# NCL Joint Formulary Committee (JFC) Meeting

**Minutes from the meeting held on Thursday 28th November 2013**

**In Foster Court, Room 132, Gower St, UCL**

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

## 2. Minutes of the last meeting

The minutes were accepted as accurate.

## 3. Matters arising

### 3.1 Overactive Bladder (OAB) Pathway

The Committee discussed feedback from consultants regarding the proposed OAB pathway. Comments included the restricted choice of anti-muscarinics (e.g. omission of trospium), consideration of modified release preparations and position of mirabegron in the pathway. Prof Macallister invited written comments and feedback from stakeholders to enable further revision of the protocol. It was agreed that the pathway would

apply to both primary and secondary care to promote uniformity in prescribing, but that niche indications (e.g. paediatrics) would be excluded.

## 4. Members declarations of relevant conflicts of interest

None were declared.

## 5. CCG-Related Medicine Applications and Reviews

### 5.1 Degarelix (Firmagon®; Ferring) for Advanced Prostate Cancer (Applicant: Dr Arya (unable to attend); Presentation: Ms R Holland)

The Committee reviewed an application for degarelix, an LHRH antagonist, for advanced hormone-dependant prostate cancer in four specific patient groups: (1) Patients with pre-existing cardiovascular disease where agonists are not appropriate (2) High risk patients with a PSA>20. (3) Patients who are unable to tolerate alternative therapies (LHRH agonists ± anti-androgens) and (4) Patients with spinal cord compression/severe bone pain in whom immediate castrate levels of testosterone are necessary.

The Committee reviewed a randomised open-label, parallel-group study by Klotz et al (n=610) which reported on the efficacy and safety of degarelix (any stage) versus leuprolide. Patients were randomly assigned to receive degarelix 240mg (initiation dose) followed by 80mg or 160mg monthly, or leuprolide 7.5mg monthly. Patients receiving leuprolide could also receive bicalutamide (50mg daily) for clinical flare protection (only 11% of patients received this at the investigators discretion). The primary endpoint of the trial was suppression of testosterone ≤0.5ng/ml at monthly measurements over the one year trial. The results showed similar median testosterone levels across the groups; 0.082ng/ml in the degarelix 240/80mg group, 0.088ng/ml in the degarelix 240/160mg group and 0.078ng/ml in the leuprolide group. The Committee considered the evidence supporting the four proposed indications in turn:

(1) *Patients with pre-existing cardiovascular disease where agonists are not appropriate.* The Committee reviewed a meta-analysis *in press* by Albertsen et al which included a cohort of 2328 patients who received either an agonist (n = 837) or an antagonist (n = 1491). The baseline incidence of cardiovascular disease was approximately 30% in both treatment groups. During the initial year of treatment, 42 men died: 22 patients who received the antagonist and 20 patients who received an agonist. During this same period, 37 patients who received the antagonist experienced a cardiac event compared with 42 patients who received an agonist. A Cox proportional hazard model estimated a 40% lower risk of a cardiac event or death (HR: 0.60; 147 95 % CI, 0.41–0.87; p = 0.02) for patients receiving an antagonist if they had pre-existing cardiovascular disease. A cardiac event was defined as arterial embolic and thrombotic events, haemorrhagic or ischaemic cerebrovascular conditions, myocardial infarction or other ischemic heart disease. The Committee were unable to determine which of these end points [if any] were driving the apparent difference in cardiac events. The Committee considered this important considering the trial was open-label and as such would place less significance to any difference in events that were subjective. This meta-analysis included 6 studies, three of whom were excluded from statistical pooling due to an absence of cardiovascular events in either arm. Two of the other three studies reported no statistical difference between antagonist and agonist therapy in cardiovascular outcomes and thus the meta-analysis was powered by a single study comparing degaralix with goserelin which appears to be unpublished. In addition, in this study about one half of enrolled patients receiving degarelix had a pre-defined break in their therapy (intermittent use). Such a trial design may thus bias outcomes in favour of the antagonist. Furthermore, the Committee noted that the trials comparing degarelix to leuprolide used a higher dose than the UK licensed dose of agonist which could again bias results in favour of antagonist therapy. The Committee considered these *post-hoc* analyses from registry studies as hypothesis-generating and not policy-defining. The Committee agreed to re-review upon full publication of the meta-analysis and the CS37 trial.

(2) *High risk patients with a PSA>20.* The Committee reviewed a study by Tombal et al which reported that patients receiving degarelix showed a significantly lower risk of PSA progression or death compared with leuprolide. PSA recurrences occurred mainly in patients with advanced disease and exclusively in those with

baseline PSA >20 ng/ml. Patients with PSA >20 ng/ml had a significantly longer time to PSA recurrence with degarelix. However, these data were generated from a *post-hoc* analysis and was limited by the small number of patients in each sub-group. The Committee again considered these data hypothesis-generating and not policy defining.

(3) *Patients who are unable to tolerate alternative therapies (LHRH agonists ± anti-androgens).* The Committee considered this reasonable considering the differing adverse event profiles.

(4) *Patients with spinal cord compression/severe bone pain in whom immediate castrate levels of testosterone are necessary.* The Committee accepted that degarelix induced castrate levels more rapidly than an agonist alone but were unsure of the clinical significance of this, particularly as the data for the small cohort (11%) of patients who received concomitant anti-androgen was not presented within the manuscript of the pivotal study. The Committee suggested that further research of the literature should be made to try and clarify if this was likely to be superior to an agonist plus anti-androgen and if this theoretical advantage has been shown to translate into any clinical advantage.

## 5.2 LHRH Analogues Review (No applicant; Presentation: Ms S Sanghvi)

The Committee reviewed available LHRH agonist preparations and prescribing patterns across the NCL CCGs. Potential cost saving opportunities were identified however the Committee considered these too difficult to implement for the degree of achievable savings and therefore it was agreed that no change would be made to current LHRH agonist prescribing.

## 5.3 Duloxetine (Cymbalta®; Eli Lilly) for neuropathic pain (Applicant: Dr W Rea (unable to attend); Presentation: Mr K Thakrar)

The National Institute for Health and Care Excellence (NICE) has recently published a clinical guideline on the pharmacological management of neuropathic pain (CG173). This guideline made the following recommendations 'all patients with neuropathic pain should be offered a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment (except trigeminal neuralgia). If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated. Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.'

Duloxetine has principally been studied in patients with diabetic peripheral neuropathy (DPN). Lunn et al conducted a systematic Cochrane review to assess the safety and efficacy of duloxetine for the treatment of chronic neuropathic pain. The study included six trials in total, of which three included patients with painful DPN and three trials were in fibromyalgia. The three trials for DPN by Raskin et al, Goldstein et al, and Wernicke et al were all double-blinded, randomised, placebo-controlled trials of similar design. The scale used to measure efficacy in most of the trials was an 11-point Likert, which has been validated to show that a reduction of two points or approximately 30% represents a clinically important difference. Inclusion criteria were participants > 18 years with an average pain score of 4 on the Likert scale. The primary end-point was > 50% improvement in pain relief compared to baseline at 12 weeks. The results of the three studies were pooled showing duloxetine to be superior when compared to placebo at reducing pain by > 50% at all doses apart from duloxetine 20mg, with an overall risk ratio estimate of 1.63 (95% CI 1.35 to 1.97). However, the Committee noted that the absolute mean difference between duloxetine 120mg daily and placebo was -1.16 (95% CI -1.49 to -0.83) thus falling short of an apparent clinical meaningful difference.

Kaur et al conducted a randomised, double-blind, cross-over trial in 58 patients to compare amitriptyline versus duloxetine in participants with DPN. Eligible patients were randomised to receive six weeks of treatment with either amitriptyline up to 50mg each night or duloxetine up to 60mg daily, with treatments reversed after a two week wash out period. The primary end point was a reduction in the median pain score from baseline (assessed using a 100-point visual analogue scale). The trial reported that the proportion of patients with a good response (defined as > 50% reduction in pain) was 59% in the duloxetine arm versus 55% (n=32) in the

amitriptyline arm; there were no difference in the proportion of patients with moderate improvements and mild response.

Lavoie Smith et al conducted a randomised, double-blind, placebo controlled, cross-over trial to determine the efficacy of duloxetine in patients with chemotherapy-induced peripheral neuropathy. The primary endpoint was a change in pain reduction, with a secondary end point of patient-reported quality of life using a FACT/GOG scale, ranging from 0 – 44. The trial reported a mean change in pain reduction of 1.06 for the duloxetine arm compared to 0.34 for placebo, representing an absolute difference of 0.73 (95% CI 0.26 to 1.20); again this absolute difference did not meet the minimal clinically significant difference (0.8). With regards to the secondary end point, the mean change in the FACT/GOG total score was 2.44 (95% CI 0.43 to 4.45) for the duloxetine arm versus 0.87 (95% CI 1.09 to 2.82) for placebo, resulting in an absolute difference of 1.58 (95% CI 0.15 to 3.0). The author pre-defined a 2-3 point change as a clinically significant improvement in QOL which was not achieved.

Tanenberg et al conducted a 12-week, open-labelled, non-inferiority study in 407 patients to assess the efficacy of duloxetine compared to pregabalin in patients with DPN. Inclusion criteria were diabetic participants aged > 18 years, who have failed gabapentin, and have a pain score of ≥ 4. Eligible patients were randomised into three groups.

Arm A - duloxetine 60mg/day monotherapy (n=138)

Arm B - pregabalin 300mg/day monotherapy (n=134)

Arm C - duloxetine 60mg/day and gabapentin ≥ 900mg/day (n=135).

The primary end point was the reduction from baseline in the pain score at week 12, measured on a 0-10 point pain scale. The authors stated a non-inferiority margin of < 0.8 between the two arms. The trial reported a mean change in pain severity at week 12 of -2.6 for the duloxetine arm compared to -2.1 in the pregabalin arm, representing an observed difference of 0.5; confirming non-inferiority between the two arms.

In terms of safety, duloxetine is metabolised via CYP-1A2 as well as a CYP-2D6 inhibitor, and thus there could be potential for drug interactions with other inducers or inhibitors. The majority of common adverse effects appear mild to moderate and most tend to subside with persisted therapy.

The trial that compared duloxetine and amitriptyline (Kaur et al) showed similar adverse event rates. The incidence of moderate to severe events was higher with amitriptyline (51% compared to 24%), which the Committee felt was consistent with the known pharmacology of both these drug classes. The Committee therefore considered that duloxetine may be useful for patients responding to amitriptyline but who experienced intolerable [anti-cholinergic] adverse events.

In terms of cost, the estimated annual cost per patient is about £330 for duloxetine, £10 for amitriptylline and £30 for gabapentin. Duloxetine was noted to be considerably less expensive than pregabalin (£330 vs £770). The Committee therefore agreed that duloxetine should be made available third-line after the two cheaper drugs. However, it was first agreed that the evidence for pregabalin be re-assessed before a final treatment algorithm is defined.

## 6. Local DTC Recommendations

### 6.1 GOSH

**Clonidine for pre-medication:** Approved at GOSH DTC. This decision was ratified by the JFC as it was restricted to patients who had experienced a paradoxical reaction to midazolam.

**Cannabidol for seizures related to Dravet or Lennox-Gastaut syndrome:** Not Approved at GOSH DTC. This decision was ratified by the JFC.

**Anti-CD45 antibodies for conditioning therapy prior to allogenic BMT:** Approved at GOSH DTC. This decision was ratified by the JFC as it was for a small niche cohort of patients unable to tolerate conventional conditioning chemotherapy.

The Committee noted that these were the first minutes provided to the JFC for ratification by GOSH and that these items did not undergo the JFC prioritisation process. Prof MacAllister agreed to meet with Dr Ancliff to discuss.

### 6.2 UCLH

**Triptorelin for preservation of ovary function:** Approved at UCLH DTC. This decision was ratified by the JFC for use at UCLH only for non-hormone sensitive cancers.

**Fampridine for treatment of down-beat nystagmus:** Approved at UCLH DTC. This decision was ratified by the JFC due to lack of treatment options and a clear protocol designed to identify potential responders.

**Kappaproct for treatment of steroid refractory ulcerative colitis:** Not approved at UCLH DTC. This decision was ratified by the JFC.

### 6.3 MEH

**Ganfort UD (Bimatoprost and Timolol) for treatment of glaucoma in patients allergic to preservative:** Approved at MEH DTC. This was ratified by the JFC as the combination product is less expensive than the individual components.

### 6.4 RNOH

**Doxycycline and Albumin for inoperable aneurismal bone cysts:** Approved at RNOH DTC. This was ratified by the JFC as it was approved under a local evaluation.

**Zoledronic Acid for paediatric osteoporosis:** Approved at RNOH DTC. This was ratified by the JFC as data has shown it non-inferior to pamidronate but more convenient to administer. It is also used at other paediatric centres including GOSH.

### 6.5 RFH

**Calcitriol injection for percutaneous injection into the parathyroid gland for hyperparathyroidism:** Approved at RFH DTC. This decision was ratified by the JFC as it was only for patients intolerant or unresponsive to oral therapy and was less expensive.

**Epoprostenol for pulmonary hypertension:** Approved at RFH DTC. This decision was ratified by the JFC as it involved a brand change to a product with greater stability.

## 7. NCL-MMC Minutes

These are available for information.

## 8. Date of next meeting: 23rd January 2013 (location TBC).

## 9. Any other Business

### 9.1 Thickeners

Mr TF Chan informed the Committee that an Enteral Feed Working Group is currently running under UCLP, and suggested that the JFC should provide input to these discussions. Dr H Taylor agreed to investigate and report back to the Committee at the next meeting.