North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 30 March 2017
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Dr R MacAllister	NCL JFC Chair	**(Chair)**
	Ms W Spicer	RFL, Chief Pharmacist	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Mr S Richardson	WH, Chief Pharmacist	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Ms K Landeryou	Patient Partner	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Dr R Sofat	UCLH, DTC Chair	
	Mr T James	MEH, Chief Pharmacist	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Dr M Kelsey	WH, Chair DTC	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr V Thiagarasah	Enfield CCG, GP	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
In attendance:	Mr A Barron	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Mr J Minshull	NCL JFC, Support Pharmacist	
	Ms Y Korimbux	NEL CSU, Senior Prescribing Advisor	
	Ms A Fakoya	NEL CSU, Senior Prescribing Advisor	
	Mr K Thakrar	UCLH, Formulary Pharmacist	
	Ms H Mehta	NMUH, Formulary Pharmacist	
	Mr G Purohit	RNOH, Deputy Chief Pharmacist	
	Dr E Kriesels	WH, Consultant Community Paediatrician	
	Dr P Cowley	UCLH, Consultant Interventional Neuroradiologist	
	Prof E Joyce	UCLH, Honorary Consultant Psychiatrist	
	Dr J Lambert	UCLH, Consultant Haematologist	
	Dr M Leandro	UCLH, Consultant Rheumatologist	
	Prof M Ehrenstein	UCLH, Consultant Rheumatologist	
	Ms L Smedts	Erasmus student, Netherlands	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Dr E Boleti	RFL, Consultant Medical Oncologist	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr P Hyatt	NMUH, DTC Chair	
	Dr S Shaw	RFL, DTC Chair	
	Ms L Reeves	C&I, Chief Pharmacist	
	Prof D Robinson	UCLH, Consultant in Respiratory Medicine	
	Prof A Tufail	MEH, DTC Chair	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Ms M Kassam	MEH, Formulary Pharmacist	
	Dr R Fox	RNOH, DTC Chair	
	Dr S Ishaq	WH, Consultant Anaesthetist	

2. Meeting observers

Ms Smedts (Erasmus student, Netherlands) was welcomed as an observer to the meeting.

3. Minutes of the last meeting

Item 7.3 'Enstilar (calcipotriol and betamethasone) cutaneous foam for psoriasis': two amendments to the draft minutes were requested by the applicant "236g vs. 193g over the duration of the *12 week* trial" and "the applicant and Leo Pharma estimate lower average Enstilar use *for the 4 week licensed duration*". The minutes were otherwise accepted as accurate.

3.1 Actions from the last meeting

Item 3.1 'Actions from the last meeting' from 23 February 2017 – Thyrotropin alfa: Specialists across NCL have advised thyrotropin alfa should be used for all patients requiring ablation because thyrotropin alfa decreases the half-life of radioactive iodine which will theoretically improve outcomes by protecting patients from unnecessarily prolonged exposure to radioactivity. This claim did not form part of the original application therefore Mr Minshull will review the evidence base and bring a summary back to the Committee for consideration.

Item 3.1 'Actions from the last meeting' from 23 February 2017 – Bisphosphonate holidays: Mr Minshull is working with NCL stakeholder to develop a local position statement. This will be brought back to the Committee for review in May 2017.

Item 7.4 'Hyacyst / Parsons solution in interstitial cystitis': Dr MacAllister informed the Committee that he has asked the Deputy Chief Executive at Whittington Hospital to review how complex lower urinary tract symptoms are managed in NCL.

4. Matters arising

4.1 NCL COPD Formularies

Mr Minshull presented a summary paper of the inhalers listed for COPD management in NCL; WH had not provided a response and Mr Richardson offered to follow-up. The majority of organisations had formularies / preferred lists compliant with the RRP recommendations with two exceptions: the addition of Symbicort and Seretide Evohaler/Accuhaler in most organisations; and the addition of three inhalers rejected by JFC that appeared on the Barnet preferred list. The Committee requested that organisations review their inhaler choice in line with the RRP recommendations.

Clarification was request about whether the Responsible Respiratory Prescribing group will be developing guidelines for the use of inhalers in children with asthma.

Action: Mr Minshull to follow-up with Dr Daff regarding aclidinium, glycopyrronium and Duaklir Genuair (formoterol and aclidinium) which appear on the Barnet preferred list however were not endorsed by JFC. Mr Minshull to seek clarification from Dr Restrick about guidance on inhaler choice for children with asthma.

4.2 NCL Sustainability and Transformation Plans (STPs)

Dr MacAllister, Dr Sofat, Ms Taylor, Mr Urquhart and Mr Bodalia (representatives of the NCL JFC and Medicines Optimisation Network) had an introductory meeting with the NCL STP Lead, Sir David Sloman. Sir David agreed with the JFC / MON delegates that collaborative working between the STP's Health and Care Cabinet and JFC would be mutually beneficial; JFC / MON would deliver the STP's Medicines Optimisation agenda and the STP would provide a more suitable governance structure. It was agreed that Mr Bodalia and Ms Taylor would approach David Stout (Programme Director, NCL STP) to discuss the NCL Medicines Optimisation Strategy proposal at the next available Health and Care Cabinet meeting.

5. NCL JFC Chair

Mr Bodalia informed the Committee that Dr MacAllister has moved onto a new role outside NCL. JFC Support wrote to paying members proposing Dr MacAllister continues to Chair the JFC until his current tenure as Chair runs out in September 2018; the ToR does not preclude a Chair from outside the region. Paying members were supportive of the proposal.

The Committee were of the opinion that Mr Bodalia's communication should have been sent to all Committee members however agreed with the recommendation that Dr MacAllister should be invited to continue as Chair.

It is currently unknown whether Dr MacAllister's new employer will support this appointment.

6. Declarations of relevant conflicts of interest

There were no declarations of interest.

7. Local DTC recommendations / minutes

7.1 Approved by local DTC

DTC site	Month	Drug	Indication	JFC outcome
RFL	Nov-16	Pegylated liposomal irinotecan **(FOC)**	Metastatic pancreatic cancer after failure of gemcitabine based therapy (used in combination with 5-fluorouracil & leucovorin)	Not approved[†]
RFL	Feb-17	Rituximab	IgG 4 disease (in line with the NHSE Commissioning Policy)	RFL only
NMUH	Dec-16	Ferinject	Iron deficient anaemia in adult outpatients only, not in patients in first trimester of pregnancy or for patient on haemodialysis	Added to NCL Joint Formulary – individual Trust to make local decisions on parenteral iron

[†]Pegylated liposomal irinotecan recently received a negative Final Appraisal Determination (NICE ID778) when used after gemcitabine and in combination with 5-fluorouracil [5-FU] & leucovorin [LV]. The Appraisal Consultation stated a lack of confidence that pegylated liposomal irinotecan offered any added value over the relevant comparator, oxaliplatin + 5-FU & LV; "pegylated liposomal irinotecan + 5-FU and LV could be considered broadly similar to oxaliplatin + 5-FU and LV". The subsequent ICER was >£100K even with the patient access scheme considered.

Action: RFL DTC to review their decision (for FOC supply) following the negative NICE FAD.

7.2 Approved Under evaluation by local DTC

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Jan-17	Brentuximab plus bendamustine	Hodgkin's lymphoma	Under evaluation at UCLH only

8. New Medicine Reviews

8.1 APPEAL: Netupitant/palonosetron for chemotherapy induced nausea and vomiting

The Committee considered an appeal of the decision made in April 2016 not to accept netupitant/palonosetron for management of chemotherapy induced nausea and vomiting. The Committee were not convinced that the evidence demonstrated any clinical advantage of netupitant/palonosetron over aprepitant and palonosetron. The appeal addressed the following issues raised by the JFC:

- When first reviewed, netupitant/palonosetron was available at a similar price to aprepitant and palonosetron, therefore offered no financial advantage. The Committee heard that the price has been reduced to £38/pack, which is less than the price of aprepitant (£44).
- There were potential safety concerns if patients attend at A&E or AAU with nausea and vomiting despite treatment with palonosetron. Prescribers would be less familiar with palonosetron and there was a risk that ondansetron be administered to a patient who had already been treated with a 5HT3 antagonist. To mitigate this risk, acute oncology guidelines currently recommend cyclizine first line. Additionally, palonosetron is not being used at the maximum dose, therefore the risk of toxicity from an overdose of 5HT3 antagonist is minimised.
- Concern was raised about staff costs involved in changing high-risk chemotherapy regimens from aprepitant/ondansetron to netupitant/palonosetron, only to have to change back again in 2018 when aprepitant is available as a generic medicine. Pharmacists in Macmillan Cancer Centre have reviewed this and determined it takes 2 hours to change all protocols.

Overall, the Committee members were not convinced that there was any real advantage from switching to netupitant and palonosetron. Even though there is a small cost saving presently, adopting this

combination now will make it difficult switch back to aprepitant and ondansetron following patent expiry of apreptant in November 2018.

Decision: Not approved

8.2 Nabilone for Tourette's syndrome [off-label] (Applicant: Prof E Joyce, UCLH)

Mr Minshull presented an application to use nabilone (a cannabinoid receptor agonist) in the management of tics in Tourette's syndrome. The Chair welcomed Prof Joyce to the Committee; Prof Joyce explained that the national Tourette's Syndrome clinic is hosted at NHNN. Some patients seen at this clinic suffer a significant burden from their symptoms and find it very difficult to perform normal daily functions; there are currently five patients for whom she would like to use nabilone. Prof Joyce explained that some patients in her clinic have used cannabis and have reported that it helps to manage their symptoms. Deep brain stimulation was previously available as a treatment option, but NHS England no longer funds this service. Cannabinoid receptor agonist is proposed as a fourth line option for a small number of patients.

The Committee discussed the available evidence for use of cannabinoid agonists to manage tics, which is limited to two, small randomised studies (one crossover study [n=12], and one double-blind RCT [n=24]), with methodological flaws. Both studies compared delta-9 tetrahydrocannabinol (not nabilone) to placebo.

The Committee discussed the findings of the double-blind RCT, which was analysed on a per-protocol basis. Different scales were reported, including the TS-CGI (-0.6 points, p=0.008) Yale Global Tic Severity Scale (YGTS, -12 points, p=0.61) and Shapiro Tourette Syndrome Severity Scale (STSS, -0.7 points, p=0.033). Videotape reported "motor tic intensity" at visit 4 showed a statistically significant difference (p=0.03), though frequency of motor tics did not show a statistically significant change.

It was noted that, in the cross-over study, a statistically significant reduction in symptoms (Tourette Syndrome Symptom List, TSSL) was self-reported (median -10 points reduction, p=0.015), however changes in rating for physician assessed scores were not statistically significant. Subjective patient experience of global improvement was reported by ten of the twelve patients following a dose of delta-9 THC (+35%, ± 28, range 20-90%), compared to three when receiving placebo (+7% ± 13.7%, range 10 – 40%). The Committee advocated caution when determining the significance of these subjective findings as it will have been difficult to maintain blinding in this study.

Prof Joyce noted that the outcome with the most meaning to patients, and therefore the one she uses in practice, is the YGTS, which Cochrane considers to be a valid and highly reliable outcome measure. Improvements on this scale translate to improvements in physical functioning and ability to socialise and work. Other scales considered useful by Cochrane are STSS and TS-CGI. Cochrane cautions that there is no evidence that TSSL has undergone rigorous psychometric validation, and that TSGS is prone to exaggerate small differences in tic severity.

The Committee noted that the evidence base for nabilone in this indication is sparse, relying on extrapolation of results from studies using a different cannabinoid. It was highlighted that a clinical trial of Sativex, another cannabinoid, is currently recruiting in Germany and it would be sensible to approach the Principal Investigator in the first instance. Prof Joyce agreed that her preference had been to use Sativex, but had written the application for nabilone when the price was much lower than for Sativex. As the price of nabilone has increased significantly, Sativex represents a more suitable alternative.

In summary, the Committee supported the evaluation of use of a cannabinoid in the management of tics in Tourette's Syndrome, with choice of agent dictated by acquisition cost. Due to the limited published evidence available, usage should be in accordance with the clinical trial protocol or an adapted local evaluation protocol.

Action: Mr Bodalia to approach the Principal Investigator of the CANNA-TICS study to explore NHNN becoming a registered centre. Mr Minshull to work with Prof Joyce to support involvement in the trial, or to establish a local evaluation.

Post meeting notes: Patients at NHNN will not be able to participate in the CANNA-TICS study as it is a single centre, non-commercial study open only to German speaking patients. Prof Joyce and Mr Minshull will develop an evaluation protocol for use at NHNN based on the CANNA-TICS trial protocol.

Decision: Approved under evaluation
Prescribing: Secondary care
Tariff status: In tariff

Funding: Hospital budgets
Fact sheet or shared care required: No
Audit required: Yes

8.3 Melatonin for children with developmental disorders [off-label] (Applicant: Dr E Kriesels, WH)

Mr Minshull presented an application to use melatonin for the treatment of insomnia in children (> 2 years) with neurological or developmental disorders. The Committee noted that use of melatonin is recommended by the Scottish Intercollegiate Guidelines Network (SIGN 145) in the management of autism spectrum disorders, and in the NICE guideline (NG 62) for the management of cerebral palsy in people under 25 years.

The Committee looked at the findings from Appleton et al (2012), who conducted a 12 week, double-blind, multicentre, placebo-controlled study to determine the efficacy and short-term safety of melatonin to manage insomnia in children with neurodevelopmental disorders. The Committee noted that all participants initially received sleep hygiene training, which resulted in 44% of those initially identified being excluded from the study, highlighting the importance of this before starting pharmacological therapy. Total night-time sleep (measured using a sleep diary) showed a mean difference of 22.43 minutes (95% CI 0.52 to 44.34 minutes, p=0.04) in favour of melatonin, and 13.33 minutes (95% CI -15.48 to 42.15 minutes) when actigraphy was used to measure sleep. Actigraphy was originally intended to be used to measure a co-primary outcome with sleep diary, but the researchers deviated from this plan after finding up to 66% missing Actigraphy data during the initial phase of the study. The Committee noted with interest the wide confidence intervals for each of these measures.

Sleep onset latency (a secondary outcome) showed a mean difference of -37.49 minutes (95% CI -55.27 to -19.71, p<0.0001) in favour of melatonin when measured using a sleep diary, and -45.34 minutes (95% CI -68.75 to -21.93 minutes, p=0.0003) in favour of melatonin when using actigraphy. The difference in change in sleep efficiency (another secondary outcome) was not statistically significant between groups.

Two other RCTs were considered by the committee, each demonstrating a modest improvement in sleep for children receiving melatonin over a short period (4 to 12 weeks).

Dr Kriesels reassured that Committee that, although there is a theoretical risk of development disorder when melatonin is used in children, this has not been conclusively proven and would be noticed at regular review. She noted that although some children may use melatonin on a when required basis, the majority will use it nightly if they respond.

The Committee discussed the large potential cost impact from melatonin prescribing; this is particularly pronounced if the dose is escalated up to 12 mg each night as was used in the Appleton *et al* study. The licensed dose in adults is 2 mg. The Committee were conscious in promoting prudent use of NHS resources. It was agreed that melatonin demonstrated modest benefits in sleep for children with developmental disorders, but its use should be carefully controlled to manage budget impact. Oral liquid formulations of melatonin are unlicensed medicines with prices much higher than the equivalent dose from the solid oral formulation. It was agreed that the licensed tablet formulation should be used where possible, crushing this if children refused to take it whole (breaking the modified-release formulation was not considered to be an issue clinically as the focus of treatment is to improve sleep onset rather than total night-time sleep).

In summary, the Committee approved the use of melatonin for specialist initiation in the management of insomnia for children (>2 years) with neurological or developmental disorders. The applicant agreed to work with the Medicines Optimisation Committee to help develop guidelines that address formulation choice, help manage dose, support evaluations of therapy and provide information about crushing tablets. GPs will be asked to take on prescribing once the dose has been stabilised.

Action: Mr Minshull to feedback to the Committee information about endogenous levels of melatonin in children.

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

8.4 Prasugrel for elective placement of intracranial stents (Applicant: Dr P Cowley, UCLH)

The Committee reviewed an application form for the use of prasugrel (instead of clopidogrel) as dual antiplatelet therapy in combination with aspirin to minimise risk of thromboembolic complications in patients undergoing endovascular therapy of unruptured intracranial aneurysms.

The Committee noted that the efficacy of clopidogrel was variable among patients, and resistance to clopidogrel was detectable by in vitro assays, most of which had not been validated clinically. Dr Cowley informed the Committee that the NHNN perform near-patient testing of platelet aggregation with the VerifyNow Assay. This determines whether a patient is clopidogrel responder or non-responder. Were a patient to exhibit in vitro clopidogrel resistance, the procedure would be rescheduled so that an alternate antiplatelet regime could be planned. This of course was inconvenient and an inefficient use of resources. The Committee had some issues with this approach (see below).

The Committee noted that the evidence for prasugrel in endovascular treatment of intracranial aneurysm is limited to one prospective open-labelled study, one retrospective analysis, and one case study only. The following studies were reviewed:

Sedat et al. (2014; n = 200) conducted a prospective study at the University Hospital of Nice to evaluate the efficacy and safety of prasugrel compared to clopidogrel (both in combination with aspirin) in patients undergoing endovascular treatment. Patients were allocated to two groups: (1) Jan 2009 to Jan 2012 - patients treated with aspirin and clopidogrel, and (2) Feb 2012 to Feb 2014 - patients treated with aspirin and prasugrel. The results showed that the total number of complications were 25 (20 intraoperative and an additional 5 within 30 days) in the clopidogrel group compared to 18 complications in the prasugrel group (12 intraoperative and 6 within 30 days). In terms of intracranial haemorrhagic complications, there was one patient in the clopidogrel group that experienced intra-operative bleeding (small-sized cerebral haematoma on awakening) compared to 2 patients in the prasugrel group (small meningeal haemorrhage and a low volume intra-ventricular haemorrhage). In terms of extracranial haemorrhage, there were four haematomas in the groin area observed in each group, with an extra patient in the prasugrel group presenting with a gastric haemorrhage. The proportion of patients with thromboembolic complications within 30 days following the procedure was higher in the clopidogrel arm (n = 17) compared to the prasugrel arm (n = 12), however this was not statistically significant (p = 0.31). The majority of the patients who experienced thromboembolic complications in the prasugrel group were small distal emboli, with no incidences of proximal artery conclusion and no stent thrombosis. In comparison, the clopidogrel group had three patients with stent thrombosis (symptomatic proximal artery thrombosis).

The committee noted that although the baseline characteristics and the size of aneurysms were similar between both groups, there were a significantly higher number of wide-necked aneurysms in the prasugrel group. In addition, there were small differences in the procedural methods with more frequent use of flow diverter stents in the prasugrel group (11 procedures) compared to the clopidogrel group (1 procedure). Finally, the study has a number of limitations including no randomisation, the comparator arm being a historical cohort of patients as opposed to a co-temporaneous control.

Ha et al. (2016; n = 194) conducted a retrospective analysis at the Seoul National University Hospital to investigate the efficacy and safety of prasugrel compared to clopidogrel in patients that underwent endovascular treatment between November 2014 and July 2015. Patients were divided into clopidogrel group or low-dose prasugrel group, both in combination with aspirin 75mg for stent assisted procedures. If the patient was a poor responder to clopidogrel (i.e. PRU > 285) cilostazol 200mg was added. The results showed no procedure-related thromboembolic events in either arm. However, there was one procedural related haemorrhage in each group; aneurysm rupture in the clopidogrel arm during the procedure leading to diffuse subarachnoid haemorrhage, and one small amount of subarachnoid haemorrhage in the prasugrel arm. There was no procedural related permanent morbidity or mortality in either group.

The Committee heard that Ha *et al.* also conducted platelet function tests using the VerifyNow P2Y12 assay to determine the extent of platelet inhibition between the two groups. The results showed P2Y12 receptor activity (PRU) were significant lower in the in the prasugrel arm (242.7 vs 125.7). The committee noted that in the cardiology literature, threshold PRU values that would classify a patients as clopidogrel resistant were reported to be above 230. However, it was again noted that the clinical relevance of these in vitro tests to short- and long-term cardiovascular outcomes was uncertain. The SPC for clopidogrel does not specify that these tests should be used to determine clopidogrel dosing regimes.

Jones et al. (2013; n = 2) published a case report of two patients treated with prasugrel and aspirin for endovascular therapy. The first patient presented on day 5 post-op with severe heachache due to a small,

right frontal subarachnoid bleed. Repeat cerebral angiography displayed significant aneurysm thrombosis when compared to the previous procedure 3 days ago, resulting in the patient continuing duel anti-platelet therapy on discharge for a total of 6 months. The second patient had no complications reported and a repeat angiogram at 6 months demonstrated no thrombosis.

In terms of safety, a retrospective study by Akbari *et al.* (2013; n = 76) examined the safety of prasugrel for neuro-interventional procedures. Patient charts were retrospectively reviewed for data collection on anti-platelet therapy and clinical/safety outcomes. All patients were loaded with aspirin and clopidogrel (n = 51) at least seven days prior to their procedure. The patients who exhibited less than 40% platelet inhibition (P2Y12 ADP receptor inhibition) were loaded with prasugrel 60mg (n = 25) prior to the procedure, and continued prasugrel 10mg daily after. The results showed a total of 86 interventions were conducted between the 76 patients. The proportion of patients with haemorrhagic complications was 19.4% with aspirin/prasugrel compared to 3.6% with aspirin/clopidogrel. A single thromboembolic complication (transient ischaemic attack) was observed in the aspirin/prasugrel group following stent assisted coiling.

The Committee discussed at length the limitations of these data. Dr Cowley agreed with the Committee that robust evidence is not available to support the use of prasugrel. Much of the practice had evolved by extrapolation from the cardiology experience.

The Committee questioned the use of near patient testing using the VerifyNow assay, highlighting in particular that the test has not been universally accepted or validated, that the clinical relevance of the result is unknown, and that it is unclear what quality assurance steps of the device are undertaken. The Committee agreed that the newer antiplatelet agents (prasugrel and ticagrelor) are more efficacious in preventing thromboembolic events due to greater platelet inhibition, however this small benefit should be offset against an increased risk in bleeding. The Committee suggested that ticagrelor be used instead of prasugrel due to a lower reported incidence of haemorrhagic events in the cardiology trials. Because of this, most cardiology practice avoids prasugrel. However, Dr Cowley informed the Committee that the experience within endovascular treatment in neurology has been with prasugrel.

In summary, the Committee agreed to include prasugrel onto the NCL JFC formulary for this indication. The Committee thought that near-patient testing with the VerifyNow Assay should be discontinued, as it wasn't likely to be useful given the lesser variability of the antiplatelet effect of prasugrel compared to clopidogrel. The Committee agreed that the initial prescription should be supplied within the hospital, with continuation in primary care with a detailed summary and treatment plan in the letter sent to the GP.

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

9. Biosimilars for all indications

Mr Thakrar provided an overview of biological medicines (biologics) and biosimilars (copy of biologics) to the Committee. Biologics are molecules produced from modified living organisms which broadly fall into two categories; proteins and glycoproteins. The former are smaller (approximately 18,000 Da) and include filgrastim, the latter are much larger (approximately 144,000 Da), have a more complex molecular structure and include the monoclonal antibodies. Unlike chemically synthesised molecules, it is not possible to manufacture exact copies of biologics which is why the term 'biosimilar' is used. The manufacturing process for biologics (both the originator and biosimilars) are tightly regulated by the EMA as changes can create molecular variability; high risk changes, such as a new cell line, require analytical, process, stability, non-clinical and potentially clinical data to be submitted to the EMA for approval. Changes to processes occur in the real world with variations of originator biologics common place in the market; Remicade® (infliximab) and Humira® (adalimumab) both underwent three high risk changes to their process with end users (prescribers and patients) uninformed of the changes.

The term biosimilar is a regulatory term: "The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods. Like the reference medicine, the biosimilar has a degree of natural variability. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness". Biosimilars are not a new concept; smaller

proteins (filgrastim and growth hormones) have been used for many years and glycoproteins (infliximab and etanercept) are in routine use in rheumatology and gastroenterology.

Biosimilars undergo a comprehensive regulatory process which demands extensive comparability studies that demonstrate similarity to reference product. There is no requirement to demonstrate clinical benefit to patients per se as this has been shown for the reference product. This underlines the fundamental difference is regulatory process between originator and biosimilar; originators must determine clinical effect, with the greatest proportion of effort spent in the clinical setting, whereas biosimilar must determine similarity, with the greatest proportion of effort spent in the analytical and non-clinical aspects of medicine development. The limited clinical requirement is to confirm the extensive analytical and non-clinical data. Most biologics are licensed for multiple indications, however, under the direction of the EMA evidence of efficacy and / or safety clinical data is not required for every indication; the EMA will identify indications with 'sensitive' (active disease, large effect size) and 'homogenous' (consistent disease activity, minimal interpatient variability) populations. If trial(s) in these populations confirm similarity, then EMA extrapolation to other less sensitive indications is regarded as justified.

The Committee agreed to support all biosimilars approved by the EMA therefore future biosimilars do not need to be reviewed by the Committee, provided the originator biologic is already on the NCL Joint Formulary. The Committee agreed that switching from an originator to a biosimilar is a priority for the NHS and there is no appetite at this stage to switch between biosimilars. The choice of specific biosimilar available across NCL should be co-ordinated by the Medicines Optimisation Committee who must involve relevant stakeholders in their decision making. To provide reassurance to the Committee on the level of detail and type of discussions that would take place, an example case of biosimilar rituximab (Truxima®) was presented (see item 9.1).

9.1 Biosimilar rituximab (Truxima®) for all indications

Truxima is the first biosimilar rituximab to enter the UK market and is licensed for the same indications as the originator product, MabThera® (EU) and Rituxan® (US).

Non-clinical methods confirmed comparative binding affinity of Truxima and MabThera/Rituxan using an array of techniques. Pharmacokinetic (PK) and pharmacodynamics (PD) data were also comparable.

The clinical data, which exists to confirm the non-clinical, PK and PD data, comprises of three studies; one Phase I study in RA (CT-P10 1.1 and CT-P10 1.3), one Phase III study in RA (CT-P10 3.2) and one Phase I/III study in follicular lymphoma (CT-P10 3.3).

CT-P10 1.1 (n=154) was a Phase I, prospective, multinational, randomised, double-blind, active-comparator controlled trial to demonstrate the PK and efficacy equivalence of Truxima to MabThera in patients with moderate-to-severe RA. Results demonstrated no significant difference in change from baseline in DAS28 by week 28; between group difference of 0.08 (95% CI: -0.39 to 0.56). More patients were re-treated after week 24 and before week 48 of the 'Core Study' in the CT-P10 arm (58%) than in the MabThera arm (45%) however the eligibility for re-treatment were met in the same proportion of patients and the time to re-treatment estimated throughout the whole trial was shorter in the CT-P10 arm than in the MabThera arm. The post-hoc analysis in patients with severe RA only, found similar proportions of patients achieved ACR20 in both treatment groups (65.9% vs. 72.5%) at week 24.

CT-P10 3.2 (n=372) was a Phase III, prospective, multinational, randomised, double-blind, active-comparator controlled trial to demonstrate the PK, efficacy and safety equivalence of biosimilar rituximab to the reference products (Rituxan and MabThera) in patients with moderate-to-severe RA. The primary aim of the study was to demonstrate non-inferiority as measured by change in DAS28 from baseline using an equivalence margin of ±0.6. Results demonstrated non-inferiority of Truxima the reference products at week 24; change in DAS28 from baseline estimated treatment difference was -0.05 [95%CI: -0.29 to 0.20] which is within the equivalence margin of ±0.6. By week 48, change in DAS28 from baseline estimated treatment difference remained within the equivalence margin [95%CI: -0.35 to 0.21]. Similar proportions of patients achieved ACR 20 at week 24. The post-hoc analysis in patients with severe RA only, was not reported in the EPAR however the manufacturer advises it showed equivalence in each group.

CT-P10 3.3 (n=121) was a Phase I/III, prospective, multinational, randomised, double-blind, active-comparator controlled trial to demonstrate the PK and efficacy equivalence of biosimilar rituximab to the reference product in patients with Advanced Follicular Lymphoma. The primary aim of was to demonstrate non-inferiority as measured by ORR (Overall Response Rate) at cycle 8. Results demonstrated similar ORR in both treatment groups were observed; 95.7% vs. 90.0% using the ITT

population. The company submission claimed non-inferiority without estimating 95% confidence intervals however the MHRA were satisfied that non-inferiority was demonstrated.

With regards to safety, the incidence of adverse events and serious adverse events were similar in all three studies.

With regards to cost-impact, the introduction of Truxima will be cost minimising; it is estimated approximately £2.6 million per annum could be saved if all MabThera supply within NCL is switched to Truxima. The majority of savings would be from UCLH's haematology department.

The Committee heard from Dr Leandro that any molecular variation between rituximab and biosimilar rituximab, which is administered every >6 months for RA, was very unlikely to affect disease control. The Rheumatology community were therefore less cautious about a rituximab biosimilar switch than anti-TNF switching. The UCLH experience for switching anti-TNFs has been overwhelmingly positive; savings of £1.7 million have been realised to date for infliximab and etanercept, with very few cases requiring switching back to the originator (approximately 5 of 490) mostly due to off-target allergic / infusion site reaction. At UCLH such cases are reviewed by a sub-group of their DTC, a process which is working successfully and has been welcomed by rheumatology / gastroenterology clinicians.

Prof Ehrenstein suggested patients with Lupus (an off-label indication) are predisposed to allergic reactions, however it was acknowledged by Dr Leandro that the incidence of allergic reactions for Truxima was very similar to the reference products.

Dr Lambert advised that ritixumab is used widely for multiple malignant haematological indications. Local and national consensus, including the Cancer Vanguard, is that practice should move towards biosimilars. Although the clinical data for cancer indications [for Truxima] was noted as being extremely limited, it was accepted that the non-clinical data confirms similarity and therefore the EMA process for biosimilar regulation / Marketing Authorisation was supported. The wider literature suggests ofatumumab, another anti-CD20 antibody, has comparable efficacy to rituximab which provides further reassurance that biosimilar rituximab can be used across all indications. The subcutaneous formulation, which is not used in NCL, is unlikely to be replaced by intravenous biosimilar rituximab. Dr Lambert stated he was not in a position to comment on the use of biosimilar rituximab in non-malignant haematology indications.

The Committee agreed to add Truxima (biosimilar rituximab) to the NCL Joint Formulary. All future biosimilars would not require evaluation by JFC and would be automatically approved, see Item 9 'Biosimilars for all indications'.

10. Magnesium aspartate (Magnaspartate®, 243 mg [10 mmol]) for magnesium deficiency

Magnesium aspartate is the first licensed oral magnesium medicine for the treatment and prevention of magnesium deficiency. Previously, the oral magnesium preparations used were magnesium glycerophosphate and magnesium oxide however both were unlicensed.

The Committee agreed to add magnesium aspartate to the NCL Joint Formulary. Magnesium glycerophosphate and magnesium oxide would remain on formulary for patients who were unable to tolerate magnesium aspartate. Given the paucity of comparative data and the variability of absorption between salts, patients who switch between products would require monitoring of serum magnesium level.

Action: Mr Minshull to ask Gastroenterology for the monitoring requirement for patients who switch between products

11. Guidelines

11.1 MEH Ocular lubricants guideline

This item was approved subject to Camden and Haringey CCG comments been incorporated into the final version.

Action: Mr Minshull to work with MEH, Camden CCG and Haringey CCG to make any final amends.

12. JFC Work plan

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

13. Next meeting

Thursday 27th April 2017, Room 6LM1, Stephenson House, 75 Hampstead Rd.

14. Any Other Business

Nil