NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 31st July 2014

Taviton Building, Room 433, 16 Taviton Street, London

Present:	Dr M Kelsey	Whittington DTC Chair	**(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 P Taylor	NHS Haringey Head of Medicines Management	
	Dr R Sofat	Consultant Clinical Pharmacologist, UCLH	
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
	Dr E Boleti	Consultant Oncologist, RFH	
	Ms J Bloom	Principal Pharmacist, Moorfields	
	Dr D Bavin	Camden CCG, GP	
	Dr C Stavrianakis	Haringey CCG	
	Dr L Wagman	Barnet CCG, GP	
	Mr T James	MEH Chief Pharmacist	
	Dr R Kapoor	Consultant Neurologist, UCLH	
	Ms W Spicer	RFH Chief Pharmacist	
	Dr A Tufail	MEH DTC Chair	
	Ms H Taylor	Whittington Chief Pharmacist	
In attendance:	Mr E Hindle	MEH Pharmacist	
	Ms I Samuel	Pharmacist, RFH	
	Mr K Thakrar	Pharmacist, UCLH	
	Dr A Grosso	Pharmacist, UCLP	
	Ms A Moore	Pharmacist, UCLH	
	Ms S Sanghvi	Pharmacist, UCLH	
	Ms A Gascoyne	Pharmacist, UCLH	
	Dr A Mohamed	Clinical Fellow Urology	
	Mr A Stein	NELCSU Medicines Management	
	Mr T Flynn	Consultant Ophthalmologist	
	Prof J Dart	Consultant Ophthalmologist	
	Dr P Dileo	Medical Oncologist, UCLH	
	Mr M Wyke-Joseph	NMUH Pharmacist	
Apologies:	Prof R MacAllister	NCL JFC Chair	
	Prof L Smeeth	NCL JFC Vice-Chair	
	Dr R Breckenridge	UCLH UMC Chair	
	Mr A Shah	RNOH Chief Pharmacist	
	Ms N Shah	NHS Camden, Head of Medicines Management	
	Mr TF Chan	BCF Chief Pharmacist	
	Dr R Fox	DTC Chair, RNOH	
	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 J Hurst	Consultant, RFH	
	Ms J Cope	GOSH Chief Pharmacist	

2. Minutes of the last meeting

Item 6: Mr A Dutt confirmed that all licensed DDP-IV inhibitors were reviewed and considered before the decision was made for sitagliptin as the sole DDP-IV inhibitor on the NCL formulary. The committee agreed with Mr Dutt.

3. Matters arising

3.1 Pregabalin Statement from Pfizer

The Committee reviewed the letter from Pfizer regarding pregabalin and agreed to draft a response to the evidence presented and outline the JFC position.

3.2 Dymista Appeal & Rebate Scheme

The Committee reviewed a second appeal for Dymista nasal spray from the RNTNE Department of Allergy. The Committee were informed that the manufacturers have reduced the cost of Dymista and introduced a rebate scheme for 2 years to facilitate cost-effective prescribing by specialists at the RNTNE.

The Committee were informed that the initial application and first appeal was rejected on the basis of lack of evidence to support the use of Dymista over the individual nasal sprays as well as Dymista (combination of fluticasone and azelastine) being marginally more expensive than the individual nasal sprays. The committee further noted that although the change in price makes it slightly cheaper, there was still an absence of data comparing it to fluticasone and azelastine nasal sprays. In addition, Dymista was still considerably more expensive then the beclomatasone and azelastine nasal spray. The Committee also expressed concerns that prescribing would run into primary care and usage would increase, with higher costs in the future.

The Committee therefore retained the original decision that Dymista should not be included on the NCL formulary.

4. Members declarations of relevant conflicts of interest

Mr P Gouldstone informed the Committee that he has participated in a pregabalin advisory board.

Mr E Hindle notified the Committee that ciclosporin eye drops are manufactured by Moorfields Eye Hospital.

5.1 Sulindac for desmoid-type fibromatosis (Applicant: Dr Palma Dileo; Presentation: Ms Sonali Sanghvi)

The Committee reviewed the use of sulindac as a first line treatment for oestrogen receptor-negative, desmoid-type fibromatosis for patients with slowly progressive, unresectable disease. The committee heard that NSAIDs are recommended by cancer networks as a less toxic treatment option in patients unsuitable for surgical resection prior to using other systemic options including hormonal therapy, chemotherapy or interferons. The exact mechanism of sulindac in the treatment for desmoid tumours is not completely understood, but is considered to be related to raised COX-2 levels in fibromatosis.

The Committee heard that desmoid tumours are extremely rare and therefore the evidence in humans is limited to case series and small retrospective studies. The Committee reviewed a study by Hansmann et al evaluating sulindac and tamoxifen combination therapy in 30 patients with either FAP-related or sporadic desmoid tumours. The results in patients with previous surgical resection compared to patients with no previous surgical resection showed progression in 44% vs 6%, static disease in 22% vs 56% and regression in 22% vs 25% respectively. The Committee noted that the positive results were for the combination of tamoxifen and sulindac, therefore the treatment effect and safety of sulindac alone could not be ascertained. In addition the study was limited by the small patient cohort, lack of information on previous systemic therapy and short term follow up which didn't allow for progression free survival analysis.

The Committee further reviewed a retrospective analysis by Nieuwenhuis et al investigating long-term outcomes in 78 FAP patients with desmoid tumours, accessed via the Dutch Polyposis Registry. The probability of progression free survival calculated by Kaplan-Meier method was predicted to be 58% for NSAIDs and 40% for hormonal or combination therapy, irrespective of previous surgery (p=0.11). The Committee questioned the validity of these results considering the small, retrospective, non-randomised design of the study and lack of specific detail about the drugs, doses and durations. In another study by Tsukada et al (n=14) 57% of patients with desmoid tumours and history of FAP responded to treatment with partial or complete reduction in tumour size.

The Committee questioned whether alternative NSAIDs with more established safety profiles and lower cost could also be effective in desmoid tumours. The Committee heard that sulindac is a long acting analogue of

indomethacin with similar biochemical actions. There are limited case reports showing benefit of indomethacin, celecoxib and other NSAIDs for desmoid tumours although the respective cardiovascular risks would also need to be considered. Dr Dileo informed the Committee that she sits on the European expert group panel for desmoid tumours and that sulindac has been established therapy due to historic prophylactic use post-surgery in FAP patients to prevent pre-cancerous lesions including desmoid tumours. Indometacin has not been used in clinical practice for approximately 30 years and also has limited evidence. Despite the lack of robust evidence the Committee agreed that NSAIDs were a reasonable initial step in place of aggressive chemotherapy or radiotherapy. Considering the small patient cohort across NCL (anticipated to be 5 patients), the favourable tolerability profile of sulindac, and the limited data available for the other NSAIDs, the Committee agreed that sulindac should be added to the formulary restricted to treatment of oestrogen receptor negative desmoid fibromatosis in patients with slowly progressive, unresectable disease. The committee agreed that consultants should liaise with the patients GP regarding prescribing in the primary care.

6 Avanafil for Erectile Dysfunction (Applicant: Dr Amr Mohamed; Presentation: Mr Kash Thakrar)

The Committee reviewed an application for avanafil; a new PDE5 inhibitor licensed for the treatment of erectile dysfunction, which was proposed for use as 2nd line therapy for patients who fail or do not tolerate first line sildenafil treatment.

The efficacy of avanafil has been studied in three pivotal randomised, double-blinded, placebo-controlled studies of similar design in patients with mild to moderate ED, but with differences in the population; general population (TA-301), diabetic population (TA-302), and ED following bilateral nerve sparing radical prostatectomy (T-303). The co-primary efficacy endpoints were SEP3, SEP2 and change in ILEF erectile function score.

In all three studies, there was a statistically significant benefit in each of the co-primary end points in favour of all three avanafil doses in comparison to placebo. The avanafil 100mg and 200mg arms were statistically superior compared to the avanafil 50mg arm, however there was no significant benefit between the avanafil 100mg and 200mg arms. A study by Rosen et al defined that the minimal threshold of a clinical relevant change from baseline for SEP3, SEP2 and ILEF score were about 23%, 21% and > 4 point, respectively. All three doses met the clinically relevant threshold. In addition, the results in the special populations such as diabetics and nerve sparing prostatectomy were smaller than those in the general population study. However, the Committee noted that these differences were also observed in the other PDE5 inhibitors as well.

The Committee also reviewed an open-labelled extension study (n = 172; 52 weeks duration) from Belkoff et al which showed that the efficacy of avanafil was sustained over a 52 week period with no significant differences between the 100mg and 200mg doses.

The Committee noted the lack of studies directly comparing avanafil to the other PDE5 inhibitors. Using a systematic review by Yuan et al, an indirect comparison of avanafil to the other PDE5 inhibitors (sildenafil, tadalafil and vardenafil) was made. For the primary endpoint of SEP3 the Committee noted that tadalafil showed a greater mean difference (36.17; 95% CI 31.89 - 39.93) compared to avanafil (22.75; 95% CI 16.48 - 28.87) and sildenafil (17.25; 95% CI 5.85 - 28.57), but acknowledged that these results should be interpreted with caution due to heterogeneity between the trials. Limitations include poor quality and reporting in original studies, differences in the general populations and dosage comparisons as well as questions over the clinical relevance of the mean difference between the PDE5 inhibitors.

In terms of safety, avanafil has a similar tolerability profile to the other PDE5 inhibitors already on the market (sildenafil, tadalafil, vardenafil), with no new safety concerns observed. For convenience, Menarini have applied to get a license for administration 15 minutes before sexual activity for avanafil. The other PDE5 inhibitors have a recommendation of 30 minutes before sexual activity.

The Committee heard that a 100% switch from tadalafil and vardenafil to avanafil would result in a saving of approximately £170K across NCL. However tadalafil is due to come off patent in 2017 and is likely to become considerably cheaper. Dr Mohamed explained that sildenafil would remain first line and that tadalafil would be used in patients post peyronie's or penile graft surgery due to its longer half-life. Avanafil is proposed as a second line option for non-surgical patients if sildenafil was ineffective or not tolerated. Dr Mohamed informed the Committee that avanafil would not replace any of the other PDE5-inhibitors and that the team at UCLH would want all PDE5 inhibitors available due to patient variability in response. The Committee questioned the value of this approach and whether availability of another PDE5 inhibitor would result in patients cycling through multiple therapies.

In summary, the Committee agreed that there was no rationale for adding avanafil to the formulary unless tadalafil could be removed. In addition tadalafil patent will expire in 2017 and would offer greater savings in the long term. Therefore the Committee agreed that avanafil should not be added to the formulary for erectile dysfunction.

7 Topical Ophthalmic Ciclosporin (Applicant: Mr Tom Flynn and Prof Dart; Presentation: Mr Edward Hindle)

The Committee considered a review for topical ophthalmic ciclosporin; a fungal antimetabolite used as an anti-inflammatory drug to treat a variety of ocular inflammatory conditions such as dry eye disease, venal and atopic keratoconjunctivitis and ocular rosacea. The Committee were informed that the alternative treatment with topical steroids results in severe ocular inflammation including cataract formation and increased intraocular pressure.

The Committee reviewed the evidence for the use of ciclosporin in dry eye disease, keratoconjunctivitis sicca, atopic keratoconjunctivitis, vernal keratoconjunctivitis and ocular rosacea and concluded that ophthalmic ciclosporin was a safe and effective treatment option for use in patients with severe disease who were at risk of adverse events from the use of long-term ophthalmic steroid use. At present there are four ciclosporin preparations available in the UK:

- Ciclosporin 0.05% eye drops (Restasis®) - licensed in the US and costs £794 per month
- Ciclosporin 0.06% eye drops manufactured by Moorfields (unlicensed) costing £87 per month
- Ciclosporin 0.2% eye ointment (Optimmune®) which is licensed as POM-V and costs £81 per month
- Ciclosporin 2% eye drops manufactured by Moorfields (unlicensed) costing £112 per month.

Prof Dart and Mr Flynn informed the Committee that patients would only be recommended ciclosporin use under supervision by a Corneal Specialist. At Moorfields Restasis® is not recommended due to the high cost and the 2% eye drops preparation are also not in use. Unpublished data from an ongoing study suggest that the tolerability of Restasis® and the 0.06% ciclosporin eye drops (Moorfields) are the same. Prof Dart and Mr Flynn further explained that there is reluctance in prescribing within the primary care and that the continuous prescriptions for ophthalmic ciclosporin at Moorfields remains impractical for the patient as well as a large cost burden on the Trust.

The Committee discussed at length regarding the practical concerns of prescribing unlicensed preparation in primary care and the potential for the acquisition price to vary from each independent pharmacy. The committee acknowledge that only ciclosporin 2% ointment has a tariff price, however were also informed that the ointment is less well tolerated in comparison to the drops.

The Committee agreed that ciclosporin was reasonable addition to the formulary for prescribing by corneal specialists but requested a strict treatment pathway, particularly for dry eyes, to avoid an increase in non-specialist prescribing and subsequent cost impact. The Committee requested agreed that ciclosporin ointment could be added to the formulary and prescribing can be continued in primary care pending a treatment pathway/protocol for dry eye with restrictions to prescribing by corneal specialist only. The Committee recommended that the logistical concerns with the other preparations that don't have a tariff price should be brought back to the Committee next month for further discussion.

8 NICE Statement on S/C Preparations- Rheumatoid Arthritis

The Committee reviewed a letter from NICE regarding subcutaneous (SC) tocilizumab for rheumatoid arthritis, which included the following statement:

> *'If the indication (target population) for the SC formulation is exactly the same as for the IV preparation, and if NICE has already had a positive appraisal (of the IV preparation) on all of the target groups covered by the planned SC indications, then the cost-savings would support a switch (assuming clinical equivalence of the IV and SC preparations) to the SC formulation.'*

On the basis of this endorsement by NICE, the Committee agreed that SC tocilizumab and SC abatacept used in combination with methotrexate should be added to the NCL formulary.

9 Home Oxygen Ordering Guide

This item was deferred to the next meeting.

10 Type II diabetes treatment pathway- Camden and Enfield pathway

This item was deferred to the next meeting.

11 Denosumab- metastatic bone disease pathway

Dr Boleti informed the Committee that there are difficulties in getting funding approval across NCL regarding the use of denosumab for metastatic bone disease in line with the NICE technological appraisal. Dr Boleti explained that zoledronic acid would remain as first line treatment in view of its cost, and recommended that denosumab should be restricted to the following group of patients:

- Patients with renal impairment
- Allergic or intolerant of IV bisphosphonates
- Patients with difficult intravenous access.

The Committee re-iterated that denosumab is in the formulary already in line with the recommendations made in NICE TA 265. The Committee would support the recommended pathway of restricting patients to the above cohort of patients to aid funding locally.

12 Local DTC Recommendations

12.1 **MEH: ATMP stem cells for ocular surface reconstruction in patients with corneal limbal stem cell deficiency –** approved pending submission of a protocol.

12.2 **NMUH: Remifentanil PCA (2nd line) where epidurals are contra-indicated in labour** - approved at MNUH. This decision was ratified by the JFC

12.3 **RNOH: Hyaluronic acid injection (Ostenil Plus) to prevent surgery -** approved under evaluation. This decision was ratified by the JFC

12.4 **RFH: Ledipasvir for Hepatitis C -** approved pending funding confirmation

RFH: Gemcitabine plus Oxaliplatin for biliary tract cancer where cisplatin is contraindicated - approved under evaluation

RFH: Alteplase for complicated visceral thrombosis - Approved under evaluation

12.5 **UCLH: UCLH: Sodium Cromoglycate for management of IBS symptoms** – not approved

UCLH: Pristinomycin for prosthetic joint infection – approved, restricted to microbiology MDT prescribing.

13 NCL-MMO Minutes

The NCL-MMO minutes were included for information.

14 NCL Dates- August 2014 to July 2015

The NCL dates were included for information.

15 Any other business

Mr A Dutt asked the Committee whether any guidance has been produced for domperidone in specialist indications following the MHRA safety alert. It was agreed that once consensus had been reached locally by Trust DTCs and CCGs, guidance should be disseminated for information, particularly concerning duration of treatment.