NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 24th October 2013

In Wilkins Garden Room, Gower St, WC1E 6BT

1. Present:	Prof R MacAllister	NCL JFC Chair
	Dr D Bavin	Camden CCG
	Dr A Tufail	MEH DTC Chair
	Mr A Dutt	NHS Islington, Head of Medicines Management
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management
	Dr M Kelsey	Whittington DTC Chair
	Dr R Urquhart	UCLH Chief Pharmacist
	Ms J Cope	GOSH Chief Pharmacist
	Ms W Spicer	RFH Chief Pharmacist
	Mr T James	MEH Chief Pharmacist
	Ms S Drayan	NMUH Chief Pharmacist
	Dr H Taylor	WH Chief Pharmacist
	Dr R Sofat	UCLH Clinical Pharmacologist
	Mr A Shah	RNOH Chief Pharmacist
	Dr R Fox	RNOH DTC Chair
	Ms P Taylor	NHS Haringey Head of Medicines Management
	Dr C Cooper	Islington CCG
	Dr C Stavrianakis	Haringey CCG
	Ms L Reeves	C&I Mental Health Trust
	Dr R Kapoor	UCLH Neurologist
	Dr J Hurst	Consultant Chest Physician, RFH
	Ms R Dallmeyer	CSU Pharmacist
In attendance:	Dr A Grosso	UCLP Pharmacist
	Ms K Chapman	JFC Support Pharmacist
	Ms S Sanghvi	UCLH Pharmacist
	Ms R Holland	UCLH Pharmacist
	Mr K Thakrar	UCLH Pharmacist
	Dr J Fullerton	UCLH SpR
	Ms I Samuels	RFH Pharmacist
	Mr E Hindle	MEH Pharmacist
	Mr S Patel	UCLH Pharmacist
	Ms L Luk	BCF Pharmacist
Apologies:	Prof L Smeeth	NCL JFC Vice Chair
	Dr A Jones	Consultant Oncologist, UCLH &RFH
	Dr L Wagman	Barnett CCG
	Dr E Boleti	Consultant Oncologist, RFH
	Dr R Breckenridge	UCLH UMC Chair
	Mr A Karr	NCL Procurement Chair

2. Minutes of the last meeting

The minutes were accepted as accurate except it was noted that Dr Hurst is not the chair of the RFH DTC.

3. Matters arising

There were no matters arising not included as an agenda item.

4. Members & applicants declarations of relevant conflicts of interest

Dr J Hurst declared honoraria/sponsorship from Almirall and BoehringerIngleheim.

5. Appeal

5.1 Aclidinium Inhaler (EkliraGenuair®; Almirall) for COPD (Applicant: Dr A Husain/Prof Wedzicha; Presentation: Ms L Luk)

The Committee considered a formal appeal against the May 2013 decision to not include the twice daily antimuscarinic, aclidinium, onto the joint formulary for COPD. The applicants based their appeal on:

1. New evidence showing longer term safety data (12 months).
2. Published data on non-inferiority to tiotropium in a 6-week study.
3. Data that detailed greater patient acceptability with the aclidinium inhaler device compared with the tiotropium handihaler was also presented. Fewer critical errors of administration were noted with the aclidinium inhaler compared to the tiotropium the handihaler.
4. The applicants also disagreed with the Committee's suggestion of inhaled metered-dose ipratropium as a suitable alternative to tiotropium in patients with dexterity issues or not tolerating anti-cholinergic side effects, quoting NICE guidance.

The appeal letter stated that patients with dexterity problems and those suffering from anti-cholinergic side effects whilst using tiotropium may benefit from the availability of aclidinium inhaler. The Committee viewed placebo devices for each product and considered their ease of use.

Professor MacAllister made the following points.

1. The 12-month safety data were dominated by the additional reassurance from 12 years of use of tiotropium.
2. There was no suggestion from the 6-week study of improved tolerability of aclidinium compared to tiotropium. The drugs have a similar anti-cholinergic adverse effect profile. It seemed very unlikely that aclidinium would be worth using in patients with anti-cholinergic adverse effects on tiotropium. Anti-cholinergic adverse effects occurring on tiotropium should discourage use of aclidinium. Ipratropium would be a safer option.
3. Despite the data indicating more critical errors of administration with the aclidinium inhaler, the 6-week study showed the two inhalers were equi-effective, which was reassuring that the critical mistakes were not especially critical.
4. NICE guidance (2010) states that patients should be offered a once daily long-acting anti-cholinergic. Aclidinium is twice daily.

After reviewing these arguments, the Committee members voted and it was unanimously agreed that the newly published evidence was insufficient to warrant a change to the previous decision.

6. CCG-related medicine applications & reviews

6.1 Overactive bladder treatment (No applicant; Presentation: Dr A Grosso)

The Committee considered a draft document clarifying the place in therapy of medications for over active bladder syndrome. The Committee suggested some minor changes, and it was agreed that an amended draft should be added to the JFC website for further stakeholder comment. It was also suggested that this consultation be extended to a Neuro-urology services for specialist input.

6.2 Eltrombopag (Refolade; GSK) and Romiplostim (Nplate; Amgen) for refractory chronic immune [idiopathic] thrombocytopenic purpura (ITP) in splenectomised patients (No applicant; Presentation: Mr K Thakrar)

The Committee considered a review of the place in therapy of thrombopoietin receptor (TPO-R) agonists for the treatment of chronic immune thrombocytopenic purpura (ITP). The Committee heard that NICE have recommended romiplostim (TA 221) and eltrombopag (NICE TA 293) as options for

treating adult patients with chronic immune ITP who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in patients who have not had a splenectomy because surgery is contra-indicated only if:

- Their condition is refractory to standard active treatments and rescue therapies, **or**
- They have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies
- **AND** the manufacturers provide eltrombopag and romiplostim with the discount agreed in the patient access scheme.

The Committee noted that these two agents were considered separately under the single Technology Appraisal programme by two different appraisal committees. Eltrombopag was originally reviewed by NICE in October 2010 where it was not recommended for the treatment of ITP on the basis of cost (cost per QALY > £30,000), however NICE reversed its decision in July 2013 after re-submission with a discount.

The Committee heard that there are no head-to-head trials comparing eltrombopag and romiplostim. NICE performed an exploratory indirect comparison between eltrombopag and romiplostim for the outcomes of durable response, overall response, and for clinically significant and moderate bleeds. NICE concluded that there was no statistically significant difference between the two agents for durable response and bleeds; however the results were in favour of romiplostim for overall response (OR 0.15; 95% CI 0.02 to 0.84). Regardless, the results should be interpreted with caution due to the uncertainties around the point estimates and high degree of heterogeneity.

With particular reference to the paediatric population, the Committee heard that evidence for romiplostimis limited to two small studies. Efficacy of eltrombopag in paediatric ITP is limited to a single case study only; however a phase II study is due to complete in April 2014.

With regard to safety, the type and incidence of adverse effects were similar in the active and placebo arms for both eltrombopag and romiplostim with the exception of hepatobiliary disorders [reversible] which was more common in patients taking eltrombopag. Due to the mechanism of action of these agents, there is an increase in the risk of thromboembolic events. The EXTEND study (2 year extension study investigating the efficacy and safety of eltrombopag) has estimated this to be approximately 3.17 per 100 patient years (95% CI 1.81 to 5.15). Paradoxically, the incidence of on-treatment serious bleeding was greater for patients taking eltrombopag compared with placebo (7% vs. <1%; p=0.03); the data for romiplostim were 12% vs. 7%, respectively. The incidence of post-treatment serious bleeding was 2% vs. 1% for eltrombopag vs. placebo, respectively. The Kuter et al studies did not report a similar analysis for romiplostim to allow for a comparison. An indirect comparison between eltrombopag and romiplostim showed no statistically significant difference between the two.

Eltrombopag is administrated orally and should be taken at least four hours before or after any products containing antacid or dairy products. Romiplostim is administered as a weekly subcutaneous injection.

The Committee agreed that eltrombopag and romiplostim appear broadly equivalent in terms of efficacy and safety for the treatment of ITP. They have both been recommended by NICE under separate TA's as an option for the treatment of ITP in adults in line with their marketing authorisation. On this basis, it was suggest that choice of TPO-R agonists be based on cost and restricted to 3rd line treatment in patients refractory to standard therapy, including rituximab. The increased incidence of bleeding on both agents was a concern, and consistent with the drugs stimulating an increase in platelet number without necessarily increasing platelet function.

With regards to paediatrics, romiplostim currently has the greatest level of supporting data. GOSH specialists prescribe this in acutely bleeding patients and the Committee asked for further information

on the use of TPO-R agents for this indication. Specifically, how quickly does the platelet count rise, and whether the increase in bleeding risk was a concern in this setting?

6.3 Rituximab (MabThera; Roche) for Neuromyelitisoptica (NMO) (Applicant: Dr S Leary; Presentation: Ms K Chapman)

The Committee considered an application for rituximab to be used for the prevention of relapse of neuromyelitisoptica (NMO) and NMO spectrum disorders (NMOSD). Neuromyelitisoptica (NMO) is a relapsing demyelinating disorder affecting the optic nerves and spinal cord and is associated with a high early morbidity and mortality rate. Studies report death in 25-30% of patients, after a mean of 5 years from onset. About half of patients develop significant walking difficulties and many patients become wheelchair-dependent. Visual impairment is also common, with blindness affecting at least one eye in about 60-70% of patients. This formulary request was for the use of rituximab as per the nationally agreed treatment algorithm for NMO.

The Committee considered a retrospective analysis of 25 patients with NMO treated with rituximab by Jacob *et al*in which two rituximab regimens were used. The first was a dose of 375m^2 infused once weekly for 4 weeks (n=18) and a second regime of 1000mg infused twice, with a 2-week interval between the infusions (n=4). 70% of these patients (14 of 20) were positive for NMO-IgG. The median annualised pre-treatment relapse rate was 1.7(range 0-3.2) which dropped to zero relapses (range 0-3.2) at a median follow up of 19 months. EDSS improved significantly in 11 patients, did not change in 9, and worsened in 5 patients, of whom two died.

An earlier open-label study by Cree *et al* evaluated eight patients with NMO who had failed other therapeutic regimens and were treated with rituximab (four infusions of 375mg/m^2 once per week). Mean follow-up time was 12 months, and 6 of 8 patients remained relapse-free. B-cell counts were evaluated bi-monthly, and patients were given the option to be retreated with rituximab when B-cell counts became detectable (two infusions of rituximab 1000mg, 2 weeks apart). Seven out of 8 of these patients went on to participate in the *Jacob et al* retrospective analysis.

More recently *Bedi et al*have conducted a retrospective study to evaluate the impact of rituximab on the relapse rate and disability in NMO. Of the 23 patients who had been treated with rituximab, 8 were treatment naïve. All 23 were scheduled to receive infusions every six or 12 months after treatment initiation with a minimum follow-up of six months (median 32.5 months, range 7-63 months). Azathioprine was stopped with the first dose of rituximab but steroids were tapered over one month after the second dose of rituximab. All acute attacks were treated with 1g methylprednisolone IV over 10 days.

Median relapse rate declined significantly from 2 relapses per patient per year to less than one relapse per patient per year. Of the 23, 17 patients remained relapse free and 6 had one relapse each and these appeared to be less severe than exacerbations before rituximab treatment. EDSS scores stabilised or improved in all patients (even those that relapsed). Median EDSS values before (7.0; range 3-9) and after treatment (5.5; range 0-8) were significantly different ($p<0.02$). A change in disability of ≥1.0 change in EDSS was considered to be meaningful for individual patients.

With regard to safety, a 2005 report on rituximab used in patients with cancer and rheumatoid arthritis concluded that overall usage is safe. Infusion related reactions were reported in 84% and included nausea, headache, fatigue, rash, flu-like symptoms. The incidence of these symptoms is highest after the first infusion and decreases with repeat administration. Infections are reported in 30% of rituximab-treated patients but only about 1-2% acquires severe infections.

The Committee heard that 8 patients have been treated at UCLH with rituximab to date. All patients have been relapse-free since starting treatment, and in 3, steroid reduction has been possible. The regime used is 2 injections every 6 months.

The NHS National Specialised Commissioning Team in the UK has acknowledged NMO as a rare neurological condition that requires specialist expertise and has funded The Walton Centre in Liverpool, and John Radcliffe Hospital at Oxford. It was not clear how this treatment will be funded

outside these centres. The Committee therefore requested that the applicants clarify the funding arrangements for potential use outside of these centres.

The Committee agreed that this is a safe and effective treatment for this highly debilitating condition and therefore decided to add rituximab onto the formulary for NMO and NMOSD, pending satisfactory clarification of funding/shared care pathways.

7. Non-CCG related medicine reviews

7.1 Epoetin (Binocrit; Sandoz) for anaemia in patients treated for hepatitis C virus (Applicant: Dr D Suri; Presentation: Ms S Sanghvi)

The Committee considered an application for epoetin in anaemic patients being treated with pegylated interferon and ribavirin (with or without boceprevir or telaprevir) for hepatitis C viral (HCV) infection. The Committee heard that anaemia is a common side effect of this treatment and the current alternative is to reduce the dose of ribavirin (RBV), which has been shown to decrease sustained viral response (SVR).

The Committee reviewed a study by Afdhal *et al* who conducted a RCT with the aim of assessing whether epoetin alfa could maintain RBV dose, improve quality of life and increase haemoglobin in anaemic HCV-infected patients. Patients infected with HCV on combination therapy who developed anaemia (Hb≤12 g/dL) were randomised to receive either 40,000 units of epoetin alfa once weekly (n=93) or placebo (n=92). After the initial 8 weeks participants began an 8 week open-label phase in which placebo patients were crossed over to receive epoetin alfa. The RBV dose could be reduced when Hb decreased to <10g/dL or when clinically indicated, at the discretion of the investigator.

At the end of 8 weeks, RBV doses were maintained in 88% of patients receiving epoetin alfa versus 60% of patients receiving placebo (P<0.001). Mean Hb increased by 2.2±1.3g/dL (epoetin alfa) and by 0.1±1.0g/dL (placebo) (P<0.001). Similar results were demonstrated in patients who switched from placebo to epoetin alfa in the final 8 weeks of the study.

The majority of patients in each group were infected with HCV genotype 1 and 64% were naïve to HCV treatment. At randomisation, patients in the epoetin alpha and placebo groups had been on HCV therapy for an average of 12 and 14 weeks, respectively, prior to receiving the first dose of study drug. Results of additional analyses showed that epoetin alfa was similarly effective in patients of different weights and RBV doses.

The Committee also heard that *Dieterich et al* randomised 64 HCV-infected patients with Hb levels of 12g/dL or less during the first 24 weeks of combination RBV/IFN therapy to receive either epoetin alfa (40,000 units) weekly or standard of care (RBV dose reduction or discontinuation/transfusions). Using an intention-to-treat analysis, the mean changes from baseline Hb levels at week 16 were +2.8 g/dl for epoetin alfa versus +0.4g/dl for standard of care (p<0.0001). Mean changes in RBV dosage were -34mg/day for epoetin alfa versus -146mg/day (p=0.060) for standard of care. At study end, 83% of epoetin alpha-treated patients maintained RBV dosages of at least 800mg/day, compared with 54% of patients receiving standard of care (p=0.022).

With regard to viral response, *Bertino et al* investigated whether epoetin alpha administration improves treatment adherence and SVR. 214 individuals underwent treatment with peg-interferon alpha-2A 190ug once weekly and ribavirin 1000-1200mg/day. Of the 174 responders, 40 completed treatment without any reduction in Hb levels and 34 developed anaemia during therapy. Anaemic responders were randomised to receive either continued therapy with the addition of epoetin alpha 10000IU twice weekly, or ribavirin dose reduction to 800-1000mg/day. Those who stayed on the initial dose but added epoetin alpha achieved higher Hb levels at end of therapy (13.8±1.2g/dl)than those who reduced ribavirin dose (11.5±0.8g/dl). Importantly, SVR was achieved by 59.7% in group 1 compared with 34.4% in group 2 (p<0.01). 60% of patients who did not develop anaemia (control) achieved SVR.

Both Afdhal *et al and* Dieterich *et al* reported that epoetin alfa was well tolerated; the most common adverse effects were headache and nausea.

The Committee agreed that introducing a once weekly injection of epoetin can increase Hb levels in anaemic patients, allowing the dosing regime to continue unaltered. The least expensive formulation was recommended for formulary inclusion. The applicants specifically recommended the use of epoetin for patients with Hb levels ≤10g/dL, rather than ≤12g/dL as used in the literature.

8. Local DTC Recommendations

8.1 NMUH: N-butyl-2-cyanoactylate (Histoacryl Glue) for upper gastrointestinal bleeding secondary to gastric varices.

In the absence of local minutes, the ratification of Histoacryl Glue was deferred.

8.2 UCLH: Triptorelin for preservation of ovary function.

In the absence of local minutes, the ratification of triptorelin was deferred.

9. Documenting informed consent

Ms J Cope asked the Committee to consider whether specific informed consent was required prior to treatment with other high risk agents such as biologics as is currently the case with chemotherapy. The Committee agreed that this is for local decision and implementation and that an NCL policy was not appropriate.

10. Date of next meeting: 21st November 2013 (location TBC).

11. Any other Business

11.1 Thickeners

The Committee agreed that RFH will review the available thickening agents, and then bring any recommendations to a future meeting.