North Central London Integrated Care System

NHS
North Central London
Medicines Optimisation Network

Joint Formulary Committee (JFC): Minutes

Minutes from the meeting held on 19th September 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 K Tasopoulos	NMUH, DTC Chair	✓	
Ms S Stern	NMUH, 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 EY Cheung	NCL ICB, Head of Quality and Improvement		✓
Ms K Petrou	NCL ICB, Community Pharmacy Clinical Lead		✓
Dr S Ghosh	Enfield Unity PCN, Clinical Director; Enfield GP Federation, Co-Chair	✓	
Dr D Heaney	UCLH, Consultant Neurologist	✓	
Mr S Jenkinson	RFL, Lead Pharmacist Cancer Services	✓	
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 H Thoong	GOSH, Formulary Pharmacist	✓	
Mr D Sergian	MEH, Formulary Pharmacist	✓	
Mr W Li	MEH, Formulary Pharmacist	✓	

Ms J Bloom	MEH, Associate Chief Pharmacist	✓	
Ms A Bathia	RNOH, Formulary Pharmacist	✓	
Ms S Ahmed	WH, Formulary Pharmacist		✓
Ms S Shah	NMUH, Formulary Pharmacist	✓	
Ms Y Lam	UCLH, Formulary Pharmacist	✓	
Ms M Thacker	GOSH, Deputy Chief Pharmacist	✓	
Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	✓	
Mr J Modha	NHSE, Specialised Commissioning Pharmacist	✓	
Mr J Flor	WH, Lead Pharmacist	✓	
Ms R Allen	UCLH, Commissioning Pharmacist		✓
Mr A Fazal	RFL, Principal Pharmacist		✓
Mr G Grewal	RFL, Deputy Chief Pharmacist	✓	
Dr B Powell	UCLH, Clinical Pharmacology Specialist Registrar	✓	
Ms J Canning	UCLH, Senior Haematology Pharmacist	✓	
Ms M Low	UCLH, Senior Haematology Pharmacist	✓	
Dr K Roy	UCLH, Respiratory Medicine Consultant	✓	
Dr A Bakhai	RFL, Consultant Cardiologist	✓	
Ms M Formica	WH, Lead Pharmacist – Respiratory and Haringey Home Oxygen Review Service	✓	
Ms C Tse	LNWH, Lead Formulary Pharmacist (Observer)	✓	
Ms M Darjee	NMUH, Gastroenterology Pharmacist (Observer)	✓	
Mr P Juneja	GSTT, Joint Formulary and Medicines Pathway Pharmacist (Observer)	✓	

2. Meeting attendees

Prof Hingorani welcomed members, observers, and applicants to the meeting (see above). The Committee acknowledged the sad news of the passing of Dr Robert Urquhart (UCLH Divisional Clinical Director) who was a member and one of the founding fathers of JFC and noted his invaluable wisdom and insight to the Committee over the years. The Committee thanked Ms Heather Weaver (NHSE Specialised Commissioning Pharmacist) for her valuable contributions to the Committee and wished her well in her retirement and welcomed Mr Jiten Modha to attend the Committee as her successor.

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 declared by members or attendees present. Ms Formica, Dr Roy, Dr Bakhai, and Dr Mallia declared interests from the manufacturer for Trixeo Aerosphere® (AstraZeneca).

4. Minutes of the last meeting

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

5. Review of action tracker

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

5.1 Eltrombopag for Aplastic Anaemia

Deferred.

5.2 Gout Treatment Algorithm: Netformulary Update

In September 2019, the Committee reviewed an application for benzbromarone for treatment-resistant gout and the decision was deferred subject to development of an NCL treatment algorithm for gout. The suggested formulary statuses and treatment hierarchy for gout were informed by British Society for Rheumatology (BSR), The European Alliance of Associations for Rheumatology (EULAR), and NICE guidelines. Following a consultation period, the relevant NCL stakeholders have agreed for the proposed formulary statuses to be adopted and Netformulary to be updated accordingly.

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

Date	Drug and Indication	DTC Decision and Details
July 2024	Alcohol Dehydrated Injection (Ethanol 100%) for ablation of cystic thyroid nodules	**Reviewed by**: RFL **Drug**: Ethanol 100% injection **Indication**: Ablation of cystic thyroid nodules **Decision**: Approved **Prescribing status**: Restricted to secondary care only **Funding source**: Divisional budget **Additional information**: Submitting application to CPPSC for governance ratification. To be referred to the LEC(s) for funding consideration **Fact sheet or Shared Care required**: N/A
January 2024	Rivaroxaban for venous thromboembolism (VTE) treatment in paediatric patients (0-18 years)	**Reviewed by**: GOSH **Drug**: Rivaroxaban **Indication**: Venous thromboembolism (VTE) treatment in paediatric patients (0-18 years) **Decision**: Approved **Prescribing status**: Restricted to secondary care only **Funding source**: In tariff **Additional information**: Brand name to be removed from drug monograph to support generic prescribing. **Fact sheet or Shared Care required**: N/A
October 2006 & May 2009	Hexaminolevulinate (HexVix®) for demarcation of carcinoma in situ, under blue light fluorescence cytoscopy, in patients with either proven or high suspicion of bladder cancers, as an adjunct to standard white light cystoscopy	**Reviewed by**: UCLH **Drug**: Hexaminolevulinate (HexVix®) **Indication**: Demarcation of carcinoma in situ, under blue light fluorescence cytoscopy, in patients with either proven or high suspicion of bladder cancers, as an adjunct to standard white light cystoscopy **Decision**: Approved **Prescribing status**: Restricted to secondary care only **Funding source**: In tariff **Additional information**: N/A **Fact sheet or Shared Care required**: N/A
July 2024	[FOC Scheme] Brigimadlin*† for MDM2 amplified/TP53 Wild Type biliary tract cancer and other solid tumours	**Reviewed by**: UCLH **Drug**: Brigimadlin tablets (unlicensed) 45mg every 3 weeks **Indication**: 1) Patients with unresectable locally advanced/metastatic, MDM2 amplified and TP53, wild type biliary tract cancer (BTC) who would meet criteria for the Brightline-2 clinical study but unable to access due to its current suspension, 2) Patients with any other solid tumour type which was MDM2 amplified and TP53 and not eligible for enrolment in any clinical trial **Decision**: Not approved **Funding status**: Free of charge scheme
July 2024	[FOC Scheme] Tinengotinib*† for FGFR2 fusion/rearrangement cholangiocarcinoma and other solid tumours	**Reviewed by**: UCLH **Drug**: Tinengotinib tablets once daily (dose TBC following confirmation of FIRST-308 part A outcome) **Indication**: Unresectable or metastatic cholangiocarcinoma (CCA) with an FGFR2 fusion or rearrangement, who do not meet criteria for the FIRST-308 study due to prior FGFR inhibitor use

		Decision: Approved **Prescribing status**: Restricted to secondary care GI oncology use only **Funding source**: Free of Charge Scheme **Additional information**: N/A **Fact sheet or Shared Care required**: N/A **Reviewed by**: UCLH **Drug**: Tinengotinib tablets once daily (dose TBC following confirmation of FIRST-308 part A outcome) **Indication**: Any other solid tumour type with an FGFR alteration, and not eligible for enrolment in a clinical trial **Decision**: Not approved **Funding source**: Free of Charge Scheme
July 2024	Baricitinib* for refractory haemophagocytic lymphohistiocytosis	**Reviewed by**: UCLH **Drug**: Baricitinib 4mg daily (up to 3 months) on advice of HLH MDT only (off-label) **Indication**: Refractory HLH - Primary HLH: in patients who have failed all standard therapies (as per HLH 2004 protocol) and require additional treatment as a bridge to allogenic stem cell transplant - Secondary HLH: patients who have failed high dose steroids, IVIG, anakinra and etoposide (or are unsuitable for etoposide) as a bridge to diagnosis/management of the underlying condition **Decision**: Conditionally approved **Prescribing status**: Restricted to secondary care only **Funding source**: Internally funded High Cost Drug **Additional information**: Conditions of approval: • All requests for baricitinib discussed and approved at HLH MDT • Baricitinib response and safety data to be collected by the HLH MDT • Submission of an NHSE policy proposal for baricitinib or ruxolitinib within the next 3 months **Fact sheet or Shared Care required**: N/A
July 2024	[FOC Scheme] Nirogacestat*† for desmoid-type fibromatosis	**Reviewed by**: UCLH **Drug**: Nirogacestat tablets (unlicensed) 150 mg twice daily **Indication**: Second line treatment option for adult patients with unresectable desmoid type fibromatosis who have progressed or relapsed following previous treatment **Decision**: Approved **Prescribing status**: Restricted to secondary care only **Funding source**: Free of Charge Scheme **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 Pathways Group

The Committee noted that the NCL Medicines Pathways Working Group is a subgroup of the NCL JFC and provides a single joint forum for the oversight and assurance of NCL treatment pathways. This aims to include ICB commissioned High-Cost Drug (HCD) pathways, primary care pathways with a medicines focus, interface prescribing and end-to-end clinical treatment pathways, but the group will initially focus on ICB commissioned HCD pathways. The Committee noted the current workplan and ratified the terms of reference for this Group. Medicines pathways will be developed by clinical working groups and will be brought to JFC for clinical sign-off.

9 Medicine reviews

9.1 [FOC Scheme] Mitapivat for transfusion and non-transfusion dependent PK-deficiency (Applicant: Dr P Eleftheriou, Mr A Tailor, Ms M Low, Ms J Canning, UCLH; Dr E Drasar, Dr R Mullaly, WH)

The Committee considered a free-of-charge (FOC) scheme *in absentia* for mitapivat tablets (initiated at 5mg twice daily up to a maximum of 50mg twice daily), a pyruvate kinase activator, licensed for treatment of pyruvate kinase deficiency in adults with haemolytic anaemia.

ACTIVATE was a 24-week, Phase III, randomized, placebo-controlled, double-blind study to assess the safety and efficacy of mitapivat in adults with pyruvate kinase deficiency (defined as the presence of at least 2 mutant alleles in the gene *PKLR* encoding pyruvate kinase, of which at least one was a missense mutation) not receiving regular red blood cell transfusions (n=80). The primary endpoint (an increase in Hb from baseline of at least 1.5g/dL), was achieved in more patients treated with mitapivat compared to placebo (40% vs 0%; adjusted difference: 39.3%, [95%CI: 24.1 to 54.6]; p<0.001). The key secondary end point, the average change from baseline in the Hb level at week 16, 20 and 24 was significantly greater for mitapivat than placebo ([1.7g/dL (95% CI: 1.3 to 2.1) vs. -0.1g/dL (95% CI: -0.6 to 0.3); least-squares mean difference: 1.8g/dL, [95%CI: 1.2 to 2.4]; p<0.001). Key limitations of the study were the limited study duration, small study population, inclusion of only transfusion independent patients, and surrogate primary and secondary endpoints.

ACTIVATE T was a 40-week, Phase III, single-arm, unblinded study to assess the safety and efficacy of mitapivat for in adults with pyruvate kinase deficiency (defined as a presence of at least 2 mutant alleles in *PKLR* of which at least one was a missense mutation) receiving regular red blood cell transfusions (n=27). Patients who were homozygous for the *PKLR* R479H mutation (1436G→A [Arg479His]) or had two non-missense mutations, without another missense mutation, in *PKLR*, were excluded from the study, because the primary response endpoint was not met in individuals with these genotypes in the DRIVE-PK study (n=5 and n=10, respectively). The primary endpoint, defined as a reduction in the number of RBC units transfused during the fixed-dose period of at least 33%, compared with the participant's individual historical transfusion burden standardised to 24 weeks, was achieved in 10 patients (37%, [95%CI: 19 to 58]; p=0.0002). The key secondary end point, the percentage reduction from the annualised number of historical RBC units transfused up to the end of the fixed-dose period was 36.6%. Six participants (22% [95% CI: 9 to 42] reached transfusion-free status during the fixed-dose period, another key secondary end point. Key limitations of the study were that this was a single-arm, open-label study conducted in a small population and was time-limited.

Grace et al (2022) reported an abstract of the long-term extension (LTE) studies for the ACTIVATE and ACTIVATE T studies. In the ACTIVATE LTE study, 13/15 (86.7%) evaluable patients on mitapivat that achieved a Hb response (≥ 1.5g/DL Hb increase from baseline) maintained this response up to 19.5 months at all time points and 2/15 patients maintained a Hb response (≥ 1g/dL Hb increase from baseline) at all timepoints. Patients randomized to the placebo arm showed similar improvements in Hb levels after switching to mitapivat. In the ACTIVATE T LTE study, 6/6 patients on mitapivat that achieved transfusion-free status maintained this status up to 21.9 months.

In terms of safety, mitapivat was reported to have a similar risk of treatment related adverse effects as placebo (88% vs 90%). Very common side effects include insomnia and nausea as per the Summary of Product Characteristics.

In terms of budget impact, mitapivat is being provided via a free of charge scheme for £1 per pack. However, the terms of supply do not fully meet the NCL Free of Charge Schemes criteria. In NCL, approximately 25 patients are expected to be enrolled on the scheme, with approximately 0-1 patient anticipated to be enrolled per annum going forward. The Committee noted that there is a very high financial risk if the FOC supply was

to end, and agreed that the FOC scheme contract, terms of supply and eligibility criteria needed further clarification before NCL Trusts would be able to sign up. The Committee also agreed that any prescribing of mitapivat under a FOC scheme would need to be subject to a patient consent form on initiation that outlines that treatment may be discontinued if the FOC stock ends.

The Committee acknowledged that PK deficiency is a rare condition, the only current alternative treatment option is transfusions and mitapivat represents a new mechanism of action with a reasonable safety profile and a reported treatment effect on haemoglobin and other markers. It was noted that further long-term safety data is expected in 2025.

However, the Committee requested clarification on the initiation criteria, and the cohort that is expected to derive the most benefit. There is a more robust evidence base for patients who are not on transfusions, and this is reflected in international guideline recommendations, however this cohort may be expected to have a milder form of the disease. The evidence in patients on transfusions is limited to the small, single arm ACTIVATE T study, however the Committee noted that this may be the cohort that represents the greatest clinical unmet need.

In summary, the Committee agreed to defer a decision on mitapivat pending further clarification on the patient initiation criteria and terms of supply for the Free of Charge scheme.

Drug: Mitapivat tablets (dose as per license)
Indication: Transfusion and non-transfusion dependent PK-deficiency patients
Decision: Deferred pending clarification on patient initiation criteria and terms of supply of the Free of Charge Scheme

9.2 Appeal: Trixeo Aerosphere® for COPD (Appellants: Ms M Formica, WH; Dr K Roy, UCLH; Dr A Bakhai, RFL; Dr M Heightman, UCLH; Dr P Mallia, RFL)

The Committee considered an appeal for Trixeo Aerosphere® (budesonide, glycopyrronium bromide, formoterol fumarate dihydrate; BGF), a triple therapy inhaled corticosteroid, long-acting beta2-agonist, and long-acting muscarinic antagonist (ICS/LABA/LAMA) pressurised metered dose inhaler (pMDI), for the licensed indication of maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD).

The proposed place in therapy was as per NCL COPD guidelines, which at the time of the meeting was being updated, with Trixeo being the first-choice triple therapy pMDI. In line with the NHS Long Term Plan and the NHSE Green Plan, prescribers have been encouraged to prescribe a dry powder inhaler (DPI) instead of an pMDI where clinically appropriate. Where this is not possible, prescribers are encouraged to prescribe a pMDI with a lower carbon footprint. Compared to Trimbow pMDI, Trixeo has a slightly lower indicative carbon footprint (12,600 vs 13,237 gCO_{2e}) but both have a much higher carbon footprint than DPIs.

NCL JFC previously reviewed Trixeo Aerosphere® for COPD in December 2022. At the time, the Committee considered evidence from the KRONOS (2018, n=1,902) and ETHOS trial (2020, n=8,509). The Committee rejected the application for Trixeo on the basis that it did not fulfil an unmet need: Trelegy Ellipta, Trimbow pMDI, and Trimbow NEXThaler are all triple inhalers available on the formulary. Moreover, the Committee discussed limitations of the clinical trial data and raised concerns about the unfair test of efficacy in the trials, which involved discontinuation of ICS, as well as some patients in certain comparator groups receiving more inhaler therapies than others.

The grounds for the appeal were:

- Claims of improved drug delivery from the Aerosphere device.
- Significant new information available requiring reconsideration. The appellants stated that new evidence available demonstrates improved all-cause mortality and cardiovascular-related mortality benefit from the use of Trixeo Aerosphere®.

In terms of claims of innovative device and the Aerosphere technology, the reviewed studies included Lechuga-Ballesteros et al (2011), Doty et al (2018), Taylor et al (2018), Usmani et al (2023), and Marshall et al (2024). The Committee were presented with evidence from Usmani et al (2023, n=20), a study evaluating lung deposition of two inhaled ICS/ LABA/ LAMA single-inhaler triple therapies using in silico functional respiratory imaging (using computational fluid dynamics). BGF pMDI demonstrated greater total, central, and small airways deposition for all components compared to fluticasone furoate/ umeclidinium/ vilanterol DPI. Key

limitations of the study were uncertainty associated with computational modelling, the lack of direct translation of results to meaningful clinical outcomes, and the choice of comparator (comparing a pMDI to a DPI device).

In terms of claims of benefit for all-cause mortality and cardiovascular-related mortality, the reviewed studies included Martinez et al (2020), Singh et al (2022), Stolz et al (2023), and Singh et al (2024). Additionally, the following abstracts were also reviewed: Pollack et al (2024) and Pollack et al (2024). Martinez et al (2020), Singh et al (2022), and Singh et al (2024), were ETHOS trial post-hoc analyses investigating reduced all-cause mortality of BGF triple therapy; effect of BGF on exacerbations, symptoms, health-related quality of life, and lung function; and effect of BGF on cardiopulmonary events in COPD patients respectively. The studies claimed that triple therapy BGF reduced the risk of death, demonstrated benefits on exacerbations and improved lung function, and was associated with reduction in risk across cardiopulmonary and traditional COPD endpoints compared to glycopyrronium/ formoterol fumarate.

In reviewing the post-hoc analyses of the ETHOS trial, the Committee were presented with limitations of the ETHOS trial design which may impact the interpretation of the reported results. In the ETHOS trial, 80% of all patients were already receiving an ICS prior to randomisation. Consequently, the ETHOS trial design resulted in a higher rate of de-escalation of ICS use in patients already on corticosteroids randomised to the LAMA/ LABA comparator arm (-80%) than escalation of ICS (~20%) in patients not on corticosteroids who were randomised to the triple therapy high-ICS dose investigational arm. Moreover, the 40% of patients who were already receiving maintenance triple therapy were at risk of a step-down in treatment intensity if they were randomised to dual therapy, either LABA and high dose ICS or LAMA/LABA comparator arms. There was a lower all-cause mortality rate of 1.5% in those randomised to the higher dose triple therapy inhaler compared to 2.1% in those randomised to the dual therapy LAMA-LABA inhaler. But this mortality difference reflects both an increase in ICS use by 20% (from 80% to 100%) in the former group; and a reduction by 80% (from 80% to 0%) in the latter.

Using the ETHOS trial investigators own published data on mortality stratified by pre-randomisation ICS use, it was possible to separate the effect of introducing and of withdrawing ICS on all-cause mortality in ETHOS. In patients already on ICS, use remained 100% among those randomised to the higher-dose triple inhaler therapy and mortality was 1.3%. However, among ICS users randomised to dual therapy LAMA-LABA, steroid use fell by 100% and mortality was substantially higher at 3%. In patients not already on ICS, use increased by 100% in those randomised to the higher-dose triple therapy inhaler but remained unchanged at 0% in those randomised to dual therapy LAMA-LABA. Yet mortality was marginally higher (not lower) at 1.8% in the former group compared to 1.2% in the latter (Figure 1c).

A lower rate of major acute cardiovascular events was also observed in the higher-dose triple therapy inhaler arm of the ETHOS trial compared to the dual therapy LAMA-LABA inhaler arm. However, this difference could also be attributed to withdrawal from ICS among existing users, rather than the introduction among non-users.

Concerns around the methodological design of COPD trials have been echoed amongst members of the respiratory community. Suissa et al (2021), in a Lancet Respiratory commentary, noted the same issues regarding the confounding effect of abrupt ICS discontinuation in 80% of patients and stepdown to dual therapy from triple therapy for patients stabilised on maintenance triple therapy prior to randomisation. Additionally, the Committee were presented with a warning letter (August 2023) issued by the US Food and Drug Administration (FDA) to AstraZeneca regarding false or misleading claims about efficacy for Trixeo (also known as Breztri® in USA). In the letter, the FDA states "*no conclusions about the effect of Breztri® on all-cause mortality can be drawn from the ETHOS trial*" due to the potential of confounding from the abrupt withdrawal of ICS. Moreover, the FDA states "*to date, no drug has been shown to improve all-cause mortality in COPD*".

The Committee heard from Ms Formica and Dr Bakhai that the updated treatment hierarchy will better align with the GOLD 2023 report which references the ETHOS and IMPACT trials as evidence that single inhaler triple therapy reduced all-cause mortality compared to single inhaler dual therapy. The appellants explained that for COPD patients, any improvement in mortality, even if modest, represents a novel development in the treatment of COPD and should be available to patients. The Committee also heard about an ongoing Phase III trial by AstraZeneca, THARROS, that will investigate the potential effect of BGF triple-combination inhaled therapy on severe cardiopulmonary outcomes in ICS-naïve patients. The Committee were informed of AstraZeneca's intention to improve the sustainability of their inhalers using new a propellant with near-zero global warming potential (GWP). However, the Committee noted that similar changes are proposed with other

inhalers and evidence of the improved sustainability and timelines for launch have not been clarified. Therefore, decisions need to be made based on existing formulations.

In camera, the Committee discussed the limitations of the clinical trial data, notably the effect on mortality of ICS withdrawal and stepping down therapy in patients established on triple therapy maintenance treatment who were randomised to dual therapy comparator arms. The Committee queried whether the results of the trial would hold true if the intervention involved an alternative triple therapy inhaler. The Committee heard about the IMPACT trial (2018, n=10,355) of the Ellipta single-inhaler triple-therapy inhaler (fluticasone furoate/ umeclidinium/ vilanterol). Like ETHOS, 77% of patients in the earlier IMPACT trial of a different triple therapy inhaler were taking an ICS prior to randomisation. Analysis of mortality data from Lipson et al (2020) stratified by pre-randomisation corticosteroid also provided evidence of an adverse effect of ICS withdrawal on all-cause mortality.

The Committee also noted that there the lack of a head-to-head trial comparing one triple therapy inhaler to another, and therefore, claims of superiority of Trixeo either on the grounds of improved device, all-cause mortality, or cardiovascular benefits could not be made and remain a research question. The committee also noted that AstraZeneca, the manufacturer of Trixeo, has embarked on the THARROS trial a Phase III randomised, double-blind, parallel group, multi-center event-driven study comparing a single inhaler tripe therapy BGF pMDI 320/14.4/9.6 micrograms twice daily with dual therapy (GFF) pMDI 14.4/9.6 micrograms twice daily in participants with COPD who are at risk of a cardiopulmonary event. The primary endpoint in the THARROS trial is time to first severe cardiac event, severe COPD exacerbation, or cardiopulmonary death. Unlike ETHOS, THARROS is excluding patients on maintenance ICS, which is consistent with the concern that ICS withdrawal may be hazardous. The Committee agreed that Trixeo did not meet an unmet clinical need as Trimbow pMDI, which is also licensed for maintenance treatment in asthma, was already on the NCL Joint Formulary. The Committee acknowledged that there may be theoretical benefits of device continuity for patients stepping up from dual therapy (Bevespi Aerosphere®) to triple therapy with Trixeo, but evidence on this was not provided and was not listed in grounds for this appeal. The importance of device continuity for patients is unknown, as patients may switch inhalers regularly throughout a treatment pathway and there are other convenience factors for consideration (e.g. ease and frequency of cleaning). Furthermore, the Committee expressed concerns with the potential impact of the inclusion of Trixeo, on the sustainability work around the promotion of prescribing DPIs. If another pMDI option is added to the NCL Joint Formulary where there is a belief of all-cause mortality and cardiovascular-related benefits, despite the lack of evidence for this claim, this may result in preferential prescribing of Trixeo over DPIs, which have a significantly lower carbon footprint and constitutes the more favourable and sustainable treatment option.

In summary, the Committee were unconvinced of the mortality or cardiovascular benefit claims made for Trixeo, nor that its improved delivery of treatment components would result in clinically meaningful outcomes for patients with COPD over existing formulary options. Trixeo does not meet an unmet clinical need as other single inhaler triple therapy options, including Trimbow pMDI, are already on the formulary. Furthermore, the Committee expressed concerns about the potential for preferential prescribing of Trixeo over DPIs, which are more sustainable. In conclusion, the Committee turned down the appeal and retained the original decision that Trixeo Aerosphere® should not be included on the NCL Joint Formulary.

Drug: Trixeo Aerosphere® (dose as per license)

Indication: Maintenance treatment in adult patients with moderate to severe COPD

Decision: Appeal not upheld

10 Position Statements and Guidelines

10.1 NCL Paediatric ONS Formulary for primary care

The Committee noted that the NCL Paediatric ONS Formulary for Primary Care had been signed off at the Medicines Clinical Reference Group and will be available as a reference on the NCL GP website.

10.2 NCL COPD Pathway (Applicants: Dr K Roy, UCLH; Ms M Formica, WH)

The Treatment Guidelines for the acute and chronic management of COPD, authored by the NCL Inhaler Sustainability Group and the NCL Respiratory Network, were presented to the Committee for ratification. The key updates include:

- Updated inhaler choices on formulary based on NCL JFC decisions (including the addition of Trixeo Aerosphere®)
- The addition of information on sustainability (including indicative carbon footprint of inhalers on the NCL Joint Formulary)
- Updated Systematized Nomenclature of Medicine (SNOMED) codes
- Creation of two separate treatment pathways including NICE guideline NG115 and the new GOLD standards document in COPD approaches
- Updated definition of airflow obstruction and severity of disease, in line with guidance from the Association for Respiratory Technology and Physiology (ARTP)
- Updated information on steroid safety cards (including which cards are available and when to provide a steroid safety card)

The Committee heard from Dr Roy and Ms Formica that the updated NCL COPD guidelines moves towards greater alignment with the GOLD treatment pathway, including removal of ICS/ LABA from the treatment algorithm. In the existing pathway, patients on dual therapy ICS/ LABA requiring a pMDI device would be on Fostair (beclomethasone/ formoterol) and would be stepped up to Trimbow pMDI (beclomethasone/ formoterol/ glycopyrronium) where clinically appropriate. However, the new pathway proposes removal of the dual therapy ICS/ LABA step, and patients requiring dual therapy on LABA/ LAMA with a pMDI device would be on Bevespi Aerosphere pMDI (glycopyrronium/ formoterol). Therefore, the proposal to include Trixeo as the first-line triple therapy pMDI would allow for continuation of the same device for patients who are requiring a step-up in treatment from LABA/ LAMA pMDI dual therapy to ICS/ LABA/ LAMA pMDI triple therapy.

In summary, the Treatment Guidelines for the acute and chronic management of COPD will require revisions following the rejection of the Trixeo Aerosphere® appeal. The authors are requested to provide an updated guideline, with the appropriate inhaler choices on the NCL Joint Formulary, and clear justification for the removal of ICS/ LABA, before the guideline is brought back to JFC for ratification.

11 NHSE Updates

Nil

12 Next meeting

Thursday 17th October 2024

13 Any other business

Nil