NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 25st September 2014

Chadwick Building, Room G07, Gower Street, UCL

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Prof L Smeeth	NCL JFC Vice-Chair	
	Dr M Kelsey	Whittington DTC Chair	
	Dr R Urquhart	UCLH Chief Pharmacist	
	Mr A Dutt	NHS Islington, Head of Medicines Management	
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management	
	Ms E Mortty	NHS Haringey Deputy Head of Medicines Management	
	Dr R Sofat	Consultant Clinical Pharmacologist, UCLH	
	Dr J Hurst	Consultant Chest Physician, RFH	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Dr E Boleti	Consultant Oncologist, RFH	
	Mr T James	MEH Chief Pharmacist	
	Ms W Spicer	RFH Chief Pharmacist	
	Dr H Taylor	Whittington Chief Pharmacist	
	Mr A Shah	RNOH Chief Pharmacist	
In attendance:	Dr F Bennett	Clinical Pharmacology Registrar, UCLH	
	Mr E Hindle	MEH Pharmacist	
	Ms I Samuel	Pharmacist, RFH	
	Dr R Stratton	Consultant Rheumatologist, RFH	
	Dr E Chung	Consultant Child & Adolescent Psychiatrist, RFH	
	Dr E Seaton	Consultant Dermatologist, RFH	
	Mr K Thakrar	Pharmacist, UCLH	
	Dr A Grosso	Pharmacist, NHNN	
	Ms S Sanghvi	Pharmacist, UCLH	
	Mr P Bodalia	Deputy Chief Pharmacist, RNOH	
Apologies:	Dr A Tufail	MEH DTC Chair	
	Dr R Breckenridge	UCLH UMC Chair	
	Ms N Shah	NHS Camden, Head of Medicines Management	
	Mr TF Chan	BCF Chief Pharmacist	
	Dr R Fox	DTC Chair, RNOH	
	Dr D Bavin	Camden CCG, GP	
	Dr C Stavrianakis	Haringey CCG	
	Dr L Wagman	Barnet CCG, GP	
	Ms R Dallmeyer	CSU Pharmacist	
	Ms S Drayan	NMUH Chief Pharmacist	
	Mr A Karr	NCL Procurement Consortia Chair	
	Dr P Ancliff	GOSH DTC Chair	
	Dr R Kapoor	Consultant Neurologist, UCLH	
	Ms P Taylor	NHS Haringey Head of Medicines Management	
	Ms J Cope	GOSH Chief Pharmacist	

2. Minutes of the last meeting

These were accepted as accurate.

3. Matters arising

3.1 Pregabalin for Neuropathic Pain

Mr Thakrar informed the Committee that discussions with pain specialists at UCLH have resulted in restriction of pregabalin use to approximately 7 pain consultants at UCLH under evaluation for 1 year. The audit results will be presented at the JFC after one year and local decisions regarding restricted use could be made at that point. Prof MacAllister reminded the Committee that pregabalin would be indicated under strict criteria for patients who fail amitriptyline and duloxetine and who have responded to gabapentin but not tolerated it due to off target adverse effects. Prof MacAllister added that he will be sending a response to the letter from Pfizer relating to the JFC decision on pregabalin. Mr Shah informed the Committee that pregabalin has been removed from the formulary at RNOH.

4. Declarations of relevant conflicts of interest

Dr E Seaton informed the Committee that he has been paid to provide lectures for Galderma relating to Mirvaso® gel.

5. New Medicine Reviews

5.1 Anakinra (Kineret; Swedish Orphan Biovitrum Ltd) for Gout (Applicant: Dr R Stratton; Presentation: Mr K Thakrar)

The Committee reviewed an application for the IL-1B antagonist anakinra for reversal of acute flares of gout (off-label). Anakinra 100mg on three consecutive days was proposed for use in hospitalised patients refractory to standard therapy including NSAIDs, colchicine and oral or intra-articular steroids.

There are no randomised controlled trials examining the efficacy of anakinra against placebo or active comparators. The Committee reviewed a multicentre retrospective study by Ottaviani et al of 40 patients with gout who had failed and/or for whom two conventional therapies were contraindicated. Of the 40 patients, 23 received anakinra 100mg s/c for 3 days, 7 received it for 3-15 days and 10 patients received it for over 15 days. Of the 23 patients who received anakinra for 3 days, 20 demonstrated good responses (defined as reduction in VAS pain score of >50%) by day 4 with mean values reducing from 73.5 (range 70-80) to 25 (range 20-32.5) ($p<0.0001$). There was also a reduction in mean CRP from 130 (range 55-238) to 16 (range 5-30) within 4 days ($p<0.0001$). After a median follow-up of 7 months (range 2-13), relapse occurred in 13 patients with a mean delay of 12 days.

The Committee further reviewed a second retrospective study by Ghosh et al of anakinra for acute gouty arthritis in 26 medically complex, hospitalised patients. The results showed 67% of patients had significant pain improvement within 24 hours and 72.5% of patients had complete resolution of any signs and symptoms of acute gout by day 5. Seven patients (27%) received multiple courses with no decrement in response with repeated treatments.

In terms of safety, the Committee heard that anakinra has been associated with a small increase in the incidence of serious infections (1.8%) vs placebo (0.7%) in patients with rheumatoid arthiritis (licensed indication). Neutropenia, lymphoma, transient elevation of liver enzymes and allergic reactions are other reported adverse effects of anakinra.

The cost of anakinra for a 3-day course would be approximately £95 and it is anticipated to be used in five patients per year at RFH.

The Committee agreed that there was a lack of robust evidence demonstrating efficacy of anakinra for gout but acknowledged the substantial treatment effect in the retrospective studies reviewed. The Committee questioned the treatment duration and retreatment approach if a patient relapsed. Dr Stratton reassured the Committee that anakinra would be reserved for use in hospitalised patients who have failed all other treatments including high dose steroids. Anakinra would be given for 3 days after which it would be stopped if ineffective. If patients responded to anakinra but relapsed after 1-2 months, a further course would be given. The Committee agreed that anakinra should be added to the NCL formulary, pending funding confirmation, restricted to use by Rheumatology consultants for patients who are hospitalised and refractory to all other treatments.

5.2 Florbetapir 18-F (Amyvid; Eli Lilly) for Alzheimer's Disease (Applicant: Dr T Wagner; Presentation: Dr F Bennett)

The Committee reviewed an application for 18F-florbetapir (Amyvid) Positron Emission Tomography (PET) imaging of ß-amyloid plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. The Committee heard that the cause of AD is unknown, but ß-amyloid plaques have been linked to the pathogenesis of AD. Currently the diagnosis of AD is based on internationally accepted and standardised clinical criteria, which carry a significant margin of error due to low sensitivity and specificity (approximately 81% and 70%, respectively).

ß-amyloid plaque density is a putative biomarker for AD-associated pathological changes, which might be useful in the diagnosis of AD. There is evidence in the literature however that correlation of Aß with cognitive status is imperfect. ß-amyloid plaque deposits have also been detected in autopsies of normal aging brains of older people without dementia.

18F-florbetapir binds to ß-amyloid plaques and the 18F isotope produces a positron signal that is detected by a PET scanner. 18F-florbetapir is indicated for PET imaging of ß-amyloid plaque density in the brains of adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive impairment. These may be patients with mild cognitive impairment without a clear diagnosis, or patients with significant cognitive impairment in whom the aetiology is not clear.

The Committee reviewed the clinical trial data from the development programme of 18F-florbetapir which was conducted by Clark et al over a period of 2 years (n=226). Patients were included if they came to autopsy within 24 months following 18-F-florbetapir PET imaging. The study tested the relationship between uptake in 18F-florbetapir PET imaging and true levels of ß-amyloid plaque determined by histopathological analysis at autopsy. The study included 2 cohorts: Cohort 1: autopsy cohort for end-of life subjects (n=59) and Cohort 2: specificity cohort of subjects aged <40 years who were cognitively and neurologically healthy (n=47). Analysis of data from the autopsy cohort showed a statistically significant correlation between the visual ratings of the PET image and the true cortical amyloid level as found on autopsy. In the specificity cohort, 100% (47/47) of young healthy control subjects were rated as negative on the visual binary reading of 18F-florbetapir PET scan. The sensitivity and specificity and accuracy for detection probable/definite ß-amyloid plaque were therefore reported as: sensitivity = 92% (95% CI: 78% to 98%), specificity = 100% (95% CI: 80% to 100%), accuracy = 95% (95% CI: 85% to 99%).

The Committee further reviewed a longitudinal study carried out on 142 subjects to evaluate the relationship between Amyvid imaging and changes in diagnostic status. Of the 142 subjects, 51 had a baseline diagnosis of mild cognitive impairment (MCI). 19 of these had a positive PET scan (sensitivity = 37%). 31 patients had a baseline diagnosis of Alzheimer's disease, and 21 of these went on to have a positive PET scan (sensitivity = 67.7%). Specificity testing was carried out using non-MCI and non-Alzheimers patients, and was found to be 69% and 75.8% respectively.

In terms of safety, no serious adverse reactions have been reported, but the drug has a black triangle status and is still subject to additional pharmacovigilance monitoring.

The Committee heard that the cost of a single dose of 370MBq of 18F-florbetapir referenced for injection time is £972. Until approval from the NHS England Commissioning Board for funding, it would only be authorised for patients with approved funding e.g. private patients/ self-funders.

The Committee discussed the fact that positive scans do not independently establish a diagnosis of AD or other cognitive disorder since plaque deposition in grey matter may be present in asymptomatic elderly patients. In addition there is a risk of interpretation errors. 18F-florbetapir PET scanning has been shown to predict the prevalence of ß-amyloid plaque found on pathological examination of the brain, but shows low sensitivity and specificity for correlation with clinical disease picture. There is no strong evidence of an improvement in the management of patients (or in patient outcomes) following PET scans with Amyvid. In addition, the usefulness of Amyvid in predicting the development of Alzheimer's disease in patients with memory problems or in monitoring patients' response to treatment has not been established.

Dr Bennett informed the Committee that she had discussed these concerns with the applicant Dr Wagner who had acknowledged the low specificity of these tests but emphasized that the PET scan results would be taken into account alongside the clinical picture and other scans.

The Committee considered the scan to be a useful research tool and biomarker for studies, however due to the low specificity and sensitivity in the prediction of AD and the unlikely impact on clinical management of patients, it was agreed not to include florbetapir 18-F on the NCL formulary. The applicants were encouraged to pursue use of florbetapir 18-F within a research remit.

5.3 Aripiprazole (Abilify; Otsuka BMS) in Children with Autistic Spectrum Disorder (Applicant: Dr C Clemente, Dr E Chung; Presentation: Ms I Samuels)

The Committee reviewed an application for aripiprazole, a third generation atypical antipsychotic, to treat irritability and hyper-arousal in children with autistic spectrum disorder (off label indication). Although the application stated that aripiprazole would replace risperidone (licensed indication), Dr Chung explained that both risperidone and aripiprazole would remain on the formulary and that choice of treatment would be based on individual patient needs and adverse effect profile.

Considering efficacy, the Committee reviewed a multicentre, randomised, double blind, placebo controlled trial by Marcus et al in 217 children/adolescents aged 6-17 years, with irritability associated with autistic disorder. Patients were randomised to receive placebo or aripiprazole (5, 10 or 15mg per day) for 8 weeks. At week 8, all aripiprazole doses produced significantly greater improvement than placebo in mean Aberrant Behaviour Checklist (ABC) Irritability subscale scores (primary outcome measure) and mean Clinical Global Impressions (CGI)-Improvement score. Discontinuation rates due to adverse events were as follows: placebo 7.7%, aripiprazole 5 mg/day 9.4%, 10 mg/day 13.6%, and 15 mg/day 7.4%. The most common adverse event leading to discontinuation was sedation. At week 8, mean weight change (last observation carried forward) was as follows: placebo +0.3 kg, aripiprazole 5 mg/day +1.3 kg, 10 mg/day +1.3 kg, and 15 mg/day +1.5 kg; all $p < 0.05$ versus placebo.

The Committee further reviewed a study by Owen et al of aripiprazole for irritability associated with autistic disorder in 98 children/adolescents aged 6-17 years old. Patients were randomised to receive either flexibly dosed aripiprazole or placebo over an 8 week period. Mean improvements in ABC Irritability subscale score were significantly greater with aripiprazole (-12.9) than with placebo (-5.0) at week 8 (95% CI -11.7 to -4.1, P<0.001). Aripiprazole also demonstrated significantly greater improvement in mean CGI score at week 8 compared to placebo with 67% of patients on the aripiprazole arm 'very much' or 'much improved' compared to 16% on the placebo arm (P<0.001).

The Committee acknowledged that aripiprazole was more effective than placebo, but that in a head to head study with risperidone by Ghanizadeh et al there was no significant differences in terms of efficacy or safety. NICE clinical guidance 170 recommendations on the management and support of children and young people on the autistic spectrum found no statistical difference in the efficacy of aripiprazole and risperidone. There was no direct comparison of the adverse effect profile, however this was noted to be similar for the two drugs. The guidance highlighted a lack of long-term data for the safety and efficacy of aripiprazole.

The most common adverse effects reported in the studies included weight gain, tremor, fatigue, hypersalivation and extrapyramidal disorders. The most common adverse event leading to discontinuation was sedation. Dr Chung informed the Committee that aripiprazole was an important treatment option due to better tolerability including a lower incidence of weight gain, QT prolongation, diabetes mellitus, reduction in prolactin, extrapyramidal side effects and sedation. The Committee noted that these are all reported adverse effects for aripiprazole too, and questioned the size of the absolute differences in adverse effects between aripiprazole and risperidone and the impact of these on clinical care. The study by Ghanizadeh et al showed no difference between the two agents in terms of safety outcomes. Dr Chung confirmed that the decision to initiate either risperidone or aripiprazole would be based on clinician's judgement and that there were no objective criteria for selection of therapy.

In terms of cost, aripiprazole liquid is currently approximately threefold more expensive than risperidone liquid; £102.90 versus £38.13, although aripiprazole is due to come off patent in 2015. The Committee expressed concern that the application was for short term use in crisis however the anticipated duration of treatment was 6-12 months. Dr Chung stated that patients would be withdrawn gradually when deemed appropriate, and may remain on treatment for one year if considered clinically appropriate. She added that prescriptions would be restricted to initiation and monitoring by CAMHS consultants with continuation in primary care under shared care.

Taking into consideration the off label use of aripiprazole versus licensed risperidone, higher cost and lack of data showing improved tolerability the Committee agreed that aripiprazole should not be included on the NCL formulary for children with autistic spectrum disorder.

5.4 Brimonidine Tartrate Gel (Mirvaso; Galderma) for Rosacea (Applicant: Dr E Seaton; Presentation: Ms S Sanghvi)

The Committee considered an application for brimonidine tartrate gel for the symptomatic treatment of facial erythema of rosacea. Brimonidine is a selective α2- adrenergic receptor agonist, and potent vasoconstrictor. It is the first licensed treatment indicated for the treatment of erythema of rosacea. Other treatments including topical metronidazole and azelaic acid gel to treat inflammatory lesions in papulopustular rosacea but do not specifically target erythema of rosacea.

The Committee reviewed the NICE evidence summary for brimonidine gel in rosacea, which was primarily based on 2 randomised, placebo controlled phase 3 trials, identical in design. There were 260 patients in trial A and 293 patients in trial B, all with moderate to severe erythema. Both trials were short term, consisting of a 4 week treatment phase where patients were randomised to either brimonidine gel or vehicle gel, with a 4 week follow-up phase thereafter. The primary efficacy end point of 'success rate' was defined as a 2-point improvement on both the clinicians' erythema assessment (CEA) and the patients' self-assessment (PSA) over 12 hours. The success rate at day 29 at 3 hours was 31.5% with brimonidine gel compared to 10.9% with placebo in trial A and 25.4% versus 9.2% in trial B respectively. The secondary efficacy end point, the '30-minute effect', defined as a 1-grade improvement from baseline on both the CEA and PSA at 30 minutes on day 1, was seen in 27.9% of the brimonidine group versus 6.9% of the placebo group in trial A, and 28.4% versus 4.8% in trial B respectively. The trials also included quality of life assessments, but there were no notable differences seen between brimonidine and placebo.

The Committee noted that brimonidine was statistically significantly more effective in terms of the primary and secondary endpoints but questioned how the results correspond to a clinically important change considering the scales used were unvalidated and subjective.

The Committee further reviewed an open-label, non-comparative 12-month study by Moore et al, in patients with moderate or severe erythema. In contrast to the RCTs, patients with 3 or more inflammatory lesions and concomitant treatment for inflammatory rosacea were included in the trial. The reduction in CEA and PSA scores seen on day 1 after the first application of brimonidine were maintained over the 12 month period and there was no evidence of tachyphylaxis.

In terms of safety, brimonidine gel was generally well tolerated in the trials. The most frequent treatment-related adverse events with brimonidine were worsening of erythema, pruritus, skin irritation and worsening of rosacea. No serious treatment-related adverse events occurred. There was no evidence of rebound erythema or tachyphylaxis during the 4-week trials, however Routt et al recently published a report of 3 patients who experienced severe erythema and burning, considered to be rebound vasodilation reactions to brimonidine. The Committee agreed that patients should be counselled about the potential for worsening erythema, use of a test area and limiting use to special occasions.

The Committee were informed that brimonidine is a once daily topical gel and that the anticipated cost per patient per year would be £240.

The Committee heard that brimonidine potentially has a transient effect on erythema but does not alter the disease course or impact on other features of the disease such as spider veins or papules. The Committee expressed concern at the relatively low response rates in the trials and potential for widespread use and increasing primary care costs. Dr Seaton reassured the Committee that brimonidine would only be used in patients with moderate to severe, persistent erythema of rosacea causing marked psychological distress or reduction in quality of life. This would be assessed using the two-item Generalised Anxiety Disorder Scale (GAD-2) and the Cardiff Acne Disability Index. He agreed that the response rates were low but argued that this could significantly improve quality of life for the small group of patients that would respond to treatment, with discontinuation if there was no benefit. He added that although rosacea is a chronic condition, patients generally use the gel on an 'as required' basis. The Committee discussed at length the cost-effectiveness of this treatment and impact on primary care and voted 7:2 in favour of brimonidine. It was therefore agreed to add brimonidine to the NCL formulary but restricted to secondary care initiation by dermatologists. The Committee also agreed that prescribing can be continued in primary care.

6 Retigabine Audit Data

This item was deferred to the next meeting.

7 Home Oxygen Ordering Guide

This item was deferred to the next meeting.

8 Type II diabetes treatment pathway – Camden, Enfield and Islington

This item was deferred to the next meeting.

9 Local DTC Recommendations

This item was deferred to the next meeting.

10 NCL Dates- August 2014 to July 2015

The NCL dates were included for information.

11 Any other business

Nil