NHS GRAMPIAN
Minute of Formulary Group Meeting held on Tuesday 18th August 2015
in the Aspen Room, Forest Grove House

PRESENT	APOLOGIES	APPROVED
Dr D Counter	Dr D Culligan	
Ms A Davie	Dr A Sun	
Ms F Doney		
Mr A Duncan		
Mrs L Harper		
Dr C Hind		
Dr A MacDonald		
Professor J McLay (Chairman)		
Mrs L Montgomery		
Dr W Moore		
Mr M Paterson		
Mr C Rore		
Mr R Sivewright		
Professor John Webster		

IN ATTENDANCE
Dr Elma Stephen, Consultant Paediatrician, Department of Paediatric Neurology RACH, for the discussion on the Medicines & Healthcare products Regulatory Agency (MHRA) advice – medicines related to valproate.
Dr Leslie Samuel, Consultant Oncologist, ANCHOR Unit, for item 8.5.

ITEM	SUBJECT	ACTION

Note some items were taken out of agenda order.

The Chairman opened the meeting, noted that a quorum was present, and welcomed members to the meeting.

3. PRESENTATIONS

3.1. MHRA ADVICE – MEDICINES RELATED TO VALPROATE: RISK OF ABNORMAL PREGNANCY OUTCOMES

Dr Stephen provided the Group with some background regarding prescribing sodium valproate for children with epilepsy, the MHRA advice issued January 2015, and the current recommendations regarding teratogenic side-effects in national guidelines, e.g. SIGN 81, and that the advice on teratogenicity may be applicable to all anti-epileptic medication.

Dr Stephen highlighted that:
- valproate is the most effective drug for genetic generalised epilepsies, and is the most commonly prescribed anti epileptic drug (AED) in many of the childhood epilepsies (44% of all AED prescriptions <16 years)
- valproate is considered a first-line AED, including epilepsies and epileptic encephalopathies which may be aggravated by other narrow spectrum drugs
- restricting the use of valproate in children who are not capable of becoming pregnant seems inappropriate
- the risks to an unborn child have been recognised for some time, and it is the responsibility of the prescribing clinician to make a judgement whether valproate is the correct medication for the individual, and this decision is made in partnership with the individual/parent etc
- the risks to the unborn child need to be counter balanced against the risk of seizures (including risks to the unborn child of maternal seizures during pregnancy), and the risk of sudden unexpected death in epilepsy (SUDEP)
- counselling regarding pregnancy and AEDs is proactive and starts in the teenage years and is the responsibility of the prescribing clinician

Dr Stephen provided an overview of:
- what the paediatric neurology service currently does in relation to counselling females of child-bearing age
- the natural history of epilepsy in children, 70-80% of children will go into remission after

two years treatment
- the positions of the North of Scotland Child and Adolescent Neurology Network (NeSCANN), British Paediatric Neurology Association (BPNA) and the International League Against Epilepsy (ILAE)

Dr Stephen confirmed that the Paediatric Neurology Service:
- has concerns about the statement "Valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated", and that it should not be interpreted to suggest that every individual female patient needs to try and fail on alternative treatments before being prescribed valproate if that is the most appropriate treatment for her epilepsy
- proposes strengthening the current arrangements for providing girls of child-bearing age (and where appropriate their parents/carers) with advice regarding the risk of valproate-related medicines, including provision of written information, documentation/written evidence of the discussion and auditing practice
- considers that valproate should remain:
  - a first-line treatment for younger girls with generalised epilepsies
  - an appropriate treatment for children with epileptic encephalopathies
  - an appropriate treatment for epilepsies that may be aggravated by other narrower spectrum drugs

It was confirmed that other Area Drugs and Therapeutics Committees (ADTCs) have or are currently considering the MHRA advice, and that Dr Mary O'Regan, Lead Clinical Scottish Epilepsy Network wrote to ADTCs highlighting the points raised locally. Scottish Paediatric Epilepsy Network (SPEN) is a national managed clinical network funded through the National Services Division. A query has been raised with SPEN and Healthcare Improvement Scotland (through the ADTC collaborative) regarding any national work regarding this issue, advice is awaited. **FD**

The Chairman thanked Dr Stephen for the update and she left the meeting.

The Group noted that valproate is also prescribed for other indications including bipolar disorder and off-label use, and the MHRA advice is relevant to all indications.
The Group discussed the position presented (supported by SPEN, NeSCANN, BPNA and ILEA), noting that this position is supported by a reasonable body of opinion, that the MHRA has not contra-indicated use and this is not a policy issue for NHS Grampian. However, as a considerable number of female patients of child-bearing age are managed in Primary Care it is important to have reassurance that local clinicians are informed of and aware of the MHRA advice. **GMMG**

3.2. DR SAMUEL FOR ITEM 8.5

Dr Leslie Samuel, Consultant Oncologist, attended the meeting to discuss the addition of bevacizumab to metastatic colorectal cancer (mCRC) chemotherapy for a small collection of patients. Bevacizumab is used in addition to backbone chemotherapy, to try and improve a patient's response to chemotherapy, as a strategy to shrink previously unresectable tumours and potentially allow resection. He left the meeting before decision-making.

8.5 FG1 371/14 – BEVACIZUMAB – BRIDGE TO SURGERY FOR MCRC

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

Reference submitted – Wong R, Cunningham D, Barbachano Y, et al. (2011), A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. *Annals of Oncology*. **22** (9), 2042–2048.

The Group noted:
- that bevacizumab is not recommended for use in NHS Scotland for mCRC - SMC 212/05 and NICE TA242

ITEM	SUBJECT	ACTION

- treatment with bevacizumab plus chemotherapy would be limited to 3-4 months in total
- the heterogeneous nature of the patients' that the submission included
- that bevacizumab plus chemotherapy could be used first-line or as a later line of therapy depending on the individual patient's disease characteristics
- that use would be limited to patients who are RAS mutant or unknown RAS status because cetuximab is accepted by SMC for use in patients with RAS wild-type metastatic colorectal cancer
- the lack of cost-effectiveness information, and that any calculations would be sensitive to the duration of treatment with bevacizumab plus chemotherapy and the curative resection rate
- the BOXER study:
  - was a multicentre, single-arm phase II study
  - aimed to evaluate perioperative capecitabine-oxaliplatin plus bevacizumab in patients with poor risk colorectal liver-only metastasis not selected for upfront resection, i.e. neoadjuvant use
  - included very small patient numbers [45]

The Group agreed that the evidence was too weak to allow inclusion of bevacizumab on the Grampian Joint Formulary when used in combination with fluoropyrimidine-based chemotherapy as a bridge to resection in adult patients with metastatic carcinoma of the colon or rectum.

The Group agreed that the evidence was not sufficiently robust to allow consideration of a Group Treatment Request. Due to the heterogeneous nature of the patient population the Group confirmed that the Individual Patient Treatment Request (IPTR)/Peer Approved Clinical System (PACS) process is the appropriate route to consider requests for individual patients. **FD**

Bevacizumab 25mg/mL concentrate for solution for infusion (Avastin®) is not included on the Grampian Joint Formulary for the indication in question.
Indication under review: in combination with fluoropyrimidine-based chemotherapy for the treatment of adult patients with metastatic carcinoma of the colon or rectum.
Restriction: for patients with RAS mutant or unknown RAS status colorectal cancers that are inoperable but with a good response to chemotherapy may become resectable after treatment with chemotherapy and bevacizumab.
It was classified 4 – evidence of efficacy not convincing enough to reach a decision on clinical effectiveness. Not included on the Grampian Joint Formulary for the indication in question. **FTeam**

1. APOLOGIES

Apologies for absence were requested and noted.

2. DRAFT MINUTE OF THE MEETING HELD ON THE 21ST JULY 2015

The Group accepted the draft note of the meeting held on the 21st July 2015 as an accurate record of the meeting subject to minor typographical changes. **FD**

The final approved minute will be published within 21 days. **FTeam**

4. MATTERS ARISING

4.1. CLARIFICATION OF STATUS OF POSACONAZOLE ORAL LIQUID FOR OROPHARYNGEAL CANDIDIASIS

At the July meeting it was highlighted that posaconazole oral liquid is the only [posaconazole] formulation that is licensed for oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor. It was confirmed that the SMC has not reviewed posaconazole oral liquid for this indication and it is not included on the Grampian Joint Formulary.

5. FORMULARY GROUP DECISIONS JULY 2015 – PUBLISHED 03/08/2015

The Group ratified the advice as published.

ITEM	SUBJECT	ACTION

6. CMO(2012)1 REPORTING FOR SCOTTISH MEDICINES CONSORTIUM (SMC) ADVICE 2015/16 – AT 03/08/2015

It was confirmed that for the SMC accepted medicines published April to July 2015 the Formulary Group audit standard for CMO(2012)1 reporting was achieved for the following criteria:

- Local decision on SMC accepted medicine published within 90 days: 32 of 32 - 100%
- FG decision published within 14 days of the decision being reached: 32 of 32 - 100%

7. OTHER BUSINESS

7.1. NICE MULTIPLE TECHNOLOGY APPRAISALS – NONE

8. NEW PRODUCT REQUESTS

Items 8.1 and 8.2 were taken together**.**

8.1. FG1 SMC 1052/15 – APREMILAST – CHRONIC PLAQUE PSORIASIS

8.2. FG1 SMC 1053/15 - APREMILAST – ACTIVE PSORIATIC ARTHRITIS

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

The Group considered the submissions from the adult Dermatology and Rheumatology Services for the new agent apremilast.

The Group noted:

- apremilast:
  - is an immunosuppressant and is the first of a new class of treatment licensed for some adult patients as a treatment option for moderate to severe chronic plaque psoriasis or active psoriatic arthritis
  - inhibits phosphodiesterase-4 (PDE4) which leads to increased intracellular cyclic adenosine monophosphate (cAMP) levels. This down-regulates the inflammatory response by modulating the expression of tumour necrosis factor alpha (TNF-α), interleukin-23, interleukin-17 and other inflammatory cytokines which have been implicated in psoriasis and psoriatic arthritis.
  - is an oral treatment option, taken as 30mg twice daily (following a 5-day titration scheme)
  - does not require monitoring, apart from regular body weight monitoring for patients who are underweight at the start of treatment
  - would replace or delay the use of biologic therapy in some patients
  - for active psoriatic arthritis is used alone or in combination with disease modifying anti-rheumatic drugs
- treatment should be reconsidered if a patient shows no benefit after 24 weeks, and treatment should be evaluated on a regular basis
- the lack of clinical experience beyond 52 weeks treatment

The Group accepted the local need for apremilast for moderate to severe chronic plaque psoriasis as outlined in SMC 1052/15, and active psoriatic arthritis as outlined in SMC 1010/14, noting that it is available as an oral formulation, it is a new class of treatment that targets a chemical pathway not covered by other agents and it will provide patients with another treatment option.

SMC 1052/15 - Apremilast 10mg, 20mg and 30mg film-coated tablets (Otezla®) ▼ is included on the Grampian Joint Formulary for the indication in question; restricted use.
Indication under review: for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA).
In two phase III, randomised, placebo-controlled studies in patients with moderate to severe plaque psoriasis, a significantly greater proportion of patients who received apremilast achieved at least 75% improvement in the Psoriasis Area and Severity Index (PASI) score at 16 weeks compared with those who received placebo. It was

ITEM	SUBJECT	ACTION

classified 1b – available for restricted use under specialist supervision and 8d - treatment may be initiated in the community on the recommendation of a consultant/specialist. Treatment should be initiated by specialists experienced in the diagnosis and treatment of psoriasis (or psoriatic arthritis). **FTeam**

SMC 1053/15 - Apremilast 10mg, 20mg and 30mg film-coated tablets (Otezla®) ▼ is included on the Grampian Joint Formulary for the indication in question; restricted use.
Indication under review: alone or in combination with disease modifying anti-rheumatic drugs (DMARDs), for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.
Restriction: for use in adult patients with active PsA who have had an inadequate response with at least two prior DMARD therapies or who are intolerant to such therapies.
In three phase III, randomised, placebo-controlled studies in patients with active psoriatic arthritis, a significantly greater proportion of patients who received apremilast achieved at least 20% improvement in the American College of Rheumatology response criteria (ACR 20) at 16 weeks compared with those who received placebo. It was classified 1b – available for restricted use under specialist supervision and 8d - treatment may be initiated in the community on the recommendation of a consultant/specialist. Treatment should be initiated by specialists experienced in the diagnosis and treatment of (psoriasis or) psoriatic arthritis. **FTeam**

8.3. FG1 SMC 943/14 – CEFTOBIPROLE – HAP (EXCLUDING VAP AND CAP)

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

The Group considered the request for ceftobiprole submitted by Dr Mackenzie on behalf of the Antimicrobial Management Team (AMT).

The Group noted that:
- the submitting company has requested that the SMC considers ceftobiprole when positioned for use in the treatment of hospital-acquired pneumonia (HAP) when activity is required against suspected methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative pathogens (including *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae*) and when combination treatment that includes vancomycin or teicoplanin is inappropriate, has not been tolerated, or treatment modification is required
- ceftobiprole:
  - is a new intravenous cephalosporin
  - will be considered a third-line option in NHS Grampian (contraindications to first- and second-line options), and use will be subject to inclusion in the 'Alert' antimicrobial policy
- the prescribing of cephalosporins is severely restricted due to the potential for *Clostridium difficile* infection and if introduced, the use of ceftobiprole would be subject to antimicrobial prescribing policies and antimicrobial stewardship

The Group accepted the local need for ceftobiprole as outlined in SMC 943/14, noting that prescribing is restricted to 'only on the advice of a Consultant/Specialist Microbiologist or infectious disease specialist', and inclusion in the 'NHS Grampian staff guidance for optimising the use of alert (restricted) antimicrobials in adults'. **AMT**

SMC 943/14 - Ceftobiprole, 500mg, powder for concentrate for solution for infusion (Zevtera®) ▼ is included on the Grampian Joint Formulary for the indication in question; restricted use.
Indication under review: Ceftobiprole is indicated for the treatment of the following infections in adults:
- **Hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP)**
- **Community-acquired pneumonia (CAP)**

Consideration should be given to official guidance on the appropriate use of

ITEM	SUBJECT	ACTION

antibacterial agents.
Restriction: for use in the treatment of HAP (excluding VAP) when activity is required against suspected methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative pathogens (including *Pseudomona aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae*) and when combination treatment that includes vancomycin or teicoplanin is inappropriate or has not been tolerated, or when treatment modification is required, i.e. as an alternative to linezolid-based regimens.
In a randomised, double-blind phase III study of patients with HAP, the clinical cure rate for empirical treatment with ceftobiprole was non-inferior to the rate associated with intravenous linezolid plus an anti-pseudomonal cephalosporin. It was classified 1b – available for restricted use under specialist supervision and 8b - recommended for hospital use only. Consideration should be given to official guidance on the appropriate use of antibacterial agents. Ceftobiprole is an 'Alert' antimicrobial available for restricted use only under the authorisation of a medical microbiologist, or infectious diseases specialist, and according to approved indications within local guidelines/policies. **FTeam**
Use of ceftobiprole is subject to inclusion in the NHS Grampian Staff Policy For Optimising Use Of Alert (Restricted) Antimicrobials **AMT**

8.4. FGA SMC 1042/15 – MAGNESIUM ASPARTATE DEHYDRATE (MAGNASPARTATE®) ▼ - MAGNESIUM DEFICIENCY

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

The Group considered the UKMI Medicines Q&A (111.5) and abbreviated submission for magnesium aspartate dehydrate for the treatment and prevention of magnesium deficiency, SMC 1042/15.

It was reported that there was an error in the costings for Magnaspartate® because the price in the BNF for Children reflected the Food for Special Medical Purpose Magnaspartate® [no longer available] not the Prescription-only medicine (PoM) product. The cost should be £8.95 for 10 sachets (not £7.95) which increases the cost for 28-days treatment to £25.06 to £50.12 (for 1 or 2 sachets daily respectively).

The Group noted that:

- the MHRA recommends that an unlicensed medicine should only be used when a patient has special requirements that cannot be met by the use of a licensed medicine
- magnesium aspartate dehydrate as PoM Magnaspartate® is the first licensed oral magnesium product available in the UK for the treatment and prevention of magnesium deficiency
- the currently available magnesium preparations require off-label use or unlicensed products, and swapping on a mmol for mmol basis may not result in an equivalent therapeutic effect as magnesium preparations have differing bioavailabilities
- introduction of PoM Magnaspartate® will not negate the need for alternate products
- local prescribing protocols will have to be reviewed in light of the introduction of PoM Magnaspartate® and the review should include provision of advice regarding the appropriateness or otherwise of switching patients currently stabilised on alternative products **MedInfo**

The Group accepted the local need for magnesium aspartate dehydrate powder for oral solution as Magnaspartate® for the treatment and prevention of magnesium deficiency. When clinically appropriate Magnaspartate® will become the preferred choice as it is the only licensed oral magnesium preparation for the treatment and prevention of magnesium deficiency.

SMC 1042/15 – Magnesium aspartate dihydrate equivalent to 243mg (10mmol) of magnesium powder for oral solution (Magnaspartate®) is included on the Grampian Joint Formulary for the indication in question.
Indication under review: for the treatment and prevention of magnesium deficiency, as diagnosed by a doctor.
Magnaspartate® is indicated in adults, children and adolescents aged from 2 years. This is the first licensed oral magnesium product to be available in the UK for the

ITEM	SUBJECT	ACTION

treatment and prevention of magnesium deficiency. Magnesium supplementation has previously been available as a food supplement. It was classified 1a – available for general use and 8e - treatment may be initiated in either hospital or community. **FTeam**

9. SCOTTISH MEDICINES CONSORTIUM PROVISIONAL ADVICE – ISSUED AUGUST 2015

The Group noted the SMC provisional advice issued August 2015.

If published next month the negative SMC recommendations, for elosulfase alfa (Vimizim®) ▼ SMC 1072/15 and avanafil (Spedra®) ▼ SMC 980/14, and the non-submission statements for ketoconazole (Ketoconazole HRA®) ▼ SMC 1100/15 and tigecycline (Tygacil®) ▼ SMC 1101/15, will not be included on the Grampian Joint Formulary for the indications in question.

10. SCOTTISH MEDICINES CONSORTIUM PRESS STATEMENTS - PUBLISHED AUGUST 2015

The Group noted the SMC advice published August 2015.

Following publication of the negative SMC recommendations for eribulin (Halaven®) ▼ SMC 1065/15 and enzalutamide (Xtandi®) ▼ SMC 1066/15, these medicines will not be included on the Grampian Joint Formulary for the indications in question. **FTeam**

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

- SMC 1028/15 tiotropium (Spiriva® Respimat®)
- SMC 1073/15 palonosetron (Aloxi®)
- SMC 1080/15 tedizolid phosphate (Sivextro®) ▼
- SMC 1081/15 darunavir/cobicistat (Rezolsta®) ▼

Local advice for these medicines and indications will be included in the August 2015 decisions as: "**not included on the Grampian Joint Formulary because clinicians have not responded to an invitation to apply for formulary inclusion for this medicine for the indication in question**." **FTeam**

11. GENERAL INFORMATION FROM SMC AUGUST 2015 – NIL OF NOTE

12. DOCUMENTS FOR INFORMATION

Items 11.1 (Drug Safety Update July 2015) and 11.2 (Grampian Medicines Management Group minute (GMMG) May 2015) were noted.

13. AOCB

The Chairman will raise the issue of lack of GP/ Integrated Joint Board input to the Formulary Group with Mr Pfleger, Chairman of the GMMG, at the September GMMG meeting. **JMcL**

DATE OF NEXT MEETING

The date of the next meeting was confirmed as Tuesday 15th September 2015 starting at 14.30 in the Aspen Room Forest Grove House.

CHAIRMAN'S SIGNATURE  **DATE 15th September 2015**