NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 27th February 2014

In Chadwick G08, Gower street, Gower St, UCL

1. Present:	Prof R MacAllister	NCL JFC Chair
	Dr R Urquhart	UCLH Chief Pharmacist
	Mr A Shah	RNOH Chief Pharmacist
	Dr D Bavin	Camden CCG
	Mr A Dutt	NHS Islington, Head of Medicines Management
	Ms N Shah	NHS Camden, Head of Medicines Management
	Mr C Daff	NHS Barnet, Head of Medicines Management
	Mr T James	MEH Chief Pharmacist
	Ms P Taylor	NHS Haringey Head of Medicines Management
	Ms L Reeves	C&I Mental Health Trust
	Dr E Boleti	Consultant Oncologist, RFH
	Dr J Hurst	Consultant Chest Physician, RFH
	Dr R Breckenridge	UCLH UMC Chair
In attendance:	Dr J Fullerton	Specialist Registrar Clinical Pharmacology
	Ms S Sanghvi	UCLH Pharmacist
	Mr K Thakrar	UCLH Pharmacist
	Ms I Samuels	RFH Pharmacist
	Mr E Hindle	MEH Pharmacist
	Ms A Moore	UCLH Pharmacist
	Mr M Wyke-Joseph	NMUH Pharmacist
	Ms Y Hossenbaccus	NHS Camden Prescribing Advisor
	Mr M Hamilton-Farrell	Co-Chair, NEL Medicine Management Network
	Mr N Marshall	RFH Pharmacist
	Dr Amr Hussain	Senior Fellow Andrology
Apologies:	Ms W Spicer	RFH Chief Pharmacist
	Dr R Fox	RNOH DTC Chair
	Dr A Jones	Consultant Oncologist, UCLH & RFH
	Dr L Wagman	Barnet CCG
	Mr A Karr	NCL Procurement Chair
	Dr A Grosso	UCLP Pharmacist
	Dr M Kelsey	Whittington DTC Chair
	Dr H Taylor	WH Chief Pharmacist
	Dr R Sofat	Consultant Clinical Pharmacologist, UCLH
	Dr R Kapoor	Consultant Neurologist, UCLH
	Dr A Tufail	MEH DTC Chair
	Ms S Drayan	NMUH Chief Pharmacist
	Prof L Smeeth	NCL JFC Vice Chair
	Dr C Cooper	Islington CCG
	Dr C Stavrianakis	Haringey CCG
	Mr TF Chan	BCF Chief Pharmacist
	Ms J Cope	GOSH Chief Pharmacist
	Ms R Dallmeyer	CSU Pharmacist
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management

2. Minutes of the last meeting

Point 3.2: The Committee were informed that the EMA now recommend that strontium (Protelos®) will not be fully withdrawn and should remain available with further restrictions applied to its use. Strontium can be considered for patients who cannot be treated with other medicines approved for osteoporosis, provided patients receive regular cardiovascular assessments. Patients with a history of certain heart or circulatory problems, such as stroke and myocardial infarction are contra-indicated. It was agreed that strontium would remain on the NCL formulary under these strict criteria.

Point 3.3: It was agreed that the updated LMWH guidance should be circulated via the JFC website.

Point 5.1: Ms Samuels informed the Committee that the application for dolutegravir applied to 3 patients at RFH who were receiving compassionate use under exceptional circumstances, and not just to a single patient. This was approved by the Committee.

Point 5.4: Ms Dallmeyer highlighted that she is unable to personally change London wide tickboxes but will raise the concerns of the Committee with the group that reviews the London wide tickbox for dose escalation in Crohn's disease and confirm the source of the time restriction to 12 weeks.

3. Matters arising

3.1 Overactive Bladder Syndrome Prescribing Guidance

The Committee were informed that Dr R Breckenridge and Dr A Grosso are meeting Mr Dan Wood to discuss the OAB prescribing guidance. They will feed back comments at the next meeting.

4. Members declarations of relevant conflicts of interest

None were declared.

5. CCG-Related Medicine Applications and Reviews

5.1 Dapoxetine (Priligy®) for premature ejaculation (Applicants: Dr D Ralph/ Dr A Husain/ Dr M King, Presentation: Ms L Reeves)

The Committee reviewed an application for the use of dapoxetine for the treatment of premature ejaculation (PE). The Committee were informed that dapoxetine is the first oral treatment licensed for PE. Dapoxetine is a short-acting selective serotonin reuptake inhibitor (SSRI) which is used when required 1-3 hours prior to sexual intercourse.

The Committee reviewed the following phase III placebo-controlled trials:

- **Study NCT00229073 (n = 1162; 24 weeks duration)** showed that the primary endpoint of Intravaginal Ejaculation Latency Time (IELT) at week 24 was increased in the dapoxetine arm 3.1 minutes (30mg) and 3.5 minutes (60mg) versus 1.9 minutes in the placebo arm ($p<0.001$).
- **Study NCT00210704 (n = 1067; 12 weeks duration, Asia-Pacific study)** showed that the primary endpoint of mean IELT at 12 weeks increased with dapoxetine in comparison to placebo; 3.9 minutes for 30mg and 4.2 minutes for 60mg versus 2.4 minutes for placebo; $p<0.001$.
- **Studies NCT00211107 and NCT00211094** (**integrated analysis, n = 2614; 12 weeks duration)** showed that the primary end point on mean IELT at week 12 was similarly increased with dapoxetine treatment in comparison to placebo; 2.78 minutes for 30mg and 3.32 minutes for 60mg versus 1.75 minutes for placebo; $p<0.001$.

The Committee heard that first line treatment includes barrier methods or anaesthetic cream. Thereafter, other SSRIs including paroxetine and fluoxetine are widely used off-label for this indication. Continual dosing is usually recommended for these SSRIs due to the long onset of action, although Dr Husain agreed that in

practice, paroxetine is also used on demand 3 to 4 hours prior to intercourse. There are a number of clinical trials that confirm the efficacy of on-demand SSRIs with a longer duration of action.

The Committee noted the lack of comparative data against current SSRIs to confirm any theoretical advantages of dapoxetine. Moreover, dapoxetine administration could not be repeated again until 24 hours had elapsed, and this was a theoretical disadvantage compared to other SSRIs with a longer duration of action. In addition, the trials were compared against placebo and not against standard of care i.e. barrier methods or EMLA.

The Committee also noted that dapoxetine has a higher incidence of syncope associated with its use, and that patients require screening for postural hypotension prior to initiation, something that is not required when using alternative SSRIs. In terms of cost-effectiveness, monthly cost for dapoxetine would be £320-£400 (based on six attempts a month) compared to £12 - £36 for fluoxetine (if taken daily) and £0.40 for paroxetine (based on six attempts a month). The difference could be potentially greater as a frequency of six attempts a month was classified as low.

The Committee discussed whether dapoxetine should be used in preference to other SSRIs because it alone had a marketing authorisation for premature ejaculation. In the end the Committee considered that longer acting SSRIs were also licenced products, and similar to dapoxetine, inhibited serotonin reuptake to achieve a pharmacological effect. The difference was that it would not be legal for the manufacturers to market these SSRIs for premature ejaculation. In addition, the Clinical Commissioning Group members agreed that the off-label prescribing of paroxetine or fluoxetine would be supported in primary care. There was no proven benefit of dapoxetine over the older SSRI's such as fluoxetine and paroxetine and a greater risk of toxicity relating to syncope. Based on the lack of data to suggest a real advantage over more cost-effective therapies the Committee recommended that dapoxetine should NOT be included on the formulary.

5.2 Pentoxifylline for Peyronie's disease (Applicant: Dr D Ralph/Dr A Husain; Presentation: Dr J Fullerton)

The Committee reviewed an application for the use of pentoxifylline for Peyronie's disease (PD). The Committee were informed that the European association of Urology (EAU) recommend oral treatment with para amino benzoate (PAB) for the treatment of PD, and recommends against the use of pentoxifylline. The Committee noted that the EAU (define) guidelines (2012) did not include the RCT conducted by Safarinejad et al (2009).

The Committee reviewed this study by Safarinejad et al which was a randomised, double-blinded, placebo-controlled study in 228 patients conducted to evaluate the safety and efficacy of pentoxifylline in patients with early chronic PD (≥ 12months) and erectile dysfunction (defined by an erectile function domain score of the International Index of Erectile Function (IIEF) of <26). Patients were randomised to receive pentoxifylline 400mg twice daily or placebo. The primary endpoints were the improvement in erectile dysfunction, penile curvature, plaque size and pain. Secondary endpoints included mean number of sexual attempts per week and treatment satisfaction.

The results showed pentoxifylline significantly reduced mean plaque area and penile deviation compared to placebo, with a positive response (defined as an objective improvement in plaque size and penile curvature) observed in 36.9% of patients in the pentoxifylline group versus 4.5% in the placebo group. Of patients in the pentoxifylline group, 12 (10.8%) experienced disease progression compared to 46 (41.8%) in the placebo group (P=0.01). The mean curvature also improved with pentoxifylline therapy with absolute difference in comparison to placebo of 5 ^{o} (ventral), 40 ^{o}; (dorsal), and 22^{o} (lateral). In term of plaque surface area, the absolute difference between the two treatments was 10mm^{2} in favour of pentoxifylline (-4mm versus +6mm, respectively). The difference in erectile dysfunction domain was 5.1 points which is greater than the minimal clinically important difference of 4 points. There was no difference in orgasmic function and sexual desire, as well as no difference in terms of pain during erection between the two treatments.

The Committee questioned the decision by the EAU not to include this trial in their recommendations. The Committee were further informed that the author Safarinejad et al has had 3 clinical studies retracted in the last 3 years. It was unusual for an investigator to have so many papers retracted, and taken with the position of the EAU, these observations cast doubt on the credibility of the results of this trial.

The Committee further reviewed the retrospective study by Smith et al. (n = 71) that showed men taking pentoxifylline were more likely to have an improvement in their calcification relative to men who did not take

pentoxifylline (69.4% vs. 33.3%, P=0.03). Furthermore, men taking pentoxifylline were more likely to have stabilisation (that is, no change) or improvement in their calcium burden relative to men not taking pentoxifylline (91.9% vs. 44.4%, P<0.001). The Committee noted the various limitations to the study in trial design, sample size, and objective measurements.

In terms of safety, pentoxifylline is generally well tolerated. Common adverse events reported in the Safarinejad et al. trial were nausea, vomiting, dyspepsia. Hypotension has also been reported as a result of its vasodilator effects.

Dr Husain explained that first line treatment for PD is surgery. Pentoxifylline is used in the acute phase of the disease for 6 months to stabilise the disease and alleviate the curvature, thus reducing the risk and complications associated with surgery.

It is anticipated that pentoxifylline would be used in 100 patients across NCL, with an annual cost per patient of approximately £155. The Committee were informed that the annual cost per patient for PAB would be £988.

The Committee discussed the basis for exclusion from the EAU guidelines. The Committee agreed to write to the EAU guideline to establish the reasoning behind exclusion of the study and pentoxifylline from the guideline. The Committee deferred deferred the decision regarding pentoxifylline to next month pending this information.

5.3 Lisdexamfetamine for attention deficit hyperactive disorder (Applicant: Dr Paschos; Presentation: K Thakrar)

The Committee reviewed an application form for the inclusion of lisdexamphetamine (LDX) for attention deficit hyperactive disorder (ADHD). The Committee were informed that LDX is a pro-drug of dexamphetamine and not a new chemical entity, with the advantage of once daily dosing.

NICE guidance recommends that methylphenidate should be used first line, with atomoxetine or dexamfetamine as second line options if the patient does not respond to methylphenidate or is intolerant to it after an adequate trial. The Committee reviewed five randomised, double-blinded, placebo-controlled trials of LDX in adolescents and children. The primary endpoint of ADHD Rating Scale was 40 units on average at baseline and decreased to 20 units with LDX versus only 5 units with placebo. The Committee were informed that all the trials were of reasonable internal validity, however trial durations were relatively short (7 weeks). The Committee questioned the eligibility criteria, which included only drug naïve patients in the studies despite the fact that LDX would be used in methylphenidate non-responders. The efficacy as a second line option in this patient group therefore remains unknown. The Committee were also informed of a direct comparison with atomoxetine which favoured LDX, however, this was a single study which again excluded non - responders and was only 9 weeks long. The efficacy in adults has been evaluated in four studies; however the license appears to require initial dosing to occur before 18.

In terms of safety, the adverse event profiles for LDX and dexamphetamine are similar. In terms of convenience, LDX has the advantage of once-daily administration compared to dexamphetamine. NICE guidance stressed the importance of once daily dosing and avoiding dosing at school due to the stigma associated with the condition.

In terms of cost, LDX is currently the more cost effective treatment in comparison to dexamphetamine (£96 vs £71), but there was some uncertainty about this.

The Committee discussed the use of LDX in a cohort of patients where the evidence is limited (i.e. methylphenidate non responders), however also acknowledged that LDX is pharmacologically the same agent as dexamphetamine. Based on frequent changes in prices for the agents the Committee agreed to defer the decision pending further comparison of cost-effectiveness.

5.4 Stribild for HIV infection (Applicant: Dr M Johnson; Presentation: I Samuels)

The Committee reviewed an application form for the inclusion of a Stribild into the formulary for the following patients:

- In ARV experienced patients with no prior history of virological failure or drug resistance, and who require a switch from their current regimen where there is a clinical advantage of Stribild over alternative switch options and where the use of the individual components is not contraindicated or
- In ARV-naïve patients with high viral loads who are not suitable for NNRTIs (or others on NNRTI who need to switch for reasons unrelated to resistance) AND
- Where the decision to prescribe Stribild has been taken after review in a Multidisciplinary HIV specialist treatment meeting and that this will be subject to clinical and commissioner audit, AND
- Where Stribild prescribing is no greater than 5% of the patients in a clinical cohort on treatment.

The Committee were informed that Stribild contains three antiretrovirals, elvitegravir, emtricitabine and tenofovir, and a booster, cobicistat. Stribild is the first single-tablet regimen to combine a once-daily integrase inhibitor (elvitegravir) which is boosted by a first-in-class pharmacoenhancer (cobicistat), plus a preferred backbone of emtricitabine and tenofovir.

The Committee reviewed two studies assessing the efficacy and safety of Stribild compared with Atripla (GS-102, n=700) and with atazanavir/ritonavir plus emtricitabine and tenofovir (GS-103, n=708) in treatment naïve patients. The primary endpoint of both studies was the proportion of patients with viral suppression (HIV RNA <50 copies/mL) at week 48. The Committee noted that the proportion of patients with HIV RNA <50 copies/mL was higher in the Stribild group up to week 16 in both studies, after which response rates between the two groups did not differ substantially In addition, few patients developed integrase resistance mutations.

The Committee further reviewed two studies assessing outcomes of switching to Stribild from Truvada/raltegravir (GS-123, n=48) and a pharmacokinetic analysis assessing switching from Atripla (tenofovir/emtricitabine/efavirenz) (Ramanathan S et al, n=32), which showed all patients maintained VL<50c/ml at 12 weeks (primary endpoint)

In terms of safety, the majority of adverse effects were mild, with diarrhoea and nausea being the most common side effects. Cobicistat is a potent inhibitor of CYP3A and can also inhibit the transporter p-glycoprotein as well as the cationic renal transport pathway for creatinine.

Stribild is taken once daily with food, although there are no specific food requirements. In addition, Stribild is a single tablet regimen which reduces the chance of unintentional or selective adherence.

The Committee were informed that the cost of Stribild is similar to the individual agents as well as the cost of the alternative regimens. As a result, the Committee agreed to recommend inclusion of Stribild into the formulary in line with the NHS England recommendations.

6. Subcutaneous Trastuzumab

In view of the NHS England recommendation, the Committee agreed to include the subcutaneous trastuzumab preparation onto the NCL formulary.

7. Local DTC recommendations

7.1. Histoacryl Glue for upper gastrointestinal bleeding secondary to gastric varices: Approved at North Middlesex hospital. This decision was ratified by the JFC.

7.2 Bifidobacterium Lactix prophylaxis against necrotising enterocolitis in high risk neonates: Approved at UCLH. This decision was ratified by the JFC.

8. Terms of reference (NHSE-commissioned medicines, CCG commissioning cycles, NELMMN

This was deferred to the next meeting

9. Membership

This was deferred to the next meeting.

10. DTC appeal process

The Committee agreed that first appeals from local hospital DTC's can be heard locally at the DTC, and that the second appeal should be referred to the JFC.

11. Any other business

Nil.