North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 18th March 2021

Present:	Dr K Tasopoulos	NMUH, DTC Chair	(Chair)
	Mr P Gouldstone	NCL CCG, Head of Medicines Management (Enfield)	
	Ms G Smith	RFL, DTC Chair	
	Mr A Dutt	NCL CCG, Head of Medicines Management (Islington)	
	Mr T Dean	Patient Partner	
	Mr S Richardson	WH, Chief Pharmacist	
	Ms W Spicer	RFL, Chief Pharmacist	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms P Taylor	NCL CCG, Head of Medicines Management (Haringey)	
	Mr S Semple	MEH, Chief Pharmacist	
	Ms R Clark	NCL CCG, Head of Medicines Management (Camden)	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Dr S Ishaq	WH, Consultant Anaesthetist	
In attendance:	Dr P Bodalia	UCLH, Principal Pharmacist	
	Mr A Barron	North London Partners, MEP Project Lead	
	Mr G Grewal	North London Partners, JFC Support Pharmacist	
	Ms M Kassam	North London Partners, JFC Support Pharmacist	
	Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr F Master	RFL, Formulary Pharmacist	
	Dr A Scourfield	UCLH, Clinical Pharmacologist	
	Dr M George	UCLH, Specialist Registrar Clinical Pharmacology	
	Ms S Amin	UCLH, Formulary Pharmacist	
	Mr S O'Callaghan	UCLH, Formulary Pharmacist	
	Ms S Maru	UCLH, Formulary Pharmacist	
	Ms P McCormick	WH, Specialist Pharmacist	
	Ms SY Tan	NEL CSU, Contracting and Commissioning Pharmacist	
	Ms A Sehmi	NMUH, Formulary Pharmacist	
	Ms H Thoong	GOSH, Formulary Pharmacist	
	Mr D Sergian	MEH, Formulary Pharmacist	
	Ms S Shah	NEL CSU, Contracting and Commissioning Pharmacist	
	Dr P Dileo	UCLH, Consultant Medical Oncologist	
	Dr K Khan	NMUH, Consultant Medical Oncologist	
	Dr D Papadatos-Pastos	UCLH, Consultant Medical Oncologist	
	Dr H Kariyawasam	RNTNE, Consultant in Allergy Medicine	
	Dr G Rotiroti	RNTNE, Consultant in Allergy Medicine	
	Ms E Gortari	UCLH, Specialist Pharmacist	
	Dr M Gandhi	RFL, Consultant in Paediatric Allergy Medicine	
	Dr J Lukawska	UCLH, Consultant in Adult Allergy Medicine	
	Dr M Dziadzio	RNTNE, Consultant Immunologist	
	Dr M Makatsori	UCLH, Consultant in Allergy Medicine	
	Dr S Berkovitz	RLHIM, Consultant in Adult Allergy Medicine	
Apologies:	Prof R Sofat	NCL JFC Chair	

Dr A Sell	RNOH, DTC Chair
Ms A Fakoya	NEL CSU, Senior Prescribing Advisor High-Cost Drugs
Ms L Reeves	C&I, Chief Pharmacist
Dr M Kelsey	WH, DTC Chair
Mr A Tufail	MEH, DTC Chair
Mr A Shah	RNOH, Chief Pharmacist
Ms S Lever	NCL CCG, Head of Medicines Management (Barnet)
Ms S Stern	NMUH, Chief Pharmacist
Ms K Delargy	BEH, Deputy Chief Pharmacist
Dr D Burrage	WH, Consultant in Emergency Medicine
Dr R Urquhart	UCLH, Chief Pharmacist

2. Meeting observers

Ms Weaver (NHSE, Specialised Commissioning Pharmacist) and Ms Shah (NEL CSU, Contracting and Commissioning Pharmacist) were welcomed as observers of the meeting.

3. Minutes of the last meeting

The minutes and abbreviated minutes of the 18 February 2021 meeting were accepted as accurate reflections of the meeting.

4. Matters arising

4.1 High frequency vedolizumab for IBD

In November 2020, the Committee deferred a decision on high frequency vedolizumab [intravenous every 4 weeks (q4w)] for patients with Ulcerative Colitis and Crohn's Disease experiencing a secondary loss-of-response to standard frequency vedolizumab [intravenous every 8 weeks (q8w) or subcutaneous every 2 weeks (q2w)], to allow time for Trusts to identify a mechanism to offset the budget impact. RFL and UCLH have confirmed this work is complete.

Decision: Restricted to Trusts who have identified a mechanism to offset the budget impact
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: Standard dose funded by CCG/NHSE (for adults and paediatrics respectively). Additional doses (needed for high frequency dosing) funded by Trusts (may not be passed through to CCGs/NHSE)
Primary and secondary care Fact sheet or shared care required: No

5. JFC Outstanding Items & Work Plan

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

6. Members declarations of conflicts of interest

Nil

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
RFL	Jan 2021	Lumasiran	EAMS: Treatment of primary hyperoxaluria type 1	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: N/A Funding: FoC Fact sheet or shared care required: No
UCLH	Jan 2021	Olaparib	FoC scheme[+]: First-line treatment of BRCA1/2 mutated metastatic cholangiocarcinoma if unsuitable for gemcitabine and platinum-based therapy	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: N/A Funding: FoC Fact sheet or shared care required: No

UCLH	Jan 2021	Olaparib	FoC scheme†: Second line treatment of BRCA1/2 mutated metastatic cholangiocarcinoma following progression with gemcitabine and a platinum-based therapy if ineligible for clinical trials and unsuitable for FOLFOX	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: N/A Funding: FoC Fact sheet or shared care required: No
UCLH	Feb 2021	Sucralfate enema	Radiation induced proctitis	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

† The relevant commissioner should be notified in line with NCL Free of Charge scheme guidance.

7.2 Approved under evaluation

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Feb 2021	Cenobamate	Pre-NICE FoC scheme†: Adjunctive treatment of refractory focal-onset epilepsy	Decision: Approved for NCL specialist epilepsy centres (RFL and NHNN) Prescribing: Secondary care Tariff status: N/A Funding: FoC Fact sheet or shared care required: No

† The relevant commissioner should be notified in line with NCL Free of Charge scheme guidance.

7.3 Not approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Jan 2021	Risdiplam	EAMS: Type 2 spinal muscular atrophy in adults	Decision: Not approved

8. New Medicine Reviews

8.1 EAMS: Pemigatinib for cholangiocarcinoma with FGFR2 fusion or rearrangement relapsed/refractory to at least one line of systemic therapy (Applicant: Dr R Gillmore, RFL)

The Committee considered an application to use pemigatinib, an inhibitor of the fibroblast growth factor receptor (FGFR) isoforms 1-3, for locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement relapsed/refractory to at least one line of systemic therapy under an Early Access to Medicines Scheme (EAMS). The applicant proposed to use pemigatinib only in patients who meet the FIGHT-202 trial inclusion.

There are no randomised controlled trials assessing pemigatinib for the treatment locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement relapsed/refractory to at least one line of systemic therapy.

FIGHT-202 was a Phase II, open label, single arm study evaluating the safety and efficacy of pemigatinib in patients with locally advanced or metastatic cholangiocarcinoma. Patients were included if they progressed after at least one prior therapy (i.e. ≥ second-line) and had an ECOG performance status ≤2. Patients were assigned to cohorts A (FGFR2 gene rearrangements/fusions), B (other FGF/FGFR gene alterations), or C (no FGF/FGFR gene alterations) and received oral pemigatinib 13.5mg once daily until disease progression/unacceptable toxicity. The primary endpoint, centrally confirmed objective response rate, was 35.5% in patients with cohort A compared to 0% cohort B & C. Overall survival was 21.1 months in cohort A, and only 6.7 and 4.0 months in cohorts B & C respectively; however, data were not fully mature at data cut off and reported following 37% of events. Key limitations of the study include: lack of comparator arm, therefore the benefit compared to best supportive care or second-line chemotherapy (commonly FOLFOX) is not known, the primary outcome is a surrogate for overall survival however initial date indicate a favourable trend and the trial recruited a healthier population.

The FDA approved pemigatinib in this setting and EMA have granted a conditional marketing authorisation. There are no licensed targeted therapies for patients with cholangiocarcinoma with FGFR2 fusion/mutation in the UK. The current first-line treatment for metastatic or locally advanced cholangiocarcinoma is cisplatin plus gemcitabine. There is no established second-line treatment, however FOLFOX is emerging as the favoured option. A naïve comparison of overall survival between pemigatinib in cohort A and the ABC-06 trial (FOLFOX vs. best supportive care), provided the Committee with reassurance that pemigatinib for a FGFR2 molecular selected cohort was likely to be therapeutically superior to existing second-line treatment options.

In terms of safety, 45% (n=65) of patients had serious adverse events, the most frequent serious adverse events were abdominal pain, pyrexia, cholangitis, and pleural effusion. Retinal detachment occurred in 4.1% of patients, of which one event was Grade 3. The MHRA concluded that given the unmet need and paucity of other treatment options, the benefit of pemigatinib outweighs the potential adverse effects. Adverse events should be manageable with regular patient monitoring and associated risk minimisation measures, including monitoring phosphate and calcium levels and routine ophthalmic monitoring;

In terms of budget impact, pemigantinib and molecular testing will be provided free of charge under the EAMS. Baseline and during treatment monitoring of ophthalmological examination, serum calcium and phosphate levels is required. Oral treatment is more convenient compared with current IV chemotherapy options.

The Committee heard from Dr Khan that pemigatinib may extend overall survival to 21 months in a small subgroup of patients who have a life expectancy of around 6 months with currently available treatments. FOLFOX may be an option following pemigantinib progression, however benefit is modest and sometimes rechallenge with cisplatin plus gemcitabine or enrolment into a clinical trial is preferred.

In camera, the Committee agreed there was a high unmet clinical need in this population and pemigatinib conferred improvements in overall survival for a targeted subgroup of patients with FGFR2 fusion/ mutation. The Committee agreed with the MHRA conclusion of a positive benefit:risk profile for pemigatinib.

In summary, the Committee agreed to add pemigatinib to the NCL Joint Formulary for cholangiocarcinoma with FGFR2 fusion or rearrangement relapsed/refractory to at least one line of systemic therapy under an Early Access to Medicines Scheme if they meet the FIGHT-202 inclusion criteria [ECOG performance status ≤1, life expectancy of >12 weeks, adequate hepatic and renal function (total bilirubin <1.5 ULN, aspartate aminotransferase and alanine aminotransferase ≤2.5 ULN and creatinine clearance >30mL/min), serum phosphate ≤upper limit to normal, serum calcium within normal range and only in patients without brain metastases (or symptomatically stable before starting treatment with pemigatinib)].

Decision: Approved
Prescribing: Secondary care only
Tariff status: N/A
Funding: Drug and molecular testing provided FoC under MHRA EAMS
Primary and secondary care Fact sheet or shared care required: No

8.2 FoC: Ripretinib for Advanced Gastrointestinal Stromal Tumours (Applicant: Dr P Dileo, UCLH)

The Committee considered a pre-NICE free of charge (FoC) scheme for ripretinib, a tyrosine kinase inhibitor (TKI), for gastrointestinal stromal tumours (GIST) following failure or intolerance to imatinib, sunitinib and regorafenib.

The INVICTUS trial was a Phase III, placebo-controlled study to assess the safety and efficacy of ripretinib for patients with GIST following progression or intolerance to imatinib, sunitinib and regorafenib, with adequate organ function and an ECOG performance status 0 to 2 (n=129). Patients were randomised 2:1 to ripretinib or placebo. The primary endpoint, median progression-free survival as assessed by a blinded independent central review (BICR), was significantly longer with ripretinib compared to placebo (6.3 months vs. 1.6 months; HR: 0.15, [95%CI: 0.09 to 0.25]). Confirmed objective response (either 'complete' or 'partial' responders) assessed by BICR was not better with ripretinib compared to placebo (8 patients vs 0 patients; p=0.0504). Median overall survival (as assessed by the double-blind and open-label periods) was improved with ripretinib compared to placebo (15.1 months vs 6.6 months); due to hierarchical

analysis, formal statistical analysis of overall survival could not be demonstrated. Key limitations of the study were the relatively small sample size, lack of a pure placebo cohort in the overall survival analysis and the statistical plan used meant that important secondary outcomes (such as overall survival or quality of life) could not have a formal statistical analysis.

In terms of safety, the most common adverse events with ripretinib include alopecia, myalgia, nausea, fatigue, diarrhoea and palmar-plantar erythrodysesthesia. Other adverse events of note with ripretinib include hypertension, increase in lipase/amylase, electrolyte abnormalities, cardiac failure and dermatologic adverse events. In terms of risk assessment, ripretinib was shown to have interactions with CYP3A inhibitors and inducers, may impair wound healing and requires dose modifications based on the type and grade of adverse event suffered.

In terms of budget impact, ripretinib is free of charge, but may result in additional appointments and assessments as compared to no treatment.

The Committee heard from Dr Dileo that having an additional line of therapy would be convenient for a population who may otherwise have a good performance status and have been living with metastatic disease for a number of years. The adverse events and risks described with ripretinib are similar for other well-known TKIs. It would be used in a limited number of patients (5-6 per annum).

In camera, the Committee acknowledged there was an unmet clinical need, and agreed that ripretinib offered an additional line of therapy to a population who otherwise have no pharmacological treatment option. The Committee understood that NICE are reviewing ripretinib for GIST in the fourth line setting also within a technology appraisal with no date currently set for publication. However, no formal statement on the free of charge agreement and funding following the decision by NICE has been provided yet.

In summary, the Committee conditionally agreed to add free of charge ripretinib to the NCL Joint Formulary for GIST following failure or intolerance to imatinib, sunitinib and regorafenib. The approval is conditional on (i) the company providing a formal statement on the free of charge agreement and ongoing funding and (ii) Trusts notifying the relevant commissioner as per the NCL Free of Charge scheme policy.

Decision: Approved (conditional on the provision of a free of charge scheme agreement and funding statement, and notification of the relevant commissioner)
Prescribing: Secondary care only
Tariff status: N/A
Funding: Free of Charge
Primary and secondary care Fact sheet or shared care required: N/A

8.3 EAMS: Nivolumab + ipilimumab for unresectable malignant pleural mesothelioma (Applicant: Dr Papadatos-Pastos, UCLH)

The Committee considered an Early Access to Medicines Scheme (EAMS) for nivolumab in combination with ipilimumab, a PD-1 and CTLA-4 immune checkpoint inhibitor respectively, as first-line treatment of adult patients with locally advanced or metastatic malignant pleural mesothelioma (MPM). Duration of treatment with nivolumab, either as monotherapy or in combination with ipilimumab, would be continued for up to 24 months, as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Malignant pleural mesothelioma affects the lining of the lung and carries a poor prognosis, the only chemotherapy approved by NICE for the first-line treatment of MPM is cisplatin (platinum-based) in combination with pemetrexed chemotherapy, which is poorly tolerated.

Checkmate 743 (n=605) was an open-label, active-comparator controlled, Phase III study designed to assess efficacy and safety of first-line nivolumab plus ipilimumab versus platinum in combination with pemetrexed chemotherapy in previously untreated locally advanced or metastatic malignant pleural mesothelioma. Only adults with an ECOG performance status ≤1, adequate haematological, renal or hepatic function were included. Patients were randomised to nivolumab 3 mg/kg intravenous infusion once every 2 weeks plus ipilimumab 1 mg/kg intravenous infusion once every 6 weeks for up to 2 years or platinum (cisplatin or carboplatin) plus pemetrexed chemotherapy every 3 weeks for a maximum of six cycles. At the prespecified interim analysis (85% of the planned number of events) the study reported a

statistically significant improvement in the primary outcome, median overall survival, for patients randomised to nivolumab plus ipilimumab (18.1 vs. 14.1 months; HR: 0.74, 96.6% CI: 0.60 to 0.91). Median progression free survival was similar between treatment groups (6.8 months with nivolumab plus ipilimumab and 7.2 months with chemotherapy; HR: 1.00, 95% CI: 0.82 to 1.21). The key limitations of the study included: the trial assessed a healthier cohort that would be seen in clinical practice, open label design may bias reporting of adverse events and the final analysis is an interim analysis, however superiority for the primary outcome is demonstrated. In terms of quality of life (QoL), data from an abstract reported that the 'definitive deterioration in QoL' was slower for nivolumab and ipilimumab than chemotherapy (HR: 0.65 (95%CI: 0.50 to 0.84).

In terms of safety, no new safety signals were identified. The frequencies of serious treatment related adverse events (21% vs 8%) and those leading to discontinuation (23% vs 16%) were higher with nivolumab plus ipilimumab than with chemotherapy. The most frequent serious adverse events with nivolumab plus ipilimumab were colitis (3%), abnormal hepatic function (1.7%), acute kidney injury (1.7%) and pneumonitis (1.7%) and infusion-related reactions (2%). In the chemotherapy arm these were anaemia (2%) and febrile neutropenia (1%). MHRA concluded that the potential adverse effects of the medicinal product are outweighed by the benefit in overall survival, allowing for a conclusion of a positive benefit:risk balance.

In terms of budget impact, nivolumab and ipilimumab will be provided free of charge under the EAMS. Patients may be maintained on treatment for longer and the trial reported greater frequency of serious adverse events with nivolumab and ipilimumab which may increase activity.

The Committee heard from Dr Papadatos-Pastos (UCLH, Medical Oncologist) that oncology teams are familiar with using these drugs, and nivolumab alone is available already for MPM during the COVID-19 pandemic. Oncology teams are able to manage side effects, including immune related adverse reactions with the majority treated as outpatients.

In camera, the Committee acknowledged the limited number of treatments available for this disease and agreed with the MHRA's conclusion that the potential adverse effects of treatment are outweighed by the benefit in overall survival.

In summary, the Committee agreed to add nivolumab and ipilimumab to the NCL Joint Formulary for first-line treatment of adult patients with locally advanced or metastatic malignant pleural mesothelioma under an EAMS.

Decision: Approved
Prescribing: Secondary care
Tariff status: N/A
Funding: FoC
Primary and secondary care Fact sheet or shared care required: No

8.4 Acarizax immunotherapy for treatment of persistent moderate to severe house dust mite induced allergic rhinitis in adults and children (Applicants: Dr G Rotiroti, Dr H Kariyawasam, Dr M Makatsori, UCLH)

The Committee considered an application for Acarizax® (12SQ-HDM), an oral sublingual immunotherapy for persistent moderate to severe house dust mite (HDM) allergic rhinitis for adults and children over 5 years, despite the use of symptom-relieving medication and where unsuitable for subcutaneous immunotherapy.

Okubo et al was a Phase III, placebo-controlled study to assess the safety and efficacy of 12SQ-HDM in adults and children over 12 years with moderate to severe HDM allergic rhinitis and no history of asthma (n=946). Patients were randomised to 12SQ-HDM or placebo. The primary endpoint, total combined rhinitis score (TCRS) at 52 weeks, was statistically improved with 12SQ-HDM compared to placebo (4.14 vs. 5.15; estimated treatment difference 1.01 [95%CI 0.51-1.49; p<0.001]). TCRS consists of assessment of four rhinitis symptoms (runny nose, blocked nose, sneezing and itchy nose) combined with a daily rhinitis medication use score. Rhinitis symptoms were rated using a 4-point scale with 0=absent and 3=severe, and medication use scores were rated 0-12; i.e., total combined score 0-24. A key secondary endpoint, acute rhinitis score (AR), was statistically improved (3.87 vs. 4.75; estimated treatment difference 0.87 [95%CI 0.43-1.32; p<0.001]). Quality of life (Japanese RQLQ) was also statistically improved (estimated

treatment difference 0.23; p=0.003). RQLQ was assessed via a questionnaire consisting of 17 questions over 6 domains (daily life, outdoors, social, sleep, tiredness and emotion), using the average of a 5-point scale with 0=nil and 4=very greatly. Key limitations of the study were assessment of rhinitis symptoms only as opposed to rhino-conjunctivitis symptoms, and the decreased use of symptom relieving medication within the Japanese population.

In terms of safety, Acarizax® is well tolerated with the most frequent adverse effects reported as oral pruritus, mouth oedema and throat irritation. There have been case reports of systemic allergic reactions and eosinophilic oesophagitis.

In terms of cost, the annual budget impact is estimated to be £66K across NCL, with an estimated 55 patients (adults & children) eligible for treatment per year.

The Committee heard from Dr Lukawska, Dr Rotiroti, Dr Kariyawasam and colleagues that the RNTNE is a tertiary referral centre and as such patients will have more severe disease than the population recruited in clinical trials, therefore treatment is likely to result in greater absolute improvement in symptoms and QoL compared to that observed in studies. There is an unmet need in this cohort of patients, particularly children where subcutaneous therapy may be distressing and requires multiple hospital attendances which could impact on schooling. It was also highlighted that early treatment in children can prevent the development of allergic asthma. With regards to subcutaneous therapy, it was estimated 40-60% of patients have an improvement of symptoms within 12 weeks, with a sustained effect observed for several years following completion of 3 years of treatment. Only 10% return for further treatment which suggests long-term effectiveness of immunotherapy.

In camera, the Committee highlighted that whilst the evidence presented was statistically significant, the clinical significance was questionable (1-point absolute difference on a 24-point TCRS scale). It was acknowledged that a 20% improvement may be clinically meaningful in patients with a high baseline disease score. The high disease burden and unmet need was accepted. It was noted that the price of subcutaneous immunotherapy had increased significantly over recent years which required further consideration. Further, a decision on Acarizax® would set a precedent for other immunotherapies (e.g. Grazax®).

In summary, based on the evidence available and the lack of clarity on the minimal clinically important difference, the Committee recommended the formation of a working subgroup to review Acarizax® and other sublingual and subcutaneous immunotherapies. The purpose of the subgroup will be to review the entire treatment pathway across NCL, establish what the minimal clinically important difference is across all allergen immunotherapies, and establish the cost-effectiveness threshold.

Decision: Deferred

9. Melatonin tablets (Slenyto®) and melatonin 1mg/mL oral solution: Use in NCL approved indications

This item was deferred to a future meeting.

10. Biosimilar teriparatide

In November 2019, JFC approved two biosimilar teriparatide products, Terrosa® and Movymia®. Terrosa® was the preferred option in new patients as the homecare service proposal was approved by the National Homecare Medicines Committee. A recent update to the homecare contract has seen a significant reduction in cost of Movymia®, which if adopted as the preferred biosimilar would result in an estimated cost saving of £1,600 per patient per 24-month treatment course. Both Terrosa® and Movymia® use the same pen technology, and is offered by the same homecare providers. The proposal was to use Movymia® in new patients, and to switch patients established on Terrosa® who have a significant duration of teriparatide therapy remaining, which is undertaken at the RNOH via a pharmacy-led telephone consultation. The Committee were supportive of using Movymia® as the preferred teriparatide option

11. NCL vitamin B_{12} guidance

The Committee heard that a position statement had been produced to support primary care to manage an unnecessary caseload of patients who do not need to visit GP practices for administration of the IM

hydroxocobalamin during the COVID-19 pandemic. The Committee agreed to extend the review date to September 2021 as the information is still pertinent at this time.

12. Next meeting

Thursday April 15th 2021