North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 17th September 2020

Present:	Dr P Taylor	NCL JFC Vice Chair	(Chair)
	Dr M Kelsey	WH, DTC Chair	
	Ms W Spicer	RFL, Chief Pharmacist	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Mr S Semple	MEH, Chief Pharmacist	
	Ms K Delargy	BEH, Deputy Chief Pharmacist*	
	Mr S Richardson	WH, Chief Pharmacist	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Ms S Stern	NMUH, Chief Pharmacist	
	Dr A Sell	RNOH, DTC Chair	
	Ms S Lever	NCL CCG, Head of Medicines Management (Barnet)	
	Ms P Taylor	NCL CCG, Head of Medicines Management (Haringey)	
	Ms R Clark	NCL CCG, Head of Medicines Management (Camden)	
	Ms L Reeves	C&I, Chief Pharmacist	
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 S Amin	UCLH, Formulary Pharmacist	
	Ms SY Tan	NEL CSU, Contracting and Commissioning Pharmacist	
	Mr D Abdulla	NMUH, Critical Care and Formulary Pharmacist	
	Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr F Master	RFL, Formulary Pharmacist	
	Ms A Fakoya	NEL, Senior Prescribing Advisor High Cost Drugs	
	Ms K Davies	NEL CSU, Deputy Director Medicines Management	
	Dr M George	UCLH, Specialist Registrar Clinical Pharmacology	
	Ms K Saxby	UCLH, Formulary Phamacist	
	Dr U McGovern	UCLH, Consultant Medical Oncologist	
	Dr R Menon	NMUH, Consultant Endocrinologist	
	Dr M Scully	UCLH, Consultant Haematologist	
	Dr A Hoisin	UCLH, Specialist Registrar Clinical Pharmacology	
	Ms S Counter	NCL STP, Senior Commissioner Transformation Delivery Manager	
	Ms L McLaughlin	NCL STP, Head of Cancer Commissioning	
	Dr A Roy	RFL, Urology Consultant	
	Ms M Thomas	UCLH, Consultant Haematologist	
	Ms R Shah	UCLH, Lead Haematology Pharmacist	
Apologies:	Dr R Sofat	NCL JFC Chair	
	Mr P Gouldstone	NCL CCG, Head of Medicines Management (Enfield)	
	Dr D Burrage	WH, Consultant in Emergency Medicine	
	Mr T Dean	Patient Partner	
	Dr K Tasopoulos	NMUH, DTC Chair	

Ms G Smith	RFL, DTC Chair
Mr A Dutt	NCL CCG, Head of Medicines Management (Islington)
Dr A Bansal	NCL CCG, GP Clinical Lead Medicines Management (Barnet)
Mr A Shah	RNOH, Chief Pharmacist
Mr A Tufail	MEH, DTC Chair

**Deputising for Committee member*

2. Meeting observers

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

3. Minutes of the last meeting

The minutes of the 20 August 2020 meeting were accepted as an accurate reflection of the meeting.

4. Matters arising

4.1 Hydrogen peroxide 1% cream for non-bullous impetigo

At the August 2020 meeting, the Committee were advised that NICE NG153 'Impetigo: antimicrobial prescribing' [non-bullous] recommended 1st line use of hydrogen peroxide 1% cream. It was queried whether the product was safe for inflammatory skin conditions. JFC Support contacted several NCL Dermatologists who confirmed in their specialist experience that hydrogen peroxide 1% cream can be used safely for patients with mild to moderate inflammatory skin conditions (and, in some cases, used on small open wounds for other indications). The Committee were reassured and agreed that hydrogen peroxide 1% cream should be added to the NCL Joint Formulary for non-bullous impetigo.

Decision: Added to NCL joint formulary
Prescribing: Primary and Secondary care
Tariff status: In tariff
Funding: Hospital and CCG
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
UCLH	August 2020	Dexmedetomidine	Part of sedation plan for patients undergoing awake craniotomy where the surgery or patient are deemed to be high risk	Decision: UCLH only Prescribing: Secondary care Tariff status: In tariff Funding: Hospital Fact sheet or shared care required: No
RFL	July 2020	Atezolizumab and Bevacizumab	EAMS: Untreated hepatocellular carcinoma	Decision: RFL only Prescribing: Secondary care Tariff status: In tariff Funding: Hospital Fact sheet or shared care required: No

8. New Medicine Reviews

8.1 Short course eltrombopag for immune thrombocytopaenic purpura

The Committee considered a retrospective review of historic off-label prescribing practice; eltrombopag for short term platelet support in 1) elective surgery and 2) during chemotherapy.

Elective surgery

The Committee heard that eltrombopag is prescribed for patients diagnosed with immune thrombocytopenia (ITP) who do not usually require treatment but be given this treatment prior to elective surgery that requires a minimum [higher] platelet count. The appropriate comparator for eltrombopag in

this setting is IVIg (NHS England funded indication) and/or corticosteroids. Platelet transfusions are administered only if other treatments have failed.

Arnold et al published a randomised, parallel arm, open-label, non-inferiority study which assessed eltrombopag compared with IVIg in patients with primary or secondary immune thrombocytopenia prior to minor or major surgery (n=74). The primary outcome was 'achievement of a specified perioperative platelet count target without rescue treatment'. Using an intention-to-treat analysis, eltrombopag was demonstrated to be non-inferior to IVIg; perioperative platelet targets were achieved for 79% of patients assigned to eltrombopag and 61% of patients assigned to IVIg ($P_{non\text{-}inferiority}$=0.005). The Treatment Satisfaction Questionnaire for Medication scores were higher for patients who received eltrombopag than for those who received IVIg (p=0.012).

In terms of safety, Arnold et al reported similar rates of severe bleeding events (24% with eltrombopag and 22% with IVIg). One patient in the eltrombopag group developed a treatment-related pulmonary embolism 14 days after minor surgery. In the eltrombopag group, two (5%) of 38 patients developed increased liver enzymes and two (5%) developed rebound thrombocytopenia after stopping eltrombopag.

It is estimated that approximately 14 patients would be eligible for treatment each year. The associated cost for eltrombopag would be £5,390 to £32,340 per annum. The alternative treatment of IVIg would cost approximately £47,325 (including daycare admission costs) therefore the net budgetary impact to the NHS as a whole would be favourable. The Committee were reminded that IVIg is commissioned by NHS England and eltrombopag would be commissioned by the CCG.

The Committee heard from Dr Scully that there is a benefit to accessing eltrombopag as a treatment option as IVIg is a scare resource and surgeons are reluctant for patients to receive high dose steroids prior to surgery as it can impact on wound healing and infections. The use of eltrombopag is restricted to patients who have elective surgery with a window of 7-14 days to allow platelet counts to rise and dosing is titrated based on response. From local experience, the failure rate and adverse events are minimal.

In camera, the Committee agreed there was a compelling evidence-base for use of eltrombopag in this cohort of patients, which is less expensive than IVIg, and potentially safer. The Committee discussed the concerns of this practice creeping into other areas of prescribing and agreed there should be a guideline in place.

In summary, the Committee agreed to add eltrombopag for short-term platelet support in ITP patients undergoing elective surgery with the caveats that a guideline is required and prescribing should be restricted to Haematology consultants only. A CCG commissioning evaluation will be required to review funding (acknowledging that a baseline spend is already in place) and CCG representatives noted that it would be for individual Trusts to decide whether to offer eltrombopag as above to patients in advance of CCG funding approval.

Decision: Deferred until a guideline is developed and approved by NCL JFC.

During chemotherapy

The Committee heard that eltrombopag is prescribed for patients undergoing chemotherapy (for solid tumour or haematological malignancies) who have a platelet-specific abnormality and a high immature platelet fraction. A small proportion of these patients do not have ITP. In a study, the appropriate comparator for eltrombopag for patients with solid tumours would be to delay chemotherapy until platelet counts have increased to >100 × 10^9/l, and for patients with haematological malignancies to provide repeated platelet transfusions.

In absence of a randomised control trial the Committee reviewed a case series. Taylor et al published a retrospective review of patients who had received eltrombopag as part of standard treatment or under special considerations (n=62). The patients were separated into three groups. The most relevant group to this application (Group 3) included patients undergoing chemotherapy (n=13). It was observed that when receiving eltrombopag, 46.2% had a complete response (platelet count >100 x 109/l), 30.8% had a response (platelet count >30 x 109/l) and 23% reported no response (platelet count <30 x 109/l).

In terms of safety, Taylor et al reported adverse events in 7 of the 62 patients including drowsiness, fatigue, skin rash, headache and disturbed sleep.

The Committee heard from Dr Scully that approximately 10 patients would be eligible for treatment each year. The budget impact for this patient cohort would be approximately £46,200 - £138,600 per annum. It was noted that patients with solid tumours have no alternative treatment (but to delay chemotherapy) and patients with haematological malignancies would otherwise receive repeat platelet transfusions. Each platelet transfusion, including day care admission costs would be approximately £830; the number of transfusions would be individual to each patient.

The Committee heard from Dr Scully that this is not a proposal to use eltrombopag for all chemotherapy patients with low platelets, but rather for a selective group with thrombocytopenia but otherwise normal blood counts. The Committee heard that the feasibility of a clinical trial in this cohort was extensively considered several years ago, however it was agreed a trial was not possible owing to the heterogeneity of the patient cohort, low patient number, and acute nature of the treatment.

In camera, the Committee noted the evidence was of low quality but agreed a trial was probably unfeasible. Similarly, the Committee agreed that concerns about delaying chemotherapy were valid however without further information on the period of delay and potential nature of disease progression the true patient was hard to quantify.. The Committee discussed that this is established practice which is tightly controlled however there were concerns that there may be potential for prescribing creep into general use.

In summary, the Committee agreed to add eltrombopag for short-term platelet support in select patients undergoing chemotherapy. The Committee requested that a guideline is developed to outline the patients who should (and should not) be offered treatment and the monitoring requirements. All prescribing and monitoring should be undertaken by a consultant haematologist. A CCG-commissioning evaluation will be required to review funding (acknowledging that a baseline spend is already in place) and CCG representatives noted that it would be for individual Trusts to decide whether to offer eltrombopag as above to patients in advance of CCG funding approval.

Decision: Deferred until a guideline is developed and approved by NCL JFC.

8.2 Tolvaptan for hyponatraemia associated (Applicant: Dr R Menon, NMUH & Dr U Srirangalingam, UCLH)

The Committee considered an application for tolvaptan, a selective vasopressin antagonist, for the treatment of hyponatraemia associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Tolvaptan was proposed for initiation under consultant supervision in euvolaemic patients with a free water clearance ratio >1 (or otherwise following a trial of 24-48 hours of fluid restriction) at a dose of 7.5mg daily for up to three days during their inpatient stay only.

The SALT-1 and 2 studies were two identical, Phase III, placebo-controlled studies to assess the safety and efficacy of tolvaptan for patients aged 18 or over who had hyponatraemia associated with SIADH, heart failure or cirrhosis (n=448). The co-primary endpoints, the change in the average daily area under the curve for the serum sodium concentration from baseline, were significantly larger with tolvaptan compared with placebo at day 4 and at day 30 [p<0.001]. The improvements were also significant when patients were stratified according to whether the degree of hyponatraemia was mild or marked [p<0.001].

Patients were followed up seven days after stopping the study drug; serum sodium in patients taking tolvaptan reverted to degrees of hyponatraemia associated with placebo. Key limitations of the study were that it was pharmaceutical-industry funded and the extensive exclusion criteria (which consisted of patients within the scope of this application, such as those with a serum sodium level <120 mmol/l). Little information was provided on concurrent diuretics or RAAS system medications. A post-hoc subgroup analysis on the SIADH population subsequently demonstrated significant improvements with tolvaptan compared to placebo in the two primary outcomes [p<0.001].

A published retrospective analysis by Tzouis et al of 61 patients given tolvaptan for two days (from two NCL centres) demonstrated an increase in serum sodium from baseline by 9±3.9 mmol/l after 24 hours and by 11.4±5.6 mmol/l after 48 hours. 49 patients were reassessed at day 3 and day 5 after stopping the study drug; there was a mean change of -3.1±5.0 mmol/l after day 3 and -3.9±6.6 mmol/l after day 5. Evidence in the paediatric cohort was limited to case studies; two trials reported conducted by the manufacturer in the paediatric cohort were terminated early due to low recruitment.

In terms of safety, in the SALT studies the desirable rates of correction were exceeded during the first 24 hours in four patients (1.8%) treated with tolvaptan and in four patients who exceeded the predefined 'potentially clinically important' serum sodium concentration. In the retrospective data, 14 patients had over-correction of serum sodium. None of the patients from the SALT studies or the retrospective data who suffered overcorrection demonstrated neurological effects reflective of osmotic demyelination.

The application specifies tolvaptan will be used at doses of 7.5mg to 15mg for of 1 to 3 days only and should not be continued post-discharge. In terms of budget impact, tolvaptan at the proposed dose and duration may be cost-minimising compared to the existing treatment option, demeclocycline.

The Committee heard from Dr Menon that there is more than 10 years' experience of using tolvaptan in the inpatient setting at the applied-for dosage (or sometimes lower). From experience, it prevents the need for hypertonic saline (which requires administration via central line in the HDU setting), and the lower dosage has a lower risk of overcorrection. Tolvaptan would not be used in emergencies (such as hyponatraemia associated with neuropathic symptoms), in which case hypertonic saline is the best course of treatment. Dr Menon noted the absence of long-term data available for tolvaptan but acknowledged that given difficulties in monitoring it would be reserved for inpatient use only. Current use at NMUH is supported by a draft hyponatraemia guideline, outlining appropriate initiation criteria and dose restrictions. In order to avoid serum sodium levels reverting to baseline, fluid restriction is commenced upon discharge; this is usually effective in maintaining serum sodium levels post discharge.

In camera, the Committee were reassured from the data that tolvaptan was safe and effective for the treatment of hyponatraemia associated with SIADH in adult patients. There was some concern in ensuring tolvaptan would be prescribed within the appropriate initiation criteria and restrictions therefore the availability of guidance for Trusts wishing to use tolvaptan was requested. With reference to the paediatric cohort, the Committee noted the lack of data. The Committee agreed that the use in the adult population was justified, and requested for more information on proposed use and dosing in the paediatric cohort.

In summary, the Committee agreed to add tolvaptan to the NCL Joint Formulary for the treatment of hyponatraemia secondary to SIADH in adult patients; the Committee requested additional information on the paediatric cohort before a decision could be reached.

Decision: Approved in adult patients, conditional on Trusts incorporating into hyponatraemia guidance (to be reviewed and approved at Trust MMC/DTCs)
Prescribing: Secondary care
Tariff status: Not routinely commissioned
Funding: Trust
Primary and secondary care Fact sheet or shared care required: No
Action: JFC Support to liaise with interested paediatricians to determine proposed use of tolvaptan in the paediatric cohort. Trust to incorporate this recommendation into local hyponatraemia guidance.

8.3 EAMS: Avelumab for locally advanced or metastatic urothelial cancer (Applicant: Dr McGovern, UCLH)

The Committee considered an Early Access to Medicines Scheme (EAMS) for avelumab, anti-PD-L1 monoclonal antibody, proposed for monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.

JAVELIN bladder 100 was a Phase III, randomised, controlled, open-label study to compare the efficacy and safety of avelumab and best standard of care (BSC) versus BSC alone in patients with locally advanced or metastatic urothelial cancer with no radiological evidence of progression after first-line platinum-based chemotherapy (n=700). A planned interim analysis was performed after 324 events (76.2% data collection) in the overall population and 143 events (65.3% data collection) in the PD L1+ population. The primary endpoint, median overall survival assessed in all randomised patients and patients with PD-L1+ tumours, was significantly longer with avelumab and BSC compared to BSC alone in both cohorts; 21.4 months vs. 14.3 months in the overall population (HR: 0.69 [95% CI: 0.56 to 0.86]) and 'not reached' vs. 17.1 months in the PD-L1+ population (n=358; HR: 0.56 [95% CI: 0.40 to 0.79]). The secondary endpoint, progression-free survival based on blinded independent central review, was significantly shorter in the avelumab and BSC arm (3.7 months vs. 2.0 months HR: 0.62; 95% CI: 0.52, 0.75). The committee considered an improvement in OS to be more relevant than the non-significant difference in PFS. Based on unpublished

data, the MHRA concluded there was no evidence of a detrimental effect on bladder cancer symptoms, functioning, health status and HRQoL.

In terms of safety, the MHRA concluded that risks associated with avelumab are generally manageable and do not outweigh the benefits. The clinical safety data in patients with advanced UC were consistent with the known safety profile of avelumab.

The Committee heard from Dr McGovern that outcomes are poor for patients with advanced urothelial cancer and there are limited treatment options. Immunotherapy is a treatment option in the second line setting (NICE TA525 & NICE TA519) however, only 50% of patients are eligible to receive immunotherapy on progression, therefore use of avelumab in the maintenance setting enables more patients to receive treatment. JAVELIN reported a greater benefit in overall survival when immunotherapy was used for maintenance compared to studies of immunotherapy in the second-line treatment of advanced urothelial cancer. In terms of safety, immunotherapy is used in a number of cancers, therefore centres are familiar with the management of toxicity. Across NCL, 25 patients are estimated to be eligible for the EAMS.

In camera, the Committee agreed results from the Phase III interim analysis showed avelumab conferred greater benefits over existing management of advanced UC in NCL, and the clinically relevant benefit outweighed the associated risks. The pending NHSE specialised commissioning letter will outline which Trusts are commissioned for the EAMS and as part of access, Trusts are required complete a Blueteq form for each patient initiated on treatment.

In summary, the Committee agreed to add avelumab EAMS to the NCL Joint Formulary for first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.

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

9. NHSE Lipid Management and Statin Intolerance Pathway

RMOC have requested feedback from Area Prescribing Committees on local adoption of NHSE AAC Lipid Management and Statin Intolerance guidance. JFC Support has provided a response to RMOC following a recent discussion at the NCL Medicines Optimisation Committee. Any further comments should be sent to Ms Kassam.

10. Nivolumab compassionate access schemes

JFC support will work to resolve this item through a virtual consultation. The resulting action points will be communicated to the Committee.

11. Priadel® (lithium carbonate) discontinuation

JFC support will work to resolve this item through a virtual consultation. The resulting action points will be communicated to the Committee.

Post meeting note: The discontinuation of Priadel is being investigated by the Competition and Markets Authority. Essential Pharma has informed Department of Health and Social Care (DHSC) that it will continue to supply the drug to facilitate discussions on pricing, removing the immediate threat to patients.

12. Ustekinumab for ulcerative colitis

NICE TA633 recommends ustekinumab as a treatment option for moderately to severely active ulcerative colitis if patients are not suitable or have failed treatment with an anti-TNF. This treatment is commissioned, and the Blueteq form is available, in advance of an update to NCL high cost drug IBD pathway.

13. Gonadotropin releasing hormone analogues - Harmonising the delivery of hormone injections across NCL for men with prostate cancer (presented by Ms S Counter and Ms L McLaughlin, North London Partners; and Dr R Roy, RFL)

The Committee were given a presentation on the work being conducted by the STP to develop a single model of delivery for gonadotrophin releasing hormone (GnRH) analogue injections used to treat men with prostate cancer across NCL. There is currently variation in the choice of GnRH analogues used in NCL; an initial scoping exercise concluded that the preferred option is triptorelin due to the flexibility in injection frequency (three-monthly and six-monthly options) and administration via the less invasive intramuscular route, though noted there may be a need for additional training for safe and effective administration. The Committee were appraised on the progress of this project to date. The commitee agreed in principle to the preferred drug and frequency proposal, which will be used to finalise cost and activity implications for harmonising the delivery of hormone injections across NCL for men with prostate cancer.

The Committee were supportive of the work being undertaken to standardise the delivery of hormone injections across NCL, and agreed that triptorelin should be used for further modelling to support standardisation. Beyond the injection itself, the Committee recommended that the project group undertake an engagement session with GP practice nurses and pharmacists to better understand capacity and practicalities with the proposed model.

14. Risk of aneurysm and artery dissection with systemically administered VEGF Inhibitors and fluoroquinolones

The NCL position statement on the safe prescribing of fluoroquinolones has been updated to include systematically administered VEGF inhibitors as an additional risk factor for aortic aneurysm and artery dissection. The minor update to the position statement was approved.

15. Updated memo: Use of corticosteroids for COVID-19

At the June JFC meeting, the UCLH memo on dexamethasone use in COVID-19 patients was presented and it was shared with other NCL Trusts for local adaptation. The UCLH formulary team have updated the memo following the recent CMO letter and a meta-analysis on the use of systemic corticosteroid therapy. This item has been circulated to NCL Trusts.

16. Next meeting: Thursday 15th October 2020

17. Any other business

Nil