NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 22nd August 2013

In UCL Room 337 David Sacks, Rockefeller Building, 21 University St, LONDON, WC1E 6DE

1. Present:	Prof R MacAllister	NCL JFC Chair
	Dr A Jones	Consultant Oncologist, RFH/UCLH
	Dr E Boleti	Consultant Oncologist, RFH
	Mr A Dutt	NHS Islington, Head of Medicines Management
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management
	Mr TF Chan	BCFH Chief Pharmacist
	Mr G Irvine	Lay Member
	Dr R Urquhart	UCLH Chief Pharmacist
	Dr R Fox	RNOH DTC Chair
	Mr A Karr	NCL Procurement Chair
	Dr L Wagman	NHS Barnet CCG
	Dr C Stavrianakis	Haringey CCG
	Dr R Breckenridge	UCLH DTC Chair
In Attendance:	Dr A Grosso	UCLP Pharmacist
	Ms I Samuels	RFH Formulary Pharmacist
	Mr M Wyke-Joseph	NMUH Formulary Pharmacist
	Ms K Chapman	MEH Formulary Pharmacist/JFC Support Pharmacist
	Ms R Holland	UCLH Formulary Pharmacist
	Mr K Thakrar	UCLH Pharmacist
	Dr R Stein	Applicant
	Dr M Chapman	Applicant
	Dr Kariyawasam	Applicant
	Mr P Bodalia	RNOH Deputy Chief Pharmacist
Apologies:	Dr M Kelsey	WH DTC Chair
	Ms W Spicer	RFH Chief Pharmacist
	Mr T James	MEH Chief Pharmacist
	Ms S Drayan	NMUH Chief Pharmacist
	Dr S Shaw	RFH DTC Chair
	Dr H Taylor	WH Chief Pharmacist
	Prof L Smeeth	NCL JFC Vice Chair
	Dr A Tufail	MEH DTC Chair
	Dr R Sofat	Clinical Pharmacologist
	Mr A Shah	RNOH Chief Pharmacist
	Dr M Broadbent	BCF DTC Chair
	Ms N Shah	NHS Camden Head of Medicines Management
	Ms P Taylor	NHS Haringey Head of Medicines Management

2. Minutes of the last meeting

It was noted that the exact place in therapy of each of the biologics recommended for use as monotherapy in rheumatoid arthritis needs to be determined in a protocol.

3. Matters arising

3.1 NOAC prescribing guides

The Committee considered the tracked changes made to the NOAC prescribing guides after the recent consultation period closed. The Committee approved the documents with minor amendments.

It was also agreed that the implementation of the NOAC pathway be reviewed by the Committee in one year.

3.2 Denosumab for bone metastases

The Committee noted that NICE has proposed a review of *TA265;Denosumab for treating bone metastases from solid tumours*. This is in response to the availability of generic zoledronic acid from various manufacturers. With zoledronic acid available at lower cost, denosumab may not be a cost-effective option for preventing skeletal related events in people with bone metastases from breast cancer and from solid tumours other than prostate.

The Committee considered a pathway showing the proposed place in therapy of bisphosphonates and denosumab for this indication, and agreed that more information is required before any proposed pathway is approved. This information includes information on safety of bisphosphonates and denosumab in renal impairment; the relative cost of each drug; how it will be funded; and which sub-groups of the population would be potentially more suited to denosumab.

Dr Boleti, Ms Samuels and Dr Jones agreed to work together to answer these questions and produce an updated pathway for review by the Committee. As denosumab is currently used at Barts Health for this indication it was also agreed that they should be contacted for information.

3.3 Membership Nomination

The Committee welcomed Dr Ross Breckenridge as a new member of the Committee. Dr Breckenridge is the new UCLH Use of Medicines Committee (UMC) Chair.

Nominations were received for the following potential new members, and these were agreed by the Committee:

- Dr R Kapoor (UCLH Neurologist)
- Dr P Belavadi (NMUH Anaesthetist)
- Dr J Hurst (RFH Respiratory Clinician)
- Dr C Cooper (MM Islington – deputising Prof L Smeeth)

4. Members & applicants declarations of relevant conflicts of interest

Dr Jones has participated in an advisory board for Celgene Ltd (manufacturers of *nab*-paclitaxel - Abraxane®).

5. CCG-related medicine applications & reviews

5.1 Dymista® appeal (Meda Pharmaceuticals) for severe seasonal and perennial allergic rhinitis (Applicant: Dr H Kariyawasam)

The Committee considered an appeal submitted by Dr H Kariyawasam and Dr G Rotiroti (applicants) regarding the June 2013 decision to not recommend Dymista® for inclusion in the NCL Joint Formulary. The Committee concluded at that time that there was insufficient evidence of increased clinical benefit of Dymista® over the individual components used separately.

In their appeal, the applicants emphasised the difficulty faced by patients with severe allergic rhinitis and suggested that restricted use of Dymista® was a necessary treatment option to improve compliance and quality of life for these patients.

The Committee reconsidered a 14-day, multicentre, randomised, double-blind study by Hampel *et al.* After a 5 day placebo lead-in, 610 patients with moderate-to-severe nasal symptoms were randomised to treatment with (1) azelastine nasal spray (2) fluticasone nasal spray (3) combination (4) placebo. All treatments were given as one spray twice daily. The primary endpoint was change from baseline in the total nasal symptom score (TNSS), consisting of nasal congestion, runny nose, itchy nose and sneezing.

All three groups were statistically superior (P ≤ .02) to placebo, and the combination was statistically superior (P ≤ .003) to either agent alone. The TNSS improved by 28.4% with the combination spray, 20.4% with fluticasone, 16.4% with azelastine, and 11.2% with placebo. The only individual component of TNSS that the combination did not show significant improvement compared with a comparator group, was that of runny nose which was not significantly improved compared to fluticasone. On Days 10 and 11 the combination group did not show statistically significant improvement compared to fluticasone alone, but did reach significance on all other study days. A statistically significant improvement in total ocular symptoms was shown by the combination group over both placebo and fluticasone (P<.01), but not the azelastine group. The Committee reiterated its view that the absence of a control group treated with azelastine and a nasal steroid administered in separate applicators was a key limitation of this trial and any data generated from it. It made any conclusions regarding better compliance to be speculative.

Whilst the Committee agreed that the cost increase of using a combined spray was likely to be minimal, there was no evidence to support increased efficacy or compliance with the combination product. The Committee also were concerned that allowing use for a niche cohort of patients at the RNTNEH would result in wider prescribing elsewhere.

In conclusion, the Committee agreed that the original decision not to recommend Dymista® for addition to the formulary should stand.

5.2 Botox® (Allergan) for sphincter of Oddi dysfunction (Applicant: Dr M Chapman; Presentation: Ms K Chapman)

The Committee reviewed an application for the use of botulinum toxin (BTX) for sphincter of Oddi dysfunction (SOD) Type 3. The Committee heard that SOD is a difficult condition to definitively diagnose and treat. There are two potential uses of BTX in SOD Type 3; firstly as a diagnostic test to identify patients whose pain is directly related to sphincter dysfunction and thus may respond to sphincterotomy, and secondly as a method of alleviating symptoms.

The Committee considered a series of 22 patients (Wehrmann *et al* 1998) with recurrent biliary colic and manometrically proven biliary sphincter of Oddi dysfunction Type 3 (BSOP>40mmHg). At the six-week check up after BTX injection, 10 patients (45%) had experienced recurrent episodes of biliary colic, whereas 12 patients (55%) were free of symptoms.

Those patients who did have symptomatic relief were not statistically different with regard to BSOP at baseline than those 10 patients who did not. 11 of the 12 responders had recurrence of biliary colic in the follow-up period (4-12months). One patient remained asymptomatic 8 months after injection.

Also 11 of the 12 BTX responders and 2 of the 10 non-responders obtained symptom relief after subsequent sphincterotomy (p=0.0015), suggesting that BTX injection may allow identification of patients with Type 3 SOD who will respond to definitive sphincter ablation (i.e. endoscopic sphincterotomy). This might avoid unnecessary procedures in patients unlikely to benefit.

The diagnostic benefit of BTX in SOD was also considered in a further prospective trial by the same author (Wehrmann *et al* 2000). 15 patients underwent endoscopic injection of 100 units of botulinum toxin into the major papilla. 15 patients had a remission of symptoms after BTX injection of 5.1 ± 2.0 months. A non-responder was defined as anyone who relapsed within 3 months of injection. After treatment with BTX, pancreatic and/or biliary sphincterotomy was performed. Only one out of three botulinum toxin non-responders benefited from endoscopic sphincter ablation, whereas all of the 11 patients who responded to botulinum toxin injection benefited (botulinum toxin responders *P*< 0.05 vs. botulinum toxin non-responder).

A retrospective clinical audit of patients with SOD was conducted in 2010 by Murray & Song. Of 64 patients, 46 (72%) had at least four pain free weeks after BTX therapy (median = 8 weeks) and 44 of these 46 patients (96%) went on to experience pain relief following endoscopic sphincterotomy.

Eighteen out of 64 patients did not report any change after BTX injection. These patients did not undergo a later endoscopic sphincterotomy.

Of those that did not respond, 72% had another functional disorder.

The applicant also presented a recently published case series abstract which shows similar results in a larger cohort of patients.

Regarding safety, Wehrmann *et al* reported two patients [out of 22] who had abdominal pain within 4 hours of BTX injection. One of these developed post-BTX injection pancreatitis (incidence 4.5%). A review by Hall *et al* states that no complications from the use of BTX have been reported. In contrast, for all patients with SOD, endoscopic sphincterotomy has been reported to result in complications in 20-30% of patients, including pancreatitis, haemorrhage and iatrogenic visceral perforation.

Endoscopic BTX injection can be provided in a day-case setting in comparison to the 1-4 day stay required when patients have ERCP.

The Committee concluded that whilst the evidence is limited, the proposed use of BTX to predict those patients who will be more likely to respond to a sphincterotomy is appropriate, when used according to the protocol provided. The use of BTX in this manner will likely defer the need for a more invasive procedure and will reduce the incidence of serious complication such a pancreatitis. Therefore, the Committee recommended inclusion of BTX onto the formulary for this indication. It was also agreed that any brand of Botutinum A Toxin would be suitable. The Committee did not approve the use of BTX for symptomatic treatment.

5.3 Calcium & Combined Vitamin D and vitamin D preparations review (Mr K Thakrar)

The Committee considered a review of the available combined calcium & vitamin D preparations and the potential cost-savings and implications upon switching. Factors such as tablet size for non-chewable tablets, and whether they are suitable for vegetarians and vegans were considered by the Committee.

It was suggested to the Committee that the preferential use of the least expensive brand [Accrete-D3] may result in considerable cost-savings across NCL (estimated at £100,000 per annum for a 50% prescribing rate). It was noted that Accrete-D3 may not be suitable for vegetarians, vegans and those with peanut or soy allergy; therefore alternative products have been identified for these groups. The pharmacy prescribing advisors raised concerns that this switch was not a high priority. In contrast, the GP members were very keen to pursue what they considered was a relatively simple change. For example, Dr Wagman suggested using the ScriptSwitch decision support software available in primary care to raise an alert for GPs at the point of next prescription. It was therefore agreed that each CCG should consider the feasibility of implementing this locally and to report back to the Committee at the next meeting.

With regard to Vitamin D preparations, a proposed rationalisation of the prescribed strengths and products was recommended. For patients initiated in secondary care, it was agreed that the most cost-effective licensed product should be preferentially used, whilst GPs initiating treatment will continue to recommend inexpensive supplements that patients can buy over the counter.

6. Non CCG-related applications/reviews

6.1 Nab-paclitaxel (Abraxane®; Celgene) for paclitaxel hypersensitivity (Applicants: Dr Jones [RFH]/Dr Stein [UCLH]; Presentation: Mr A Grosso)

The Committee reviewed two applications (UCLH & RFH) for Abraxane® to be added to the formulary for patients with breast cancer and hypersensitivity to taxanes, in three situations (adjuvant or neoadjuvant therapy and metastatic disease). These indications are now all reimbursable by NHS England.

Although paclitaxel and docetaxel have significant activity against breast cancer and other solid tumours, data indicates that the solvents polyethylated castor oil and polysorbate 80 directly contribute to hypersensitivity reactions. These solvents have been included because these taxanes are highly hydrophobic and solvents allow parenteral administration. *nab*-Paclitaxel (Abraxane®) is an albumin-bound particle form of paclitaxel developed to avoid the need of such solvents.

The Committee considered evidence from the open-label, industry sponsored Phase III study by Grandishar *et al*. Patients were randomly assigned (1:1) to receive treatment every three weeks with either Abraxane®(260mg/m^2 intravenously over 30 minutes without corticosteroid or antihistamine pre-medication) or standard paclitaxel (175mg/m^2 intravenously over 3 hours with pre-medication). The study was designed as a non-inferiority study to demonstrate that Abraxane® (n=229)was at least 75% as active as standard paclitaxel (n=225). The ORR was reported to be significantly greater for Abraxane® than for standard paclitaxel 33% vs. 19%; P=0.001).

The incidence of hypersensitivity reactions (any grade) was low for both arms (<1% for Abraxane®and 2% for standard paclitaxel). No grade 3 or 4 treatment-related hypersensitivity reactions occurred in any of the patients in Abraxane® arm despite the absence of pre-medication. Grade 3 standard hypersensitivity reactions occurred in the standard paclitaxel arm despite pre-medication. However, it was not clear from the studies whether hypersensitivity was due to the solvent or taxane moiety itself (the Committee noted that other studies have shown significant cross-reactivity between the two taxanes which contain different solvents).

In conclusion, the Committee agreed to include Abraxane® onto the formulary for all three indications. The Committee agreed that hypersensitivity should be a minimum of Grade 3 to be considered for this more expensive treatment option.

7. Local DTC recommendations

7.1 MEH: Sodium Hyalorunate/Xanthan Gum (Lubristil® Gel;Moorfields Pharmaceuticals) for insertion of scleral lenses. Lubristil® Gel was reviewed by Moorfields DTC where this lubricant was recommended prior to insertion of scleral lenses only. The Committee agreed with this decision.

8. NCL-MMC minutes

The Committee heard that there is ongoing discussion regarding the proposed addition of all items funded by NHS England to be added to the Red List.

9. Date of next meeting: 26th September 2013 (location TBC).

10. Any other Business