North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 29 September 2016
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof L Smeeth	NCL JFC Vice-Chair	**(Chair)**
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Ms K Landeryou	Patient Partner	
	Ms W Spicer	RFL, Chief Pharmacist	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr R Fox	RNOH, DTC Chair	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Dr M Kelsey	WH, Chair DTC	
	Ms S Ceci	WH, Formulary Pharmacist (on behalf of Mr I Man)	
In attendance:	Mr E Hindle	MEH, Formulary Pharmacist	
	Mr J Minshull	NCL JFC, Support Pharmacist	
	Mr A Barron	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFL, Formulary Pharmacist	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Ms M Kassam	MEH, Formulary Pharmacist	
	Mr P Liu	Islington CCG, Prescribing Advisor	
	Ms G Bhudia	UCLH, Respiratory Nurse	
	Mr A Raheem	UCLH, Consultant Andrologist	
	Dr Balakrishnan	RFL, Consultant Microbiologist	
Apologies:	Prof R MacAllister	NCL JFC Chair	
	Mr T James	MEH, Chief Pharmacist	
	Prof A Tufail	MEH, DTC Chair	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Dr V Thiagarasah	Enfield CCG, GP	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr P Hyatt	NMUH, DTC Chair	
	Dr C McGuinness	Patient Partner	
	Mr TF Chan	RFL, Deputy Chief Pharmacist	
	Dr S Shaw	RFL, DTC Chair	
	Dr R Sofat	UCLH, Consultant Clinical Pharmacologist	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Dr R Breckenridge	UCLH, DTC Chair	
	Prof D Robinson	UCLH, Consultant in Respiratory Medicine	
	Ms H Taylor	WH, Chief Pharmacist	
	Mr I Man	WH, Interim Deputy Chief Pharmacist	
	Dr C Cooper	Islington CCG, GP	

2. Meeting observers

Prof Smeeth welcomed Mr P Liu (Prescribing Advisor, Islington CCG), Ms M Kassam (Formulary Pharmacist, MEH) and Ms G Bhudia (Respiratory Nurse, UCLH) as observers of the Committee and explained the role of Joint Formulary Committee in NCL.

3. Minutes of the last meeting

The minutes were accepted as an accurate record of the meeting.

4. Matters arising

There were no matters arising.

5. Declarations of relevant conflicts of interest

No conflicts of interest relevant to the agenda were declared by the Committee members.

For item 7.2 'Xiapex® for Peyronie's Disease'; Mr D Ralph (applicant) and Mr A Raheem (attendee in support of the application) both declared they were Advisors for Swedish Orphan Biovitrum Ltd (Sobi).

6. Local DTC recommendations / minutes

6.1 Approved by local DTC

DTC site	Month	Drug	Indication	JFC outcome
MEH	July-16	Tacrolimus ointment	Atopic dermatitis [atopic eczema] on eye lids	Added to NCL Joint Formulary
RFL	Aug-16	Rituximab	Granulomatous–lymphocytic interstitial lung disease' (GLILD)	RFL only*
RFL	Aug-16	Treatment pathway including oxybutynin MR	Primary generalised hyperhidrosis	Deferred

**Funding for rituximab for granulomatous–lymphocytic interstitial lung disease (GLILD) is via IFR to NHS England.*

Refer to October 2016 minutes for an update

A treatment pathway for primary generalised hyperhidrosis was approved by RFL. This pathway may be relevant to other Acute Trusts and drugs will be continued in primary care, therefore it was requested the treatment pathway be brought to the next JFC meeting.

6.2 Deferred by local DTC

DTC site	Month	Drug	Indication	JFC outcome
MEH	July-16	Tacrolimus ointment	Atopic Keratoconjuctivits (AKC)	Deferred pending local decision

7. New Medicine Reviews

7.1 Rituximab for myositis (dermatomyositis and polymyositis) (Applicant: Prof M Ehrenstein, UCLH)

The Committee discussed an application for rituximab for the treatment of dermatomyositis (DM) and polymyositis (PM) in adults. The eligibility criteria, stopping criteria, re-treatment criteria and dosing regimen was consistent with NHS England Commissioning Policy 16036/P. The Chair welcomed Prof Ehrenstein from UCLH to answer the Committee's questions about the application.

The Committee reviewed evidence from one multicentre, double-blind, randomised, placebo-controlled trial comparing early (week 0 & 1) with late (week 8 & 9) administration of rituximab in patients with myositis. Eligible patients were adults with either DM or PM, or paediatrics with PM, with refractory myositis and active disease. The primary endpoint was the 'time to definition of improvement [DOI]', secondary endpoints included 'time to 20% improvement in Manual Muscle Testing [MMT-8] score' and the 'proportion who achieve DOI at week 8'. Results found no difference in the primary endpoint of 'time to DOI' between early and late rituximab (mean: 20.2 vs. 20.0 weeks, p=0.74), additionally there were no differences in either secondary endpoints. Additional analyses found mean steroid doses reduced in both treatment arms (from 20.8 mg to 14.4 mg), however there was no significant difference in the steroid reducing rate between both arms.

Explanations for the failure to observe a treatment effect include potential flaws in the study design; the power calculations assumed a rapid treatment response to rituximab (50% achieving DOI by week 8), however the study revealed a slower therapeutic response (50% achieving DOI by week 20). The study also revealed a high placebo response which further underpowered the study; an explanation for the high placebo response rate was not offered in the literature.

With regards to safety, the pivotal trial reported only 1 patient withdrew due to adverse effects and 26 patients developed serious drug related adverse effects which were predominantly infections. There were more infusion reactions with rituximab than placebo during the first infusion, however not with the second infusion. It was noted that rituximab is a high-risk drug with the proposed usage being for an off-label indication; risk management strategies will be taken from the established rheumatoid arthritis treatment protocols.

The drug costs for one treatment course (2 x 1g infusions) is £2,096 administered over two day-case admissions. The application anticipates 5 patients per annum and an infusion frequency of one cycle per annum. Funding will be via NHS England in line with the Commissioning Policy.

The Committee heard from Prof Ehrenstein that myositis is a rare condition which makes recruitment to randomised controlled trials challenging; therefore the pivotal study was designed with two active treatment arms to maximise recruitment. The true comparator for rituximab is IVIg which is considerably more expensive hence using rituximab may be cost-minimising. Rituximab for myositis will be restricted to specialist centres and only used in-line with the Commissioning Policy. Treatment courses will be up to a maximum of two cycles per annum, which will remain cost-minimising compared to IVIg. Biosimilar rituximab, due to reach the UK market in 2017, will be adopted for these patients when launched.

In camera, the Committee raised concerns that the pivotal trial appeared to show no benefit of rituximab, however were assured by the NHS England re-treatment criteria which guaranteed only patients who derived benefit would be eligible to remain on treatment. It was acknowledged that alternative treatments were either more expensive or more toxic, and doing nothing was not a viable option for these heavily pre-treated patients with severe active myositis.

In summary, the Committee agreed to add rituximab to the NCL Joint Formulary for dermatomyositis and polymyositis in adults, in line with the NHS England Commissioning policy.

Decision: Approved
Prescribing: Secondary care only
Tariff status: PbR excluded
Funding: NHS England
Fact sheet or shared care required: No
Audit required: No

7.2 Xiapex (collagenase) for Peyronie's disease (Applicant: Mr D Ralph, UCLH)

Refer to October 2016 minutes for an update

The Committee discussed an application for the administration of collagenase clostridium histolyticum (Xiapex) injections into penile plaques in Peyronie's disease. The Chair welcomed Mr Amr Raheem from UCLH to answer the Committee's questions about the application.

Peyronie's disease is caused by fibrous plaques depositing in the penile shaft, causing painful curvature of the erect penis, which has a reportedly profound effect on the sexual and emotional experience of the sufferer. Xiapex is licensed for treating mature, non-calcified plaques of 30° to 60° curvature using a regimen of 2 x 0.58mg injections one to three days apart for four cycles of treatment. Each cycle is separated by approximately six weeks. In contrast with the submitted application, Mr Raheem clarified that the intended use would be one 0.9mg injection (one full vial) administered for up to three cycles of treatment for a total of 50 patients per annum. Patients would then be issued with a vacuum pump to support remodelling of the penis. Mr Raheem explained that after the first injection, most men experience some oedema making it challenging to inject accurately into the plaque the second time. For this reason in his practice [outside of UCLH] he administers the single, larger injection. Mr Minshull highlighted that this regime is supported only by an abstract for a conference presentation given by Mr Raheem. Mr Raheem explained that he had further data, which had been presented at a more recent conference, demonstrating a mean 34% reduction in curvature in 40 men. Mr Raheem assured the Committee that in his experience the higher dose has not been linked with any additional adverse events to the patients.

It was noted that, although this intervention is mentioned in the European guideline on management of curvature, no hierarchy of treatment options is provided. Surgery is currently the only option available to

Refer to October 2016 minutes for an update

treat affected men. Mr Minshull presented a summary of the evidence, based on the double-blind, placebo-controlled (sham injection) IMPRESS-1 and IMPRESS-2 trials, that demonstrated a modest efficacy for this intervention when used according to the licensed regimen in 832 middle aged men.

Men enrolled in the IMPRESS trials had an average penile curvature of 50° at baseline. The co-primary endpoints in the trials were the improvement from baseline in penile curvature and change in Peyronie's Disease bother score values. The results from IMPRESS-1 and IMPRESS-2 were pooled together for analysis. These trials demonstrated a mean penile curvature decrease of -17.0° in the active treatment arm, and -9.3° in the placebo arm ($p<0.0001$). This represented a difference in -7.7° between arms. The Committee acknowledged that the process of physical manipulation of the penile plaque following injection was likely to have led to this large placebo response.

Considering the secondary outcomes, the Committee did not feel that a difference of one point between the active and placebo arms in the reduction of Peyronie's Disease bother score, a sixteen-point, subject measurement, was a compelling reason to use this intervention (-2.8 vs -1.8, $p<0.0037$), although the Phase 3 open-label study (NCT01243411) did show a slightly larger benefit in terms of bother.

The Committee asked Mr Raheem whether an average reduction of 17° from an average curvature of 50° degrees (the baseline of men entered into the trials) represents a *clinically* meaningful reduction in curvature for patients. Mr Raheem explained that should a man want a perfectly straight penis, surgery would be the only viable treatment option; however, most men are content with some residual curve, therefore Xiapex would be suitable.

With regards to adverse effects of collagenase treatment, the larger proportion of patients in the active arm reporting effects (84% vs 36%) was noted. Of the serious adverse events noted, Mr Raheem explained that corporeal rupture was likely to have been caused by misapplication of the drug, rather than by the drug itself.

In camera, the Committee discussed the uncertainty around the proposed treatment regimen and the absence of submitted data to support this off-label regime. The CCG members highlighted that this drug is not routinely commissioned, and was unlikely to be considered a priority for commissioning. Although the applicant anticipated this would be used as an alternative to surgery, it was noted that most men would be willing to consider any treatment option that would allow them to avoid or postpone surgery, therefore there was risk of this intervention being used routinely prior to the established surgical procedure. The Committee concurred that if patients are currently not eligible for surgery, this cannot be considered a cost saving strategy for the NHS. The Committee agreed that there were a number of outstanding questions and an absence of data to support the application as proposed by Mr Raheem in order to make a decision. Mr Minshull was asked to gain the following further information:

1. Clarify the current cost of surgery for Peyronie's Disease
2. Obtain from Mr Raheem the unpublished data (informing on efficacy and safety) of the proposed regimen of Xiapex for the treatment of Peyronie's Disease
3. Define the exact patient cohort that this will be used in to avoid creep, with reference to the prevalence of this condition (423 per 100,000)
4. Identify how other urology centres in NCL would use Xiapex

Decision: Deferred

7.3 Clomifene and tamoxifen for male hypogonadism (Applicant: Mr D Ralph, UCLH)

The Committee discussed an application for clomifene and tamoxifen for symptomatic hypogonadism (e.g. erectile dysfunction, decrease in energy and libido) in adult males who would otherwise be eligible for exogenous testosterone, however desire to preserve fertility. Exogenous testosterone therapy impairs spermatogenesis by suppressing pituitary gonadotropin secretion (LH and FSH) therefore the European Association of Urology (EAU) contraindicates testosterone for men who have an active desire to have children. The application was not for the treatment of male infertility, or to increase the success rate of Micro-TESE. Mr Amr Raheem from UCLH was in attendance to answer the Committee's questions about the application.

The first study was of randomised, double-blind, placebo-controlled, crossover design in a single centre where patients received 2 months of treatment with clomifene or placebo. Men with erectile dysfunction for >6 months and secondary hypogonadism were included. Of the 21 patients who qualified for inclusion 19 entered the study and results were only presented for the 17 *per protocol* patients. Results showed a significant increase in serum LH, FSH and total testosterone (TT) with clomifene compared with baseline

and placebo. Patient sexual dysfunction questionnaires revealed both treatments lead to improvements from baseline, however outcomes for clomifene were no better than placebo.

The second study was of 12-week, randomised, double-blind, controlled design in a single centre which compared clomifene with anastrazole. Inclusion criteria were men aged 18 to 40, with hypogonadism and serum LH levels in the low or normal range who were unable to conceive after 1 year. Results at week 12 showed an increase in TT levels for both interventions from baseline; however the increase was higher with clomifene. LH also increased significantly in both groups and there was no significant difference between therapies at week 12. The quantitative-ADAM score, a symptom score used in hypogonadism, showed no overall change in patient reported outcomes. No change was observed in the 'International Index of Erectile Function (IIEF) scale' or 'Erection Hardness Scale' (EHS)'.

A third study was a prospective observational cohort trial from a single centre with a mean follow-up of 19 months. Younger men with low TT levels, symptoms consistent with hypogonadism or erectile dysfunction or infertility, and who received clomifene were included in the analysis. Of the 102 patients, data from 86 (84%) were analysed; 9% were excluded because they had not received ≥6 months of treatment and 7% withdrew consent "owing to dissatisfaction with therapy, despite good LH and TT responses". After a mean follow-up of 19 months, TT, FSH and LH levels all increased significantly with clomifene. The proportion of patients who reported problems for each question in the ADAM questionnaire reduced significantly after treatment. The observational nature of the study makes it impossible to determine causality of the objective improvements observed. A fourth study from the same centre as the third, but with a longer follow-up period, found that the non-quantitative ADAM score initially decreased but then increased again over the 36-month follow-up period despite persistently raised TT.

There were no trials investigating the efficacy of tamoxifen for this indication. Two trials investigating the efficacy of enclomifene did not collect data on improvement in hypogonadism symptoms; the FDA had major concerns about these trials and did not grant enclomifene a licence.

With regards to safety, there is very little long-term safety data for clomifene and tamoxifen in men. Clomifene or tamoxifen for this indication is not included in EAU guidelines.

The Committee heard from Mr Raheem that, in contrast to the submitted application, he would not recommend clomifene as an alternative to exogenous testosterone in patients with symptomatic hypogonadism. All patients with symptomatic hypogonadism should be started on exogenous testosterone and when a patient wants to conceive, testosterone should be stopped and Pregnyl (LH) commenced to restart spermogenesis. The role of clomifene in andrology is for the treatment for men with primary testicular failure who present to infertility clinics; clomifene increases serum testosterone to improve semen parameters, or increase success rate of Micro-TESE. Longer term risks of clomifene and tamoxifen may include gynaecomastia due to the oestrogenic effects and visual field defects due to hyperstimulation of pituitary gland.

In camera, the Committee considered the application for symptomatic secondary hypogonadism and agreed clomifene or tamoxifen improved biochemical markers, however there was no evidence either drug improved symptoms of hypogonadism. There was concern that body weight was not reported in the clinical trials as oestrogenic effects may increase weight which could worsen hypogonadism. The treatment of hypogonadism in the obese must include weight-loss which was not described in the treatment algorithm provided by the applicant.

In summary, clomifene and tamoxifen for symptomatic secondary hypogonadism in adult men who want to preserve fertility was not approved. The Committee encouraged a new submission for short-term clomifene to improve semen parameters, or success rates of Micro-TESE in men with primary testicular failure.

Decision: Not approved

7.4 Ceftolozane-taxobactam (Zerbaxa®) for multidrug resistant Gram negative organisms (Applicant: Dr I Balakrishnan, RFL)

The Committee discussed an application for ceftolozane-taxobactam for multi-resistant Gram negative organisms. Ceftolozane-taxobactam is licensed for complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI) however the application was for a broader indication. The Chair welcomed Dr Balakrishnan from RFL to answer the Committee's questions about the application.

The licensing study for cUTI found empirical ceftolozane-tazobactam to be non-inferior to levofloxacin and similarly the licensing study for cIAI found empirical ceftolozane-tazobactam plus metronidazole to be non-inferior to meropenem.

The licensed dose for ceftolozane-taxobactam is 1.5g thrice-daily; however there is an ongoing randomised controlled study and several case studies that are investigating the use of 3g thrice-daily for respiratory infections. The appropriate dose in paediatrics and patients on haemofiltration has not been adequately determined.

In vivo testing by Public Health England found 58% of referred ESBL-positive *E. coli* and Klebsiella *spp.* were susceptible to ceftolozane-tazobactam however their data suggest impermeability, the main source of ertapenem resistance in ESBL producers, can also compromise ceftolozane-tazobactam. Impressive activity was observed for *P. aeruginosa*; among the 206 referred samples, 80% were susceptible to ceftolozane-tazobactam and half of the 80 isolates that were non-susceptible to all other penicillins, cephalosporins and carbapenem were also susceptible.

With regards to safety, the most common adverse effects include nausea, headache, constipation, diarrhoea and pyrexia. A decline in renal function has been seen in patients receiving ceftolozane-tazobactam.

With regards to risk assessment, the Committee felt that there is a high potential for risk of confusion between ceftolozane-tazobactam (Zerbaxa) and ceftazidime-avibactam (Zavicefta) irrespective of whether the generic or branded names were used, therefore each Acute Trust will need to take steps to minimise this risk. This risk is particularly prominent as these two drugs have different spectrums of activity.

With regards to cost, ceftolozane-tazobactam at 1.5g thrice-daily costs £1,696 for a 7 day course, however the higher doses (3g thrice-daily) will be required for respiratory infections which would cost £3,392. The application suggests that use of this agent (at its low-dose) would be cost-neutral in comparison with the current alternatives, colistin + tigecycline or colistin + IV fosfomycin.

The Committee heard from Dr Balakrishnan, that ceftolozane-tazobactam would not be effective against carbapenemase producing organisms; however the majority of local carbapenem resistant organisms were not resistant via this mechanism. It was clarified that ceftolozane-tazobactam would be reserved for infections resistant to all other antibiotics, or where the only active agents were colistin, tigecycline or fosfomycin. Limitations of currently available alternative treatments was as follows: tigecycline is not renally excreted so cannot be used for urosepsis and the FDA warn of an increased risk of death with this agent; colistin is associated with neuro and nephrotoxicity and requires therapeutic drug monitoring via an external reference laboratory; fosfomycin is not licensed in cIAI. Treatment with ceftolozane-tazobactam would be based on finding an isolate which is known to be susceptible and where other therapeutic options are unsuitable or unavailable.

In camera, the Committee discussed that the lifespan of this drug would likely be short as metallo-beta-lactamases are likely to become more prevalent in the UK, however in the mid-term, ceftolozane-tazobactam would serve as a useful agent. Ceftolozane-tazobactam is unlikely to be cost-neutral as a proportion of patients will require the high dose which is not accounted for the in the budget impact assessment.

In summary, the Committee agreed to add ceftolozane-tazobactam to the NCL Joint Formulary for multi-resistant Gram-negative organisms that have proven susceptibly to ceftolozane-tazobactam and where the only alternative active agents, if any, are limited to colistin, tigecycline and fosfomycin. Usage should be restricted to Microbiology approval only.

Decision: Approved
Prescribing: Secondary care only
Tariff status: In tariff
Funding: Secondary care
Fact sheet or shared care required: No
Audit required: No

8. Guidelines

No guidelines were considered at this meeting.

9. Minutes of NCL Medicines Optimisation Network June 2016

This item was included for information only.

10. JFC Work-plan

Mr Minshull informed the Committee that the amended DOAC documents are likely to be presented at the October JFC meeting.

Prof Smeeth requested that WH prioritise their melatonin application as GPs are being asked to prescribe for children and adolescents.

11. Next meeting

Thursday 27th October 2016, Room 6LM1, Stephenson House, 75 Hampstead Rd.

12. Any Other Business

Mr Minshull explained to the JFC that there was a typo in the July minutes in relation to the COPD patient population eligible for treatment with the LABA/LAMA combination inhaler. After discussion with the applicant, it was determined that the minutes should also be updated to clarify patient cohorts according to their GOLD stage. The approved cohort eligible for treatment with umeclidinium and vilanterol combination will now read:

> *The intended patient group is those with COPD who decline on or cannot tolerate inhaled corticosteroids (ICS) and have:*
>
> *(a) FEV1 <50% and persistent breathlessness despite PRN short-acting beta-agonist or short acting antimuscarinic (patients could be in GOLD stage C or D)*
>
> *(b) FEV1 ≥ 50% predicted who are experiencing exacerbations, or have breathlessness despite maintenance with LAMA, will also be considered for treatment with combination, especially if there isn't a clear need for ICS (patients could be GOLD stage B, C or D)*

Mr Minshull agreed to communicate this change with the Camden, Haringey and Islington Responsible Respiratory Prescribing group, as they are currently working on a COPD prescribing guideline.