North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 18 June 2020

Present:	Dr R Sofat	NCL JFC Chair	(Chair)
	Dr P Taylor	NCL JFC Vice Chair	
	Dr M Kelsey	WH, DTC Chair	
	Ms G Smith	RFL, DTC Chair	
	Mr P Gouldstone	NCL CCG, Head of Medicines Management (Enfield)	
	Mr A Dutt	NCL CCG, Head of Medicines Management (Islington)	
	Ms W Spicer	RFL, Chief Pharmacist	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Ms R Clark	NCL CCG, Head of Medicines Management (Camden)	
	Ms P Taylor	Haringey, Head of Medicines Management	
	Ms S Lever	Barnet CCG, Pharmaceutical advisor	
	Mr A Tufail	MEH, DTC Chair	
	Ms K Delargy	BEH, Deputy Chief Pharmacist*	
In attendance:	Mr A Barron	NCL MEP, Project Lead	
	Ms M Kassam	NCL JFC, Support Pharmacist	
	Mr G Grewal	NCL JFC, Support Pharmacist	
	Ms K Saxby	UCLH, Formulary Pharmacist	
	Ms S Amin	UCLH, Formulary Pharmacist	
	Ms A Fakoya	NEL, Senior Prescribing Advisor	
	Ms H Thoong	GOSH, Formulary Pharmacist	
	Mr D Abdulla	NMUH, Critical Care and Formulary Pharmacist	
	Mr B O'Farrell	RFH, Critical Care Pharmacist	
	Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	
	Mr J Flor	WH, Formulary Pharmacist	
	Ms Z Zhao	RFL, Medical Student	
	Mr J Yates	RFL, Medical Student	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Mr A Adlakha	RFL, ICU Consultant	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Ms H Thoong	GOSH, Formulary Pharmacist	
	Mr F Master	RFL, Formulary Pharmacist	
	Ms P McCormick	WH, Lead Pharmacist Integrated Medicine	
	Mr R Brenner	RFL, MS Consultant	
	Dr W Brownlee	UCLH, MS Consultant	
	Ms K Dhadwal	RFL, ICU Consultant	
	Ms H Yeoh	RFL, Specialist Pharmacist	
	Mr S O'Callaghan	UCLH, Medicines Information and Governance Pharmacist	
	Prof D Hochhauser	UCLH, Consultant Medical Oncologist	
	Dr R Gillmore	RFL, Consultant Medical Oncologist	
Apologies:	Mr C Daff	NCL CCG, Head of Medicines Management (Barnet)	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr S Semple	MEH, Chief Pharmacist	

Dr K Tasopoulos	NMUH, DTC Chair
Dr A Bansal	Barnet CCG, GP Clinical Lead Medicines Management
Mr R Urquhart	UCLH, Chief Pharmacist
Mr A Shah	RNOH, Chief Pharmacist
Mr S Tomlin	GOSH, Chief Pharmacist
Mr T Dean	Patient Partner
Mr S Richardson	WH, Chief Pharmacist
Dr A Sell	RNOH, DTC Chair

*Deputising for Committee member

2. Meeting observers

Dr Sofat welcomed Ms Weaver (NHSE, Specialised Commissioning Pharmacist) as an observer of the meeting.

3. Matters arising

3.1 Evaluation: Nebulised iloprost in COVID-19 data

The Committee heard an evaluation of nebulised iloprost for COVID-19 associated ARDS at RFL (n=5). Outcomes were variable and no conclusions could be drawn in terms of efficacy. The Committee thanked RFL for their review and agreed nebulised iloprostol and epoprostenol, and inhaled nitric oxide should continue to be available to NCL Trusts in line with guidance from NHS England. However, a randomised placebo-controlled trial remained necessary to establish the efficacy and safety for these interventions and the Committee recommended that a trial proposal is submitted to the NIHR via the Urgent Public Health application portal. Dr Dhadwal and Dr Adlakha agreed to lead on the clinical trial proposal.

4. JFC Outstanding Items & Work Plan

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

5. Members declarations of conflicts of interest

Prof Hochhauser for olaparib was the PI for POLO trial at UCLH.

6. New Medicine Reviews

6.1 Pre-NICE FoC scheme: Siponimod for Secondary Progressive MS (Applicant: Dr W Brownlee)

The Committee considered an application for a pre-NICE free of charge (FoC) scheme for siponimod for the first-line treatment of secondary progressive multiple sclerosis (SPMS) in patients with active disease, as evidenced by relapses or active lesions.

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator. It is very similar in its mechanism of action to fingolimod which is used in highly-active relapsing remitting MS (RRMS).

The Committee reviewed the EXPAND study, a randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of siponimod in patients with SPMS (n=1651). Inclusion criteria were adults (<60 years) with a diagnosis of SPMS (defined as a progressive increase in disability, of at least 6 months' duration, in the absence of relapses in the last 3 months) and an Expanded Disability Status Scale (EDSS) score of 3.0-6.5. The primary endpoint was time to 3-month Confirmed Disability Progression (CDP) of the EDSS. At baseline, median time since conversion to SPMC was 2.5 years with a median ESDD score of 6.0. After a median time on study of 21 months, the primary endpoint was observed in 26% of patients treated with siponimod compared to 32% with placebo; absolute risk reduction 6% (HR = 0.79; p=0.013). There was also the preferred endpoint of 6-month CDP; 20% of patients treated with siponimod compared to 26% with placebo; absolute risk reduction 6% (HR = 0.74; p=0.0058). There was no improvement in other clinically relevant secondary endpoints, including walk test, walking scale & QoL (as measured by EQ-5D).

During product licensing, in its review the EMA commented that population recruited into EXPAND reflected "early" disease rather than the entire population with SPMS. Moreover the EMA found that siponimod was not effective in patients with 'no relapses in the prior 2 years and no gadolinium enhancing lesions at baseline' (HR=0.93; p=0.622). A post hoc analysis for patients with 'relapses in the prior 2 years and/or gadolinium enhancing lesions at baseline' (47% of the overall population) showed siponimod was effective in this subgroup (HR = 0.69; p=0.009). The product license was subsequently

granted for this subgroup only. The EMA also had concerns over trial conduct including risk of unblinding however were satisfied that this did not bias results for the subjective endpoints.

With regards to safety, siponimod appeared relatively well tolerated (rate of serious ADRs was 18% vs. 15% in placebo). A high-level of pre-initiation and maintenance monitoring is required (including metabolism testing, ophthalmic, ECG, FBC and LFTs) however this is broadly similar monitoring requirements to other disease modifying treatment (DMT) prescribed by the MS service.

The drug is currently being provided as part of a FoC scheme. In the event of a negative NICE TA, the manufacture's FoC scheme provides treatment to patients already on the scheme for up to 3 years only. The publication date of the NICE review is unknown. The committee heard the number of patients expected to be treated across NCL by May 2021 would be ~40, with a maximum annual theoretical budget impact of over £1 million.

The Committee heard from Dr Brownlee that for the EXPAND subgroup eligible for treatment under the FoC scheme; the primary endpoint was observed in 30% of patients treated with siponimod compared to 41% with placebo; absolute risk reduction 11%. Dr Brownlee and Dr Brenner commented that there was a high unmet for patients with active/early SPMS. Assurance was provided that a diagnosis active SPMS could be made, and this is in keeping with the trial where SPMS was diagnosed after a median of 2.6 years after 'time since conversion to SPMS'. On commenting on its place in therapy and comparing to other medicines, Dr's Brownlee and Brenner said that interferon beta was not used routinely in clinical practice, in part due to adverse effects (inc. flu-like symptoms) and the requirement to self-inject three-times per week.

In camera, the Committee remained unclear how to differentiate between 'late RRMS' and 'early SPMS'. It was considered that the introduction of siponimod could bring forward the timing of diagnosis of SPMS, as early diagnosis currently precludes active treatment with drugs other than interferon beta. It was unclear to the Committee whether the population of interest were (i) not receiving DMT or (ii) receiving DMT due delayed SPMS diagnosis. This distinction is important in establishing the appropriate comparator for siponimod and in establishing whether the FOC scheme addressed unmet clinical need. The Committee agreed there was a high unmet need for patients who were not receiving DMT and that siponimod would likely provide a modest benefit in those patients (11% improvement; equivalent to treating 9 patients for 21 months to avoid 1 case of confirmed disease progression). The Committee compared siponimod to fingolimod agreeing that the main difference was the product license without a significant degree of innovation. When considering the cost-effectiveness of siponimod compared to placebo, the high cost and absence of an improvement in EQ-5D, meant siponimod was unlikely to be cost-effective at list-price. The committee therefore considered the terms of the FoC scheme in the absence of a NICE TA, which stated that patients would only receive FoC supply for three years. The committee considered it inappropriate to stop a medicine after three years where patients and/or their clinician believed it was making a difference. If Trusts were to continue siponimod beyond 3 years, it would present a significant cost pressure to NCL. Moreover, the 3 year 'FOC scheme exit strategy' which was inconsistent with the RMOC recommendation 5.1.1 "where NICE do not recommend the treatment… the company will continue to supply it FOC until the clinician and the patient decide that the treatment should be stopped". It was understood the ABPI were a stakeholder in the RMOC guidelines and there was an expectation that all pharmaceutical companies should follow this guidance. The Committee was made aware that the manufacturer recently received a negative NICE TA based on cost-effectiveness for a novel anti-migraine drug.

The Committee agreed to defer their decision for up to 3 months to:

1. Establish when NICE are expected to publish the Technology Appraisal (TA) for siponimod
2. For the applicant to provide clearer eligibility criteria for patients at highest unmet need [which may be narrower to the FOC scheme eligibility criteria]
3. For the Novartis to change their FOC scheme allow continued provision of drug, in the event of negative NICE TA, until the clinician and the patient decide that the treatment should be stopped.

Decision: Deferred

Post meeting note: *Siponimod received a negative Appraisal Consultation Document (ACD) from NICE. NICE state that "because of the limited clinical evidence [no evidence directly comparing siponomid to*

interferon beta-1b], the cost-effectiveness estimates are uncertain" and that "none of the [health economic] analyses reflected the committee's preferred assumptions". NICE considers interferon beta-1b and best supportive care to be relevant comparators but acknowledge few people take interferon beta-1b.

6.2 FoC scheme: Sorafenib for relapsed/refractory FLT3-positive acute myeloid leukaemia (Applicant: Prof A Khwaja)

The Committee considered an application for sorafenib in patients with acute myeloid leukaemia and a mutation in the FLT3 gene, who have relapsed and/or refractory to conventional chemotherapeutics from the age of 13 upward. The proposal was to use sorafenib in three different positions – before stem cell transplant (pre-HSCT), after stem cell transplant (post-HSCT) and as bridging therapy to transplant.

The Committee reviewed eight studies; one was a phase I/II study in the pre-HSCT cohort, and seven were retrospective analyses in the post-HSCT cohort. All but one of these retrospective studies formed a favourable conclusion; however, these were generally single-centre, single-arm studies with low patient numbers and a lack of control of many variables. There was a lack of studies focusing on patients receiving sorafenib as a bridging strategy to stem cell transplant, though few patients in the pre-HSCT and post-HSCT studies progressed to consolidation therapy with stem cell transplant. Experience at UCLH with sorafenib (n=8) was also considered.

The Committee considered an alternative FLT3-inhibitor, gilteritinib, which is licensed for the proposed indication but has a negative draft NICE TA as the high cost was not justified by the improvement in overall survival.

Commonly reported adverse events from studies include cytopaenias, hyperbilirubinaemia and transaminitis. The company could not provide reassurance for how long the therapy would be available for, and the cost for eight patients per month was considered.

The Committee heard from Prof Khwaja that gilteritinib was now available via the Cancer Drugs Fund for adult patients with relapsed or refractory acute myeloid leukaemia (pre/post transplant).

In camera, the Committee agreed that the quality of evidence supporting sorafenib for this indication was very low however took reassurance from the positive gilteritinib (a different FLT3 inhibitor) data which showed an improvement in overall survival. The Committee agreed whilst gilteritinib is available via CDF, it should be used instead of sorafenib. Where gilteritinib is not available, the Committee agreed there was high unmet clinical need, sorafenib was likely to have a positive risk/benefit profile, and the FOC scheme had favourable terms.

In summary, for patients with relapsed or refractory acute myeloid leukaemia (pre/post transplant) who cannot access gilteritinib (either not eligible under the terms of the CDF, or gilteritinib is removed from CDF and not otherwise commissioned) then sorafenib FOC was added to the NCL Joint Formulary.

Decision: Approved (for patients who cannot access gilteritinib only)
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: NA (free-of-charge)
Primary and secondary care Fact sheet or shared care required: No
Additional notes: Typical dose 400mg twice daily

6.3 Pre-NICE FoC Scheme: Olaparib for locally advanced or metastatic pancreatic cancer (Applicant: Dr R Gillmore)

The Committee considered a pre-NICE free of charge scheme for olaparib for maintenance therapy, after first line treatment with a platinum based chemotherapy, in metastatic pancreatic cancer with BRCA1/2 gene mutation.

POLO was a Phase III, double-blind, randomised controlled trial to assess the safety and efficacy of Olaparib versus placebo in patients with metastatic pancreatic adenocarcinoma and a deleterious germline mutation in BRCA1 or BRCA2 whose disease had not progressed following ≥16 weeks of first-line platinum-based chemotherapy. The median progression-free survival (performed after 68% data maturity) was significantly longer in the olaparib group than in the placebo group (7.4 months vs. 3.8

months respectively; hazard ratio: 0.53, 95% confidence interval [CI]: 0.35 to 0.82). The difference in median overall survival was not significant (conducted at data maturity of 46%) and no clinically meaningful change from baseline was noted in the EORTC QLQ-C30 global health related quality-of-life score in either group.

Grade ≥3 adverse events occurred in more patients receiving olaparib than placebo (40% vs. 23%). The most common grade 3/4 adverse event was anaemia with 11% of patients experiencing this. Overall adverse effects were broadly in line with those from other olaparib trials.

The Committee heard from Dr Gillmore and Prof Hochhauser that there was variability in the treatment pathway for this cohort, however treatment typically involved FOLFIRINOX for ~12 infusions (as per 2011 NEJM protocol), followed by a treatment break until progression, followed by subsequent chemotherapy. FOLFIRINOX causes adverse effective which have a significant impact on patients QoL including neuropathy and diarrhoea.

In camera, the Committee agreed there was a high unmet clinical need in this population, with a median survival of only 18 months. Olaparib was unlikely to offer a survival advantage which was disappointing for patients with such a poor prognosis. In terms of QoL, the trial showed no measurable disadvantage over placebo whilst on treatment (providing assurance that olaparib does not cause significant harm), however there was no data to support a claim that QoL is improved over the patient's lifetime. There was no evidence to know whether 'time on second chemotherapy' (which is associated with significant adverse effects) was impacted by olaparib. The Committee therefore agreed the only therapeutic advantage with olaparib was delaying time to adverse effects from second chemotherapy. The Committee agreed there was high unmet clinical need in this population, olaparib had a borderline but positive risk/benefit profile, and the FOC scheme had favourable terms.

In summary, the Committee agreed to add olaparib FOC to the NCL Joint Formulary for patients with metastatic pancreatic cancer with BRCA1 or BRCA2 mutations.

Decision: Approved
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: NA (free-of-charge)
Primary and secondary care Fact sheet or shared care required: No

7. IV to SC switch: Infliximab

The Committee reviewed a proposal to use subcutaneous infliximab (Remicade®) for patients with rheumatoid arthritis in whom shielding from coronavirus is recommended by Public Health England, as an alternative to intravenous infliximab. The aim is to reduce hospital attendance for vulnerable patients and is consistent with guidance from NICE and NHS England. A single high-quality study confirmed non-inferiority of the subcutaneous product although there was a higher risk of injection-site reaction. The higher cost of subcutaneous Remicade® compared with intravenous Zessly® means subcutaneous infliximab would not be approved under usual circumstances. It was noted that not all patients in whom shielding is recommended comply with advice, and in such patients, switching to the subcutaneous product would unlikely offer a meaningful advantage in terms of risk-reduction.

In summary, the Committee agreed subcutaneous infliximab could be only offered to patients who are actively following PHE advice to shield, provided they meet NICE criteria for biologic therapy. This recommendation is a short-term approval for rheumatoid arthritis only when used at a dose of 120 mg every other week. Patients who stop actively shielding (either through choice or a change in government recommendations) should be switched back to cost-effective infliximab infusion after their supply of the subcutaneous product has finished; this expectation should be clearly communicated to patients.

Decision: Short-term approval only (see details above)
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: CCG
Primary and secondary care Fact sheet or shared care required: No

Post meeting note: *Shielding is expected to be paused from 1st August 2020 therefore this interim approval will also pause on this date. CHMP have also recommended a license extension to include treatment of adult patients with Crohn's disease, ulcerative colitis; approval for this cohort will be subject to a further review in the event that shielding is unpaused again.*

8. IV to SC switch: Vedolizumab

The Committee reviewed a proposal to use subcutaneous vedolizumab for patients with ulcerative colitis or Crohn's disease in whom shielding from coronavirus is recommended by Public Health England. The aim is to reduce hospital attendance for vulnerable patients and is consistent with guidance from NICE. There were no comparative non-inferiority studies for the subcutaneous and intravenous products, therefore the Committee could not definitively confirm equivalence between the two. A crude comparison of placebo-controlled trials provided reassurance that the two products were likely to be similarly safe and effective (except a higher risk of injection site reaction). The subcutaneous product was available at a lower cost therefore concerns over possibility of reduced efficacy were further reduced. The Committee were satisfied that the patent expiry for intravenous vedolizumab was far enough into the future such that it should not inform decision making.

In summary, the Committee agreed subcutaneous vedolizumab could be offered to all patients eligible for intravenous vedolizumab. Owing to initially limited stock availability, Trust procurement department should work with the manufacturer to agree the number of patients who can be treated.

Decision: Approved
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: CCG
Primary and secondary care Fact sheet or shared care required: No

9. IV to SC switch: Belimumab

The Committee reviewed a proposal to use subcutaneous belimumab for patients with systemic lupus erthyematosus in whom shielding from coronavirus is recommended by Public Health England, as an alternative to intravenous belimumab. The aim is to reduce hospital attendance for vulnerable patients and is consistent with guidance from NICE. There were no comparative non-inferiority studies for the subcutaneous and intravenous products, therefore the Committee could not definitively confirm equivalence between the two. An indirect comparison of placebo-controlled trials provided reassurance that the two products were likely to be similarly safe and effective (except a higher risk of injection site reaction). The manufacturer has agreed to a short-term supply to the UK of the subcutaneous product. NHS England has agreed to Trusts using the subcutaneous product.

In summary, the Committee agreed subcutaneous belimumab could be offered to patients whilst supplies are available. The short-term nature of this supply, and the eventual requirement to revert back to intravenous belimumab, should be clearly communicated to patients.

Decision: Approved
Prescribing: Secondary care only
Tariff status: Excluded from tariff
Funding: NHS England
Primary and secondary care Fact sheet or shared care required: No

10. Next meeting

Thursday 2nd July

11. Any other business

Dexamethasone for hospitalised adults with suspected or confirmed COVID-19 requiring oxygen therapy.

UCLH have developed a guideline to implement the recent CMO alert (CEM/CMO/2020/026). The guideline was developed by a multidisciplinary team including trialists, infectious diseases, intensive care and hyperinflammation specialist. The Committee agreed the guideline was useful and UCLH agreed to share across NCL.

The Committee agreed there was an urgent need for RECOVERY data to be published in a peer-reviewed journal as it is unknown whether there is a mortality advantage across relevant subgroup e.g. advanced age, history of diabetes, mental health conditions.