shared care required: No
Additional notes: Omacor for this indication can be prescribed at doses 2-6g per day; high doses increase the risk of gastrointestinal adverse effects.

9. Brivaracetam outcomes (Applicant: Prof M Koepp, UCLH)

In October 2016 the JFC received an appeal to review the previous decision of 'not approved' for brivaracetam as an adjunct for partial onset seizures. The 'not approved' decision was based on a consideration of the evidence that brivaracetam did not offer any clinical advantages over levetiracetam. The Committee noted in the appeal that no new data was presented to inform the value of brivaracetam compared with levetiracetam, the key driver behind the previous decision of non-approval.

The Committee however appreciated the dilemma presented regarding the local cohort of patients with highly-refractory epilepsy and were persuaded by the high standard of medicines governance demonstrated by the epilepsy service over recent years to support an evaluation. JFC supported the NHNN epilepsy service to evaluate brivaracetam in a cohort of patients with refractory epilepsy who responded to levetiracetam, but had to stop due to off target effects.

Between the period of January 2017 and July 2018 a total of 50 patients at UCLH were approved by JFC to commence brivaracetam, with data collected prospectively at baseline, 3 months and 6 months. The data collected included numbers of seizures, tolerability to levetiracetam and tolerability to brivaracetam. Nine patients did not commence brivaracetam and four patients did not have 3 months data available, these patients were excluded from the results. 37 patients had data available for evaluation.

The results collected from the patients initiated on brivaracetam indicated the efficacy in some patients, at month 3, 81% of patients had a documented efficacy with brivaracetam. At month 6, 66% had a documented positive effect however 5 patients did not have results available from the 3 month cohort. Regarding tolerability at 3 months; 78% of patients reported no side effects when administering brivaracetam, 22% of patients reported side effects in which 20% withdrew from treatment. The remainder that reported side effects continued treatment with brivaracetam due to the positive effect from therapy, although 6 month data was not available for these patients. Retention at 3 months was 75% and this reduced to 53% at 6 months.

Whilst the dataset included only patients with intolerance to levetiracetam, the Committee requested information on the efficacy of brivaracetam in pharmacoresistant epilepsy patients. The audit was not designed to answer this question although the mean number of previous AEDs in the 'responder' group was 9 compared to 11 with the 'non-responder group.'

This evaluation provided the JFC with real world data in a cohort of patients that accurately reflects the patients managed by the NHNN epilepsy service. The results indicated that 53% of patient experienced a sustained positive response with brivaracetam at month 6 (reduction in seizures and well tolerated), with one patient becoming seizure free and able to drive which was not achieved with levetiracetam. Inappropriate initiation and appropriate continuation of brivaracetam was aided by use of the audit forms, supported by JFC Secretariat.

The Committee heard from Prof Koepp that the main adverse effect responsible for intolerance to levetiracetam is aggression or change in behaviour; as these adverse effects commonly develop before efficacy is evident it is these patients who are considered eligible to receive brivaracetam. It was clarified that prescribing of brivaracetam has been and should be restricted to the consultants at the epilepsy specialist service at NHNN and RFL and restricted to patients who have tried but are unable to tolerate levetiracetam. Ongoing prescribing in primary care is considered appropriate if therapy is effective and tolerated after 6 months. The audit report highlighted that antiepileptic drugs are reviewed closely when initiated and stopped appropriately for lack of efficacy or reported side effects, with collection of outcome data at month 3 and month 6 for all patients newly initiated on brivaracetam.

In camera, the Committee agreed that brivaracetam may be of value for a specific cohort of patients as described within the audit and recommended that the same selection criteria and process which formed the evaluation to be retained for future patients.

Decision: Approved with restrictions
Prescribing: Primary and secondary care
Tariff status: In tariff
Funding: CCG and hospital funding
Fact sheet or shared care required: No
Additional notes: This is approved only for patients with partial onset refractory epilepsy who have not been able to take an optimal dose of levetiracetam due to off target effects before effectiveness could be established. Selection criteria and process which formed the evaluation should continue for future patients.

10. **Eslicarbazepine audit proposal**

At the July 2016 JFC meeting, the Committee did not approve eslicarbazepine for prescribing in partial epilepsy on the basis that eslicarbazepine (ES) was not found to be superior to oxcarbazepine (OXC), and that any advantage was considered to be minor and theoretical, which would be offset by the greater cost. A subsequent discussion took place in September 2017 where Prof Koepp proposed a prospective switching evaluation of eslicarbazepine in patients who experience adverse side effects from oxcarbazepine in order to test the hypothesis that eslicarbazepine will be better tolerated than oxcarbazepine due to the differences in pharmacokinetics between the two agents. The Committee were supportive of this evaluation provided this could be undertaken via the 'n-of-1' methodology including double-blinding and an evaluation plan is submitted for approval. The JFC suggested that the Secretariat support Prof Koepp in setting up this evaluation.

The Committee welcomed Prof Koepp to discuss an update on the above proposal. The evaluation plan indicated an evaluation of 20 to 30 patients over a 1 year period who have not tolerated OXC; patients will be initiated on ES with data collected prospectively at baseline, month 3 and month 6. The outcomes collected include: change in seizure frequency and seizure-free days; adherence to medication; frequency and type of adverse events; and emergency / hospital admissions. Costs incurred from adverse events including admission to A&E, appointments with healthcare professionals and hospital stays will be analysed.

Eligible patients include those seen by the NHNN Epilepsy Service (Queen Square or Chalfont) and fulfil all of the following:

- Are currently taking OXC, but not tolerating the current dose or the required BD or TDS regime;
- Are experiencing dose-dependent adverse effects;
- Have an agreement with their GP to continue the prescription of ES after the 6-month observation period, if proven to be beneficial.

Prof Koepp advised that the medication (OXC and ES) will be provided free-of-charge as part of this evaluation for all patients for 6 months by Bial Pharma UK Ltd, however undertaking the evaluation via the suggested n-of-1 design will not be possible due to the cost of over-encapsulation being prohibitively expensive (circa £100k and not willing to be funded by Bial Pharma).

In camera, the Committee remained of the opinion that OXC and ES are pharmacologically indistinguishable; ES is structurally similar to OXC, with an active metabolite profile which is extremely similar. The Committee referred to their previous decision that there is no clinical evidence of superiority of ES compared to OXC, although were willing to explore the hypothesis of improved tolerability of ES versus OXC through a blinded structured evaluation. The Committee reiterated the past JFC decision which concluded that the most effective way to evaluate this hypothesis given the subjective endpoints collected would be to undertake a double-blinded evaluation.

In summary, although the Committee appreciated the terms of the proposal in order to test the hypothesis, it was agreed that a non-blinded evaluation would not be suitable given the considerable risk of bias when evaluating a subjective endpoint. The Committee remained supportive of Prof Koepp running a blinded evaluation and would welcome a plan which included this to be brought back to a future JFC meeting for agreement; should it be approved, prescribing will remain in secondary care until the results of the evaluation have been analysed.

11. **Ciclosporin eye preparations fact sheet [Update] – for approval**

The fact sheet document was presented to the committee following approval from the shared care and fact sheet working group. The document was approved for use.

12. **Linaclotide for IBS-C fact sheet [New] – for approval**

The fact sheet document was presented to the committee following approval from the shared care and fact sheet working group. The document was approved for use.

13. **Riluzole shared care document [New] – for approval**

The shared care document was presented to the committee following approval from the shared care and fact sheet working group. The document was approved for use.

14. **Sub-regional Immunoglobulin assessment panels**

NHS England has recommended the establishment of sub-regional immunoglobulin panels to oversee the current issues and pressures surrounding supply and cost implications of immunoglobulins. The North

Central London sub-regional IVIG committee will be hosted by RFL with a Chair appointed from UCLH. A meeting will be held later this week and the Committee will be updated following this.

15. **Next meeting**

Monday 19th November, 4.30 – 6.30pm, LG01 Farr Institute of Health Informatics Research

16. **Any other business**

WH have requested for flixonase nasules for nasal polyps to be added to the NCL Joint Formulary. Flixonase for nasal polyps is currently on the formulary at UCLH and RFL. This matter was deferred to the next meeting.