North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 27 October 2016
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Ms L Reeves	C&I, Chief Pharmacist	
	Mr T James	MEH, Chief Pharmacist	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Dr V Thiagarasah	Enfield CCG, GP	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Dr C McGuinness	Patient Partner	
	Mr TF Chan	RFL, Deputy Chief Pharmacist	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Dr R Sofat	UCLH, DTC Chair	
	Prof D Robinson	UCLH, Consultant in Respiratory Medicine	
	Dr H Taylor	WH, Chief Pharmacist	
	Dr M Kelsey	WH, Chair DTC	
In attendance:	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 D Ralph	UCLH, Consultant Andrologist	
	Dr A Fayaz	UCLH, Consultant Anaesthetist	
	Dr A Drebes	RFL, Consultant Haematologist	
	Ms C Gates	UCLH, Anticoagulation Pharmacist	
	Dr D Heaney	UCLH, Consultant Neurologist	
	Ms H Mehta	NMUH, Formulary Pharmacist	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Prof A Tufail	MEH, DTC Chair	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Mr G Kotey	NMUH, Chief Pharmacist	
	Dr P Hyatt	NMUH, DTC Chair	
	Ms K Landeryou	Patient Partner	
	Ms W Spicer	RFL, Chief Pharmacist	
	Mr A Shah	RNOH, Chief Pharmacist	
	Dr R Fox	RNOH, DTC Chair	
	Dr S Shaw	RFL, DTC Chair	
	Dr R Kapoor	UCLH, Consultant Neurologist	
	Dr S Ishaq	WH, Consultant Anaesthetist	

2. Meeting observers

Prof MacAllister welcomed Dr Muduligo (FY2, UCLH), Ms Sainz De Vicuna (Pharmacist, UCLH) and Ms Staines (Pharmacist, UCLH) as observers of the meeting and explained the role of Joint Formulary Committee in NCL. Prof MacAllister informed the Committee that following a round of interviews, Dr Sofat has been offered the position of UCLH DTC Chair.

3. Minutes of the last meeting

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

4. Matters arising

4.1 Oxybutinin (IR and MR) for hyperhidrosis

The pathway for the use of oxybutynin IR and MR for Primary Generalised Hyperhidrosis treatment has been deferred until the RFL evaluation for oxybutynin MR has concluded.

4.2 Xiapex® (collagenase) for Peyronie's disease (Mr D Ralph, UCLH)

The Chair welcomed Mr Ralph, who attended to present the additional information requested following review of the application at the last meeting.

1. Cost of surgery:

Mr Minshull advised the Committee that the PbR tariff codes for urological surgery are as follows, however, he has not yet received confirmation of which code is used in treatment of Peyronie's disease:

LB47Z	Major Open Penis Procedures	£3,728
LB48Z	Intermediate Open Penis Procedures	£1,850
LB56A	Minor Penis Procedures, 19 years and over	£767

2. Data on off-label dosing regimen:

Evidence of efficacy of a modified treatment protocol (one Xiapex 0.9 mg injection administered at four weekly intervals for three cycles) was presented in the form of a poster the applicant had presented at 20th World Meeting on Sexual Medicine in September 2016. The modified protocol was being used in practice as it is difficult to follow the licensed injection schedule (two injections per cycle separated by a couple of days) and it is less expensive to deliver a 0.9 mg dose than to deliver two 0.58 mg doses. To date, twenty-eight patients have been enrolled in this open-label, single arm study. Twenty three of the patients received three injections, whereas five of the patients received six injections in total.

The mean baseline curvature was 53.9°, reducing by 15.5° (range: 0° to 40°) to 38.4° (range: 12° to 75°) following treatment with Xiapex ($p<0.001$). In the five patients who received six injections, an additional improvement of 10.4° (range: 0° to 30°) was reported. Using a subjective assessment (Global Assessment of Peyronie's Disease Questionnaire), the majority of patients reported some improvement, with only three patients reporting "stayed the same" and 1 patient reporting "a little worse". Erectile function and intercourse satisfaction were also reported to improve following treatment with Xiapex.

3. Patient cohort:

The Committee acknowledged the applicants view that Xiapex will not be suitable for patients wanting a perfectly straight penis, and is most likely to have a role in those with a baseline curvature of 45° to 60°; the aim is to reduce the curvature to less than 45° to meet the patient's needs. Regarding clinically relevant outcome of Xiapex administration, of the fifty patients treated so far in private practice, only 3 have gone on to have surgery suggesting satisfaction with the result. The Committee were assured by the applicants confirmation that Peyronie's disease is not a relapsing condition, although 2% of men may experience Peyronie's again through recurrence.

4. Access within NCL:

The Committee noted that the modified protocol would have to be discussed with the other urology centres in NCL who want to use Xiapex, due to the unlicensed nature of the regimen under discussion. Mr Ralph will be asked to produce a treatment protocol to share with other urology centres.

Based on the unpublished data considered, the Committee agreed that Xiapex administration in accordance with this modified treatment protocol seemed almost as effective as when used according to the licensed indication, equally safe, and more cost-effective. There was a real possibility that Xiapex might reduce the number of penile operations, and that this was both desirable and measurable. The Committee agreed to include Xiapex on the NCL Joint Formulary.

Decision: Approved (pending business case)
Prescribing: Secondary care only
Tariff status: PbR-excluded (when administered as outpatient)
Funding: CCG
Fact sheet or shared care required: N/A
Audit required: No

4.3 Appeal: Brivaracetam for partial onset epilepsy (Dr D Heaney, UCLH)

At the April 2016 meeting the JFC reviewed an application for the use of a new anti-epileptic drug (AED), brivaracetam, within in licensed indication. A decision of 'not approved' was reached on the basis that the data considered failed to demonstrate any clinically significant benefit over levetiracetam. This comparison was made as the Committee noted that brivaracetam is structurally and pharmacologically similar to levetiracetam. The Committee also noted that the proposed advantage of brivaracetam over levetiracetam, lower incidence of psychological disturbance, postulated as the target population within the application, has not been demonstrated in the clinical setting, whilst the SPC for brivaracetam continues to warn clinicians about the risk of suicidal ideation.

Dr Heaney, in his capacity as Lead consultant for Clinical and Experiment Epilepsy at NHNN / RFL, presented an appeal to the above decision based on the following:

- Patients with refractory epilepsy are a major cost pressure to emergency services
- Epilepsy trials fail to achieve the levels of funding needed to conduct robust clinical trials with clinically meaningful outcomes (as required by the Committee) and hence are conducted in accordance with regulatory requirements
- The Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) have considered the evidence for brivaracetam since the JFC review and have approved the drug
- Other specialist epilepsy units (such as King's College Hospital) have approved brivaracetam; as such it is proving difficult for the epilepsy service at NHNN / RFL to provide advice to other centres on the use of this new AED as they are unable to prescribe it
- Brivaracetam offers mechanistic differences from levetiracetam such as higher affinity for synaptic protein 2A and no involvement in AMPA-gated currents or calcium currents, although it was accepted that there is currently no evidence to demonstrate the benefit of these differences
- The epilepsy service at NHNN / RFL operates a high standard of medicines governance and implements a robust medicines management strategy:
    - All patients commenced on a new AED are placed on a register and reviewed at 3, 6 and 12 months
    - Drugs are stopped where benefit is not seen

Dr Heaney explained to the Committee that the neurology specialists had initially been concerned that this was a levetiracetam "me-too" and are well aware that they have been stung by emergent side-effects from novel AEDs in the past. However, the NHNN and RFL have a number of patients with highly-refractory epilepsy (inadequate response to > 6 AEDs) who consume a lot of NHS resource in terms of emergency attendances; approximately 50 patients under their care meet these criteria for whom brivaracetam would offer an opportunity to attempt seizure control. He further explained that the robust medicines management processes that the neurologists employ will prevent this drug being used in less refractory patients. Evidence from local prescribing data [not presented during the meeting] has demonstrated this with other drugs such as lacosamide, zonisamide and perampanel.

Dr Heaney acknowledged to the Committee his awareness of publications, and indeed his experience, which suggest that once patients have tried multiple AEDs their likelihood of achieving seizure freedom from a new AED diminishes; approximately 20 – 30% chance of significant improvement in seizures and possibility of 3 – 4% chance of seizure freedom. However, there remains a cohort of patients within NCL who are not tolerating current treatment and have a 1% chance of dying from seizures. This population have more refractory epilepsy than those considered within the trials. As the neurology community in NCL is very small, if this were to be made available for their use, all patients can be added to a registry

when brivaracetam is started. The registry would help build on the experience from the short-term licensing studies, as it allows regional data collection on real world use of AEDs.

The Committee acknowledged the positive work that the epilepsy service at NHNN / RFL undertake to curate introduction of new AEDS, however, remained of the view that brivaracetam was almost indistinguishable from levetiracetam. With reference to the data considered previously, the licensing trials showed that when brivaracetam was given to patients on concomitant levetiracetam they experienced no additional benefit. Despite the lack of treatment options for this refractory population, until a head-to-head comparison of off-target effects and safety is conducted between brivaracetam and levetiracetam, it was agreed that there will be no way to know if there is any true benefit of this new AED in terms of toxicity and safety. Dr Heaney suggested that brivaracetam may differ from levetiracetam clinically because of the differences in metabolism and pharmacological effect although he would require availability for it to be prescribed in order to build local experience of it. The Committee suggested that brivaracetam could be approved on an individual patient basis in the rare circumstances that a patient may be experiencing off-target effects from, but had been responding to, levetiracetam; this would not require formulary approval but could be monitored by the JFC Pharmacists. Dr Heaney explained that engaging with the one-off process for each patient is far from ideal and likely to be cumbersome.

In camera, the Committee noted that no new data were presented that informed on the value of brivaracetam compared with levetiracetam, the key driver behind the previous decision of non-approval. Further, the decisions by the AWMSG and SMC followed a review which included comparators that were indicated only for adjunctive therapy; this included a sponsor submitted network meta-analysis, which based on its design, excluded generic drugs like levetiracetam from the analysis. The Committee however appreciated the dilemma presented regarding the local cohort of patients with highly-refractory epilepsy and were persuaded by the high standard of medicines governance demonstrated by the epilepsy service over recent years. Based on the above, the Committee voted on whether to approve brivaracetam for addition to the NCL Joint Formulary:
Approve: 0
Approve under Evaluation: 4
Not Approve: 8
Abstention: 3

Decision: Not approved

Post-meeting notes: To support the NHNN Epilepsy Service to gather data on the benefits of brivaracetam in patients with refractory epilepsy who responded to levetiracetam, but had to stop due to off target effects, individual patient approval for this drug can be obtained from the JFC Pharmacists on behalf of UCLH / RFL. This reduce the administration burden of this process, the registry data collected by the team could be shared.

The following data will be requested before individual patient approval will be given:

- *Patient name and hospital number*
- *Other antiepileptic drugs patient has received (including start and stop dates)*
- *Date levetiracetam started*
- *Date levetiracetam stopped*
- *Off-target effects experienced with levetiracetam*
- *Baseline scores (see below)*

Three and six months after treatment has been initiated, the following data from the epilepsy register held at NHNN will be requested for each patient:

- *Physician and patient global impression*
- *Impact on duration and severity of seizure*
- *Impact on number of seizures*
- *Impact on seizure freedom*
- *Impact on A&E attendances*

5. Declarations of relevant conflicts of interest

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

For item 4.2 'Xiapex® for Peyronie's Disease'; Mr Ralph declared he was an Advisor for Swedish Orphan Biovitrum Ltd (Sobi). For item 4.3 'Appeal: Brivaracetam for partial onset epilepsy'; Dr Heaney declared he was an Advisor for a levetiracetam generic manufacturer.

6. Local DTC recommendations / minutes

6.1 Approved by local DTC

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Sep-16	Hydromorphone (intrathecal)	Intractable cancer pain	UCLH only
RFL	Aug-16	Genvoya® (emtricitabine, elvitegravir, cobicistat, tenofovir alafenamide fumarate [TAF])	HIV in line with NHS England Commissioning Policy	Added to NCL Joint Formulary in line with NHS England Commissioning Policy

6.2 Not approved by local DTC

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Jun-15	Dornase alfa + alteplase	Intrapleural fibrinolysis	Not approved[†]
UCLH	Sep-16	Dactinomycin	Relapsed/refractory acute myeloid leukaemia (AML)	Not approved outside of the context of a clinical trial

[†] *RFL are considering a similar application to that originally reviewed at UCLH. The RFL applicant has been asked to work with the original UCLH applicant to develop a joint appeal. The appeal will be heard at JFC.*

7. New Medicine Reviews

7.1 Hyaluronidase for epidurolysis (Applicant: Dr A Fayaz, UCLH)

The Committee discussed an application for hyaluronidase for epidurolysis (epidural lysis of adhesions, adhesiolysis) for the treatment of chronic pain in patients presenting with radicular pain. The Chair welcomed Dr Fayaz to answer the Committee's questions about the application.

Kim et al. report a prospective un-blinded, randomised, single-centre, active-comparator controlled trial in South Korea in patients with 'Failed Back Surgery Syndrome' (n=60). Patients were randomised to triamcinolone + bupivacaine (TB), bupivacaine + hyaluronidase (BH) or triamcinolone + bupivacaine + hyaluronidase (THB). At baseline, median VAS was approximately 7. Results found TB was associated with a significantly decreased score on the Visual Analogue Scale (VAS) by week 2 which persisted until week 12 (7.2±2.04 to 5.5±1.51, $p<0.001$), BH did not significantly reduce from baseline and THB had the largest reduction in VAS by week 2 and by week 12 (7.34±2.12 to 3.82±1.95, $p<0.001$). The study had many weaknesses; the method of randomisation was not described, primary outcomes measure was not described, power calculations were not performed and the statistical analyses were crude. There was also a high risk of bias given the un-blinded natured of the study which was of particular concern as outcomes were patient-reported subjective measures..

Rahimzadeh et al. report a double-blind, randomised, single-centre, active-comparator controlled trial in Iran in patients with 'Failed Back Surgery Syndrome' (n=25). Patients were randomised to triamcinolone + bupivacaine + hypertonic saline (TBS) or triamcinolone + bupivacaine + hypertonic saline + hyaluronidase (TBSH). Following the procedure, patients with VAS scores >3 were prescribed celecoxib. The primary outcome measure was a reduction in the 'without moving' [when the patient is stationary] VAS from baseline by week 4. Secondary outcomes included celecoxib dose. At baseline, median VAS was approximately 3. Results at week 4 showed the VAS was 2.5 and 1.5 and with TBS and TBSH respectively ($p=0.02$). The mean celecoxib use was also higher with TBS compared to TBSH (1420mg vs. 780mg per week, $p=0.01$).

Ko et al. report a double-bind, randomised, single centre, active-comparator controlled trial in Korea in patients with radicular pain in the presence of radiographically confirmed lumbar spinal stenosis and lumbar disk herniation (n=252). Patients were randomised to triamcinolone + bupivacaine (TB) or triamcinolone + bupivacaine + hyaluronidase (TBH). At baseline, mean VAS was 7.6. Results at week 12

showed an improvement in VAS from baseline that was similar between groups (TB; 7.6 to 2.2, TBH; 7.6 to 2.5). In group TB, VAS decreased at 2 weeks, then increased over weeks 2–4, and then decreased thereafter whereas in group TBH, VAS decreased from 2 weeks and was maintained thereafter. These differences were minor.

With regards to safety, the overall reporting of adverse effects is poor however one study identified a higher risk of rash and itching in the hyaluronidase arm. Hyaluronidase via the epidural route is off-label and Trusts must complete individual risk assessments; UCLH have risk assessed Hyalase® (Wockhardt UK Ltd) and consider it suitable for epidural administration. The budget impact is expected to be £5,000 annually across NCL.

The Committee questioned the mechanism by which hyaluronidase exerted a prolonged therapeutic effect on the basis that fibrous tissue is a composite with a minor contribution from hyaluronic acid and the half-life of hyaluronidase is limited to minutes. The Committee heard from Dr Fayaz that the predominate action was unlikely to be releasing trapped nerves, but rather improving the distribution of the corticosteroid and local anaesthetic to the affected area. The improved distribution is visible via routine imaging throughout the procedure. Hyalurondiase also permits the catheter, which is inserted in the cordial space, to move further up the epidural space to where the therapeutic substance is needed.

In camera, although unclear on the mechanism of action that hyaluronidase offers, the Committee agreed that the resultant improved distribution of the therapeutic substances to the affected site was likely to be beneficial. Concern was still raised that the largest study showed a trivial treatment effect. The overall risks of the procedure, both in terms of adverse effects and budget impact were considered low. The Committee agreed to add hyaluronidase to the NCL Joint Formulary for epidurolysis, for the treatment of chronic pain in patients presenting with radicular pain.

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

7.2 Melatonin for insomnia in learning disability (Applicant: Prof A Hassiotis, C&I)

The Committee discussed an application for melatonin to be used in patients with chronic insomnia that have learning disabilities. Melatonin is only licensed for the short-term management of primary insomnia in adults aged at least 55 years, but is also available on the NCL Joint Formulary for use in sleep disorders caused by visual impairment, REM sleep behaviour disorders and circadian rhythm disorders.

The request is in line with NICE Guideline 11 (Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges), which recommends considering melatonin if a drug is required to help with sleep problems. This should follow behavioural interventions and consultation with a psychiatrist or specialist paediatrician with experience of using melatonin in people with learning disability. The evidence review conducted by NICE for its 2015 guideline identified four relevant randomised controlled trials, which the Committee considered.

The most relevant study included by NICE was Gringras *et al* (2012). They conducted a 12-week, randomised, double-blind, placebo controlled study, including 146 children (age 3 years to 15 years 8 months) with neurodevelopmental problem. Melatonin was initiated at 0.5 mg daily, and could be escalated to 12 mg based on response and tolerability. This study measured total sleep time (using a sleep diary) as the primary outcome. Secondary outcomes included total sleep time (actigraphy), sleep onset latency (diaries/actigraphy), and Composite Sleep Disturbance Index (CSDI) and Epworth Sleepiness Scale (ESS).

The total sleep time (sleep diary) increased by mean 40.5 minutes in melatonin treated patients, compared to 12.5 minutes in placebo patients (difference of 28 minutes, adjusted difference 22.4 minutes) ($p=0.04$). Sleep onset latency was statistically significantly lower in the melatonin group compared to placebo group when measured both using sleep diary (-37.5 minutes, $p<0.001$) and actigraphy (adjusted difference -45.3 minutes, $p<0.001$). CSDI and ESS showed a statistically significant improvement for melatonin compared to placebo. CSDI (a 12 point scale) was an additional 1 point lower in the melatonin group compared to placebo (lower score better). The ESS was an additional 1.6 points lower in the melatonin treated group compared to the placebo patients (lower score better). Scores that

measured individual behaviours that challenged (e.g. irritability, agitation, hyperactivity) did not differ between melatonin and placebo treated patients.

The Committee acknowledged that, although this intervention is support by NICE guidance, it is off-label, and will require GP prescribing to support ongoing care. However, there is little known about the long-term safety of this drug. Theoretical concerns about impact on fertility have been raised, though there is no robust evidence to suggest that use of melatonin in children is currently affecting fertility. Discontinuations due to adverse events in general are no more likely for melatonin than for placebo.

NICE Guideline 11 states that melatonin tablets are likely to be a cost-effective intervention in this indication. Melatonin oral suspension and oral solution are not cost-effective compared to tablets because they are considerably more expensive. The Committee acknowledged the added cost of non-tablet oral formulations, and recognised that these should be strictly reserved for patients who cannot use tablets. The Committee noted that the dose listed in the application was very low (2 mg daily), and agreed that as the Gringras study used larger doses, there was justification for using doses up to 12 mg daily where necessary.

The Committee agreed to add melatonin tablets and oral formulations to the formulary in this indication. GPs will require clear guidance on monitoring requirements, including how to review therapy and stop melatonin if appropriate. This will be referred to the Medicines Optimisation Network to produce the shared care or fact sheet.

Decision: Approved
Prescribing: Specialist initiation and continuation by GP under shared care
Tariff status: In-tariff
Funding: Hospital and GP prescribing budgets
Fact sheet or shared care required: Yes – format to be agreed at MON
Audit required: No

7.3 Parsons Solution for interstitial cystitis (Applicant: Mr J Ockrim, UCLH)

The Committee discussed an application for Parsons solution (a mixture of heparin, lidocaine and sodium bicarbonate) for intravesical administration in patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Parsons solution is to be administered either twice weekly for three weeks, or thrice weekly for two weeks (maximum 6 doses).

The committee noted the product applied for is one of many options listed in international guidelines on the management of BPS. It is proposed that administering a combination of heparin, lidocaine and sodium bicarbonate intravesically will benefit patients with IC/BPS via the anaesthetic effect of lidocaine, and a protective effect from heparin on the glycosaminoglycans layer of the bladder. Sodium bicarbonate acts as an alkalizing agent to enable passage of drug through the bladder endothelium.

The evidence base for this intervention mostly consists of short duration, small, open-label studies. There is one small, double-blind trial that demonstrated Parsons solution is more effective at reducing pain and improving global assessment of response than placebo instillation. All of the quoted studies demonstrated a positive effect from Parsons solution, with no serious side effects listed. Each study had serious methodological weaknesses.

Parsons *et al* (2012) conducted a small (n=18), multi-centre, placebo-controlled, double-blind cross-over study in patients with interstitial cystitis and a high symptom burden (pelvic pain and urgency/frequency) at screening (scoring 5 out of 10 on pain and urgency scores). Patients were excluded if they were also taking opioid analgesics, tricyclic antidepressants or gabapentin, which may limit the external validity of this trial as patients treated following a neuropathic route may have been treated with TCA or gabapentin. Analysis was on a per-protocol basis. For the primary outcome of mean % change in pain by 12 hours, there was a statistically significant better response to Parsons solution (42% reduction) than to placebo (21%), though the committee were conscious of the large placebo response and short time period over which the outcome is measured.

Parsons (2005, n=82) had previously conducted an open label, uncontrolled study in patients newly diagnosed with interstitial cystitis were administered an intravesical mixture of heparin, sodium bicarbonate and lidocaine. The intervention formulation was changed part way through the study (lidocaine increased from 1% to 2%), with n=47 receiving the lower concentration of lidocaine, and n=35 receiving the higher concentration. Those receiving 1% lidocaine received just one dose of treatment, whereas participants in the 2% group were given the option to be treated 3 times per week for 2 weeks.

Pain and urgency relief was assessed within 20 minutes of administration for all patients. Patients in group two were also assessed by telephone follow up at 24 to 48 hours to determine the extent of their relief. The predefined end point was ≥ 50% improvement ("significant improvement") in symptoms using the PORIS scale (Patient Overall Rating of Improvement of Symptoms). 75% of patients in the first group (1% lidocaine, n=35/47) experienced "significant improvement" in pain and urgency when they were asked about it 20 minutes after the instillation. 94% of patients in the second group (2% lidocaine, n=33/35) experienced "significant improvement" at the 20 minutes post-instillation point. Twenty eight of the thirty five patients in group two completed the telephone consultation; half experienced at least 4 hours of symptom relief. Twenty patients then went on to receive 6 doses of this mixture; 80% of whom reported sustained relief in pain and urgency at 48 hours after the last instillation following two weeks of treatment.

The committee noted the methodological limitations inherent when measuring a subjective outcome in an open-label study. It was also concerning that the follow-up period was so short for an intervention used to treat a long-term condition, and these newly diagnosed patients were unlikely to be representative of the cohort likely to receive this intervention.

The Committee also considered the findings of Nomiya *et al* (2013), as this open-label, uncontrolled study (n=32 patients, 90% female) followed up refractory interstitial cystitis patients initially for 12 weeks of treatment and then for 6 months following treatment. The primary outcome considered was the Global Response Assessment (GRA), which asks patients to assess their symptoms compared to baseline using a seven-point scale ranging from markedly worse (-3) to markedly improved (+3).

This study considered any positive patient rating ("slightly improved", "moderately improved", "marked improvement") as a responder to treatment, and reported a response rate of 33% at week one, increasing to 77% at week twelve. Response rates were 90% one month after treatment, but had fallen to 17% after 6 months. Although the longer-term nature of the follow-up was noted, the subjective outcome measured in an open label study was of limited usefulness.

The most notable adverse event noted was bladder pain and burning on administration, which was experienced by up to 13% of the treatment arm patients. Clotting (aPTT and PT) were not altered, though in one study 4 patients experienced gross haematuria on the day of administration.

Two options for delivery of the mixture were proposed: either administration from a pre-prepared combination, or from a mixture made up from the raw materials. The pre-prepared formulation has the advantage that it doesn't require nurses to make up the mixture, but it comes at an increased cost and is not available as a terminally sterilised formulation. The Committee noted that the cost impact for this in-tariff intervention could be almost £250,000 + VAT per annum if 120 patients are treated.

The Committee acknowledged that because there are various treatment options available for management of this condition, it is not possible to consider Parsons Solution in isolation. This together with the poor quality of the data, meant that it was not approved for addition to the formulary. The Committee asked for a IC/PBS treatment pathway to be presented at a future meeting.

Decision: Not approved

Action: Mr Minshull to liaise with the applicant to ask that a pathway be proposed that compares all of the available treatment options for IC/PBS

8. Guidelines

8.1 Ciclosporin Eye Preparations – Fact Sheet (amendment)

The amendment was approved and the new version of the ciclosporin fact sheet will be uploaded onto the NCL JFC website.

9. NCL DOAC documents

The Chair welcomed Dr Drebes (RFL) and Ms Gates (UCLH) to the meeting.

Mr Minshull explained that since the last time these documents were presented at the JFC, the authors have made a significant number of amendments based on extensive stakeholder engagement. A link to the NICE patient decision aid has been added. Prescribing recommendations in patients with renal impairment relate to CrCl rather than eGFR, as this is the measure used in most of the trials; a link to a renal function calculator that was recommended by the Renal Pharmacist at RFL has been included. These documents do not cover education and competency standards for people providing anticoagulation services, as this was out of scope of the project.

Dr Drebes updated the Committee that a number of sections have been updated and added, included the clinical pathways, thrombosis dosing, switching between warfarin and DOACs. Dr Drebes explained that where the document refers to an anticoagulation clinic, this does not differentiate or specify whether the service is primary care, secondary care or GP delivered; asterisk to specify that this refers to any appropriately trained clinical to be added. Information on follow up to be added to the checklist.

When a patient is transferred back into primary care, it will be assumed that the GP will take on prescribing. Providing one month of treatment before referring back to the GP is responsive to patient needs; previously patients were all seen twice in clinic, but experience is that 80-90% of patients are fine at 4 weeks, therefore there is no need for all patients to have further follow up.

It was highlighted that the documents recommend DOAC for someone who has had a previous bleed, yet the committee noted that these patients were excluded from pivotal trials, therefore it isn't known that a DOAC will be safe for them; this would require MDT assessment, therefore should not be a blanket recommendation to DOAC in the guidance.

The Committee thanked Dr Drebes and Ms Gates for their hard work producing these documents and agreed to approve them following minor amendments.

Action: AD and CG to make minor amendments and seek Chair's action

10. JFC Work-plan

This item was included for information only. Any questions should be directed to Mr Barron.

11. Next meeting

Thursday 24th November 2016, Room 6LM1, Stephenson House, 75 Hampstead Rd.

12. Any Other Business

Eculizumab (compassionate use scheme) for Cold Agglutinin Disease was approved by UCLH in June 2016 and restricted to 'UCLH only' by JFC in July 2016. The RFL also require access to eculizumab therefore eculizumab (compassionate use scheme) for Cold Agglutinin Disease was added to the NCL Joint Formulary.

Mr Minshull informed the JFC that retigabine, an antiepileptic drug used in the treatment of partial onset epilepsy, has been discontinued by the manufacturers for commercial reasons. There is currently very little use in NCL. Any patients on this drug will need to have their treatment reviewed by a specialist.

Refer to November 2016 minutes for an update

Prof Robinson informed the JFC that Relvar inhalers (fluticasone furoate/vilanterol trifenatate) have recently had a price decrease, making them less expensive than both Seretide MDI and Sirdupla MDI. The JFC did not approved Relvar inhalers in September 2015 as the Committee wanted to see how the generic salmeterol/fluticasone propionate market developed. As the price of Relvar has fallen further than generic salmeterol/fluticasone propionate, the Committee agreed to approve Relvar to support cost minimisation. Prof Robinson should liaise with the Responsible Respiratory Prescribing group to discuss how this will fit into their guidelines. In the interim, this will be restricted to prescribing by Prof Robinson for patients seen in his specialist clinic.