Joint Formulary Committee (JFC): Minutes

Minutes from the meeting held on 20th June 2024

		Present	Apologies
Members			
Prof A Hingorani (Chair)	NCL JFC Chair	✓	
Dr B Subel	NCL JFC Vice Chair	✓	
Ms L Coughlan	NCL ICB, Deputy Chief Clinical Officer & ICS Chief Pharmacist		✓
Ms W Spicer	RFL, Chief Pharmacist		✓
Dr P Jasani	RFL, DTC Chair		✓
Dr K Boleti	RFL, DTC Chair		✓
Dr A Scourfield	UCLH, DTC Chair	✓	
Mr J Harchowal	UCLH, Chief Pharmacist		✓
Dr R Urquhart	UCLH, Divisional Clinical Director		✓
Dr K Tasopoulos	NMUH, DTC Chair	✓	
Ms S Stern	NMUH, Chief Pharmacist	✓	
Ms A Stein	NMUH, Deputy Chief Pharmacist		✓
Dr M Kelsey	WH, DTC Chair	✓	
Mr S Richardson	WH, Chief Pharmacist	✓	
Dr S Ishaq	WH, Consultant Anaesthetist	✓	
Dr A Worth	GOSH, DTC Chair		✓
Ms J Ballinger	GOSH, Chief Pharmacist		✓
Dr M Henley	RNOH, DTC Chair	✓	
Mr A Shah	RNOH, Chief Pharmacist	✓	
Prof A Tufail	MEH, DTC Chair		✓
Ms N Phul	MEH, Chief Pharmacist		✓
Ms K Delargy	NLMHP, Partnership Deputy Chief Pharmacist	✓	
Ms L Reeves	NLMHP, Chief Pharmacist		✓
Dr L Waters	CNWL, Consultant Physician in HIV		✓
Ms R Clark	NCL ICB, Assistant Director of Medicines Optimisation		✓
Ms M Kaur-Singh	NCL ICB, Head of Medicines Planning & Operations	✓	
Dr D Roberts	NCL ICB, Clinical Director (Islington)	✓	
Ms C Weaver	NCL ICB, Senior Prescribing Advisor (deputising for Ms R Clark)	✓	
		✓	
Attendees			
Ms S Sanghvi	IPMO Programme Team, JFC Principal Pharmacist	✓	
Ms S Amin	IPMO Programme Team, Lead Pharmacist	✓	
Ms S Maru	IPMO Programme Team, JFC Support Pharmacist	✓	
Ms K Leung	IPMO Programme Team, JFC Support Pharmacist	✓	
Ms M Butt	IPMO Programme Team, Director	✓	
Ms I Samuel	RFL, Formulary Pharmacist	✓	
Mr H Shahbakhti	RFL, Formulary Pharmacist	✓	
Mr A Barron	UCLH, Principal Pharmacist	✓	
Mr S O'Callaghan	UCLH, Formulary Pharmacist	✓	
Ms C OBeirne	UCLH, Formulary Pharmacist		✓
Ms H Matthews	UCLH, Formulary Pharmacist		✓
Ms H Thoong	GOSH, Formulary Pharmacist		✓
Mr D Sergian	MEH, Formulary Pharmacist		✓

Ms A Bathia	RNOH, Formulary Pharmacist	✓	
Ms S Ahmed	WH, Formulary Pharmacist		✓
Ms N Patel	NMUH, Formulary Pharmacist	✓	
Ms M Thacker	GOSH, Deputy Chief Pharmacist		✓
Ms H Weaver	NHSE, Specialised Commissioning Pharmacist		✓
Ms EY Cheung	NCL ICB, Head of Medicines Quality & Improvement		✓
Dr J Ross	UCLH, Clinical Pharmacology Registrar	✓	
Dr S Eriksson	UCLH, Consultant Neurologist	✓	
Prof M Walker	UCLH, Consultant Neurologist	✓	
Ms L Stockford	UCLH, Specialist Neurology Pharmacist	✓	
Mr H Hossenally	WH, Specialist in Special Care Dentistry	✓	
Dr H Jayaram	MEH, Consultant Ophthalmic Surgeon	✓	
Dr S Ghosh	NCL ICB, General Practitioner and Clinical Director (Observer)	✓	
Ms A Bishop	NCL ICB, Medicines Optimisation Technician (Observer)	✓	

2. Meeting attendees

Prof Hingorani welcomed members, observers, and applicants to the meeting (see above). Dr Raman (RNOH DTC Chair) was thanked for his valuable contributions to the Committee over the years as he has stepped down from his role. Dr Henley (RNOH DTC Chair) was welcomed as a new member of the Committee.

3. Members' declaration of interests

The Declarations of Interests register for Committee members was included for information. No further interests relevant to the agenda were raised.

4. Minutes of the last meeting

Minutes and abbreviated minutes of the May 2024 meeting were ratified.

5. Review of action tracker

Action tracker included for information. Closed actions have been updated on the tracker.

6. JFC Outstanding items and workplan

These items were included for information only. Any questions should be directed to Ms Sanghvi.

7. Local DTC recommendations/minutes

DTC site	Month	Drug	Indication	JFC Outcome
UCLH	May 2024	[FOC Scheme] Navitoclax and Venetoclax†	Relapsed/ refractory B-cell acute lymphoblastic leukaemia (B-ALL) and T-cell acute lymphoblastic leukaemia (T-ALL)	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: FOC Scheme **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	Sodium Cromoglicate capsules	Gastrointestinal symptoms in systemic mastocytosis	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	Misoprostol	For termination of pregnancy (1st trimester)	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A

UCLH	May 2024	Misoprostol	For cervical ripening prior to surgical termination of pregnancy (1st trimester)	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	Misoprostol	For the medical management of missed miscarriage (1st trimester)	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	Misoprostol	For the cervical ripening prior to surgical management of missed miscarriage (1st trimester, under general anaesthesia)	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	Misoprostol	For the treatment of postpartum haemorrhage	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	Misoprostol and ergometrine	For the prevention and management of haemorrhage during surgical management of miscarriage (1st trimester, under general anaesthesia)	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	Misoprostol and ergometrine	For the medical management of miscarriage in haemodynamically unstable patients	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	Misoprostol and ergometrine	For prevention of haemorrhage during surgical management of caesarean scar ectopic pregnancy	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	L-arginine injection, suspensions, and tablets	Stroke-like migraine attacks after radiation (SMART)	**Decision:** Not approved
UCLH	May 2024	Apraclonidine 0.5% eye drops	Diagnosis of Horner syndrome	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A

UCLH	May 2024	Sucralfate oral suspension	Emergency management of button battery ingestion (in line with NPIS; via Toxbase)	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
UCLH	May 2024	Tacalcitol (Curatoderm®) Lotion	Management of scalp psoriasis (in line with NICE CG153)	**Decision**: Approved **Prescribing status**: Suitable for initiation in primary and secondary care **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A
RFL	April 2024	Indocyanine Green injection	Common bile duct (CBD) and biliary visualisation	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: Conditionally approved pending specific intended indication for use and review by the RFL Clinical Consumables Committee **Fact sheet or shared care required**: N/A
MEH	June 2024	Mydrane	Intracameral anaesthesia during topical anaesthesia cataract surgery	**Decision**: Approved **Prescribing status**: Secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or shared care required**: N/A

*Subject to funding consideration; †The relevant commissioner should be notified in line with NCL Free of Charge scheme guidance. Approval is conditional on the provision of a free of charge scheme agreement and funding statement.

8. Matters arising

8.1. NCL ICS Medicines Optimisation Governance Review

The Committee reviewed a draft NCL ICS medicines optimisation governance structure. The Committee were supportive of the structure and the proposition for JFC to have oversight of three groups: i) Shared Care Group (established), ii) Medicines Pathways Working Group (new), and iii) NICE TA Implementation Group (new).

8.2. JFC New Members: Expressions of Interest Forms

The Committee were informed that an Expression of Interest form for JFC membership (including a lay member) was circulated via email. The Committee was requested to share the email with their networks and interested colleagues.

9. Medicine reviews

9.1. Targinact® (Oxycodone hydrochloride/ Naloxone hydrochloride) for symptomatic treatment of severe to very severe idiopathic restless legs syndrome (Applicants: Dr S Erikkson, Prof M Walker, Ms L Stockford (UCLH))

The Committee considered an application for Targinact® (Oxycodone hydrochloride / Naloxone hydrochloride prolonged-release tablets), an opioid combined with an opioid antagonist, for licensed use as second-line symptomatic treatment of adults with severe to very severe idiopathic restless legs syndrome (RLS) after failure of dopaminergic therapy. The application was brought for discussion at JFC as part of the draft RLS pathway. RLS is a neurological disorder characterised by the impulse to move the legs during rest or inactivity, in severe cases associated with discomfort pain and poor sleep.

Since naloxone undergoes first pass metabolism, the rationale of combining it with an opioid in Targinact® is to counteract the local constipating effect of opioids in the gut, without counteracting the systemic analgesic effect. However, in previous trials comparing Targinact® with prolonged release oxycodone the need for laxatives was not removed in the Targinact® group, and the small difference in bowel function improvement score in favour of the Targinact® group was considered to be biased because of a suboptimal laxative regime in the oxycodone prolonged release group (Drugs and Therapeutics Bulletin (DTB), volume 48, number 12, Dec 2010).

The rationale for considering an opioid in severe Restless Legs syndrome is to reduce the associated pain, discomfort and poor sleep. The trial evidence used in support of the Targinact licence for Restless Legs Syndrome, which the committee considered was Trenkwalder et al (2003; n= 304), a 12-week double-blind, placebo-controlled RCT with a 40-week open-label extension phase. The study investigated the efficacy and safety of a fixed-dose combination of prolonged-release oxycodone-naloxone preparation for patients with severe RLS inadequately controlled by previous, mainly dopaminergic, treatment. Patients were randomised to either oxycodone 5mg with naloxone 2.5mg twice daily or matched placebo, with the dose of the study drug being up-titrated according to investigator's opinion up to a maximum dose of oxycodone 40mg and naloxone 20mg twice daily. The primary endpoint was mean change in severity of symptoms according to the International RLS Study Group severity rating scale sum score at 12 weeks. The International RLS Study Group severity rating scale is a validated symptom rating scale from 1 to 40 which gives an indication of the severity of RLS: mild 1-10; moderate 11-20; severe 21-30; very severe 31-40. At baseline, the mean International RLS Study Group severity rating scale sum score was 31.6 (SD 4.5); mean change after 12 weeks was -16.5 (SD 11.3) in the prolonged-release oxycodone-naloxone treatment group and -9.4 (SD 10.9) in the placebo group (mean difference between groups at 12 weeks was 8.15 [95% CI 5.46 to 10.85; p<0.0001]). In the open-label extension phase (n= 197), 157 patients completed 40 weeks of treatment. Patients received a mean daily dose of Oxycodone 18.1mg ± 10.5mg and Naloxone 9.1mg ± 5.3mg for a median of 281 days. However, the study was at high risk of bias due to the large proportion of participants who withdrew from treatment.

In terms of safety, Trenkwalder et al (2003; n= 304) found prolonged-release oxycodone-naloxone had a higher risk of adverse events compared to placebo (RR 1.22 [95% CI 1.07 to 1.39]). 30 patients (9.8%) withdrew from the study due to drug-related adverse events. Reported adverse events were consistent with the safety profile of opioids. Drug withdrawal symptoms were reported in one patient after 12 weeks and two patients following one year of treatment with prolonged-release oxycodone-naloxone. However, the trial duration was insufficient to provide evidence on the risk of physical or psychological dependence with prolonged use.

In terms of budget impact, prolonged-release oxycodone-naloxone is expected to cost an additional £11,000 up to £16,500 per annum for 10 patients per annum. Oxycodone-naloxone combination products are included on the NHSE 'Items which should not routinely be prescribed in primary care: policy guidance'. This is due to the significant cost of oxycodone-naloxone combination products and unclear role and benefits of combination products compared to oxycodone and laxatives prescribed separately.

The Committee heard from Dr Eriksson who highlighted RLS symptoms can be severe, life-long and have a profound impact on patients' quality of life for the intended RLS population. Prof Walker explained that prolonged-release oxycodone-naloxone potentially addresses RLS symptoms beyond pain (such as poor sleep) but acknowledged that trials investigating the role of opioids in the treatment of RLS were very poor.

The Committee discussed the following limitations of the evidence:

The absence of an active comparator, for example oxycodone and laxatives prescribed separately

The substantial dropout rate of a third of participants, noting that this study was also identified by Cochrane to be low quality evidence due to attrition bias.

The small reported difference in the primary outcome but no significant change in quality-of-life scores for participants in the study.

The Committee questioned the value of the combination product rather than using opioids plus laxatives separately and tailoring according to patient need. The applicants noted that the application for Targinact was based on it being a licensed option for RLS, however they would consider prescribing the separate components instead if suggested as a more cost-effective option.

The Committee also raised concerns about how the well documented risks related to long-term opioid treatment (including adverse effects, tolerance and dependence), would be managed for this patient cohort. There was uncertainty about whether patients who lost response would be weaned from treatment, or whether the dose would be escalated, including uncertainty about a maximum dose threshold. The Committee

suggested that involvement of pain clinics in managing long-term opioid use, as well as offering non-pharmacological support for pain management, would be beneficial for this cohort. The applicants stated that they would be happy to work in collaboration with pain clinics.

Prof Walker also clarified that whilst the intention was to transfer prescribing of prolonged-release oxycodone-naloxone to primary care after patients are stabilised on treatment, patients would continue to be followed up in secondary care in RLS clinics. The Committee noted the recommendation in NHSE guidance that Targinact should not be routinely prescribed in primary care, and highlighted risks with the transfer of long-term opioid prescribing to primary care. It was suggested that management of opioid dose, adverse effects and wraparound care would be better supported by the specialists in conjunction with the pain clinic, and that the pathway should be amended to reflect this.

In camera, the Committee discussed the following concerns when considering Targinact® as a treatment option for RLS:

i) The weak evidence base for the efficacy and safety of Targinact® in patients with severe to very severe RLS is limited to a single placebo-controlled rather than an active comparator RCT, which had a high risk of attrition bias, which has been deemed low quality evidence by Cochrane.

ii) The lack of data regarding the long-term safety profile for Targinact® in RLS patients. The limited short-term evidence for efficacy did not appear to outweigh the known risks associated with long-term opioid use.

iii) The uncertainty regarding weaning criteria and a treatment dose threshold. These were considered to be to reduce risk of withdrawals and dependency. The committee were of the view that holistic management of symptoms and risks would benefit from specialist pain clinic expertise.

iv) If opioids were considered necessary in a small subset of patients with severe symptoms, Targinact is a more costly treatment option compared to using opioids and laxatives separately, with no clear advantage of the combination product in terms of efficacy or safety.

In summary, based on the limited evidence available and safety concerns concerning the long-term use of opioids, the Committee could not recommend the use of Targinact®. However, the Committee were supportive of the applicants collaborating with specialist pain services to provide support in the holistic management of pain for patients with severe to very severe RLS.

Drug: Targinact®; licensed use
Indication: Second-line symptomatic treatment of adults with severe to very severe idiopathic restless legs syndrome
Decision: Not approved

9.2. Remimazolam for sedation in dental procedures (Applicants: Mr H Hossenally; WH)

The Committee considered an application for Remimazolam (at a dose of 2.5-20mg IV titrated according to response), an ultra-short-acting benzodiazepine, for licensed use in dental procedures carried out under conscious sedation. The application proposed remimazolam as an alternative to IV Midazolam for conscious sedation where more rapid and full recovery is beneficial, for example in shorter procedures, for older or frail patients, and for patients with physical, intellectual or sensory impairments (or a combination of such conditions).

The Committee considered three prospective, randomised, phase III, placebo-controlled trials with an additional open-label midazolam arm (all of which were conducted by the manufacturer):

- Rex et al (2018; n= 461) included patients undergoing colonoscopy
- Rex et al. (2021; n= 79) included high-risk patients undergoing colonoscopy
- Pastis et al. (2019; n= 431) included patients undergoing bronchoscopy

In each study, all patients received pre-treatment intravenous fentanyl for analgesia; if sedation was deemed to be unsuccessful with the assigned treatment, rescue sedation with midazolam could be used to complete the procedure. The studies tested the superiority of remimazolam compared to placebo but were not designed to compare remimazolam with midazolam. The primary outcome in the studies was a composite endpoint which consisted of: (i) completion of the procedure, (ii) no requirement for rescue midazolam, and (iii) no requirement for >5 doses of remimazolam or placebo within any 15-minute window or no requirement of >3

doses of midazolam within any 12-minute window. The difference in the primary outcome was primarily driven by the need for rescue medication. Procedure completion rates were similar across each arm.

Dao et al (2022, n= 986), a post-hoc analysis of the above RCTs reported remimazolam had faster time to full alertness compared to real-world midazolam (rescue for placebo) (p< 0.0001), but this was not statistically significant when compared to on-label midazolam (p= 0.16). For time ready for discharge, a secondary outcome, patients who received remimazolam had faster times to discharge compared to real-world midazolam (p<0.0001), however the Committee noted that the absolute difference was only 6 minutes and questioned whether this would have a significant impact on patient throughput. For mean fentanyl used, remimazolam patients received 78.2 micrograms compared to real-world midazolam patients who received 113.6 micrograms (p<0.0001). However, the Committee noted that there were significant differences in the initial dosing regimens between the two arms that limited interpretation of these results. The study protocol used a higher initial dose of remimazolam compared to midazolam, and there was variation in the top-up doses permitted, which may have caused a slower onset of sedation and recovery in the midazolam arms as a result of the study protocol design.

Two further independent trials were also considered by the Committee. Kim et al (2023; n= 100) was a prospective randomised parallel group study with patients undergoing bronchoscopy. The primary outcome of interest was time to end of procedure to full alertness. Patients who received remimazolam had faster neuropsychiatric recovery time (2 minutes; IQR 1-5 minutes) compared to midazolam (5 minutes; IQR 1-12 minutes) but this was not statistically significant (p= 0.035). Li et al (2023; n= 83) was a prospective RCT that involved patients undergoing dental procedures. The primary outcome of interest was median onset timewhich was significantly shorter for remimazolam (0.57 minutes; IQR 0.53-0.63 minutes) compared to midazolam (9 minutes; IQR 8-12 minutes) (p=0.001). Median recovery time for remimazolam was also significantly shorter (5 minutes; IQR 4-6 minutes) compared to midazolam (20 minutes; 17-26.5 minutes) (p= 0.001). The Committee questioned why the difference in outcomes of this smaller study were significantly higher than in the much larger manufacturer studies (Dao et al) and whether the faster onset and recovery were linked to the higher doses of remimazolam permitted in the protocol.

The Committee noted that there is an ongoing prospective blinded RCT at GSTT comparing recovery after conscious sedation for dental extractions between remimazolam and midazolam; the REMIDENT study (NCT05220462). This is expected to complete in September 2024 and may provide relevant efficacy and safety data once published.

In terms of safety, Remimazolam is expected to have a similar risk and safety profile compared to midazolam. Kim et al (2023; n= 183) reported only mild adverse drug reactions in both treatment groups with more cases of adverse drug reactions (ADRs) in the midazolam group compared to the remimazolam group (p= 0.001). The midazolam arm showed a higher rate of antidote administration compared to the remimazolam arm, however, the difference was not statistically significant (15.7% vs. 4.1%; p= 0.092).

In terms of cost, remimazolam is more expensive compared to midazolam. The Scottish Medicines Consortium (SMC) concluded that it could not recommend the use of remimazolam within NHS Scotland based on cost-effectiveness. Pedersen et al (2023), developed a cost model (funded by manufacturer) that estimated remimazolam to offer cost savings compared to midazolam in colonoscopy and bronchoscopy procedures, based on hospital costs, however the assumptions and findings of the manufacturer funded analysis were disputed by the SMC. The anticipated budget impact for NCL of remimazolam is £5156 per annum for 275 patients per annum.

The Committee heard from Mr Hossenally that the Community Dental Service serves a diverse patient population, including those with anxiety, severe learning disabilities, and dementia. Drawing from his experience using remimazolam at other sites, Mr. Hossenally explained that it allowed for some cases considered too high-risk for general anaesthesia or midazolam to be performed with remimazolam, due to a faster and more predictable recovery. While the goal of introducing remimazolam focuses on safety and enhancing post-procedural care for high-risk patients, it would also improve throughput, as community dental clinics lack dedicated recovery spaces, though this was not the primary motivation for the application. The Committee noted that there was currently no evidence to suggest an improvement in clinical turnaround. In addition, the Committee raised concerns about the potentially overstated benefits of remimazolam reported in the manufacturer-sponsored trials, due to bias in the treatment protocol. The slower onset of sedation, greater need for top ups ('rescue medication') which formed part of the prespecified end-point and slower recovery from sedation could all have arisen because the comparator groups received either no, or a suboptimal initial dose of midazolam. The committee also noted that, despite this, the difference between groups in readiness for discharge was no more than 11 minutes.

In camera, the Committee agreed that the evidence presented did not offer a fair comparison with midazolam due to dosing protocols, and that the time for recovery and discharge was not clinically significantly different. There was no direct evidence that remimazolam would offer a reduction in complications or improved clinical throughput, and the SMC review of cost-effectiveness was not favourable.

The Committee raised concerns about the current clinical practice with midazolam and high use of flumazenil, and suggested that a review of the midazolam dosing protocol and clinical practice in collaboration with anaesthetists was warranted to support safer sedation practice. The Committee also recommended that frail patients or those with a particular safety concern for sedation should be referred for anaesthetist delivered sedation. The Committee noted potential risks in similar drug names 'remimazolam' and 'remifentanil' and also the potential for scope creep beyond dental procedures, which may result in significant budget impact.

In summary, based on the limitations of the evidence available and lack of clear safety, efficacy or cost-effectiveness advantage over midazolam, the Committee could not recommend the use of remimazolam. The Committee noted the ongoing REMIDENT study, and suggested that if the published results of this study supported use of remimazolam, the applicants could appeal on the basis of new evidence.

Drug: Remimazolam
Indication: Dental procedures carried out under conscious sedation
Decision: Not approved

9.3. Latanoprost-netarsudil drops for open-angle glaucoma and ocular hypertension (Applicant: Mr Hari Jayaram; MEH)

The Committee considered an application for latanoprost-netarsudil eye drops (administered as one drop into the affected eye(s) each night), a prostaglandin analogue combined with a Rho-kinase and norepinephrine transporter inhibitor, for licensed use as the preferred second-line alternative treatment option in patients with open angle glaucoma and ocular hypertension in whom ß-blockers are contraindicated.

This application was approved at the Moorfield's Eye Hospital Drugs and Therapeutics Committee (MEH DTC) pending clarification of place in therapy, development of a treatment pathway, consideration of primary care budget impact and presentation of audit finding at the DTC in 12 months. An amber prescribing status (specialist initiation and primary care continuation) was suggested by MEH.

This application was brought for discussion to the JFC to consider:

- Suitability of the amber prescribing status
- Suitability of addition to formulary ahead of a NICE TA that has been in development since 2020 with an unknown publication date.
- Inclusion of prescribing interest and consideration of impact of the decision for other NCL ophthalmology services (NMUH and RFL).

MERCURY-1 (12-months) and -2 (3-months) were phase 3, active-controlled, double-blind studies comparing the efficacy and safety of latanoprost-netarsudil to latanoprost or netarsudil monotherapy in adults with open-angle glaucoma and ocular hypertension. These studies were reviewed but not considered further in evidence evaluation as two pressure-lowering drugs together are expected to lower pressure to a greater extent than each drug given alone.

MERCURY-3 was a 6-month, phase 3, active-controlled, double-bind study comparing the efficacy and safety of latanoprost-netarsudil to bimatoprost-timolol in adults with open-angle glaucoma and ocular hypertension. The primary endpoint, change in mean intraocular pressure (IOP) change from baseline to 3 months, was met and clinical non-inferiority of latanoprost-netarsudil was demonstrated compared to bimatoprost-timolol. This is because an IOP ≤ 1.5mmHg was achieved at all nine time points and ≤ 1.0mmHg at a minimum of six out of nine timepoints at the upper limit of the 95% confidence interval difference. The secondary outcome, mean percent change in diurnal IOP from baseline to 3 months was not significantly different for latanoprost-netarsudil compared to bimatoprost-timolol (-36.7% vs – 38.6%; 95% CI [-0.39 to 4.05]; p=0.1056). Key limitations of the study were the short study duration and that it was manufacturer funded.

Singh et al (2020; 1004) reported the pooled efficacy data from the ROCKET 1-4 studies. These were phase 3, double-blind, parallel group, non-inferiority, randomised, active-comparator controlled trials comparing the safety and efficacy of netarsudil montotherapy to timolol monotherapy in adults with open-angle glaucoma or ocular hypertension. The primary endpoint, mean IOP reductions from baseline to 3 months in patients with baseline IOP < 25mmHg, met the criteria for clinical non-inferiority (IOP ≤ 1.5mmHg at all nine timepoints) with netarsudil monotherapy and timolol monotherapy (reductions up to -4.8mmHg and -5.0mmHg respectively).

In per-protocol patients, a ≥20% reduction in mean diurnal IOP at month 3 was significantly greater with netarsudil monotherapy than timolol monotherapy in patients with baseline IOP <23mmHg (57.2% vs 45.6%) but significantly lower in patients with baseline IOP <30mmHg (45.0% vs 53.4%). Key limitations of the study were that efficacy results were reported for the per-protocol population and only over 3 months due to varying individual study durations. Additionally, the study was manufacturer funded.

In terms of safety, majority of the adverse effects reported for latanoprost-netarsudil across the various studies were ocular in nature and of mild-moderate severity. Latanoprost-netarsudil had a higher risk of conjunctival hyperemia (30-60% vs 9%), conjunctival verticillate (10-20% vs 0%) and conjunctival haemorrhage (10-17% vs 2%) compared to bimatoprost-timolol across the studies. There was a greater discontinuation rate reported in the MERCURY-1 and -3 studies of latanoprost-netarsudil of approximately 20% compared to 2% with bimatoprost-timolol.

In terms of budget impact, latanoprost-netarsudil is expected to cost £84,000 per annum in year 1, with cumulative costs anticipated each year due to long-term continuation of treatment. These costs exclude the costs offset by not using other combination therapies.

The Committee heard from Mr Jayaram that latanoprost-netarsudil offers an additional treatment option for patients contraindicated to receive B-blockers in a second line setting while providing improved convenience and adherence due to its availability as a once-daily fixed dose combination product compared to the currently available combinations of prostaglandin analogues with carbonic anhydrase or alpha-adrenergic agonists. Mr Jayaram noted that while there was no evidence of superiority of latanoprost-netarsudil to prostaglandin analogues given with carbonic anhydrase inhibitors or alpha-adrenergic agonists, it provides a novel mechanism of action that targets 75% of the fluid outflow from the eye. Additionally, the aim of treatment is to delay the need for invasive surgery. The Committee queried whether early surgery may in fact provide a more cost-effective option compared to long-term eye drops but acknowledged that this data is not available.

The Committee acknowledged that while latanoprost-netarsudil provides a novel mechanism of action with convenience advantages, it confers no efficacy advantage compared to latanaprost-timolol in patients that can tolerate beta-blockers, and has not been tested against regimens involving latanoprost and either carbonic anhydrase inhibitors or alpha-adrenergic agonist therapies, which are the current second line agents in patients that cannot tolerate beta-blockers. The committee also noted uncertainties on the long-term safety of the new agent, and that latanoprost-netarsudil drops contain benzalkonium preservatives to which some patients are sensitive. Since alternative second line regimes that do not include beta-blockers are available, the committee considered that there was no significant urgent unmet clinical need. The committee noted the high cost of the latanoprost-netarsudil which could impose a significant budget impact ahead of a pending NICE TA publication. Mr Jayaram agreed that it may be appropriate to restrict use to a more defined cohort of patients, with initiation by glaucoma specialists only.

In camera, the Committee concluded that based on the evidence available of lack of superioprity against latanoprost-timolol and the absence of comparative evidence on other second line regimens currently in use, the lack of long-term safety data, lack of comparative efficacy data against current alternatives, lack of an urgent unmet clinical need, significant budget impact and a pending technology appraisal, the Committee could not recommend the use of latanoprost-netarsudil ahead of the NICE TA publication. The NCL Glaucoma Guidelines should be revised to exclude the latanoprost-netarsudil eye drops in the interim. However, the Committee recommended that applicants discuss an NCL consensus formulary position for latanoprost-netarsudil once details of the NICE TA recommendation are known, for review by JFC.

The Committee suggested that MEH DTC and specialists may wish to review the formulary position in the interim, and if further prescribing was supported ahead of a NICE TA that this should be retained within secondary care, restricted to MEH glaucoma specialist prescribing, and the criteria for use be refined, noting that latanoprost-netarsudil would be unsuitable for patients with preservative intolerance, and that it should be considered only after current second-line alternatives (i.e. prostaglandin analogues in combination with carbonic anhydrase inhibitors/alpha-adrenergic agonists) had been exhausted.

Drug: Latanoprost-netarsudil eye drops
Indication: Preferred second-line alternative treatment option in patients with open angle glaucoma and ocular hypertension in whom ß-blockers are contraindicated.

Decision: Not approved ahead of NICE TA publication. NCL Glaucoma Guidelines should be revised to exclude the latanoprost-netarsudil eye drops in the interim, but applicants should consider an NCL consensus formulary position for latanoprost-netarsudil once details of the NICE TA recommendation are known. Recommendation for MEH DTC to review formulary position as per suggestions in JFC minutes.

10. Position Statements and Guidelines

10.1. NCL Glaucoma Guideline

Following the decision to not approve the use of latanoprost-netarsudil eye drops, the NCL Glaucoma Guidelines will be revised and presented at JFC at a future date.

11. NHSE Updates

11.1. NHSE Specialised Commissioning NICE Appraisals Update

Nil.

11.2. NHSE New Restrictions on Use of Puberty Suppressing Hormones

The Committee noted that NHSE had published new government restrictions on the use of gonadotrophin releasing hormones (GnRH) analogues used to suppress puberty as part of treating gender incongruence or gender dysphoria in children and young people under the age of 18 years. This has taken effect since early June and implementation across NCL Trusts and primary care should be underway. The NCL Netformulary will need to be updated in line with the advice.

12. Next meeting

Thursday 18th July 2024

13. Any other business

Nil