NHS GRAMPIAN
Minute of Formulary Group Meeting
Tuesday 15 September 2020 at 14:30 via Microsoft Teams

PRESENT	APOLOGIES	APPROVED
Ms F Doney	Ms A Davie	
Dr L Elliot	Mr C Rore	
Dr J Fitton		
Ms M Galvin		
Mrs L Harper		
Professor J McLay (Chairman)		
Dr Malcolm Metcalfe		
Mrs L Montgomery		
Mrs K Neave		
Mr M Paterson		
Mr R Sivewright (until item 3)		
Dr A Sun (from item 3)		

IN ATTENDANCE
Dr Henry Watson, Consultant Physician (for item 8.1).
Ms Caitlin Wilkinson, Formulary Team administrator.

Note some items were taken outwith the agenda running order.

ITEM	SUBJECT	ACTION
	The Chairman welcomed members, opened the meeting and noted that a quorum was present.	
1.	**APOLOGIES**	
	Apologies for absence were requested and noted.	
2.	**DRAFT MINUTE OF THE MEETING HELD 18 AUGUST 2020**	
	The Group accepted the draft note of the meeting subject to minor typographical changes. The corrected final approved minute will be in the public domain within 21 days of approval.	**FD**
3.	**DISCUSSION - SMC 2273 ANDEXANET ALFA**	
	Dr Henry Watson, Consultant Physician, attended the meeting to discuss the submission for SMC 2273 andexanet alfa for adult patients treated with a direct Factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Dr Watson provided the Group with an update on a new molecule, andexanet alfa, its mechanism of action and the study data to support licensing. He reminded the Group that andexanet alfa comes to market on the background of increasing use of direct-acting oral anticoagulants (DOACs). Dr Watson reported that: • andexanet alfa is a site inactivated molecule that mimics native activated FXa [the active site serine was substituted with alanine, rendering the molecule unable to cleave and activate prothrombin]. The molecule is modified such that it looks enough like activated FXa to allow molecules to bind to it but it has none of the functional activity of FXa. • the predominant mechanism of action of andexanet alfa is the binding and sequestration of the FXa inhibitor • in the context of bleeding, andexanet alfa binds the FXa inhibitor freeing up the native FXa to function, i.e. restoration of thrombin generation	

- licensing is based on an open-label (ongoing) phase III study, ANNEXA-4
- ANNEXA-4:
  - - n = 352 patients who had acute major bleeding within 18 hours after administration of a FXa inhibitor [apixaban, rivaroxaban or edoxaban at any dose or enoxaparin at a dose of at least 1mg/kg of body weight per day]; mean age 77 years and most had substantial cardiovascular disease. Atrial fibrillation (AF) was the primary indication of anticoagulation in 80% of patients, i.e. in line with clinical population.
    Bleeding was predominantly intracranial [in 227 patients; 64%] or gastrointestinal [in 90 patients; 26%] and the indication for rapid reversal.
  - - co-primary outcomes were percentage change from baseline to nadir in anti-FXa activity [92% reduction] and percentage of patients with excellent or good haemostatic efficacy at 12 hours after andexanet alfa - 82% of patients [204 of 249] showed excellent or good homeostasis
  - - within 30 days, death occurred in 14.6% [49] of patients and a thrombotic event in ~10% [34]
  - did not include a surgical treatment arm, so andexanet alfa is not suitable for pre-treatment of urgent surgery [not licensed]
- outcomes are poor for very high-risk individuals, e.g. elderly patients with vascular disease who require anticoagulation for whatever reason. If these patients go on to have a major bleed that would benefit from reversal, potentially no matter what you do in this situation there is probably an all-cause mortality of ~15%, and after the reversal procedure (or not) the patients have an increased risk of thrombotic events.

Dr Watson answered questions from members and confirmed that:

- andexanet alfa for edoxaban reversal - there is very limited data, it has gone through animal studies but there is insufficient information in human subjects to allow application as an agent to reverse edoxaban.
  For the moment, other strategies possibly combined with the off-label use of Beriplex® would be available.
- in DOAC reversal, Beriplex® is used (off-label) with reservations as patients do not have a substrate deficiency they have a FXa inhibitor on board
- meta-analysis/systematic reviews confirm that the rate of major and fatal bleeding is lower for patients on any DOACs compared with those on warfarin
- post-licensing andexanet alfa remains under increased pharmacovigilance - there are concerns about the thrombosis rates and death rates
- use to facilitate urgent surgery is not supported (or licensed) due to the lack of evidence for the use of andexanet alfa in this situation. This is at odds with the 2016 British Committee for Standards in Haematology (BCSH) guideline on perioperative management of anticoagulant and antiplatelet therapy. However, the BCSH guideline is over 4 years old and the position may be revised with the publication of ANNEXA-4.

Given the limited data and concerns about the use of andexanet alfa Dr Watson proposed that, until further data is available, andexanet alfa should only be used in line with licensing and that other strategies (potentially including using off-label Beriplex®) should be used for edoxaban reversal.

The Chairman thanked Dr Watson for attending the meeting, and Dr Watson left the meeting before decision-making.

There were no declarations of interest recorded in relation to this product.

The Group considered the SMC advice for andexanet alfa for the treatment of adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, SMC 2273.

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The Group noted:

- andexanet alfa:
  - is accepted by SMC on an interim basis subject to ongoing evaluation and future reassessment
  - has a conditional marketing authorisation from the European Medicines Agency (EMA)
- the sparse data available for the licensed population (small patient numbers), and the lack of data for individuals taking edoxaban. Ongoing studies are due to report in 2023.
- that reversal of FXa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease, and a pro-thrombotic effect of andexanet alfa cannot be ruled out
- the possible higher risks of andexanet alfa when used at higher dose and when used in patients over the age of 75 years (risks of mortality and thrombosis)
- that edoxaban is NHS Grampian's preferred DOAC for AF patients, but unlike the other DOACs, edoxaban does not have a licensed reversal agent
- that andexanet alfa used for edoxaban reversal would be off-label use. There is no data to support use, however due to the mechanism of action [of andexanet alfa] there is reason to believe it would work.
- the governance concerns regarding the off-label use of a medicine when a licensed medicine is available, and the first-line use of a DOAC that does not have a licensed reversal agent
- if the Health Board was to continue promoting edoxaban as the first-choice DOAC, then consideration has to be given to accepting off-label use of andexanet alfa for reversal

The Group accepted that andexanet alfa has positive and negative effects, it has the potential to be a life-saving drug but carries mortality and thrombosis risks. It gained a conditional licence from the EMA and post-licensing it remains under increased scrutiny whilst additional data is collected [studies due to report 2023].

Mindful of the limited data for licensing and lack of data in some populations the Group requested that:

- Dr Watson and Ms Doney contact colleagues in other Health Boards for information regarding their approach to the introduction of andexanet alfa **HW/FD**
- Ms Doney produce a paper for the Grampian Area Drug and Therapeutics Committee (GADTC) and Clinical Governance Committees to consider the points raised at the meeting **FD**
- an update is provided at the October meeting **FD**

4. MATTERS ARISING

4.1. ACTION LOG

The Action log was noted.

Ms Doney confirmed that the Action log was reinstated from the August 2020 meeting, with some items deferred or delayed since March.
No additional items were identified that should have been included on the agenda.

4.2. FORMULARY GROUP REGISTER OF INTERESTS

The Group reviewed the proposed summary register of members' conflicts of interest.

Ms Doney confirmed:

- the data will be held for five years
- the register will be hosted on the Formulary Group intranet web space, with the data organised by calendar year
- there are no plans to publish the register on a publicly-facing website, however the

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register will be available for request under the Freedom of Information (Scotland) Act (2002)

The Group accepted the proposed register and hosting arrangements.

A link to the Formulary Group Register of interests' intranet web space will be available at the next meeting. **FD**

5. FORMULARY GROUP DECISIONS AUGUST 2020 – PUBLISHED 31 AUGUST 2020

5.1. FORMULARY GROUP DECISIONS AUGUST 2020

Members ratified the decisions of the August 2020 meeting as published. **FTEAM**

6. NETFORMULARY/FORMULARY REVIEW

6.1. FORMULARY GROUP INTRANET SITE AND WORK PROGRAMME

Ms Doney provided members with a brief demonstration of the Formulary Group intranet website.

7. OTHER BUSINESS

7.1. SCOTTISH GOVERNMENT HEALTH AND SPORT COMMITTEE

The Chairman highlighted publication of the Scottish Parliament Health and Sport Committee report 'Supply and demand for medicines'.

Ms Doney confirmed that the GADTC is taking forward the actions from this report.

8. NEW PRODUCT REQUESTS

8.1. SMC 2273 - ANDEXANET ALFA (REVERSAL OF RIVAROXABAN AND APIXABAN)

This was discussed under item 3.

8.2. SMC 1254/17 - GLYCOPYRRONIUM ORAL SOLUTION (SEVERE SIALORRHOEA IN CHILDREN AND ADOLESCENTS)

There were no declarations of interest recorded in relation to these products.

The Group considered the request for glycopyrronium oral solution for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

The Group noted that:

- glycopyrronium is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine
- glycopyrronium is available as licensed and unlicensed formulations (tablets)
- July 2017, following an abbreviated submission glycopyrronium oral solution, as Sialanar® [glycopyrronium bromide 400microgram/mL], was accepted for use in NHS Scotland. Since 2017, a generic glycopyrronium bromide 1mg/5mL oral solution preparation has received a marketing authorisation.
- hyoscine patches have also been used for sialorrhoea. The service prefers to use glycopyrronium oral solution because the patches are circular and for younger children the patches were cut into different sizes, so the dosing is not accurate. Also the patches are stuck behind the ear but sweating caused the patches to fall off.
- patient numbers across Grampian are relatively small but there is a significant financial impact related to the use of glycopyrronium. The financial burden will fall on Primary Care as the specialist Community Child Health and Medical Paediatrics Team is not based in the hospital.
- there is a risk of prescribing error including dosing errors (under- or over-dosing):
  - the dosing tables for the oral solutions are only available in the relevant

SmPCs/Patient Information Leaflets, the dosing [for the oral solutions] is not specified in the BNF for Children
- the two licensed oral solution products come as different strengths per millilitre, express the dose differently [glycopyrronium base versus glycopyrronium salt (bromide)], and have different dose titration steps [16micrograms versus 20micrograms glycopyrronium bromide dose titration steps].
  In the SmPCs, Sialanar® dosing is expressed as glycopyrronium base, whereas the generic 1mg/5mL oral solution expresses the dose as glycopyrronium salt.

Dr Sun confirmed that colleagues in the Community Child Health and Medical Paediatrics Team prefer Sialanar® as it allows dosing with a much smaller volume, so is easier to administer for individuals with neurodisability.

The Group accepted the restricted local need for glycopyrronium bromide oral solution for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. The Group noted the potential for confusion and prescribing errors, under- or over-dosing, with the different products, and an additional risk due to the presentation of the glycopyrronium bromide dosing information in the BNF for Children.

The Group supported prescribing of glycopyrronium as the salt, glycopyrronium bromide, not as the base. Ms Doney will liaise with colleagues in paediatrics to confirm if there is a preferred glycopyrronium oral solution. **FD**

Glycopyrronium bromide oral solution is routinely available in line with local guidance.
Indication under review: for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.
It was classified 1b - available for restricted use under specialist supervision and 8d - treatment may be initiated in community on the recommendation of a consultant/specialist. Glycopyrronium bromide should be prescribed by physicians experienced in the treatment of paediatric patients with neurological disorders. **FTEAM**

8.3. SMC 2234 - BLINATUMOMAB (ACUTE LYMPHBLASTIC LEUKAEMIA (ALL))

There were no declarations of interest recorded in relation to this product.

The Group considered the request for blinatumomab as monotherapy for the treatment of adults with Philadelphia chromosome negative, CD19 positive, B-precursor acute lymphoblastic leukaemia (ALL).

The Group noted:
- blinatumomab:
  - is accepted by the SMC for restricted use, limited to patients in first complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
  - [for this indication] was accepted for use in NHS Scotland following the output from the PACE process and application of the appropriate SMC modifiers
  - [for this indication] meets SMC end of life and orphan criteria
  - is given as a continuous infusion during a treatment cycle of 4 weeks. Patients are treated for up to three additional treatment cycles, each one given after a 2-week treatment-free interval.
  - in the phase II study patients showed a high response rate (78% of patients did not have measurable residual cancer cells after 1 cycle)
  - [for this indication] may provide patients with a potential for cure
  - represents a new cost to the service with minimal offset available from FLAG-IDA

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(fludarabine, cytarabine, G-CSF factor, idarubicin)

- for patients achieving complete response (CR), persistence of MRD is the strongest prognostic feature for relapse after achieving CR regardless of treatment choice or risk classification system, and patients who are highly responsive to induction chemotherapy and achieve an MRD level below 1 x 10^{-4} (MRD-negative) have a favourable prognosis
- the cost of treatment is high but patient numbers are expected to be very small
- the SMC advice takes account of the benefits of a PAS that improves the cost-effectiveness of blinatumomab
- the service has experience in the use of blinatumomab

The Group accepted the restricted local need for blinatumomab as monotherapy for the treatment of adults with Philadelphia chromosome negative, CD19 positive, B-precursor ALL in first complete remission with MDR greater than or equal to 0.1%, as outlined in SMC 2234.

SMC 2234 - Blinatumomab 38.5micrograms powder for concentrate and solution for solution for infusion (Blincyto®) ▼ is routinely available in line with national guidance (SMC 2234).
Indication under review: as monotherapy for the treatment of adults with Philadelphia chromosome negative, CD19 positive, B-precursor acute lymphoblastic leukaemia (ALL) in first complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
In a single arm phase II study of patients with B-cell precursor ALL in first or later complete remission and with persistent or recurrent MRD, blinatumomab was associated with clinically relevant complete MRD response rates.
This advice applies only in the context of an approved NHS Scotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.
This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting. It was classified 1b - available for restricted use under specialist supervision and 8b – recommended for hospital use only. Treatment should be initiated under the direction of and supervised by physicians experienced in the treatment of haematological malignancies. **FTEAM**

8.4. SMC 2111 - CICLOSPORIN (SEVERE VERNAL KERATOCONJUNCTIVITIS (VKC))

There were no declarations of interest recorded in relation to this product.

The Group considered the request for ciclosporin 0.1% eye drops, as Verkazia®, for the treatment of severe vernal keratoconjunctivitis (VKC) in children and adolescents.

The Group noted:

- Verkazia®:
  - is licensed for the treatment of severe VKC in children and adolescents from 4 years of age to <18years
  - [for this indication] has been designated an orphan medicine by the European Medicines Agency (EMA) and meets SMC orphan criteria
- VKC is a rare but serious, allergic inflammatory disease that affects the eyes of children and adolescents. It mainly affects boys from the age of 5 to 12 years and commonly resolves at puberty. If left untreated there is an increased risk of sight loss.
- patient numbers are small
- the different licensed indications and dosing regimens for Verkazia® and Ikervis®. Verkazia® is given as one drop four times a day or twice a day, whereas Ikervis® is licensed for severe keratitis in adult patients with dry eye disease and is given once a day.

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The Group accepted that there might be cases where VKC continues into adulthood, and for these patients the Group supported continued [off-label] use of Verkazia® as a means to minimise the potential for dosing errors.

The Group accepted the restricted local need for ciclosporin 0.1% eye drops, as Verkazia®, for the treatment of severe VKC in adolescents and children from 4 years of age, as outlined in SMC 2111.

SMC 2111 - Ciclosporin 1mg/mL (0.1%) eye drops emulsion (Verkazia®) is routinely available in line with national guidance (SMC 2111).
Indication under review: for the treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.
It was classified 1b - available for restricted use under specialist supervision and 8c - treatment to be initiated in hospital prior to handover. Verkazia® treatment must be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology. **FTEAM**

8.5. SMC 2253 - FAMPRIDINE (MULTIPLE SCLEROSIS (MS))

The Group discussed fampridine, a medicine licensed for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS [expanded disability status scale] 4-7).

Fampridine is accepted for use within NHS Scotland following a second resubmission. A local request for formulary inclusion will be considered at a future meeting.
The Chairman highlighted that the introduction of fampridine will have significant service implications for the Neurology department.

The Group requested that colleagues from Neurology department are invited to discuss the formulary submission and service development required to support the safe introduction of fampridine. **FTEAM**

9. SCOTTISH MEDICINES CONSORTIUM PROVISIONAL ADVICE – SEPTEMBER 2020

The Group noted the SMC provisional advice issued September 2020.

10. SCOTTISH MEDICINES CONSORTIUM PRESS STATEMENTS – SEPTEMBER 2020

The Group noted the SMC advice published September 2020.

The following SMC accepted medicines have not been processed within a 60-day timescale:

- SMC 2260 fluocinolone acetonide (Iluvien®)
- SMC 2263 cannabidiol (Epidyolex®) (submission expected)
- SMC 2262 cannabidiol (Epidyolex®) (submission expected)
- SMC 2257 pembrolizumab (Keytruda®) (submission expected)
- SMC 2247 pembrolizumab (Keytruda®) (submission expected)
- SMC 2252 gilteritinib (Xospata®) ▼ (submission expected)
- SMC 2258 esketamine (Spravato®) ▼ (submission expected)
- SMC 2272 brolucizumab (Beovu®) ▼ (submission received)
- SMC 2266 caplacizumab (Cablivi®) ▼ (submission expected)
- SMC 2261 ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar®) ▼
- SMC 2282 polatuzumab vedotin (Polivy®) ▼ (submission received)
- SMC 2284 pertuzumab (Perjeta®) (submission expected)
- SMC 2288 sodium zirconium cyclosilicate (Lokelma®) ▼ (submission received)
- SMC 2287 semaglutide (Rybelsus®) ▼ (submission expected)

Local advice for these medicines and indications will be included in the September 2020

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decisions as 'Not routinely available as the ADTC is waiting for further advice from local clinical experts'. FTEAM

11. GENERAL INFORMATION FROM SCOTTISH MEDICINES CONSORTIUM – SEPTEMBER 2020

None

12. DOCUMENTS FOR INFORMATION

ITEM 12.1 (DRUG SAFETY UPDATE AUGUST 2020)

The Chairman highlighted the article *"Clozapine and other antipsychotics: monitoring blood concentrations for toxicity"* to the Group.
Ms Doney confirmed that the Mental Health Operational Medicines Management Group has discussed the article, and will disseminate information as necessary.

Items 12.2 (MedWatch newsletter August 2020) and 12.3 (Grampian Primary Care Prescribing Group minute July 2020) were noted.

13. AOCB

PRIADEL 200MG, 400MG TABLET TO BE DISCONTINUED

Ms Doney confirmed that lithium carbonate as Priadel® 200mg and 400mg modified release tablets are being discontinued. Priadel® is the first-line choice lithium preparation in NHS Grampian and discontinuation will have a significant impact. There is a need to manage the change as safely as possible.

A summary of the financial impact will be presented at the October meeting. FD

EUROPEAN SOCIETY OF CARDIOLOGY CONGRESS 2020

Dr Metcalfe highlighted that two sodium-glucose co-transporter-2 (SGLT2) inhibitor studies, presented at the European Society of Cardiology Congress, have been received positively. The data may drive a new standard of care for patients with heart failure [with or without diabetes].

DATE OF NEXT MEETING

Tuesday 20 October 2020 starting at 14.30 via Microsoft Teams.

CHAIRMAN'S SIGNATURE _____ **DATE 20 OCTOBER 2020**