North Central London
Joint Formulary Committee

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on Thursday 24th September 2015
Room 6LM1, Stephenson House, 75 Hampstead Rd

Present:	Prof R MacAllister	NCL JFC Chair	**(Chair)**
	Mr P Gouldstone	NHS Enfield, Head of Medicines Management	
	Ms N Shah	NHS Camden, Director of Quality & Clinical Effectiveness	
	Mr B Sandhu	NEL CSU, Assistant Director Acute Services	
	Mr J Paszkiewicz	NEL CSU, Senior Prescribing Advisor	
	Dr D Bavin	Camden CCG, GP	
	Dr M Kelsey	Whittington, DTC Chair	
	Ms P Taylor	NHS Haringey, Head of Medicines Management	
	Ms S Drayan	NMUH, Chief Pharmacist	
	Mr A Shah	RNOH, Chief Pharmacist	
	Ms W Spicer	RFH, Chief Pharmacist	
	Ms L Reeves	C&I Mental Health Trust, Chief Pharmacist	
	Mr A Dutt	NHS Islington, Head of Medicines Management	
	Dr R Urquhart	UCLH, Chief Pharmacist	
In attendance:	Mr J Minshull	NCL JFC, Support Pharmacist	
	Ms I Samuel	RFH, Formulary Pharmacist	
	Mr P Bodalia	UCLH, Principal Pharmacist	
	Mr A Barron	NCL JFC, Support Pharmacist	
	Mr E Hindle	MEH, Formulary Pharmacist	
	Dr M Griffiths	UCL, Clinical Teaching Fellow	
	Ms H Amer	UCLH, Registrar, Clinical Pharmacology	
	Dr R Sofat	UCLH, Consultant Clinical Pharmacologist	
	Dr A Shah	UCLH, Registrar, Clinical Pharmacology	
	Dr C Cooper	London Respiratory Network GP (Islington)	
	Prof D Robinson	UCLH, Consultant Respiratory Medicine	
	Dr S Naik	UCLH, Consultant Diabetologist	
	Dr M Rosenthal	RHF, Consultant Diabetologist	
Apologies:	Prof L Smeeth	NCL JFC Vice-Chair	
	Dr R Breckenridge	UCLH, DTC Chair	
	Mr T James	MEH, Chief Pharmacist	
	Dr R Fox	RNOH, DTC Chair	
	Mr C Daff	NHS Barnet, Head of Medicines Management	
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	Dr A Stuart	NHS Camden, GP Clinical Lead Medicines Management	
	Mr T James	MEH, Chief Pharmacist	
	Dr V Thiagarasah	NHS Enfield, Medicines Management GP	
	Mr I Man	WH, Interim Deputy Chief Pharmacist	
	Dr M Griffiths	UCL, Clinical Teaching Fellow	

2. Meeting observers

Dr R Sofat welcomed the applicants and observers to the meeting.

Dr Bavin informed the Committee that she will be stepping down as the GP representative for Camden CCG and will be succeeded by Dr Stuart. Ms Drayan informed the Committee that she will be leaving her post as Chief Pharmacist for NMUH at the end of the month; an appointment to her post has not yet been made. The Committee thanked both members for their contributions and wished them well for the future.

3. Minutes of the last meeting

The last sentence of item 7 was amended to: "The Committee agreed to replace EpiPen with Emerade on the NCL Joint Formulary".

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

4. Matters arising

4.1 Relvar [APPEAL] (Applicant: Prof Robinson, UCLH)

The Committee considered an appeal for Relvar (inhaled fluticasone furoate / vilanterol trifenatate) for patients with severe asthma who are failing to comply with twice-daily Seretide Accuhaler (fluticasone propionate/salmeterol xinafoate).

The Committee heard from Prof Robinson his proposal that once-daily Relvar would optimise treatment adherence in approximately 10-20 patients with poor adherence to twice-daily therapy. The Committee were informed that the RASP-UK study in Belfast had received funding to assess adherence to inhaled therapy; however there was no evidence presently available for the Committee to review that once-daily dosing improved compliance or outcomes. The colour of the Relvar inhaler device had been changed from blue to yellow in order to prevent patients mistaking this as being a reliever inhaler.

The Committee acknowledged that whilst Relvar is currently cheaper than Seretide Accuhaler, the introduction of generics to the market is likely to reverse this over the coming months. The Committee thought it best to see how the generics market will develop.

Based on the absence of evidence to demonstrate that Relvar improves adherence and / or outcomes, the Committee agreed that Relvar should not be added to the NCL Joint Formulary for the above indication.

4.2 Dymista [APPEAL] (Applicant: Prof Robinson, UCLH)

The Committee considered an appeal for Dymista (nasal fluticasone propionate/azelastine hydrochloride) for allergic rhinitis.

The Committee heard that the NHS price for Dymista has been reduced to £14.80 with a manufacturer guarantee for 5 years. The Committee were aware that the price for generic fluticasone nasal sprays have also recently reduced and so requested confirmation that Dymista remained cheaper than the constituent components.

On the proviso that Dymista would be cost-minimising, the Committee agreed that Dymista should be added to the NCL Joint Formulary as a third-line therapy when 1st line betamethasone monotherapy and 2nd line fluticasone monotherapy have failed.

Action: Mr Barron and Ms Taylor to establish the current costs of the constituent components used in combination

Post-meeting note: Rhinolast (1 spray to both nostrils twice-daily) used in combination with fluticasone (2 sprays to both nostrils once-daily [Flixonase, Nasofan, Avamys]) costs £16.93-£19.31. Dymista should therefore be added to the NCL Joint Formulary.

4.3 Insulin degludec [APPEAL] (Applicant: Dr Rosenthal, RHF and Dr Naik, UCLH)

See Section 7.4

5. Declarations of relevant conflicts of interest

None were declared

6. New Medicine Reviews

6.1 Methotrexate for severe asthma (Applicant: Prof Robinson, UCLH; Presentation: Ms Amer)

The Committee reviewed an application for methotrexate as an oral corticosteroid sparing agent in patients with severe asthma where omalizumab is contraindicated, or not appropriate, or where treatment with omalizumab has failed. Although the use of oral corticosteroids is an established treatment modality for asthma, they are associated with an increased risk of osteoporosis, cataracts, weight gain and diabetes.

The Committee reviewed the evidence from a Cochrane Collaboration systematic review and meta-analysis. The systematic review included 10 studies; 3 parallel-group and 7 cross-over, randomised, double-blinded, placebo-controlled trials (RCTs). There were a total of 218 patients enrolled within the trials reviewed; of these 32 withdrew (14.6%). The minimum oral corticosteroid dose at baseline was prednisolone 7.5mg/day in all trials however the mean doses ranged from 10.9mg/day to 30.8mg/day. Reduction in oral corticosteroid use was the primary outcome measure in all the trials reviewed. Meta-analyses were performed separately on parallel and cross-over studies; the mean reduction in prednisolone dose was -4.1mg/day (95% CI: -6.8 to -1.3) and -2.9mg/day (95% CI: -5.5 to -0.2) for parallel and cross-over trials respectively. A secondary outcome for efficacy was change in FEV_1 which showed no difference between arms (mean difference = 0.12 [95% CI: -0.21 to 0.45).

The Committee also reviewed a retrospective analysis of 15 patients with severe asthma who were prescribed methotrexate as an oral corticosteroid sparing agent. The mean maintenance dose of oral prednisolone at baseline was 15mg/day. Of the 15 who started methotrexate, 2 (13%) withdrew from therapy by month 4. The mean reduction in prednisolone for the remaining 13 patients was 9.03mg/day or 58.75% (p=0.01). FEV_1 remained unaffected despite oral corticosteroid reduction.

With regards to safety, the Cochrane review found that treatment discontinuation due to hepatotoxicity and hepatic adverse events were particularly prominent with methotrexate. GI side effects were more commonly reported with methotrexate, including nausea, oral ulceration or stomatitis and other gastro-intestinal issues. Rash and alopecia were also more common with methotrexate.

The Committee heard from Prof Robinson that patients on long term oral corticosteroids have a strong desire to reduce their dose with a reduction of 5mg being considered as beneficial. The Severe Asthma service has adapted Rheumatology guidance on the management of patients on methotrexate and all monitoring would remain in clinic (not for Shared Care with GPs). The Committee noted that another treatment for severe asthma, mepolizumab, delivers a greater reduction in corticosteroid dose as well as improved FEV1 outcome, however, it is currently undergoing assessment by NICE. Prof Robinson confirmed that assuming NICE recommend this treatment late next year it will likely supercede the use of methotrexate, however as it is not currently available there is still a place for methotrexate.

In summary, the Committee were satisfied that methotrexate would reduce oral corticosteroid use in patients with severe asthma, however were mindful that very small reductions in some patients may not justify ongoing methotrexate use. Therefore the Committee agreed that a stopping rule should be applied whereby methotrexate would be discontinued if the maintenance dose of prednisolone has not reduced by at least 5mg after a 2 month trial period. Subject to this stopping rule, the Committee agreed to add methotrexate on the NCL Joint Formulary restricted to the Severe Asthma Service only. It was agreed that methotrexate for this indication is not suitable for Shared Care.

6.2 Tiotropium for severe asthma (Applicant: Prof Robinson, UCLH; Presentation: Mr Minshull)

The Committee reviewed an application for Tiotropium Respimat as an option for patients with severe asthma currently treated with a combination of inhaled corticosteroid (≥ 800 micrograms budesonide or equivalent per day) plus long-acting beta agonist, and have experienced ≥ 1 severe exacerbations in the previous 12 months. This application was in line with the licensed indication for the drug. Prescribing would be restricted to the Severe Asthma Clinic.

The Committee acknowledged that the goals of asthma management are symptom control, maintaining normal activity, minimising the risk of exacerbations, minimising fixed airflow limitations and trying to avoid adverse effects of treatment. The Committee were informed that an article recently published in the Drug and Therapeutics Bulletin considered a minimum important FEV1 difference to be approximately 10% and the minimum patient perceivable difference to be approximately 230 mL.

The Committee considered the efficacy evidence for tiotropium for this indication from two randomised, placebo-controlled trails, a randomised, cross-over study and a meta-analysis of RCTs. The Committee

reviewed the results from two replicate randomised controlled trials (48 weeks) which were reported together and included a total of 912 adult patients with ≥ 5 year history of asthma, and persistent airflow limitation, having suffered ≥ 1 severe exacerbation in the last year. Patients were randomised to self-administer 5 mcg tiotropium or placebo each morning using a soft-mist inhaler.

The average improvement to *peak* FEV1 at 24 weeks was 86 mL [95% CI 20 to 152 mL, p<0.05] in trial one and 154 mL [95% CI 91 to 217 mL, pp<0.001] in trial two. Similar figures were reported at week 48. The average improvement to *trough* FEV1 at 24 weeks was 88 mL [95% CI 27 to 149 mL, p<0.01] in trial one and 111 mL [95% CI 53 to 169 mL, p<0.001]; results at 48 weeks were not significant in trial one and 92 mL (95% CI 32 to 151 mL, p<0.01] in trial two. Time to first severe exacerbation (initiation of doubling of systemic steroids for at least 3 days) was increased to 56 days with tiotropium compared to placebo, representing a reduction in the risk of severe exacerbation in the tiotropium arm (HR 0.79; 95% CI 0.62 to 1.00; p=0.03). Minimum clinically important changes to ACQ-7 (measure of asthma symptoms) and to asthma quality of life (AQLQ) were not reached in either trial.

The Committee then reviewed a meta-analysis of six RCTs comparing tiotropium to placebo in patients aged ≥ 12 years with a diagnosis of symptomatic asthma despite treatment with ICS or ICS/LABA (including two RCTs reviewed above). A total of 1,648 patients were included in this analysis. Statistically significant differences were reported between tiotropium and placebo for peak FEV1 [weighted mean difference 130 mL, 95% CI 9 to 180 mL, p<0.001] and trough FEV1 [WMD 100 mL, 95% CI 6 to 140 mL, p<0.001]. The Committee also considered that statistically significant improvements were seen with tiotropium treatment for morning and evening PEF, peak and trough FVC and improvements to FVC in the first three hours after dosing. Asthma control (ACQ-7) did not reach a clinically significant threshold of a 0.5 unit change, despite a statistically significant reduction for tiotropium treatment (WMD -0.12, 95% CI -0.21 to -0.03, p=0.01). No difference in quality of life (AQLQ) or use of reliever was reported for tiotropium treated patients compared to placebo. The effect of tiotropium treatment of rate of exacerbations, or mortality was not reported.

In February 2015, MHRA published an update to its 2010 Drug Safety Update, advising that there is no significant difference in the risk of death from any cause between patients with COPD treated with tiotropium Respimat or tiotropium HandiHaler; CV history needs to be taken into account for all patients in whom tiotropium is being considered.

Prof Robinson explained to the Committee that tiotropium will be reserved for patients with difficult to treat asthma; the important outcome for these patients is not the change in FEV1, but the 21% reduction in exacerbations as the only other agents capable of achieving this is are biologics which can achieve approximately 50% reduction at a far greater cost. Exacerbation rates over the six to twelve month period will be measured to determine efficacy of tiotropium. He explained that some patients are already coming to his clinic having been started on tiotropium in primary care. Regarding alternative therapies recommended by BTS/SIGN as part of step 4 of the asthma guidelines, Prof Robinson proposed that the evidence actually suggests they are effective at step 3, but offer little benefit at step 4. Prof Robinson quoted data published in the Lancet that suggests there is no additional benefit gained by adding montelukast. The Committee questioned whether there is a need for another tiotropium inhaler given that the HandiHaler dry powder inhaler is already available on the formulary. Prof Robinson advised that the HandiHaler uses a different dose of tiotropium than the Respimat device due to delivery of a dry powder compared with a fine mist and that is not licensed for use in asthma, however, he agreed that he would be happy to use this inhaler if that is what is made available. The Respimat device is currently priced the same as the HandiHaler refills although the tiotropium patent is due to expire in 2016 so prices may fall.

In summary, the committee agreed that tiotropium would be beneficial in severe asthma to reduce severe exacerbations, however, it was not thought that the Respimat device should be added to the formulary as a Handihaler dry powder inhaler is already available. Initiation of tiotropium for severe asthma is restricted to the Severe Asthma Service only.

6.3 Symbicort as sole inhaler for asthma (Applicant: Prof Robinson, UCLH; Presentation: Mr Minshull)

The Committee reviewed an application to use Symbicort as reliever inhaler therapy in patients with asthma at BTS/SIGN guideline step 3 or above, where there is difficulty with compliance or using a metered dose inhaler (MDI) with a spacer.

At Step 3 of the BTS/SIGN Asthma Guideline recommends that adults receive treatment with a regular inhaled corticosteroid (ICS) and a long-acting beta-2 agonist (LABA). This medication is invariably administered as a fixed dose combination (FDC). A short-acting beta-2 agonist (SABA) is used for PRN symptom relief. This application was to use the FDC (budesonide/formoterol) as the reliever.

The evidence reviewed was from two Cochrane systematic reviews and meta-analyses and a 12-month, double-blind, parallel-group study.

A total of 13,152 adult patients were included in a systematic review of 13 trials of the use of budesonide/formoterol as a reliever. Studies compared this approach with the standard approach (that uses SABA as reliever). Nine open-label studies compared budesonide/formoterol reliever therapy to "current best practice", which was combination LABA/ICS for most patients. A further three studies compared sole budesonide/formoterol inhaler therapy to a higher dose of ICS and one study compared it to the same dose of ICS. Patients in comparator arms for each study were issued with a reliever inhaler (salbutamol or terbutaline).

A significant reduction in exacerbations requiring oral steroid treatment was seen using budesonide/formoterol reliever therapy compared to best practice (OR 0.83, 95% CI 0.7 to 0.98, NNT=90) and compared to high dose ICS and SABA alone (OR 0.54, 95% CI 0.45 to 0.64, NNT=14). There was not a significant impact on hospitalisations. Odds of withdrawing due to adverse events were higher with budesonide/formoterol reliever therapy when compared to best practice (2.85, 95% CI 1.89 to 4.3), but was lower when compared to high dose ICS alone (0.57, 95% CI 0.35 to 0.93).

A more focussed meta-analysis compared budesonide/formoterol reliever therapy to maintenance treatment with combination budesonide/formoterol plus a SABA reliever inhaler, where steroid doses in the comparator arm was higher than in the SMART arm. This included four double-blind, parallel group, controlled studies that lasted at least 12 weeks. A total of 9,120 patients were included in this analysis. Patients receiving budesonide/formoterol reliever therapy had fewer severe exacerbations (OR 0.72, 95% CI 0.57 to 0.90), fewer non-severe exacerbations (OR 0.75, 95% CI 0.65 to 0.87), and reported a lower overall dose of inhaled corticosteroids. It was inconclusive whether budesonide/formoterol reliever therapy was associated with more or fewer severe adverse events, and it was not possible to determine specifically the impact on admission to hospital, as outcomes were combined with A&E attendances. There was no suggestion that any improvement was due to improved compliance, and one study suggested that changing from a metered dose inhaler to a dry powder inhaler may have been responsible for an increase in adverse events occurring when patients were not sure how to use their device.

The Committee also considered a 12-month, double-blind, parallel group study (n=3,394). In this study all patients were on background budesonide/formoterol therapy and one of terbutaline, formoterol or budesonide/formoterol as reliever. This study had been excluded from the meta-analyses described above. At the end of twelve months, the FEV1 was 30 mL greater in formoterol reliever patient arm compared to terbutaline reliever (p=0.043), and the FDC reliever group had and FEV1 that was 80 mL greater compared to terbutaline (p<0.0001) and 50 mL greater compared to formoterol (p=0.00014). Use of reliever budesonide/formoterol reduced the number of inhalations (by 0.86 inhalations/day compared to 0.65/day in the terbutaline arm). Using reliever budesonide/formoterol reduced the rate of severe exacerbations (HR 0.55, 95% CI 0.45 to 0.68, p<0.0001) and mild exacerbations (HR 0.88, 95% CI 0.8 to 0.97, p=0.0075), when compared to terbutaline. By comparing this combination to formoterol alone as a reliever, the study indicates that the use of when required ICS is contributing to this effect.

Budesonide/formoterol is more expensive than treatment with individual inhalers and may be associated with an increased adverse event profile.

Prof Robinson reported that in his clinical practice he has found that some patients achieve control with budesonide/formoterol reliever therapy when they had not using other regimens, which he believes is due to adherence to therapy. As many patients with chronic diseases only take their medication when they feel like it, this approach therapy provides them with a dose of steroid, which is likely to benefit them in terms of exacerbation. He also described that even small reductions in the number of exacerbations requiring oral steroid would be clinically important and valuable to patients; the cost avoided by reducing these exacerbations should be balanced against the increased drug cost.

Fostair (a combination of beclometasone dipropionate and formoterol) is already available on the NCL formulary for use in asthma and is less expensive than Symbicort. This inhaler is also licensed for maintenance and reliever therapy. Prof Robinson explained that, although he hasn't used this combination inhaler, he tends not to use beclometasone in practice because he finds it to have higher systemic absorption.

The Committee came to the conclusion that some patients do better if they take a combined steroid/beta 2 agonists inhaler as a reliever, almost certainly because they receive a bigger dose of inhaled steroid using this schedule. The Fostair inhaler would be adequate to fill this niche indication within NCL so the FDC of budesonide/formoterol was not included on the formulary.

7. NCL guidelines for insulin and adjuvant therapy in Type 1 diabetes (Applicant: Dr Rosenthal, RHF and Dr Naik, UCLH; Presentation: Mr Barron)

The Committee reviewed a guideline for insulin and adjuvant therapies in Type 1 diabetes. The guideline was developed jointly by the Camden IPU and JFC support pharmacists, and had been sent to all provider Trusts in NCL for comment.

7.1 Bolus insulin

The Committee heard that rapid-acting insulin analogues are used exclusively in Type 1 diabetes. Rapid-acting analogues offer the convenience of dosing with meals (rather than soluble insulin which require dosing 40 minutes before a meal) and form an integral part of training programmes such as DAFNE whereby patients are taught to adjust their insulin dose according to the number of carbohydrates to be consumed. Furthermore, the meta-analysis performed by NICE demonstrated a small but statistically significant improvement in HbA1c and a reduced incidence of severe and nocturnal hypoglycaemia. The price of the analogue insulins range from £182 to £197 per annum compared to £123 per annum for soluble insulin.

The Committee discussed that the superior outcomes with rapid-acting analogues identified by NICE was limited to insulin lispro studies and there was no evidence of superiority for insulin aspart. A meta-analysis by the Cochrane Collaboration in 2009 combined all rapid-acting analogue data and found only a very small improvement in HbA1c with no overall improvement in hypoglycaemia. The uncertainty in clinical benefit was compounded by the open-label study designs which are open to bias when interpreting subjective outcome data such as hypoglycaemia.

Overall, the Committee was satisfied that the benefit to patients of injecting bolus insulin with meals was sufficient to support the use of rapid-acting insulin analogue (insulin lispro [Humalog] and insulin aspart [NovoRapid]).

7.2 Basal insulin

The Committee heard that the guideline recommends 1st line insulin glargine and 2nd line twice-daily insulin detemir. Insulin detemir is more expensive than glargine and is subsequently reserved for patients who require a high level of flexibility with their insulin regimen.

The Committee heard that the NCL guideline differs to NICE NG17 which recommends 1st line twice-daily detemir and 2nd line once-daily glargine. The NICE recommendations were rejected as they were based on the outcome of a cost-effectiveness analysis which had three flaws (i) the results relied on inputs that are non-statistically different (ii) the impact of biosimilar insulin glargine 100iU/mL had not been considered therefore incremental cost between once-daily glargine and twice-daily detemir was underestimated (iii) it known that twice-daily detemir is associated with a higher total daily dose of insulin which was not considered in the model, thereby further underestimating the incremental cost between once-daily glargine and twice-daily detemir.

The Committee reviewed the evidence for biosimilar glargine (Abasaglar®) which was launched in the UK at a 15% price reduction compared to branded glargine (Lantus®). The safety and efficacy of Abasaglar was demonstrated in two non-inferiority studies; one 52-wk study in Type 1 diabetes and one 26-wk study in T2DM. Both studies compared Abasaglar to Lantus. The results demonstrated no statistically significant differences in HbA1c and furthermore there were no statistically significant differences in overall hypoglycaemia, severe hypoglycaemia and nocturnal hypoglycaemia. There were trends towards slightly fewer episodes of hypoglycaemia with Abasaglar and trends towards slightly more weight gain (+200 to +350g) and (+1%) injection site reaction. It was noted that withdrawal due to adverse events and injection site reactions were equivalent but numerically fewer with Abasaglar.

The Committee heard that patients would be considered for Abasaglar during their routine clinic appointments, following adequate counselling on the similar, but different, pre-filled pen (Lantus SoloStar to Abasaglar KwikPen). It was confirmed that Abasaglar was not suitable for switching via ScriptSwitch.

The Committee heard from Dr Rosenthal and Dr Naik that patients with well managed Type 1 diabetes are typically seen in clinic every 6 months for approximately 15 minutes per appointment. Trying to switch stable patients from Lantus to Abasaglar during this short appointment would be difficult given the time restraints. It was proposed that new patients and patients who require more intensive care would be most suitable for initiation with Abasaglar. It was acknowledged that the cost-savings were significant and therefore uptake of Abasaglar should be encouraged. The Committee heard that moving patients from Lantus to Abasaglar would require individual training from a diabetic specialist nurse; however this should be done proactively in a phased approach.

The Committee agreed biosimilar glargine (Abasaglar) was the same molecular entity as Lantus and agreed to add Abasaglar to the NCL Joint Formulary. The Committee also agreed that a pragmatic phasing of Abasaglar was appropriate which would require a proactive approach with suitable investment to achieve the savings.

Action: Camden diabetes IPU to discuss with NCL Heads of Medicines Management

7.3 Adjuvant therapies

The Committee reviewed results from a meta-analysis which that underpinned NICE NG17. The analysis found adjuvant metformin was successful at reducing the mean daily insulin dose and reduced body weight by -1.75kg (95% CI: -3.31 to -0.17kg). There was no impact on glycaemic control and subsequently metformin was recommended by NICE for patients with a BMI >25kg/m^2 (23 kg/m^2 for people from South Asian and related minority ethnic groups) who want to achieve weight loss. The Committee agreed to add metformin onto the NCL Joint Formulary for the above indication.

The guideline included a recommendation for liraglutide as adjunctive therapy in Type 1 diabetes for patients with a BMI >30kg/m^2. The Committee heard that NICE had included liraglutide in their literature review but concluded that there was insufficient evidence to support its use. The Committee also heard that there were 13 recorded trials of liraglutide in Type 1 diabetes with many of the studies still ongoing or not published in full.

The Committee reviewed the evidence from LIRA-1, for which results were only from a poster presentation. LIRA-1 was a 26-wk, randomized, double-blinded, placebo-controlled, single-centre intervention trial (n=100). Inclusion criteria was Type 1 diabetes >1 year, age >18 years, BMI >25 kg/m^2, HbA1c >8.0%. Patients were randomized 1:1 placebo or liraglutide 1.8mg as add-on to insulin therapy. Insulin doses adjusted according to a treat-to-target protocol. The results at 26-wks concluded that liraglutide did not improve in HbA1c compared to placebo (-6 mmol/mol vs -4 mmol/mol, p=-0.146) however it successfully reduced body weight from baseline compared to placebo (-5.59 kg vs. +0.23 kg, p<0.0001) and the total daily insulin dose from baseline (+4.04 units vs. +13.61 units, p<0.0001). There was no difference in hypoglycaemia (+0.08% vs +2.92%, p=0.349). With regards to adverse events, nausea occurred more frequently in the liraglutide group (48% vs 7%). Heart rate also increased with liraglutide from baseline (+4.75 bpm vs. +0.24 bpm, p=0.005) however there was no difference in blood pressure (+1.55 mmHg vs. -0.91 mmHg, p=0.169).

The Committee also heard that other smaller and shorter studies had found results consistent to the LIRA-1 results.

The Committee heard from Dr Rosenthal and Dr Naik that very few patients were already on treatment with liraglutide and furthermore the potential for creep was very low due to the added injection burden. It was clarified that patients with proven insulin resistance (e.g. ≥2iU/kg) were most likely to benefit from treatment therefore patients who are both obese and insulin resistant would be prioritised for liraglutide.

In summary, the Committee agreed it was premature to consider liraglutide for this indication and deferred their decision until after publication of the LIRA-1 study.

7.4 Insulin degludec [APPEAL]

The Committee considered an appeal for insulin degludec for Type 1 diabetes with problematic hypoglycaemia. The appeal was centred around three key arguments; (i) the high cost of hypoglycaemia, (ii) the proportion of patients that were excluded from the NCL pathway for hypoglycaemia and (iii) a request to report the event rates (and rate ratios) rather than the proportion of patients who experienced an event in (and relative risks).

New evidence that had not been published at the time of the original review was discussed. Extension studies for the 26-wk Mathieu et al. (BEGIN-Flex T1) and 52-wk Heller et al. (BEGIN Basal-bolus T1) were reviewed. These studies found no difference in HbA1c between degludec and glargine at 52-wks and 102-

wks for BEGIN-Flex T1 and BEGIN Basal-bolus respectively. There were no differences in confirmed hypoglycaemia. A reduction in nocturnal hypoglycaemia remained statistically significant in both studies, amounting to a 25% reduction in the event rate per patient year of exposure (PYE). In terms of absolute difference in event rates, 2 and 3 nocturnal hypoglycaemic episodes were avoided in 52-wks and 102-wks studies respectively. The limitations of the open-label design were noted.

Dr Rosenthal stated that patients experiencing recurrent severe hypoglycaemia were referred to a specialist service which offered insulin pumps and continuous blood glucose monitoring (CGM). Patients with irreversible hypoglycaemia would be considered for NHS England funded Islet cell or pancreas transplantation. It was noted that patients with recurrent severe hypoglycaemia were a large burden on the healthcare sector despite comparatively small prescribing costs. It was proposed that elderly and frail patients, or those with cognitive impairment are frequently not suitable for insulin pumps or CGM and these patients may benefit from insulin degludec. It was also proposed that prior to starting an insulin pump, patients could be trialled on insulin degludec. It was explained that the true comparator for insulin degludec was not insulin glargine, but rather intensive clinic supervision, possible insulin pump and possible transplantation.

The applicants discussed that patients with severe recurrent hypoglycaemia were specifically excluded from the clinical trials, this being precisely the population being considered for degludec under the appeal. This made the Committee doubtful whether the small and uncertain difference in nocturnal hypoglycaemia would lead to meaningful benefits in this population.

The Committee considered the economic analysis by Parekh et al which estimated the cost of hypoglycaemia in the UK. As the inputs were not populated with data from a systematic literature review the Committee felt that the values presented are unlikely to reflect real-world costs.

In summary, the Committee were not satisfied that insulin degludec would offer any clinically meaningful benefit in the proposed population and furthermore did not believe that tight blood glucose control was necessary in elderly, frail and cognitively impaired patients. The Committee agreed that patient education and a comprehensive MDT approach would be more effective in reducing severe recurrent hypoglycaemia. In summary, the Committee agreed that insulin degludec should not be added to the NCL Joint Formulary for problematic hypoglycaemia.

8. Ciclosporin 1mg/1mL eye drops fact sheet

Comments should be sent to Mr Minshull and Dr Hindle by 2nd October 2015. The fact sheet would be approved via Chair's action.

Action: Mr Minshull and Mr Hindle to collate feedback. The final version to be uploaded to JFC website.

9. Process for NHS England Commissioning Policies

This item was deferred to the October 2015 meeting.

10. Pfizer UK patient for Lyrica (neuropathic pain)

The Committee noted that further advice from NHS England was required and that no change to practice was necessary at the present time.

11. Local DTC recommendations / minutes

Month	DTC site	Outcome
June 2015	WH	Silfex to replace Mepitel as wound contact dressing of choice Atrauman to replace Jelonet as low adherence dressing of choice

12. Next meeting

Thursday 29th October, Room 6LM1, Stephenson House, 75 Hampstead Rd.

13. Any Other Business

Nil