NHS GRAMPIAN
Minute of Formulary Group Meeting
Tuesday 21 March 2023 at 14:30 via Microsoft Teams

PRESENT	APOLOGIES	APPROVED
Miss R Anderson	Ms L Cameron	
Dr V Chieng	Ms A Davie	
Ms F Doney (Vice-Chair)	Mrs S Howlett	
Dr E Elias		
Dr L Elliot (Chair)		
Mrs G McKerron		
Dr M Metcalfe (Vice-Chair)		
Mrs K Neave		
Dr J Newmark		
Mr M Paterson		
Mr R Sivewright		

ITEM	SUBJECT	ACTION

WELCOME

The Chair 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 21 FEBRUARY 2023

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 final approval. **FD**

3. PRESENTATION

None.

4. MATTERS ARISING

4.1. ACTION LOG

The action log was noted.

No additional items were identified for discussion at the meeting.

5. FORMULARY GROUP DECISIONS FEBRUARY 2023 - PUBLISHED 06/03/2023

Members ratified the decisions of the February 2023 meeting as published.

6. NETFORMULARY/FORMULARY REVIEW

6.1. FORMULARY UPDATES – MARCH 2023

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

The Group reviewed the Formulary Team's summary document highlighting discontinued medicines.

ITEM	SUBJECT	ACTION

The Group supported the changes proposed by the Formulary Team:

- minor change to the current website entry for ciprofloxacin 3mg/mL/dexamethasone 1mg/mL ear drops (Cilodex®), remove the brand name as this product has been replaced by a generic product
- minor change to the current website entries for the non-formulary medicines darvadstrocel (Alofisel®) and eluxadoline (Truberzi®), amend to note that these products are now withdrawn from use/discontinued
- create new entries for the discontinued products - fluoxetine 10mg film-coated tablets (current entry does not include this formulation), and Insuman® Comb 25, Insuman® Basal and Insuman® Rapid. Insuman® stocks are expected to be exhausted by May/June 2023. **FTEAM**

6.2. NICE - THERAPEUTICS FOR PEOPLE WITH COVID-19 [ID4038]

Ms Doney confirmed that National Institute for Health and Care Excellence (NICE) issued draft Multiple Technology Appraisal guidance, ID4038, Therapeutics for people with COVID-19.
The final appraisal document is expected to be published on 29 March 2023.
Information will be sent to the Antimicrobial Management Team (AMT) for local comment. **FTEAM**

7. OTHER BUSINESS

7.1. DECLARATIONS OF INTEREST REGISTER 2022

Ms Doney requested that members' check and if necessary update their conflicts of interests for the calendar year 2022. The Group's Register of Interests [for 2022] will be published on the Formulary Group intranet site by the end of April. **FTEAM**

8. NEW PRODUCT REQUESTS

8.1. NCMAG 103 - LENALIDOMIDE (PREVIOUSLY UNTREATED MULTIPLE MYELOMA)

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

The Group reviewed the National Cancer Medicines Advisory Group (NCMAG) advice document for the off-patent licensed use of lenalidomide, in combination with dexamethasone, for the treatment of adults with previously untreated multiple myeloma who are not eligible for transplant and are suitable for thalidomide-containing regimens.

The Group noted that:

- NCMAG supported the routine off-patent use of generic lenalidomide for this indication
- December 2015, SMC issued 'accepted restricted' advice for use in patients who were not eligible for transplant and unsuitable for thalidomide-containing regimens (SMC 1096/15)
- multiple myeloma is an incurable haematological cancer. Initial treatment for myeloma is divided into two categories, those that are eligible for high dose chemotherapy and autologous stem cell transplantation, and those that are ineligible for transplantation.
- [within Scotland] routinely available treatments for transplant ineligible patients are cyclophosphamide, thalidomide and dexamethasone attenuated (CTDa), or melphalan, prednisolone and thalidomide (MPT). Both regimens are considered to have similar efficacy.
- lenalidomide:
  - is an immunomodulatory drug, and combining lenalidomide with corticosteroids has a synergistic effect and increases efficacy
  - has serious teratogenic effects and must be prescribed via a pregnancy prevention programme
- lenalidomide plus dexamethasone (Rd):
  - is given continuously until disease progression or intolerance (Rd continuous)

ITEM	SUBJECT	ACTION

- is supported as a treatment option for this patient group in national and international guidelines
- key evidence for this indication comes from the final analysis of the phase III FIRST study (versus MTP), but there are no direct data versus CTDa
- FIRST study:
  - final data cut-off, January 2016, median duration of follow-up 67.2 months, progression-free survival (PFS) improved with Rd continuous versus MPT (median PFS 26.0 versus 21.9 months (hazard ratio [HR], 0.69; 95% confidence interval [CI] 0.59 - 0.79, P<0.00001))
  - four-year PFS rate also favoured Rd continuous (32.6% versus 13.6%)
  - there was a significant increase in median overall survival (59.1 months versus 49.1 months (HR 0.78, 95% CI 0.67-0.92))
  - median time to next treatment was longer with Rd continuous (36.7 months versus 26.7 months)
- the NCMAG Council was satisfied that the case for cost-effectiveness had been made for generic lenalidomide in combination with dexamethasone [for this population]
- patient numbers are expected to be small and costs are already in the system from the current extant NCMAG advice (that expires at the end of March 2023)
- lenalidomide is now available as generic products, and a switch to generics is anticipated with the launch of an appropriate pregnancy prevention programme (Data Protection Impact Assessment (DPIA) awaited)
- the service has significant experience using lenalidomide, and the adverse event profile is considered to be manageable and acceptable
- Rd continuous provides an all-oral treatment option, with benefits for patients and the service

The Group accepted the restricted local need for lenalidomide in combination with dexamethasone for the treatment of adults with previously untreated multiple myeloma who are not eligible for transplant and are suitable for thalidomide-containing regimens.

NCMAG 103 - Lenalidomide 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg, 25mg hard capsules is routinely available in line with national guidance (NCMAG 103). Indication under review: in combination with dexamethasone for the treatment of adults with previously untreated multiple myeloma who are not eligible for transplant and are suitable for thalidomide-containing regimens.
It was classified 1b - available for restricted use under specialist supervision and 8b - recommended for hospital use only. Treatment should be supervised by a physician experienced in the use of anti-cancer therapies. — **FTEAM**

8.2. FG1 444/21 - ANDEXANET ALFA (OFF-LABEL USE, REVERSAL OF EDOXABAN)

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

Mr Paterson declared a personal, non-specific interest in AstraZeneca UK Limited, and took part in the discussion and decision-making.

The Group considered the request to include andexanet alfa on the formulary as a reversal agent for edoxaban.

The Group noted that:
- andexanet alfa:
  - is a specific reversal agent for direct factor Xa inhibitors
  - is licensed for hospital use only, and is included on the formulary (as licensed) for the reversal of the direct factor Xa inhibitors, apixaban and rivaroxaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding
  - for edoxaban reversal would be an off-label use

ITEM	SUBJECT	ACTION

- there are limited data for andexanet used in patients with acute major bleeding whilst taking edoxaban, however specific reversal of the anticoagulant activity of edoxaban with andexanet alfa is pharmacologically plausible (significant decrease in antifactor Xa activity)
- treatment is not recommended if the last dose of direct factor Xa inhibitor was taken more than 18 hours previously (exclusion criteria in the pivotal study, ANNEXA-4)
- andexanet alfa is administered as an intravenous bolus followed by administration of a continuous infusion as low dose or high dose regimens:
  - LOW dose (5 vials) - 400mg bolus followed by 480mg infusion over 2 hours
  - HIGH dose (9 vials) - 800mg bolus followed by 960mg infusion over 2 hours
- the low dose regimen is used for patients who received up to 30mg edoxaban less than 8 hours previously or at an unknown time, and those who took edoxaban ≥8 hours previously
- the high dose regimen is used for patients who received >30mg or an unknown dose of edoxaban less than 8 hours previously or at an unknown time
- Autumn 2020, andexanet alfa was included on the formulary in line with licensing and the SMC interim accepted advice (SMC 2273)
- local haematologists who specialise in haemostasis and thrombosis:
  - confirm that there is a local need for the off-label use of andexanet alfa for edoxaban reversal, and that there is national support from the thrombosis leads in other Scottish centres, e.g., NHS Tayside and NHS Greater Glasgow and Clyde
  - support use in line with guidance used in other Health Boards
- the cost of treatment, and that there is already a significant spend on andexanet alfa

Members noted the high spend on andexanet alfa and discussed the potential that it might be used inappropriately. Off-label use of andexanet alfa for edoxaban reversal was supported subject to the following:

- provision of guidance to support appropriate use, including audit of use
- treatment should only be prescribed following discussion with a Consultant Haematologist

The Group accepted the restricted local need for the off-label use of andexanet alfa for adults treated with edoxaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Use is subject to provision of local guidance to support appropriate use of andexanet alfa. This decision is subject to review on reassessment of the current interim SMC advice for andexanet, SMC 2273.

FG1 444/21 - Andexanet alfa 200mg powder for solution for infusion (Ondexxya®) ▼ is routinely available in line with local guidance.
Indication under review: [off-label use] for adults treated with the direct factor Xa inhibitor edoxaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Restriction: to patients who present within 18 hours after administration of a factor Xa inhibitor.
It was classified 3b - licensed product requested for unlicensed use and 8a - licensed for hospital use only. Treatment should only be prescribed following discussion with a Consultant Haematologist.
Informed consent should be obtained and documented. — **FTEAM**

Items 8.3 and 8.4 were taken together.

8.3. SMC 2478 - OZANIMOD (MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS) AND

8.4. SMC 2510 - UPADACITINIB (MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS)

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

ITEM	SUBJECT	ACTION

The Group considered the requests to include ozanimod and upadacitinib on the formulary for the treatment of adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

The Group noted that:

- the global prevalence of UC is increasing
- UC is an immune-mediated chronic inflammatory bowel disease that affects the rectum and colon and is characterised by remissions and exacerbations. Symptoms include recurrent episodes of diarrhoea, rectal bleeding and abdominal pain, and patients are at an increased risk of perforated bowel, toxic megacolon and colorectal cancer.
- the treatment goal for patients with active disease is to induce and maintain remission and mucosal healing. A significant number of patients with moderate to severe UC do not respond, lose response or are intolerant to currently available therapies.
- treatments available for moderately to severely active UC include corticosteroids, immunosuppressants such as thiopurines and ciclosporin, tumour necrosis factor-alpha inhibitors (TNFi (adalimumab, golimumab or infliximab)), the anti-integrin vedolizumab, the interleukin-12/23 antagonist ustekinumab, and JAK inhibitors (tofacitinib and filgotinib)

Ozanimod

The Group noted that:

- October 2022, following a full submission reviewed by the SMC executive, ozanimod was accepted for use within NHS Scotland for the treatment of adults with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent (SMC 2478)
- ozanimod:
  - is a new drug class [selective sphingosine 1-phosphate (S1P) receptor modulator] for the management of UC
  - is already included on the formulary for the treatment of adults with relapsing remitting multiple sclerosis (SMC 2309)
  - is available as a 'Hospital-only pack' and supply via a homecare arrangement is anticipated
- evidence for ozanimod for UC comes from TRUENORTH (n = 645) a randomised, double-blind, phase III study which comprised of induction (10 weeks) and maintenance (+ 42 weeks) periods
- TRUENORTH:
  - the primary outcome for the induction (at week 10) and maintenance (at week 52) periods was the proportion of patients in clinical remission
  - for the induction period, clinical response was achieved in 18% and 6% of patients for ozanimod and placebo respectively
  - for the maintenance period, clinical remission was achieved in 37% and 19% of patients for ozanimod and placebo respectively
  - in the maintenance period, in TNFi-experienced patients (n=145), clinical remission at week 52 was achieved by 29% (22/76) of patients receiving ozanimod compared with 10% (7/69) of patients in the placebo group
- there are no data versus comparators. A Bayesian network meta-analyses compared ustekinumab, vedolizumab and tofacitinib and suggested no evidence of a difference between ozanimod and these comparators in the TNFi-experienced population.
- the recommended dose is 0.92mg ozanimod daily, with dose escalation from day 1 to 7 (7-day titration initiation pack available)
- the SMC advice takes account of the benefits of a simple finance-based PAS that improves the cost-effectiveness of ozanimod
- costs will be cumulative as ozanimod is potentially a long-term treatment option
- there are additional costs expected in relation to laboratory tests and ECGs, and

monitoring and review of adverse events
- new and additional pressures are expected on other services - the need for consultation with cardiology and a baseline electrocardiogram (ECG); people with diabetes, uveitis, or retinal disease require a pre-treatment ophthalmologic examination
- at initiation, some patients require hourly heart rate and blood pressure monitoring for at least the first 6 hours. Some patients also require a repeat ECG 6 hours after the first dose.
- members queried the arrangements for pre- and post-treatment assessment, and ongoing monitoring

Upadacitinib
The Group noted that:
- October 2022, following an abbreviated submission reviewed by the SMC executive, upadacitinib was accepted for use within NHS Scotland for the treatment of adults with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent (SMC 2510)
- the SMC advice takes account of the benefits of a simple finance-based PAS that improves the cost-effectiveness of upadacitinib, and supply via a homecare arrangement is anticipated
- upadacitinib is the third Janus kinase (JAK) inhibitor licensed for UC and accepted for use in NHS Scotland. Tofacitinib and filgotinib are already included on the formulary for UC.
- The European Medicines Agency (EMA) safety review of JAK inhibitors states that - *these medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer. JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible*.
- upadacitinib:
  - (like the other JAK inhibitors) is licensed for UC induction and maintenance of remission, and would provide an alternative oral JAK inhibitor, with a simple once-daily dosing regimen
  - preferentially inhibits JAK1 over JAK2 and JAK3
  - is available as 15mg, 30mg and 45mg prolonged-release tablets. The 45mg strength is only used for the induction dose (45mg daily), and upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.
- cost will be cumulative, as if effective upadacitinib is potentially a long-term treatment option
- members noted the lack of head-to-head data for the three JAK inhibitors, and queried what clinical characteristics would direct choice to one JAK inhibitor over another, and if three JAK inhibitors were needed on formulary?

Member agreed that:
- generally both ozanimod and upadacitinib would be used in TNFi experienced patients, and cost offset would be available from displacement of alternative treatment options
- efficacy and safety data in the maintenance setting was limited, there is a lack of long-term efficacy data, and insufficient data to know if there will be a treatment waning effect

ITEM	SUBJECT	ACTION

The Group deferred decision-making pending confirmation of the queries posed in the reviews, and/or the requestor to attend a future meeting.

SMC 2478 - Ozanimod 0.23mg, 0.46mg, 0.92mg hard capsules (Zeposia®) ▼ decision deferred to future meeting.
Indication under review: for the treatment of adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.
In a randomised, double-blind, phase III study in patients with moderately to severely active UC, clinical remission was achieved by a significantly greater proportion of patients who received ozanimod compared with placebo after induction and maintenance treatment.
This advice applies only in the context of an approved NHS Scotland Patient Access Scheme (PAS) arrangement delivering the economic results upon which the decision was based, or a PAS/ list price that is equivalent or lower.
Decision deferred to future meeting. **FTEAM**

SMC 2510 - Upadacitinib 15mg, 30mg, 45mg prolonged-release tablets (Rinvoq®) ▼ decision deferred to future meeting.
Indication under review: for the treatment of adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.
Upadacitinib offers an additional treatment choice in the therapeutic class of janus kinase inhibitors.
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.
Decision deferred to future meeting. **FTEAM**

9. SCOTTISH MEDICINES CONSORTIUM PROVISIONAL ADVICE ISSUED - MARCH 2023

The Group noted the SMC provisional advice issued March 2023.

If the negative SMC recommendation is published next month, this medicine will not be included on the formulary for the indication in question.

10. SCOTTISH MEDICINES CONSORTIUM ADVICE PUBLISHED - MARCH 2023

The Group noted the SMC advice published March 2023.

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

- SMC 2520 - bulevirtide (Hepcludex®) ▼ (submission expected)
- SMC 2513 - nintedanib (Ofev®) (submission expected)
- SMC 2496 - pralsetinib (Gavreto®) ▼ (clinicians not responded)

Local advice for these medicines and indications will be included in the March 2023 decisions as 'Not routinely available as the ADTC is waiting for further advice from local clinical experts'. **FTEAM**

10. GENERAL INFORMATION FROM SCOTTISH MEDICINES CONSORTIUM - MARCH 2023

None.

11. DOCUMENTS FOR INFORMATION

Items 12.1 (Drug Safety Update February 2023), 12.2 (Drug Safety Update (published

ITEM	SUBJECT	ACTION
	14/03/2023 - Pholcodine-containing cough and cold medicines: withdrawal from UK market as a precautionary measure), 12.3 MEDwatch Volume 4 Issue 1 March 2023 were noted.	

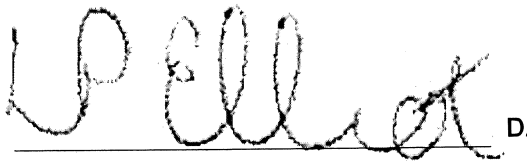
12. AOCB

THANK YOU AND BEST WISHES

The Chair confirmed that Mrs Neave was going off on maternity leave and this would be her last meeting for a while. Members wished her well for the future.

DATE OF NEXT MEETING

Tuesday 18 April 2023 starting at 14.30 via Microsoft Teams

CHAIR'S SIGNATURE  **DATE 18 APRIL 2023**