North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 15th July 2021

Present:	Prof R Sofat	NCL JFC Chair	(Chair)
	Dr K Tasopoulos	NMUH, DTC 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)	
	Dr A Sell	RNOH, DTC Chair	
	Mr S Semple	MEH, Chief Pharmacist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Mr S Richardson	WH, Chief Pharmacist	
	Ms W Spicer	RFL, Chief Pharmacist	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Ms P Taylor	NCL CCG, Head of Medicines Management (Haringey)	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Dr A Scourfield	UCLH, Interim DTC Vice Chair	
	Ms M Singh	NCL CCG, Head of Medicines Management (Barnet)	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Mr T Dean	Patient Partner	
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	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr F Master	RFL, Formulary Pharmacist	
	Ms S Amin	UCLH, Formulary Pharmacist	
	Ms S Y Tan	NEL CSU, Contracting and Commissioning Pharmacist	
	Ms A Fakoya	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 J Bloom	MEH, Deputy Chief Pharmacist	
	Dr A Hosin	UCLH, Clinical Pharmacology Registrar	
	Mr S O'Callaghan	UCLH, Medicines Safety Officer	
	Ms C Gates	UCLH, Specialist Pharmacist	
	Dr A Drebes	RFL, Consultant Haematologist	
	Prof D Hughes	RFL, Professor of Experimental Haematology	
	Mr O Ogunleye	Clinical Pharmacologist	
Apologies:	Dr M Kelsey	WH, DTC Chair	
	Ms R Clark	NCL CCG, Head of Medicines Management (Camden)	
	Ms S Stern	NMUH, Chief Pharmacist	
	Dr D Burrage	WH, Consultant in Emergency Medicine	

2. Meeting observers

Dr Ogunleye (Clinical Pharmacologist, Lagos State University College of Medicine & Lagos State University Teaching Hospital) was welcomed as an observer of the meeting.

3. Minutes of the last meeting

The minutes and abbreviated minutes of the 17 June 2021 meeting were accepted as accurate reflections of the meeting.

4. Matters arising

4.1 NCL spinal anaesthesia flowchart

JFC Support co-ordinated the development of an NCL flowchart to clarify the place in therapy for bupivacaine, prilocaine and chloroprocaine for spinal anaesthesia. This has been created in consultation with consultant anaesthetists and specialist pharmacists. The Committee approved the treatment pathway.

Drug: Chloroprocaine for spinal anaesthesia in day case procedures as per NCL spinal anaesthesia flowchart
Decision: Approved
Prescribing: Secondary care
Tariff status: In tariff
Funding: Trust
Primary and secondary care Fact sheet or shared care required: No

Drug: Prilocaine for spinal anaesthesia in day case procedures as per NCL spinal anaesthesia flowchart
Decision: Approved
Prescribing: Secondary care
Tariff status: In tariff
Funding: Trust
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	May 2021	Eltrombopag	Interim NHSE Clinical Commissioning Policy: First line therapy for new or relapsed immune thrombocytopenia in adults and children over the age of 1 year during the COVID-19 pandemic	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: Excluded from Tariff Funding: NHSE in paediatrics; CCG in adults Fact sheet or shared care required: No
RFL	May 2021	Romiplostim	Interim NHSE Clinical Commissioning Policy: First line therapy for new or relapsed immune thrombocytopenia in adults and children over the age of 1 year during the COVID-19 pandemic	Decision: Added to the NCL Joint Formulary Prescribing: Secondary care Tariff status: Excluded from Tariff Funding: NHSE in paediatrics; CCG in adults Fact sheet or shared care required: No

UCLH	June 2021	Pyrantel pamoate	Second line option for the treatment of threadworm infections	Decision: UCLH only (restricted to Hospital of Tropical Disease) Prescribing: Secondary care Tariff status: In Tariff Funding: Trust Fact sheet or shared care required: No Additional information: Initiation by infectious disease team only
UCLH	June 2021	Sirolimus	First line prophylaxis of Graft versus Host Disease in adult sickle cell patients undergoing haematopoietic stem cell transplantation	Decision: UCLH only Prescribing: Secondary care Tariff status: Excluded from Tariff Funding: NHSE for first 100 days; Trust thereafter Fact sheet or shared care required: No
UCLH	June 2021	Sirolimus	Second-line prophylaxis of Graft versus Host Disease in adult and adolescents who develop serious adverse drug reactions	Decision: UCLH only Prescribing: Secondary care Tariff status: Excluded from Tariff Funding: NHSE for first 100 days; Trust thereafter Fact sheet or shared care required: No
JFC	July 2021	Chloramphenicol eye drops containing borax or boric acid buffers	Use in children <2 years for ocular infections (updated following advice from the MHRA)	Decision: Added to the NCL Joint Formulary Prescribing: Primary and Secondary care Tariff status: In Tariff Funding: Trust and CCG Fact sheet or shared care required: No
JFC	July 2021	Hydroxychloroquine 300mg tablets	For use in line with the DMARDs quick reference guide	Decision: Added to the NCL Joint Formulary Prescribing: Primary and Secondary care Tariff status: In Tariff Funding: Trust and CCG Fact sheet or shared care required: Available on the NCL MON website
JFC	Sept 2019	Trimbow Nexthaler	Triple therapy for use in COPD	Decision: Added to the NCL Joint Formulary Prescribing: Primary and Secondary care Tariff status: In Tariff Funding: Trust and CCG Fact sheet or shared care required: No
JFC	-	Nizatidine or Famotidine (alternative H_2-antagonists)	Gastroprotection in patients taking acalabrutinib in whom antacids alone are not effective	Decision: Added to the NCL Joint Formulary Prescribing: Primary and Secondary care Tariff status: In Tariff Funding: Trust and CCG Fact sheet or shared care required: No
JFC	Feb 2019	Opicapone	Second-line COMT inhibitor for patients with Parkinson's disease and end-of-dose motor fluctuations/OFF periods who do not respond to, or tolerate entacapone (previously restricted to RFL and NHNN only)	Decision: Added to the NCL Joint Formulary Prescribing: Primary and Secondary care Tariff status: In Tariff Funding: Trust and CCG Fact sheet or shared care required: No

C&I	Sept 2014	Nicotine oral spray	Nicotine replacement therapy	Decision: Added to the NCL Joint Formulary Prescribing: Primary and Secondary care Tariff status: In Tariff Funding: Trust and CCG Fact sheet or shared care required: No

8. New Medicine Reviews

8.1 Andexanet alfa for reversal of anticoagulation with apixaban or rivaroxaban (Applicant: Dr A Drebes, RFL)

The Committee considered the evidence underpinning the NICE TA for andexanet alfa, a recombinant form of factor Xa, which (i) recommended use for the reversal of anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled gastrointestinal bleeds, and (ii) recommended 'only in research' in adults with life-threatening or uncontrolled intracranial haemorrhage. The review follows consensus amongst NCL haematology specialists that the evidence for andexanet alfa was not sufficiently robust and may lead to inappropriate use if added to the NCL Joint Formulary without due consideration.

ANNEXA-4 was a multi-centre, single-arm study to assess the safety and efficacy of andexanet alfa, when used in combination with best-supportive care, for the treatment of acute major bleed in patients taking anticoagulation (n=352, of which 227 had intracranial haemorrhage [ICH] and 90 had gastrointestinal [GI] bleed). Patients were included if they had potentially life-threatening bleed; exclusion criteria were patients with surgery planned within 12 hours, patients with GCS <7 or haematoma >60mL, expected survival less than one-month, thrombotic events in the previous two weeks, or use of other anticoagulants or blood products within one week. In the efficacy analysis, 98 patients (28%) were excluded retrospectively following administration of andexanet alfa as their anti-factor Xa activity was below a pre-specified threshold and/or they were adjudicated to not having met the bleeding criteria. In the first co-primary outcome, anti-factor Xa activity following bolus of andexanet alfa reduced by 92% in patients who were taking apixaban or rivaroxaban at baseline respectively. In the second co-primary outcome, haemostatic efficacy assessed at 12 hours post-infusion, 82% of patients taking any anticoagulant at baseline were adjudicated as having either 'excellent' or 'good' haemostatic efficacy. The authors determined there to be no association between haemostatic efficacy and reduction in anti-factor Xa activity in the overall population. Key limitations of the study were the lack of an appropriate comparator, the exclusion of patients with poorer prognosis, limited follow-up, the exclusion of 28% of andexanet alfa recipients from the primary efficacy analysis (leading to generalisability concerns), and haematological outcomes used were surrogates of patient-oriented outcomes (the ideal outcomes being mortality and quality of life).

The NICE TA was published in April 2021. It establishes that current practice uses prothrombin complex concentrate (PCC), though considered this off-label with limited clinical evidence to support its use. The Evidence Review Group (ERG) decided that evidence from ANNEXA-4 be limited to 30-day mortality (a safety outcome obtained from the overall cohort, including the 28% of patients administered andexanet alfa who were excluded from the primary efficacy analysis). The ERG reviewed three additional pieces of evidence which are not publicly available: a propensity-matched comparison of patients from ANNEXA-4 with the ORANGE study; a real-world analysis of andexanet alfa in patients with GI bleeding; and an analysis of Rockall scores and mortality in patients with GI bleed from the ANNEXA-4 study. Whilst the propensity-matched comparison demonstrated reduced mortality with andexanet alfa compared to PCC, the ERG understood limitations in evidence. The real-world analysis and analysis of Rockall scores from ANNEXA-4 provided reassurance to the NICE Committee to approve the use of andexanet alfa in patient with a life-threatening GI bleed. The data for ICH was unclear due to patients with a poorer prognosis excluded from ANNEXA-4 and the benefit on disability being unclear, which led to NICE developing a research recommendation.

In terms of safety, ANNEXA-4 observed two safety outcomes. Andexanet alfa administration led to thrombotic events within 30 days in 10% of all patients, and 30-day mortality was observed in 14% of all patients. Using the NPSA risk assessment tool, andexanet alfa is a high-risk injectable medication with risk of mild to moderate infusion reactions. The reconstitution and administration of andexanet alfa can be complex for clinicians not familiar with the medication.

In terms of budget impact, andexanet alfa is expected to cost an additional £156,000 for the initial stockholding across NCL Acute Hospitals, and up to £454,000 per annum from year 3 of use onwards as estimated by NICE.

The Committee heard from Dr Drebes that there is no comparative data for andexanet alfa versus placebo or PCC. There is not enough information from the ANNEXA-4 trial whether patients had additional surgical intervention in addition to andexanet alfa. Dr Drebes was concerned of the high number of patients given andexanet alfa despite not being therapeutically anticoagulated, and this practice would occur in the real-world setting. Current treatment involves giving fluids, blood and PCC (to replenish coagulation factors II, VII, IX and X), whilst andexanet alfa would only bind and sequester rivaroxaban and apixaban. Anti-factor Xa activity in ANNEXA-4 demonstrates that activity returns to levels that is deemed therapeutic from 4 hours after the end of the infusion. For these reasons, haematologists are likely to opt to use PCC; the large spend on stockholding for all NCL Trusts may not therefore be justified. A similar agent to reverse effects of dabigatran is on the RCEM/NPIS antidotes list; JFC Support was informed that andexanet alfa is likely to be added to the list of antidotes held within each acute hospital later this year.

In camera, the Committee agreed with the concerns raised by NCL Haematologists, several of which were also raised as part of the NICE TA consultation process. Main areas for concern include:

- Single-arm study design; no randomisation between intervention and relevant comparator (with arms otherwise treated equally i.e. degree of interventional endoscopy)
- TA'd indication represents a small subgroup of the overall study (n=90; 26%)
- Co-primary efficacy outcomes were not suitable to inform NICE TA
- Possibility of future RCTs for this indication undermined
- Unknown risk associated with using a short-term reversal agent (4 hours) as compared to replenishing coagulation factors
- Risk of creep in other indications (e.g. pre-surgery in patients taking factor Xa inhibitors)

The Committee agreed despite the lack of robust evidence, the presence of a NICE TA and subsequent addition to RCEM/NPIS antidotes list necessitates compliance and the JFC is best placed to facilitate this. The Committee therefore agreed to add andexanet alfa to the NCL Joint Formulary for 'the reversal of anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled gastrointestinal bleeds' restricted to Consultant Haematologist recommendation only, acknowledging that in practice PCC would be recommended first. The decision about where to stock andexanet alfa was delegated to the NCL Provider Chief Pharmacist Group; who would balance the need for urgent supply with the need to minimise wastage from holding stock which could expire before being used. JFC Support will seek the views of relevant clinical teams and return these to the next meeting.

Decision: Approved for the reversal of anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled gastrointestinal bleeds

8.2 Bevacizumab for eyes with late wet AMD and visual acuity better than 6/12 (Applicant: Dr A Tufail, MEH)

The Committee considered bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), for eyes with late wet age-related macular degeneration (AMD) and visual acuity above the NICE threshold of 6/12. Bevacizumab intraocular injection is on formulary for this indication at RFL and MEH (in tariff funding) however is newly being considered as a commissioned treatment as part of the updated NCL wet AMD pathway.

Ranibizumab, aflibercept and brolucizumab are licensed for wet AMD (any degree of visual acuity) however are only recommended by NICE for visual acuity between 6/12 to 6/69. People with wet AMD and visual acuity better than 6/12 have no effective commissioned licensed treatment options, therefore treating with unlicensed bevacizumab intraocular injection is justified.

There are no RCTs examining the effectiveness of anti-VEGF therapy for visual acuity better than 6/12, however there is a wealth of observational studies. NICE NG82 states that anti-VEGF treatments are clinically effective and cost-effective (depending on the regimen) for visual acuity better than 6/12. The Committee heard evidence underpinning NG82:

1) Anti-VEGF agents are equivalent in terms of efficacy and safety

Moderate to high quality evidence from a network meta-analysis showed that there is no difference in visual acuity between people receiving different anti-VEGF treatments up to 2 years' follow-up. In terms of safety, the Committee heard the safety profile of anti-VEGF agents is well established and the adverse event profile is similar.

2) Anti-VEGF agents are recommended for wet AMD where visual acuity is better than 6/12
Observational studies with duration of 2 to 3 years, suggested that treating wet AMD when visual acuity is better than 6/12 leads to the eye maintaining good visual acuity for longer and may lead to fewer injections being required overall.

3) Cost-effectiveness of early treatment varies due to costs of different agent and regimen used
NICE modelling suggested extending current practice to treat eyes with visual acuity better than 6/12 consistently produced additional QALYs. Bevacizumab 1.25mg every 2 months had an ICER of £17,895 per QALY, which is cost-effective compared with current visual acuity thresholds (considered as below £20,000) and therefore the health benefits gained represent good value for money.

In terms of budget impact, bevacizumab 1.25mg every 2 months is estimated to cost up to £23,000 in drug costs and £148,500 in additional activity (total of £171,500) across NCL in Year 1. Cost-offsets from delaying the time to costly NICE TA'd anti-VEGF treatment is expected but is not modelled.

The Committee heard from Prof Tufail that the NICE TA visual acuity thresholds is based on RCT inclusion criteria however patients with better visual acuity often gain more from anti-VEGF treatment as vision is better for longer. Waiting until vision deteriorates to worse than 6/12 is significantly problematic for patients' independence and means the patient does not meet driving standards; treating earlier can delay patients reaching this stage. Most patients considered for bevacizumab are already eligible for NICE TA'd products in their 'bad eye' with bevacizumab used for their 'good eye'; in practice therefore both drugs will be administered in the same clinic appointment and the proposal will not significantly increase activity or associated costs.

In camera, the Committee were satisfied that the proposed use of bevacizumab every 2 months is clinically effective and would result in direct patient benefit. Owing to the minimal expected increase in activity, and very low cost of the intervention, the Committee agreed it represented good value for money by simultaneously improving health and delaying future costs to a point which biosimilars may be available.

In summary, the Committee clinically approved the proposal to add bevacizumab 1.25mg intraocular injection every 2 months to the NCL Joint Formulary for eyes with late wet AMD and visual acuity better than 6/12 (pre-NICE TA thresholds). Commissioning implications would be deferred to NEL on behalf of NCL CCG.

Decision: Clinically approved, funding approval required
Prescribing: Secondary care
Tariff status: Excluded from tariff
Funding: CCG
Primary and secondary care Fact sheet or shared care required: No

8.3 EAMS: Cipaglucosidase alfa with miglustat in the treatment of enzyme replacement therapy-experienced late-onset Pompe disease (Applicant: Prof D Hughes, RFL)

The Committee considered an Early Access to Medicines Scheme (EAMS) for cipaglucosidase alfa (an enzyme replacement therapy, or ERT) and miglustat (a pharmacological chaperone to aid stability of cipaglucosidase alfa) for the treatment of Late Onset Pompe Disease (LOPD) who have received previous ERT treatment for two years or more.

Data was not published in a peer-reviewed journal but was supplied with the EAMS documentation. ATB200-02 was a 52-week, phase I/II, single-arm study to assess the safety and efficacy of cipaglucosidase alfa and miglustat for four cohorts; cohorts were based on whether the patient was ambulatory or not and their level of previous ERT-experience (n=29). The first outcome of interest, the 6-minute walking distance test, was improved following treatment with cipaglucosidase alfa and miglustat (mean change 33.5m [95% CI 7m to 60m]). The second outcome of interest, percent predicted forced vital capacity was not different from baseline (mean change -1.3% [95% CI -4% to 2%]). Key limitations of the study were that it was non-randomised open-label study, there was no comparator and it is unpublished or peer-reviewed.

ATB200-03 was a 52-week, Phase III, active-comparator controlled, double-blind study to compare the efficacy and safety of cipaglucosidase alfa with miglustat and alglucosidase alfa and placebo for patients with LOPD who were either ERT-experienced or ERT-naïve (n=123). The primary endpoint, the 6-minute walking distance test, was not better with cipaglucosidase alfa and miglustat compared to alglucosidase alfa and placebo (difference in least square means 13.5m [p=0.071]). Statistical testing was hierarchical and therefore further outcomes (such as the percent predicted forced vital capacity) could not statistically tested. A subgroup analysis of the 6-minute walking test in the ERT-experienced patients (n=95) was significantly longer with cipaglucosidase alfa with miglustat compared to alglucosidase alfa with placebo (difference in least square means 16.8m [p=0.047]). Key limitations of the study were that the study was unpublished and not peer-reviewed and it was unclear whether any protocol amendments were made.

In terms of safety, there were 76 infusion reaction events in ATB200-02 and 97 infusion reaction events in ATB200-03. Two discontinuations occurred due to infusion reactions across both studies. There were no life-threatening or fatal infusion reactions. The administration was assessed as being high-risk, but no different than current standard of care alglucosidase alfa.

In terms of budget impact, cipaglucosidase alfa and miglustat will be available free of charge. As all patients will be ERT-experienced with a majority currently receiving alglucosidase alfa via homecare, there is not expected to be an impact on homecare services. Patients will require at least their first infusion in hospital, which was deemed to be a minimal impact on healthcare resource.

The Committee heard from Prof Hughes that the subgroup analysis from ATB200-03 was the most relevant data for the intended population, and it is expected to be used in 15 patients in total as it is a rare disease. A single day-case administration is required though this is offset by the savings made in drug spend. An EAMS for avalglucosidase (another ERT) was recently approved at RFL DTC but was not utilised as a homecare service was not available and hospitals did not have the capacity for ongoing administrations. Patients would be consented to the EAMS scheme in case NICE did not approve the drug combination.

In camera, the Committee discussed the quality of available evidence and the current unmet need, in particular when patients lose efficacy with alglucosidase alfa over time and have no alternatives available. The Committee was cautious that if a homecare option was to become available for avalglucosidase alfa, then a pathway of treatment options would be required. The Committee was otherwise supportive of the application.

In summary, the Committee agreed to add cipaglucosidase alfa and miglustat to the NCL Joint Formulary for patients with LOPD who have received previous ERT treatment for two years or more.

Decision: Approved
Prescribing: Secondary care
Tariff status: Excluded from Tariff
Funding: Free of Charge
Primary and secondary care Fact sheet or shared care required: No

9. COVID Monoclonal antibody Delivery Units (CMDU): ICS proforma

The Committee heard that delivery units are being scoped out to deliver intravenous or subcutaneous neutralising monoclonal antibodies for COVID-19 (products include Regeneron). A NCL working group has been established. Supporting evidence base will be brought to Committee for review and approval.

10. Dexmedetomidine for sedation of adult ICU patients – usage report

In January 2019, JFC approved dexmedetomidine for light sedation in mechanically ventilated adult patients with CAM ICU positive agitated delirium where agitation precludes weaning and extubation only after standard sedative agents had been trialled. The Committee requested that individual Trusts put in place methods for limiting and monitoring use and asked for usage to be monitored collectively after 12 months.

The Committee heard spend was <£20 000 in most of the NCL acute Trusts over the past 12 months, UCLH had a higher spend than other Trusts. Higher spend was correlated with COVID-19 surges and reflected the increase demand on ITU.

Action: NCL Trusts to continue to individually dexmedetomidine monitor usage and prescribing creep

11. Anti-hyperglycaemic agents for Type 2 diabetes interim NCL guidance

The Committee approved the updated guideline. Updates included adding information relating to personalised HbA1c targets.

12. NCL guideline for glucose & ketone monitoring for adults with diabetes

The Committee approved the updated guideline. Changes included updated Type 2 meter choices, updated Type 1 meter choices, additional advice for the prescribing of SMBG strips in combination with Freestyle Libre or continuous glucose monitoring (CGM) or insulin pumps, added gestational diabetes to scope, new advice on Diasend and GDm-Health app compatibility, new advice for the safe initiation of SGLT2i in certain cohorts and revised DVLA guidance.

13. NCL MON annual report 2019-2021

The Committee heard a summary of the Committee's output for the two-year period 2019/20 and 2020/21. Members were asked to contact Mr Barron with any suggestions for improvement. A final version of the report will be brought back to Committee for approval next month.

14. Next meeting

Thursday 19th August 2021