NCL Joint Formulary Committee (JFC) Meeting

Minutes from the meeting held on Thursday 27th June 2013

in the Moorfields Eye Hospital Boardroom, 2nd Floor, 15 Ebenezer St, N1

1. Present:	Prof R MacAllister	NCL JFC Chair
	Prof L Smeeth	NCL JFC Vice Chair
	Mr A Dutt	NHS Islington, Head of Medicines Management
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management
	Mr TF Chan	BCFH Chief Pharmacist
	Ms N Shah	NHS Camden, Head of Medicines Management
	Mr G Irvine	Lay Member
	Ms S Drayan	NMUH Chief Pharmacist
	Mr A Shah	RNOH Chief Pharmacist
	Mr T James	MEH Chief Pharmacist
	Dr A Tufail	MEH DTC Chair
	Dr M Kelsey	WH DTC Chair
	Ms W Spicer	RFH Chief Pharmacist
	Dr C Stavrianakis	NHS Haringey, CCG
In Attendance:	Dr A Grosso	UCLP Pharmacist
	Dr R Sofat	UCLH Clinical Pharmacologist
	Ms K Chapman	MEH Formulary Pharmacist
	Ms S Sanghvi	UCLH Formulary Pharmacist
	Ms R Holland	UCLH Formulary Pharmacist
	Dr J Brazier	UCLH Applicant (Aprokam)
	Dr M Cohen	BCF Applicant (Degludec)
	Ms E Mortty	Haringey Medicines Management
	Ms P Shah	WH Formulary Pharmacist
Apologies:	Dr H Taylor	WH Chief Pharmacist
	Dr D Bavin	Camden CCG
	Dr R Fox	RNOH DTC Chair
	Dr P Ancliff	GOSH DTC Chair
	Dr A Jones	Consultant Oncologist, RFH/UCLH
	Dr T Sadhu	NHS Enfield
	Dr L Wagman	NHS Barnet CCG
	Dr R Urquhart	UCLH Chief Pharmacist
	Dr P Taylor	NHS Haringey, Head of Medicines Management
	Dr S Shaw	RFH DTC Chair
	Dr E Boletti	Oncology RFH

2. Minutes of the last meeting

The previous meetings minutes were accepted as accurate. It was agreed that more detailed information on local DTC decisions would given on the JFC Agenda and Minutes.

The Committee was informed that the NOAC paperwork is not yet finalised and will be circulated when available.

3. Matters arising

3.1 MHRA Strontium ranelate warning

At the June meeting, the Committee agreed to contact the MHRA for confirmation on whether 'age' was considered as a risk factor by the MHRA and for a clarification on their definition of 'severe' osteoporosis.

A response from the MHRA stated that 'severe' osteoporosis is not defined in the current product information for Protelos®. The severity of osteoporosis should be determined by the physician on an individual patient basis. Age is not currently included in the list of examples of significant risk factors for cardiovascular events provided in the product information. Age should be considered as part of the individual patient's overall risk of cardiovascular events. The response goes on to state that further clarification may become available following the European evaluation of the benefits and risks of Protelos® in the approved indications which is currently being conducted. The outcome of this review will be communicated to health professionals when available.

4. Members & applicants declarations of relevant conflicts of interest

Insulin degludec applicant Dr M Cohen declared that Novo Nordisk provide a Diabetic Specialist Nurse at Edgware Hospital on a temporary basis.

5. Medicine applications & reviews

5.1 Insulin Degludec (Tresiba®; Novo Nordisk) for diabetes mellitus (Applicant: M Cohen; Presentation: R Sofat)

The Committee considered an application for the long-acting insulin analogue, insulin degludec, to be added to the NCL Joint Formulary for patients who have experienced nocturnal hypoglycaemia with other long-acting insulin analogues.

The Committee heard that once daily insulin degludec has been compared to once daily insulin glargine in a series of open-label, company-sponsored [BEGIN]trials which confirm non-inferiority to insulin glargine with respect to the primary endpoint of reduction in HbA1c from baseline. Both Type 1 and Type 2 diabetics were assessed with regard to this primary endpoint and also secondary endpoints of incidence of severe, nocturnal and overall hypoglycaemia and weight change. The studies were powered for an endpoint difference in HbA1c of 0.4%; study length ranged from 26-52 weeks. A local meta-analysis shows that the mean difference in HbA1c was 0.13% [95% CI; 0.09-0.17] favouring glargine over degludec when all trials were considered.

The Committee heard that in both Type 1 and 2 BEGIN trials, insulin degludec appeared to show a small benefit over insulin glargine in reducing the incidence of nocturnal hypoglycaemia (OR 0.85 [0.72, 1.00]), particularly with regard to Type 2 diabetics in the BEGIN Basal-bolus Type 2 study (OR 0.73 [0.54, 0.97]). However, differing insulin degludec and glargine dosing regimens may have contributed to this outcome; in all studies insulin degludec was administered in the evening but insulin glargine could be given at any time of the day. Another important factor is the open-label nature of the trial, allowing patients to be aware of which insulin they were using, possibly introducing bias. A benefit in Type 2 diabetes is of less importance as the application focuses on degludec use in Type 1 diabetes.

The Committee concluded that there does not appear to be a substantial difference between insulin degludec and glargine with regard to the rates of severe hypoglycaemia. The Committed note that patients with recurrent severe hypoglycaemia were excluded from the BEGIN trials, so relevance in the proposed patient populations remains unknown. It was also noted that any reduction in the risk of hypoglycaemia was larger in patients with Type II (who have a lower incidence of hypoglycaemia) compared to Type I diabetes (higher incidence of hypoglycaemia). This observation increased the uncertainty whether there would be advantage of insulin degludec in Type I patients with frequent nocturnal hypos. Unlike other insulins on the UK market, the Committee heard that insulin degludec is available in two different strengths; 100 units per mL and 200 units per mL, and has been subject to an MHRA safety notice to highlight this to both prescribers and pharmacists. The FDA (November 2012) has also raised concerns about a potential increase in major adverse cardiovascular events (MACE) compared to comparator (hazard ratio of 1.3 [95% CI 0.88-1.93])).

The Committee was presented with a cost-comparison for the different long-acting insulin, showing insulin degludec to be almost double the cost of both insulin detemir and glargine.

The Committee heard anecdotal evidence from the applicant, who reported that he had successfully reduced nocturnal hypoglycaemia in private practice with insulin degludec. The dangers and distressing nature of hypoglycaemia were acknowledged by the Committee; however this needs to be balanced against available evidence and the increased cost of insulin degludec.

In summary, insulin degludec has been shown to be non-inferior to insulin glargine with regard to reduction in HbA1c – the primary endpoint of the currently available trials. There may be a small advantage in the reduction of nocturnal hypoglycaemia, a secondary endpoint of these trials; the Committee therefore considered such data hypothesis-generating and not policy-defining. It is important to note other limitations, the potential for bias in open-labelled trials and that patients with frequent hypoglycaemic episodes and hypoglycaemic unawareness were excluded.

The Committee therefore concluded that there is insufficient evidence of cost-effectiveness to recommend the prescribing of insulin degludec.

5.2 Intra-cameral cefuroxime (Aprokam®; Spectrum Thea) for prophylaxis post-cataract surgery (Applicant: J Brazier; Presentation: A Grosso)

The Committee reviewed an application for intra-cameral cefuroxime for antibiotic prophylaxis post-cataract surgery. The application submitted was for the only UK licensed preparation, Aprokam®, which is reconstituted to a 50mg in 5mL preparation prior to surgery, from which 0.1mL is injected intra-camerally to give a dose of 1mg. Many other centres around the UK, including Moorfields Eye Hospital, currently use unlicensed intra-cameral preparations which are available as a pre-filled syringe, requiring freezer storage and thawing to room temperature prior to administration.

The Committee heard that the use of antimicrobial prophylaxis is commonplace in cataract surgery despite the lack of a definitive protocol – largely because it reduces the rate of infective endophthalmitis - one of the most serious complications of cataract surgery which can be sight-threatening.

The Committee were told that the current practice at UCLH is to use sub-conjunctival cefuroxime for the same indication which is reconstituted prior to surgery from the IV preparation. Whilst this is a very cost-effective prophylaxis regime, current practice in the UK has moved toward intra-cameral prophylaxis.

The Committee heard evidence from a single-centre UK retrospective analysis (Yu-Wai-Man et al, 2008) of all presumed infectious endophthalmitis cases from January 1, 2000, to December 31, 2006. The rate of presumed infectious endophthalmitis in patients receiving sub-conjunctival cefuroxime (n= 19,425) was compared with those receiving intra-cameral cefuroxime (n= 17, 318) at the end of surgery.

The incidence of presumed infectious endophthalmitis was lower in patients who had received intra-cameral cefuroxime (0.46 per 1000 cases) than in those who had received sub-conjunctival cefuroxime (1.39 per 1000 cases), and this difference was statistically significant (OR, 3.01; 95% CI, 1.37-6.63; P = 0.0068).

The Committee noted that as this is a retrospective analysis over 6 years, many other changing factors – including surgeon, operating theatre and training changes – could have affected this result, although the authors note that there were no other changes in protocol during this period.

A further study by the European Society of Cataract & Refractive Surgeons (ESCRS, 2007) randomly assigned patients to 1 of 4 treatment groups of approximately equal sizes. Group A received no peri-operative antibiotic prophylaxis, Group B received the intra-cameral cefuroxime treatment only, Group C received topical levofloxacin 0.5% administered 1 drop 1 hour before surgery, 1 drop 30 minutes before surgery, and 3 drops at 5-minute intervals commencing immediately after surgery, and Group D received both intra-cameral cefuroxime and topical levofloxacin treatments. The levofloxacin treatment was masked; with patients receiving placebo or antibiotic drops from bottles supplied as part of the study. The use of cefuroxime was not masked; surgeons were requested to

give patients who had been randomly allocated to Groups B and D the intra-cameral injection at the end of surgery. The results obtained show that Groups B and D had the lowest rates of endophthalmitis, and that intra-cameral injection of cefuroxime had a statistically significant effect in reducing the risk for endophthalmitis after cataract surgery by phacoemulsification with 0.049 (95% CI; 0.118-0.453) and 0.025 (95% CI; 0.001-0.137) proven cases respectively in the intention to treat population.

With regard to safety, the cumulative experience in other studies confirms that intra-cameral cefuroxime has a broad spectrum, a reliable safety profile, and does not result in anterior segment toxicity. Corneal endothelial toxicity has not been reported at the recommended concentration of cefuroxime; nevertheless, this risk cannot be excluded. Special care is indicated in patients who have experienced an allergic reaction to penicillins or any other beta-lactam antibiotics as cross-reactions may occur.

The Committee agreed that considering the lack of licensed alternatives and the evidence of efficacy and safety of cefuroxime intra-cameral injection, Aprokam® is a reasonable option to replace sub-conjunctival cefuroxime for antibiotic prophylaxis post cataract surgery in patients not allergic to penicillins/cephalosporins.

The Committee also agreed that due to the large volume of cataract surgeries conducted at Moorfields, the Trust should be able to choose to continue using the unlicensed pre-filled syringe manufactured by Moorfields Pharmaceuticals.

5.3 Azelastine hydrochloride and fluticasone propionate (Dymista®; Meda Pharmaceuticals) for severe seasonal and perennial allergic rhinitis (Applicants: Dr G Rotiroti& Dr H Kariyawasam. Presentation: R Holland)

The Committee considered an application for a nasal spray containing azelastine hydrochloride and fluticasone propionate (Dymista®) for the treatment of seasonal and perennial allergic rhinitis if monotherapy with either component alone has failed or is ineffective.

The Committee reviewed evidence from Carr et al, comparing the efficacy of Dymista® with fluticasone propionate (FP),azelastine hydrochloride(AZ) and placebo in 3398 patients with moderate-to-severe seasonal allergic rhinitis (AR) in 3multi-centre, randomised, double-blind, placebo-controlled, parallel-group trials over a 14 day treatment period. The primary efficacy endpoint was the mean change in 12 hour rTNSS from baseline to day 14. The rTNSS is a sum of nasal symptoms; congestion, itching, rhinorrhoea, sneezing on a four-point scale (0=no symptoms, 1=mild, 2=moderate, 3=severe). Patients recorded application time and symptom scores in a diary, twice daily, with a maximum daily rTNSS of 24.Results from the intention to treat meta-analysis population show that Dymista® significantly reduced the average rTNSS when compared with FP (p=0.001), AZ (p<0.001) and placebo (p<0.001).

Hampel et al's proof-of-concept study showed similar results; all three active treatments were significantly superior to placebo in improving the rTNSS (p<0.001), however there was not a statistically significant improvement from baseline rTNSS when Dymista® was compared to FP or AZ alone.

The Committee considered the secondary efficacy endpoints of overall change from baseline in the instantaneous TNSS (iTNSS) and reflective total ocular symptom score (rTOSS). Dymista® showed a statistically significant reduction in the iTNSS than FP (P<0.022), AZ (P<0.001) and placebo (p<0.001) and in reduction of rTOSS when compared to FP (p=0.003) and placebo (<0.001).The improvement in AR symptoms occurred more rapidly with Dymista® than FP (up to 5 days faster, p<0.33), and 7 days faster than AZ (p<0.001).Quality of life was assessed using the Rhinitis Quality of Life Questionnaire (RQLQ) and showed all active treatment significantly improves patients quality of life when compared to placebo (p<0.001).

When considering safety, the Committee heard that the meta-analysis showed adverse events are comparable across all active groups, however long-term safety data are lacking. Price et al considered the long term safety of Dymista® in 612 patients affected with chronic rhinitis or vasomotor rhinitis. This open-label, active-controlled, parallel group study examined patients on Dymista® versus FP alone. Safety and tolerability assessments were made at months 1, 3, 6, 9 and 12. Patients were well matched for baseline characteristics; however 99.5%-100% of patients were of Asian origin. No serious adverse events were noted, and discontinuation due to adverse effects was less than 3% in both groups. The most commonly reported adverse events were dysgeusia (2.5% vs. 0.5%, Dymista®, FP) and headache (1% vs. 4.3%).

The Committee reviewed the convenience and cost of Dymista compared with other AR treatments. All have a dosing regimen of 1 spray per nostril twice daily. The monthly cost of Dymista® is £18.91, compared to £14.83-£17.20 (average £16) for the individual components administered separately. Annual cost impact is difficult to assess as this will depend on length of treatment, which will be subject to intra-patient variability. Dymista® may be a more manageable treatment regimen and it could be suggested that it would improve compliance with a reduced number of nasal sprays used daily. In comparison, the cost of beclometasone dipropionate nasal spray is £2.44 for one month treatment. This has been shown to have a higher rate of systemic absorption than other agents.

In conclusion, the Committee decided that there is currently insufficient evidence of increased clinical benefit of Dymista® over the individual components used separately. The Committee therefore agreed that Dymista® should not be recommended for prescribing.

6. Local DTC recommendations

6.1 RNOH: Barium sulphate (Baritop® 100 liquid and EZ-HD powder) for video-fluoroscopic swallowing exam

6.2 UCLH: Regorafenib (Stivarga®) for gastrointestinal stromal tumours (GIST)

Regorafenib is a novel oral multikinase inhibitor which has potent anti-tumour and anti-angiogenic activity. Regorafenib is available from Bayer Healthcare Ltd for use in a compassionate basis until it has obtained marketing authorisation. The compassionate supply is to continue for patients already commenced on treatment until progression of disease. Regorafenib is restricted for use at UCLH as a third line option for patients with metastatic or unresectable GIST who have failed on, or are intolerant to imatinib and sunitinib.

6.3 RFH: Ferric carboxymaltose (Ferinject®) for iron-deficiency anaemia

Ferinject® is already approved at RFH - this is to extend its use to liver transplant patients with iron deficiency anaemia. The decision was deferred by the RFH DTC whilst clarification is sought as to whether this proposal represents an audit or a research submission.

The European Medicine Association has issued guidance reminding prescribers that all intravenous iron preparations can cause serious hypersensitivity reactions which can be fatal.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Intravenous_iron-containing_medicinal_products/human_referral_000343.jsp&mid=WC0b01ac05805c516f&source=homeMedSearch&category=human

6.4 RFH: Mitotane (Lysodren®) for adrenocarcinoma

Mitotane removed from April 2013 CDF, this is for one urgent case.

6.5 WH: 'Fast-Mix' (lidocaine 2%, sodium bicarbonate 8.4%, epinephrine 1:1000) for conversion of labour epidural analgesia to epidural anaesthesia for CS.

The fast mix solution of lidocaine, epinephrine and bicarbonate is effective and safe for conversion of labour epidural analgesia to epidural anaesthesia for emergency caesarean section. Lidocaine/Epinephrine solutions provide a significantly faster onset of surgical block compared to both epidural top up solutions currently used at the Whittington. The addition of bicarbonate further shortens the time of onset. This may be crucial for a subset of emergency caesarean sections.

7. NCL-MMC minutes

Provided for information only.

8. Horizon scanning, proactive JFC consideration & collaborative working

The Committee considered a proposal by Anthony Grosso to move away from the current reactive process of considering Formulary applications. This would involve a change in activity, whereby the Committee would horizon-scan for new medications and indications as they come to market, before reviewing and discussing their inclusion onto the Joint Formulary.

The Committee agreed that there are benefits and limitations to this proactive approach, and suggested continuing with the current applicant-based system for a further 6 months, before reviewing the process.

The Committee were reminded that currently each Trust produces a six-monthly horizon-scanning document for the relevant CCG's. It was considered sensible to remove any duplication of effort and therefore the Committee will produce a joint horizon-scanning document (next due in September) for CCG notification.

9. Date of next meeting: 25th July 2013. Location to be confirmed.

10. Any other Business

10.1 Adoption of the Moorfields Eye Hospital Ophthalmic Formulary

The Committee agreed that the MEH Ophthalmic Formulary should be adopted across all NCL Trusts, with any restrictions to be agreed locally where appropriate. The Moorfields Ophthalmic Formulary is available on the following web address:

http://www.moorfields.nhs.uk/Publicationsandresources/Medicines

10.2 Updated guidance on the management and treatment of *Clostridium difficile* infection

The Committee considered the updated Public Health England guideline with relation to an earlier JFC decision to restrict fidaxomicin to microbiologist recommendation for patients with multiple recurrent infections [at least 3] or for patients in extremis. The Committee concluded that this early decision is in line with the updated guidance and no modifications to the fidaxomicin formulary status are necessary.