North Central London
Medicines Optimisation Network

Joint Formulary Committee (JFC): Minutes

Minutes from the meeting held on 19th January 2023

		Present	Apologies
Members			
Prof A Hingorani	NCL JFC Chair		✓
Dr B Subel	NCL JFC Vice Chair	✓	
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; NCL ICS, Interim Chief Pharmacist	✓	
Dr R Urquhart	UCLH, Divisional Clinical Director	✓	
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		✓
Mr V Raman	RNOH, DTC Chair	✓	
Mr A Shah	RNOH, Chief Pharmacist	✓	
Prof A Tufail	MEH, DTC Chair		✓
Ms N Phul	MEH, Chief Pharmacist		✓
Ms K Delargy	BEH, Chief Pharmacist	✓	
Ms L Reeves	C&I, Chief Pharmacist		✓
Dr L Waters	CNWL, Consultant Physician in HIV	✓	
Ms R Clark	NCL ICB, Head of Medicines Management (Camden)		✓
Mr P Gouldstone	NCL ICB, Head of Medicines Management (Enfield)	✓	
Ms E Mortty	NCL ICB, Interim Head of Medicines Management (Haringey)	✓	
Ms M Singh	NCL ICB, Head of Medicines Management (Barnet)	✓	
Mr A Dutt	NCL ICB, Head of Medicines Management (Islington)	✓	
Dr D Roberts	NCL ICB, Clinical Director (Islington)	✓	
Mr T Dean	Patient partner		✓
Attendees			
Ms S Amin	IPMO Programme Team, JFC Principal Pharmacist	✓	
Mr G Grewal	IPMO Programme Team, JFC Support Pharmacist	✓	
Ms S Maru	JFC Support Pharmacist	✓	
Ms P Varu	JFC Support Pharmacist	✓	
Ms I Samuel	RFL, Formulary Pharmacist	✓	
Mr H Shahbakhti	RFL, Formulary Pharmacist	✓	
Ms H Bouattia	RFL, Formulary Pharmacist	✓	
Mr A Barron	UCLH, Principal Pharmacist		✓
Mr S O'Callaghan	UCLH, Formulary Pharmacist		✓
Ms A Sehmi	NMUH, Formulary Pharmacist	✓	
Ms H Thoong	GOSH, Formulary Pharmacist	✓	

Mr D Sergian	MEH, Formulary Pharmacist	✓	
Ms H Weaver	NHSE, Specialised Commissioning Pharmacist	✓	
Ms A Blochberger	NHSE, Specialised Commissioning Pharmacist		✓
Ms A Fakoya	NCL ICB, Contracts & Commissioning Pharmacist	✓	
Dr A Hosin	UCLH, Clinical Pharmacology Registrar	✓	
Ms EY Cheung	NCL ICB, Deputy Head of Medicines Management (Camden)		✓
Ms K Mistry	RNOH, Formulary Pharmacist	✓	
Ms S Ahmed	WH, Formulary Pharmacist	✓	
Mr J Flor	WH, Finance, Business and Performance Pharmacist	✓	
Ms M Thacker	RFL, Clinical Lead Pharmacist	✓	
Mr G Purohit	RNOH, Formulary Pharmacist		✓
Ms J Bloom	MEH, Associated Chief Pharmacist	✓	
Prof M Scully	UCLH, Consultant Haematologist	✓	
Ms R Burgoyne	UCLH, Haematology Pharmacist	✓	
Mr A Tailor	UCLH, Haematology Pharmacist	✓	
Dr C Kortsalioudaki	UCLH, Consultant Neonatologist	✓	
Ms A Hussain	UCLH, Womens Health Pharmacist	✓	
Ms P Stepney	UCLH, Neonatal Dietician	✓	
Dr J O'Nions	UCLH, Consultant Haematologist	✓	
Dr P Kumar	RFL, Consultant Haematologist	✓	
Dr R Crowley	UCLH, Senior Clinical Fellow (Neonatal unit)	✓	
Ms L Garubova	WH, Formulary Pharmacist	✓	
Dr K Stringaris	UCLH, Consultant Haematologist	✓	
Ms R Allen	UCLH, Specialised Clinical Commissioning Pharmacist	✓	
Mr A Fazal	UCLH, Specialised Clinical Commissioning Pharmacist	✓	
Ms C OBeirne	UCLH, Formulary Pharmacist	✓	

2. Meeting observers and members

Dr Subel welcomed members, applicants and observers to the meeting (see above).

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.

4. Minutes of the last meeting

Minutes and abbreviated minutes were accepted as an accurate reflection of the December 2022 meeting.

5. Matters arising

Nil

6. Review of action tracker

Action tracker included for information.

7. JFC Outstanding Items & Work Plan

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

8. Local DTC recommendations / minutes

8.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
RNOH	May 2022	Intravesical gentamicin	Recurrent UTIs in spinal cord injury patients (protocol for research purposes only)	**Decision:** RNOH only **Prescribing:** Secondary care **Tariff status:** N/A – charity funded **Funding:** N/A – charity funded **Factsheet or shared care required:** N/A

UCLH	Nov 2022	Hyperthermic intraperitoneal cisplatin	Ovarian cancer	**Decision:** UCLH only **Prescribing:** Secondary care **Tariff status:** Not routinely commissioned **Funding:** Trust **Factsheet or shared care required:** N/A
UCLH	Nov 2022	FOC scheme: Pembrolizumab*† (in combination with platinum chemotherapy)	Recurrent persistent or metastatic PD-L1 positive (CPS≥1) cervical cancer	**Decision:** Added to the NCL Joint Formulary **Prescribing:** Secondary care **Tariff status:** N/A – Free of Charge Scheme **Funding:** N/A – Free of Charge Scheme **Factsheet or shared care required:** N/A
UCLH	Nov 2022	Dexrazoxane*	Preventing anthracycline-induced cardiotoxicity in adult sarcoma patients (25 years or older)	**Decision:** UCLH only **Prescribing:** Secondary care **Tariff status:** Not routinely commissioned **Funding:** Trust **Factsheet or shared care required:** N/A **Additional information:** Approved clinically, deferred to the High-Cost Drugs Panel for internal funding decision
UCLH	Dec 2022	(Appeal) FOC scheme: Zanidatamab*	Locally advanced or metastatic HER2+ biliary tract cancer for patients who have progressed following first line chemotherapy, when enrolment into a clinical trial is not available and either: • Trastuzumab/ pertuzumab is not available via a free of charge scheme, OR • The patient has not responded to prior trastuzumab/ pertuzumab therapy	**Decision**: UCLH only **Prescribing**: Secondary care only **Tariff status**: N/A – Free of Charge Scheme **Funding**: N/A - Free of Charge scheme **Fact sheet or shared care required**: N/A
UCLH	Dec 2022	Carbamazepine	Trigeminal neuralgia	**Decision**: Added to the NCL Joint Formulary **Prescribing**: Primary and Secondary care only **Tariff status**: In tariff **Funding**: Trust **Fact sheet or shared care required**: N/A **Additional information:** Conditionally approved pending development of a formal guidelines including safety checks and monitoring requirements

UCLH	Dec 2022	Oxcarbazepine	Trigeminal neuralgia	**Decision**: Added to the NCL Joint Formulary **Prescribing**: Primary and Secondary care only **Tariff status**: In tariff **Funding**: Trust **Fact sheet or shared care required**: N/A **Additional information:** Conditionally approved pending development of a formal guidelines including safety checks and monitoring requirements
UCLH	Dec 2022	Lamotrigine	Trigeminal neuralgia	**Decision**: Added to the NCL Joint Formulary **Prescribing**: Primary and Secondary care only **Tariff status**: In tariff **Funding**: Trust **Fact sheet or shared care required**: N/A **Additional information:** Conditionally approved pending development of a formal guidelines including safety checks and monitoring requirements
UCLH	Dec 2022	Pregabalin	Trigeminal neuralgia	**Decision**: Added to the NCL Joint Formulary **Prescribing**: Primary and Secondary care only **Tariff status**: In tariff **Funding**: Trust **Fact sheet or shared care required**: N/A **Additional information:** Conditionally approved pending development of a formal guidelines including safety checks and monitoring requirements
UCLH	Dec 2022	Gabapentin	Trigeminal neuralgia	**Decision**: Added to the NCL Joint Formulary **Prescribing**: Primary and Secondary care only **Tariff status**: In tariff **Funding**: Trust **Fact sheet or shared care required**: N/A **Additional information:** Conditionally approved pending development of a formal guidelines including safety checks and monitoring requirements
UCLH	Dec 2022	Phenytoin	Trigeminal neuralgia	**Decision**: Added to the NCL Joint Formulary **Prescribing**: Primary and Secondary care only **Tariff status**: In tariff **Funding**: Trust **Fact sheet or shared care required**: N/A **Additional information:** Conditionally approved pending development of a formal guidelines including safety checks and monitoring requirements
UCLH	Dec 2022	Baclofen	Trigeminal neuralgia (MS patients only)	**Decision**: Added to the NCL Joint Formulary **Prescribing**: Primary and Secondary care only **Tariff status**: In tariff **Funding**: Trust **Fact sheet or shared care required**: N/A **Additional information:** Conditionally approved pending development of a formal guidelines including safety checks and monitoring requirements. Restricted to MS patients only.

C and I	Aug 2022	Zaponex (Clozapine) orodispersible tablets	For existing NCL approved indications for patients with adherence issues or swallowing difficulties in the community	**Decision:** Added to the NCL Joint Formulary **Prescribing:** Secondary care **Tariff status:** In tariff **Funding:** Trust **Factsheet or shared care required:** N/A **Additional information:** Restricted for use on a named patient basis only, requiring a non-formulary request form

† 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. * Subject to funding consideration.

8.2 Not approved

DTC site	Month	Drug	Indication	JFC outcome
C and I	Aug 2022	Denzapine (Clozapine) suspension	For existing NCL approved indications for patients with adherence issues or swallowing difficulties in the community	**Decision:** Not approved

9. New Medicine Reviews

9.1 Eltrombopag and romiplostim for immune thrombocytopenia (ITP) within six months of diagnosis (Applicant: Prof M Scully, UCLH)

The Committee considered an application for thrombopoietin (TPO)-agonists – eltrombopag (an oral tablet given as 25-75mg daily, adjusted according to response) and romiplostim (a subcutaneous injection given as 1microgram/kg, adjusted according to response), for immune thrombocytopenia (ITP). Both agents have positive NICE TA recommendations for use in chronic ITP; pivotal studies which informed the NICE TAs defined chronic ITP as >6 months since diagnosis (therefore patients with newly diagnosed or persistent ITP 0-6 months since diagnosis is not commissioned). During the COVID-19 pandemic, NHSE published an interim clinical commissioning policy for the use of TPO-agonists in newly diagnosed or relapsed ITP patients aged 1 year or older. This policy was withdrawn in June 2022, and from that point eltombopag and romiplostim were no longer considered to be on Formulary. The Committee considered the use of TPO-agonists as an option for patients with incomplete response or relapse following initial conventional treatments (e.g., corticosteroids or IVIG), irrespective of the time since diagnosis.

The NHSE interim clinical commissioning policy considered three studies. Arnold et al was a randomised, active-comparator controlled, unblinded study to determine if perioperative eltrombopag was non-inferior to IVIG for adult patients with primary or secondary ITP and platelet counts <100 x 109/L before major surgery, or <50 x 109/L before minor surgery (n=74). Patients were randomised to eltrombopag 50mg for 28 days (D21 pre-op until D7 post-op) or IVIG 1-2g/kg for 7 days. The primary endpoint, achievement of perioperative platelet targets, was non-inferior between eltrombopag and IVIG (79% vs 61% [p value for non-inferiority = 0.005]). Key limitations of the study were the relatively small sample size, the variable IVIG dose and it was pharma funded.

Kuter et al was a pooled analysis of 9 studies in which patients who failed first-line treatments were treated with romiplostim, placebo or standard-of-care (SOC). A subgroup analysis was conducted of patients who had a duration of ≤1 year vs >1 year since ITP diagnosis. In 311 patients who had ITP <1 year, response (defined as platelets ≥50 x 10^9/L) was better with romiplostim than placebo and SOC combined (86% vs 62%). In other important outcomes, there was a higher proportion of patients who had ITP <1 year in remission with romiplostim compared with placebo and SOC (16% vs 6%). Key limitations of the study were that it was a retrospective post-hoc analysis, it included extension studies (with no detail how duplication was avoided) and it combined placebo and SOC results together.

Newland et al was a single-arm study to assess the safety and efficacy of romiplostim in adults with primary ITP (platelets <30 x 10^9/L) within 6 months of diagnosis (n=75). The primary endpoint, cumulative months of

response (platelets <50 x 10^9/L), was reached in 70 patients (93%). Key limitations of the study were the lack of comparator and the relatively short duration.

In addition to the data reviewed by NHSE, the Committee were provided with updated information from the EMA, who had recently reviewed and approved a licence variation for the use in patient's refractory to other treatments, irrespective of the time since diagnosis. Data considered included real-world data (response rate range from 115 patients in 3 prospective studies: 67% to 76%), and a subgroup analysis from the EXTEND study which demonstrated a higher response rate in ITP patients <6 months since diagnosis with eltrombopag compared with placebo (56.3% vs 33.3%). The EMA also considered data from an ongoing, phase II, open-label, single-arm study in adult ITP patients who relapsed after or refractory to corticosteroids, with or without IVIG, and grouped by the duration since ITP diagnosis (n=105). Platelet response (platelets ≥50 x 10^9/L), partial platelet response (platelets ≥30 x 10^9/L) and complete response (platelets ≥100 x 10^9/L) was similar between groups, regardless of time since diagnosis. Key limitations include that the study has not been published in a peer-reviewed publication, only interim results available, and the single-arm design open-label design.

In terms of safety, the adverse effect profile is well known as the same medications are used in the chronic ITP setting. It was highlighted that the use of TPO-agonists may reduce the need for corticosteroids, which itself carries long-term risks of adverse effects.

In terms of budget impact, eltrombopag and romiplostim are expected to cost between £10,800 to £11,300 per patient per 6-month period. This cost is substantially less than the cost of IVIG (£44,000 per patient per 6-month period) and avoids the need for hospital attendance and associated costs with infusion and nursing time. However, the budget impact is further complicated as TPO-agonists are funded by the ICB whereas IVIG is funded by NHSE (therefore the drug acquisition cost is not offset by savings generated).

The Committee heard from Prof Scully that there is much experience in the use of TPO-agonists since the pivotal licensing trials. The use of TPO-agonists in newly diagnosed patients (after corticosteroids/IVIG) has been used in practice successfully since the NHSE interim clinical commissioning policy, and clinicians tend to use lower doses (and hence not expected to reach the higher end of the budget impact range). The Committee queried whether IVIG would be devolved to ICBs, though it was confirmed that no specialised commissioning services would be devolved in 2023/24.

In camera, the Committee considered the potential budgetary risk to Trusts (as the current block payment arrangement with the ICB may not be sufficient to cover the potential spend on TPO-agonists across NCL). The Committee agreed it could review the application clinically, with funding decisions devolved to Trust High-Cost Drug Panels for consideration. Both medications appear to work effectively in ITP patients within six months of diagnosis. The Committee understood there had been several changes to the way TPO-agonists are used in NCL over recent years and requested the development of a guideline to support the use of TPO-agonists (to include the review indication, as well as previous JFC decisions from September 2020 on the use of eltrombopag as a short-course to support platelet counts during elective surgery and during chemotherapy).

In summary, the Committee clinically approved the use of eltrombopag and romiplostim for ITP, irrespective of the time from diagnosis (i.e., for use in newly diagnosed and persistent ITP in months 0-6 from diagnosis) following incomplete response or relapse with initial conventional treatments (e.g., corticosteroids or IVIG). Addition to the NCL Trust Formularies is conditional on the development of an NCL guideline to outline the use of TPO-agonists for ITP and approval from each NCL Trust High-Cost Drug Panel.

Decision: Approved clinically; subject to development of an NCL guideline to outline the use of TPO-agonists for ITP and approval from each NCL Trust High-Cost Drug Panel

Prescribing: Secondary care only

Tariff status: In tariff

Funding: Trust (not routinely commissioned)

Fact sheet or shared care required: N/A

9.2 Appeal: ProPrems® to prevent necrotizing enterocolitis (Appellant: Dr C Kortsalioudaki)

The Committee considered an appeal for ProPrems® given as 1 sachet dissolved in water for injection or breast milk daily, to prevent the incidence of necrotizing enterocolitis (NEC) in very preterm (<32 weeks gestational age) and/or very low-birth-weight (<1.5kg) neonates, and continued until 34 weeks gestational age. ProPrems® is a probiotic (classified as a food supplement) and is therefore treated as an unlicensed medicinal product. ProPrems® was reviewed and not approved by NCL JFC in February and April 2022 due to concerns relating to limitations in the evidence base. The pivotal "ProPrems®" study which was reviewed was noted to have reported a significantly lower risk of NEC incidence, though this was a secondary endpoint,; the Committee

also had concerns with why GIRFT had set the use of probiotics in standard practice despite limitations in the evidence. As the Committee were not assured that the efficacy and safety data was sufficient, ProPrems® was not approved.

The appeal was made on several grounds:

- The original application had interest from several NCL Trusts. However, the appellants proposed to use ProPrems® at the UCLH level 3 neonatal unit only, in order to build experience before it is considered for use in NCL Level 2 neonatal units.
- The Committee had previously queried the feasibility of a clinical trial. Input was provided from a UK clinical expert regarding the information and data available, and that whilst further research is needed there is data to support the intervention. This can often lead to challenging discussions with parents, particularly as it is now a national recommendation through GIRFT to make probiotics available.
- The UK clinical expert stated that parents should have the choice provided to them – not that the child should receive ProPrems® – but that the parents should be given the information and have the option to use ProPrems®.
- The request to use ProPrems® was supported by several NCL lead clinicians and experts in neonatal medicine, due to an increase in evidence over time and a strong steer nationally to use the intervention. It would be monitored at an NCL level by the Operational Delivery Network.
- Further feedback from the UK clinical expert stated that other GIRFT recommendations had previously been implemented based on limited data (e.g., the use of Donor Human Milk), and felt that the same criteria for approvals should apply with ProPrems®.
- Additional evidence post-JFC review was presented to the Committee:
    a) WHO have published their recommendations for the care of preterm or low birth weight infants, which includes a recommendation for probiotics in human-milk-fed very preterm infants <32 weeks gestational age, conditional on shared decision making with parents, and using products formulated specially that meet regulatory standards. The evidence of benefit was based on similar data to that reviewed by JFC. The WHO concluded the evidence of benefit was of moderate certainty, with no evidence of harm and little to no effect on neurodevelopment, and no evidence of any other critical outcome.
    b) A retrospective cohort study (Mitha et al, n=345) was presented, in which the authors reviewed the Swedish National Quality Registry for very preterm infants (gestational age 28-31 weeks) in Swedish NICUs. The authors compared 139 patients who received ProPrems® with 206 patients who received no supplementation. ProPrems® was associated with a non-significant reduction in the composite outcome of death, sepsis or NEC (4.3% vs 9.2% [95% CI 0.18 to 1.08; p=0.08]). It was acknowledged that the study was limited by the retrospective and unblinded design in a relatively small population.
- The JFC previously interpreted baseline data at UCLH as being within the national average despite probiotics not in use. However, the appellants argued that a more appropriate interpretation would only be found by comparing centres that offer probiotics versus those that do not; unfortunately, this data is not available. Therefore, an assumption that neonatal units are performing optimally, or that the incidence of NEC cannot be reduced further, should not be made. GIRFT suggests that if uptake in breast milk and probiotics increases, then the incidence of NEC could potentially be avoided in >100 babies per year in the UK with a concurrent reduction in mortality rate.
- The appellants considered the data described to JFC previously and felt that whilst the ProPrems trial was a pivotal study for the particular product requested for use, the Committee should consider the results from the Cochrane review by Sharif et al. The forest plots from the review were presented to the Committee, which demonstrated that compared with control, probiotics were associated with an overall significant reduction in incidence of NEC, mortality and invasive infection in very preterm or very low birth weight infants. Probiotics were associated with a non-significant reduction in incidence of NEC, mortality and invasive infection in extremely preterm (<28 weeks) or extremely low birth weight (<1kg) infants, though could potentially be due to a substantially lower number of patients in studies.
- The recommendations from GIRFT were summarised but highlighted that it was also supported by recommendations from ESPGHAN, WHO and MatNeoSIP (a national initiative to reduce neonatal death, led by the National Patient Safety Team).

- The product choice was reaffirmed to the Committee; ProPrems® was chosen as it is made in accordance with GMP standards and the manufacturer can provide a certificate of analysis with each batch to help with internal Trust QA processes. The composition of ProPrems® is the only combination recommended by ESPGHAN and there are no known issues in supply of ProPrems® with reassurance provided by the company that they are able to meet demand. It was acknowledged that it is more expensive than other probiotics. Additionally, there is a risk of contamination in wards (as with any probiotic), and therefore caution and risk mitigation measures (e.g., appropriate training) should be applied.
- The Committee were informed of the use of probiotics in other NHS Trusts. Further information was sought and responses from six Trusts was presented. Five out of six Trusts use ProPrems® also, and there were no concerns, incidents, or infections reported in their use. One Trust had collected data which demonstrated a decrease in late onset sepsis. One network had implemented ProPrems® in three Level 3 neonatal units and six Level 2 neonatal units, and had the lowest incidence of NEC nationally.
- The Committee had previously raised concerns around microbiological infection, and to allay these concerns the appellants reiterated that the risk of invasive infection was low from the Cochrane review (favouring probiotics), no risks were identified from Trusts who have implemented probiotics, and the appellants plan to implement ESPGHAN/WHO recommendations for shared decision making with parents (i.e., to inform them of any potential risks prior to initiating treatment).
- The JFC previously had concerns around the timing and duration of probiotics as there was no information on long-term risks or harm. This remains true, although ESPGHAN do recommend for individual units to determine the start and duration of treatment based on their population and ongoing risk of disease. The appellants would work with other centres who have implemented probiotics to share their learning, and there is alignment in that every centre usually treats until 34 weeks gestational age.
- The appellants had originally overestimated the number of patients which ProPrems® would potentially be used in. An analysis of patients over one year demonstrated that ProPrems® would potentially be used in 149 patients. Based on the NNT from the ProPrems trial, ProPrems® could potentially avoid 3 incidences of NEC per year. Each incidence adds lifelong healthcare costs, and if the patient survives, they could develop neurodevelopmental and cognitive outcomes. In the previous 2 years, there had been 17 incidences of NEC at UCLH. This has led to substantial increases in healthcare resource utilisation (e.g., lengthy inpatient admissions in the paediatric ITU and HDU, prolonged use of TPN, mortality). The cost of ProPrems® would be £35,000 in 149 patients per annum, though this could easily be offset if two incidences of NEC were avoided per annum (not including lifetime costs associated once an incidence of NEC is observed).
- The UCLH neonatal team plan to collect data to monitor the use of ProPrems® and for patient outcomes. This can be compared with the current baseline incidence rate of 9.8%. The appellants provided the Committee with an audit form for consideration.

The Committee heard from Dr Kortsalioudaki that there is a strong feeling in the neonatal community that ProPrems® should be available, as it offers an option to prevent NEC, which itself is a serious and life-threatening condition. Level 3 neonatal units are planning to collaborate to produce national guidance and are also planning to collectively gather data on the use of probiotics to support its position. The Committee enquired whether the use of probiotics in preterm neonates had been adopted in Australia (as pivotal studies with ProPrems® were undertaken there), and it was demonstrated to be implemented for use where consent is provided.

In camera, the Committee remained uncertain of the evidence from the ProPrems® trial, but agreed that the Cochrane review does demonstrate some degree of signal overall for probiotics. The Committee was given confidence from the endorsements from international organisations (particularly from ESPGHAN), and the use of a standardised product manufactured to cGMP standards. Due to the uncertainties remaining with the data, and with knowledge that probiotics may be recommended to Level 2 neonatal units in the near future, the Committee requested that data is collected under an evaluation for one year and brought back to JFC for reassurance prior to any further decisions being made.

In summary, the Committee agreed to add ProPrems® to the UCLH formulary for the prevention of necrotizing enterocolitis in very preterm (<32 weeks) or very low birth weight (<1.5kg) neonates. The approval was subject to minor amends to the proposed audit form (i.e. to include gestational age/weight at time of ProPrems® initiation if different to birth, gestational age/weight at time of treatment cessation, and clarity on continuation of treatment if the patient is discharged to a local neonatal unit up until week 34 and how this data is reported back into the UCLH team).

Decision: Approved under evaluation

Prescribing: UCLH only

Tariff status: In tariff

Funding: Trust

Fact sheet or shared care required: N/A

9.3 Venetoclax with either low- or high-intensity chemotherapy regimes for relapsed/refractory acute myeloid leukaemia (Applicant: Dr J O'Nions, UCLH)

The Committee considered an application for venetoclax in combination with low-intensity (azacitidine or low-dose cytarabine [AZA/LDAC]) or high-intensity (fludarabine + cytarabine + idarubicin [FLA-Ida]) chemotherapy regimens, intended to be administered with a dose range of 50-400mg daily for a duration of 7-21 days per cycle, to treat refractory/relapsed acute myeloid leukaemia (R/R AML). Venetoclax is a targeted drug therapy (BCL2 inhibitor which is a key protein regulator of apoptosis) available as oral tablets. It is licensed for use in combination with a hypomethylating agent (e.g., AZA) or LDAC to treat adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy. Venetoclax is not currently licensed for use in patients with R/R AML; the low-intensity regime is in use at other London Trusts, though the high-intensity regime is not.

There are no randomised controlled trials for the use of venetoclax in combination with low- or high-intensity chemotherapy regimens for R/R AML patients. Data was mostly limited to retrospective cohort studies with small patient numbers.

The evidence for the low-intensity regimen consisted of 19 retrospective cohort and case-series studies (n range=22–126) which included R/R AML patient numbers to varying degrees. The low-intensity chemotherapy regimens in the studies included venetoclax monotherapy or venetoclax in combination with AZA, decitabine, LDAC or AZA and giteritnitib. The reported outcomes of complete response (CR) and complete response with incomplete count recovery (CRi) rates varied across all the studies, with a range of 12.4–72%. The average CR/CRi rate across the studies was 44% (median 46%), compared to a baseline CR of 19% with AZA monotherapy.

For the high-intensity regimen, the available evidence consisted of 2 studies. The highest-level of evidence was reported from a Phase I/IIB study. The phase IB stage enrolled R/R AML patients (single arm) to identify a maximum tolerated dose and dose-limiting toxicities. The phase IIB stage enrolled patients into two arms (ND-AML [newly diagnosed AML] and R/R-AML) to evaluate response and time-to-event end points; both arms received the same chemotherapy regimen, with some differences in dosing. The composite complete remission rate (CRc – which includes CR, CRi and CRh [CR with partial haematologic recovery]) of 75% for Phase IB arm (n=12) and 61% for the Phase IIB arm (n=14). This is in comparison to a complete remission (CR) rate of 37% reported when FLA-Ida was used alone. However, it is important to note that these are not directly comparable as CRc is a composite of several types of response, whereas CR is complete remission only. The second study was a retrospective observational cohort-controlled study comparing FLA-Ida vs. FLAVIDA (FLA-Ida and venetoclax) (n=13). The study reported haematological recovery parameters (such as neutrophil and platelet count) which were similar between both groups. The overall response rate following one ch

emotherapy cycle was reported as 69% and 47% for FLAVIDA and FLA-Ida, respectively.

Limitations of the low and high-intensity studies include the lack of available randomised evidence, the lack of an active comparator and heterogeneity in the treatment regimens and outcomes used across the studies.

In terms of safety, the limited data available from the venetoclax SPC does not indicate a significantly increased risk of adverse effects when used in combination with the low-intensity regime (AZA/LDAC). The safety data for the combination of venetoclax with the high-intensity regime (FLA-Ida) is not well documented. Some of the safety data reported from the low and high- intensity regimens included the following: tumour lysis syndrome, infections, febrile neutropenia, thrombocytopenia, pneumonia, anaemia, neutropenia, pancytopenia, hypotension, typhlitis, bacteraemia and sepsis.

In terms of budget impact, the potential additional cost of venetoclax was calculated to be between £25,000 - £150,000 per annum, calculated as an average dose of 100mg OD for 21 days, for between 2 to 12 cycles in 20 patients (although there may be very small patient numbers in other NCL Trusts). The Committee were informed that the wide range in potential budget impact was due to variation in treatment duration and dose used because of interpatient variability (e.g., response to treatment, disease progression, concomitant medicines etc).

The Committee heard from Dr O'Nions that all R/R AML patients will require treatment with either AZA alone or intensive chemotherapy. Achieving CR sooner with venetoclax-based combination regimens can have additional healthcare resource benefits such as maintaining transfusion independence and regaining count recovery, which has the potential to offset the cost of medication. This is particularly relevant in patients eligible for allogenic haematopoietic stem-cell transplant (AlloHSCT) which is the only curative treatment available. Dr O'Nions clarified that the actual budget impact was likely to be less than the estimated cost owing to; (i) a shorter cycle length in the low-intensity setting from cycle 2 onwards (21 days to 14 days), and (ii) a shorter cycle length in the high-intensity setting (21 days to 7 days).

Dr O'Nions recapped internal data (n=60) that demonstrated response rates of up to 65% (and in some cases up to 85% in patients with specific genetic subtypes) demonstrating the beneficial effect of the addition of venetoclax. The use of venetoclax in combination with AZA/LDAC (low-intensity regime) is considered an alternative option for patients, who would have otherwise used FLA-Ida to achieve remission, with a reduced risk of toxicity. The high-intensity regime is a newer strategy for managing R/R AML patients and is therefore supported by fewer studies. Updates from the recent American Society of Haematology conference suggest venetoclax duration is reduced to 7 days when given in combination with high-intensive chemotherapy in order to reduce the risk of toxicity. The applicant shared their experience of using a lower total dose of venetoclax compared to the recommended dose in the SPC.

In general, venetoclax-based regimens would not be used if a patient had previously received it in the first-line setting (although this will depend on whether previous treatment was stopped due to patient preference as opposed to clinical reasons, and the patient is identified as likely to be highly responsive).

Dr O'Nions confirmed that the regimens are not currently being considered by NICE and are not being considered for inclusion on the CDF. The manufacturer is undertaking real-world data collection in the US and Israel, with no plans for formal clinical trials.

In camera, the Committee highlighted the importance of reviewing the budget impact to ensure an accurate representation of intended usage, stratified by updated patient numbers for the low- and high-intensity setting respectively, based on time to AlloHSCT (where eligible) and using the updated dosing regimens. There were concerns with the rationale from the company not to pursue a formal evidence base; NHSE specialised commissioning representatives offered to raise this with NHSE cancer commissioning pharmacists for their input. It was acknowledged that the available data is limited and not sufficiently robust. Further clarification was sought from other London Trusts/ICS areas that have added venetoclax in this setting to their local formularies, in terms of the evidence base and budget impact they considered in their reviews.

In summary, the Committee deferred the decision for the use of venetoclax in combination with low-intensity (AZA/LDAC) and high-intensity (FLA-Ida) chemotherapy regimens for R/R AML patients pending further review of the budget impact, an update on the NHSE position and clarification on the evidence base used for approval in other areas of London.

Decision: Deferred

Actions:

(i) JFC support to approach SEL ICS and Royal Marsden formulary teams to better understand the rationale supporting formulary inclusion.

(ii) JFC support to work with the applicants to review, update and stratify the potential budget impact based on the updated chemotherapy regimens for both the low- and high intensity regimes.

10. For noting: Bempedoic acid monotherapy for treating primary hypercholesterolaemia or mixed dyslipidaemia

Deferred to the February 2023 JFC meeting.

11. For noting: Cannabis-based medicinal products position statement and Sativex shared care

The Committee were informed that NHS England have stipulated a mandatory requirement that all patients prescribed cannabis-based products for medicinal use (CBPMs) should be entered onto a national patient registry to collect further observational data. The registry should be updated by the initiating prescriber (or their team) at each clinician/patient contact and contact details were provided to organise training and technical support on using the registry for lead clinicians and prescribers of CBPMs. Any prescriptions written in primary care for medicinal cannabis are under shared care protocols and so the responsibility to update the registry remains with the initiating specialist doctor. This has been updated on the NCL cannabis-based medicinal products position statement. The Sativex shared care factsheet will be updated and presented at the next shared care meeting. Further clarification has been sought from NHSE England on whether secondary care

clinicians (within the context of a tertiary-to-secondary care shared care model) can take responsibility for updating the register, and if the registry requires updating each time a prescription is written in primary care. These updates will be brought back to a future meeting.

12. Next meeting

Thursday 16th February 2023

13. Any other business

13.1 Asthma guideline update: alcohol content in Salamol®

JFC Support were recently informed that Salamol® contains a small amount of alcohol. Whilst it is not large enough to have clinical impact, it is inappropriate in some patients for cultural, religious, or personal reasons. The Committee were provided with a minor update to the current NCL adult asthma inhaler guidance to reflect this information. The Committee approved the minor amends.