AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

One Wales Medicines Assessment Group (OWMAG)

Minutes of the virtual (Teams) meeting held Monday 28 November 2022

Members in attendance:
John Watkins, Consultant in Public Health, OWMAG Chair
Andrew Champion, Assistant Director, Evidence Evaluation, representative WHSSC
Alan Clatworthy, Clinical Effectiveness and Formulary Pharmacist, representative Swansea Bay
Joe Ferris, Operations Manager, ABPI Cymru Wales
Teena Grenier, Medicines Governance Lead, representative Betsi Cadwaladr
Malcolm Latham, Community Health Council, Lay representative
Hywel Pullen, Assistant Director of Finance, Finance Directors representative
Berni Sewell, Senior Lecturer, Health Economist, Swansea University
Jonathan Simms, Clinical Director of Pharmacy, representative Aneurin Bevan
William King, Consultant in Public Health, representative Powys
Michael Thomas, Consultant in Public Health, representative Hywel Dda
Ian Campbell, Hospital Consultant CAV, representative NMG

AWTTC:
Tony Williams, Senior Appraisal Pharmacist, Team Leader
Gail Woodland, Senior Appraisal Pharmacist
Clare Elliott, Senior Appraisal Scientist
Rosie Spears, Senior Appraisal Scientist
David Haines, Medical Writer
Carolyn Hughes, Medical Writer
Rachel Jonas, Medical Writer
Bridget-Ann Kenny, Medical Writer
Laura Phillips, Admin Supervisor
Jessica Morgan, Senior Communications Officer

Clinical experts:
Dr Joanita Ocen, Consultant Medical Oncologist, Velindre University NHS trust
Valerie Harris, Macmillan Immunotherapy Lead Nurse, Velindre University NHS trust

Patient organisation representative:
Jackie Hodgetts, Melanoma Focus Helpline Support Manager & Nurse Clinician at the Christie Hospital in Manchester

Observer(s):
Julie Wilson-Thomas, prospective new lay member

List of Abbreviations:

ABPI	Association of the British Pharmaceutical Industry
AWTTC	All Wales Therapeutics & Toxicology Centre
CEMT	Chief Executive Management Team
ESR	Evidence Status Report

IPFR	Independent Patient Funding Request
NICE	National Institute for Health and Care Excellence
NMG	New Medicines Group
OWMAG	One Wales Medicines Assessment Group
SPC	Summary of Product Characteristics
WHSSC	Welsh Health Specialised Services Committee

1. Welcome and Introduction

The Chair opened the meeting and welcomed members. The Chair welcomed prospective new lay member Julie Wilson-Thomas as an observer.

2. Apologies

Kathryn Howard, Head of Pharmacy, Royal Glamorgan Hospital, representative Cwm Taf Morgannwg
Brian Hawkins, Chief Pharmacist Medicines Governance, alternate representative Cwm Taf Morgannwg
Bethan Tranter, Chief Pharmacist, representative AWPAG/Velindre
James Coulson, Clinical Pharmacologist, Cardiff and Vale
Richard Hain, Consultant in Paediatric Palliative care, representative Cardiff and Vale

3. Declaration of Interests/Confidentiality

The Chair reminded members that all OWMAG proceedings are confidential and should not be disclosed outside of the meeting. Members were reminded that declarations of interest and confidentiality statements are signed by each member on an annual basis. The Chair invited any declarations of interest; there were none.

4. Chair's report

The Chair informed members that the minutes of the September meeting were agreed and are available on the AWTTC website.

The Chair informed members that since the last virtual face-to-face meeting we have received endorsement from the Chief Executive Management Team (CEMT) for the medicines considered at that meeting in September 2022 (abiraterone acetate for the treatment of non-metastatic and locally advanced high-risk, hormone-sensitive prostate cancer and vonicog alfa (Veyvondi®) for on-demand treatment of non-surgical and surgical (elective and emergency) bleeding episodes in children aged up to 17 years with von Willebrand disease).

The Chair informed members that we are awaiting endorsement of the three reviews that were considered at the October meeting: bendamustine and rituximab for treatment of indolent lymphomas and for treatment of mantle cell lymphoma and low dose bevacizumab for treatment of ovarian cancer.

To date AWTTC have performed seven reviews (two internally) in 2022 and an additional three new medicines and one review will be considered by OWMAG in December this year.

The Chair informed members that the recommendations from today's meeting will be forwarded to the Chief Executive Group for their consideration on 20 December 2022.

From early 2023, the recommendations from OWMAG will no longer be forwarded to the Chief Executives but will be sent to the following AWMSG meeting and subsequently to Welsh Government for ratification. The Chair informed members that these changes were not expected to affect OWMAG's process and if members had any queries to please contact the One Wales team in AWTTC. Comments were provided at the meeting regarding access arrangements and it was agreed that these would be followed up by AWTTC to seek further clarification on the process.

The Chair outlined the sequence of events for the meeting. As the clinical experts and patient organisation representative were the same for both assessments; the two assessments were to be discussed in full and members asked to vote for both once the clinical experts and patient organisation member had left the meeting. Each assessment was to be taken in turn and discussed on their own merit with separate votes for each.

Set up of hybrid meetings was discussed in relation to a concern that virtual attendees may not be able to have equal hearing with attendees in person. It was made clear that virtual attendees would feature prominently on TV screens within the venue.

5. Assessment one

Infliximab for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids.

The Chair welcomed clinical experts, Dr Joanita Ocen, Consultant Medical Oncologist, Velindre University NHS trust and Valerie Harris, Macmillan Immunotherapy Lead Nurse, Velindre University NHS trust. The Chair described the role of the clinical expert as an invited observer of the OWMAG meeting to answer questions and input into discussions to enable members to gain a better understanding of the clinical context. The Chair highlighted that clinical experts were nominated by their specialist group or network and should not express personal opinion or promote the use of a medicine.

The Chair welcomed also the patient organisation representative Jackie Hodgetts, Melanoma Focus Helpline Support Manager & Nurse Clinician at the Christie Hospital in Manchester. The Chair described the role of the patient organisation representative as providing the patient perspective and highlighting social issues for both assessments.

The Chair invited any declarations of interest specific to this assessment; Jackie Hodgetts in receipt of honorarium from Bristol-Myers Squibb Pharmaceuticals Ltd and Merck Sharp & Dohme Ltd for speaking and giving educational

sessions. No further declarations made.

The Chair further outlined the roles of the clinical experts and the patient organisation representative for both assessments that were being considered.

Rosie Spears presented an overview of the clinical background information pertinent to both assessments before presenting key aspects of the infliximab evidence status report.

The Chair invited the clinical expert, Dr Joanita Ocen, to give an overview of the disease and medicine being considered. The clinical expert detailed the typical clinical pathway; intravenous steroids are commonly used for all of grade 2-4 toxicities initially, if no clinical improvement after 48-72 hours, second line immunosuppression is considered. Flexible sigmoidoscopy with biopsy is arranged in collaboration with gastroenterology. The clinical expert stated that first line steroids work in the majority (80%) of cases. However, in the small proportion of patients who are refractory, infliximab is considered second line, pre-screening (including CMV, HIV and TB) would be undertaken. A new immunotherapy clinic has been developed at Velindre (covering the South East population of Wales) with the development of an internal pathway to allow ease of administration of infliximab, which works well. For the vast majority of patients receiving infliximab, symptoms settle and resolve.

The Chair asked for details about how the response to infliximab is monitored. The clinical expert stated that the team consider clinical symptoms corroborated on clinical examination, imaging (including abdominal X-ray and CT scans) and faecal calprotectin measurements. Weekly reviews are carried out while a patient receives steroids or infliximab for colitis.

The Chair invited the clinical expert, Valerie Harris, for further input. The clinical expert shared a patient perspective based on past experience within the unit at Velindre. Noting significant improvements in quality of life, the reduction in bowel movements meant that patients were able to sleep at night and allowed swifter hospital discharge. Infliximab can now be administered as a day case reducing hospital stays further. Infliximab is enabling patients to receive subsequent cancer treatments, titrate steroids down and to carry on with their lives at home. The team at Velindre are interested in ascertaining the dose required and further outcomes, specifically the impact on inflammatory markers in the bowel, which are being measured to inform practice.

The Chair invited the patient organisation representative, Jackie Hodgetts, to comment further on the patient perspective and impact on quality of life. The patient organisation representative supported what had been offered by both clinical experts and stated that the given scenarios are very real for patients who may be in hospital for several weeks with refractory diarrhoea.

The patient organisation representative provided further insight relating to patients whose symptoms respond to high dose steroids very quickly but, as steroids are reduced, symptoms recur. Before infliximab availability, this cohort would bounce in and out of hospital (up to eight times) as a cycle of steroid

reduction and symptom recurrence occurred. Currently, patients are discharged on a reducing dose of steroids, if symptoms recur, steroids are increased again slightly but, if symptoms recur a second time following steroid reduction, these patients are brought into the hospital as a day case for infliximab treatment after which they can return home. Generally, as stated by the clinical experts, the patient organisation representative shared that infliximab works very quickly for this indication. For those patients for whom infliximab is refractory, vedolizumab has been effective.

The Chair opened general discussion relating to the clinical effectiveness of infliximab.

The Chair asked the clinical expert whether the patient numbers provided were consistent with those seen in clinical practice. The clinical expert stated that currently one to two patients commence infliximab each month. Members asked whether the patient number provided in the evidence summary may be an underestimate. The clinical expert, Dr Joanita Ocen, stated that the number of potential patients will most likely increase given the increasing use of immunotherapies for various indications and that the given estimate is possibly a conservative estimate for all of Wales. AWTTC noted that patient numbers will be picked up at the 12-month review, alongside dosing regimens from data collected by the cancer centres. A follow-up question asked whether it was possible to know which immunotherapies/immunotherapy combinations were most likely to result in this toxicity. The clinical expert and patient representative agreed that combination treatment was more likely to result in this reaction than single agents.

Members asked for more detail relating to the timeline of this toxicity's occurrence and reoccurrence in relation to immunotherapy treatment. The clinical expert, Dr Joanita Ocen, stated that it presents earlier, particularly with combination treatment. The patient organisation representative supported this view, adding that it normally presents within the first two to three months of treatment. When this toxicity occurs in patients receiving immunotherapy treatment long term, it has been found to be more difficult to manage.

Members asked for any information relating to patient demographics and characteristics. The patient organisation representative stated that younger patients generally experience more severe toxicity however no gender differences have been noted.

The industry representative asked, given this use of infliximab is off-licence, whether any indication of licensing is on the horizon, particularly considering the anticipated increasing use of immunotherapies. AWTTC confirmed that there is currently no indication that a licence would be sought.

The Chair, acknowledging the lack of cost-effectiveness evidence, invited comment on potential assumed downstream cost benefits with the clinical experts and patient organisation representative's shared experience of a reduction in hospitalisation and reduction in symptoms alongside improved quality of life following infliximab treatment. The patient organisation

representative supported this assumption, adding that improved patient health would further contribute to cost benefits by, for example, facilitating steroid reduction which would otherwise contribute to significant health issues. The clinical expert, Dr Joanita Ocen, highlighted the severity of treatment options prior to infliximab availability by sharing the case which emphasised infliximab's potential to prevent significant resource use in terms of negating prolonged admissions and surgery. No further questions on cost effectiveness were raised.

The Chair invited discussion on budget impact. Members queried the impact infliximab may have on patient discharge and a potential resultant decrease in healthcare resource use. The patient organisation representative indicated, as a result of infliximab availability for this indication, patients can return home earlier and re-admission (staying within the hospital for up to three weeks) can be prevented as infliximab treatment for symptom flares can be given as a day case.

Members asked for more information relating to treatment cost and biosimilar use. It is assumed that the biosimilar with the lowest acquisition cost would be preferentially used.

The Chair invited discussion on the patient and public perspective. The lay representative highlighted issues relating to equity of access and standardisation of treatment both in terms of where a patient may live within Wales and funding pathway differences. A positive recommendation may also build a stronger evidence base, especially important as the use of immunotherapies is anticipated to increase. The personal benefits to individual patients and their family and friends was also acknowledged. It was widely acknowledged that, without a viable treatment option, this toxicity can exacerbate isolation issues for immunotherapy patients. This relates to an increased need and urgency for bathroom facilities when not at home as a result of this toxicity. Patients can become housebound and isolated for weeks or months if symptoms are not controlled.

The Chair invited discussion on any outstanding wider societal and health and social care issues. No questions were raised.

6. Assessment two

Vedolizumab (Entyvio®) for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable.

Rosie Spears presented key aspects specific to the vedolizumab evidence status report.

The Chair reminded members that, although both medicines are for the same indication they are separate considerations and that they are judged on their individual merit.

The Chair asked the clinical experts for their experience of using vedolizumab as opposed to infliximab and also the post treatment landscape in relation to steroids, for either medicine. The clinical expert, Dr Joanita Ocen, shared that experience is limited, treatment was undertaken in collaboration with gastroenterology. Similarly to infliximab, vedolizumab would assist with a rapid wean from steroids which would reduce the risks associated with long-term steroid exposure. It would also reduce the risk of more surgical intervention. The clinical expert, Valerie Harris, added that vedolizumab's gut specificity would be particularly beneficial for this toxicity. The patient organisation representation supported the comments of the clinical experts.

The Chair invited discussion on clinical effectiveness. Members asked whether a patient would receive three doses of infliximab if insufficient clinical response before being moved to vedolizumab. The clinical expert, Dr Joanita Ocen, stated that decisions on switching treatment would be made on a case-by-case basis. Generally, if there is a modest response, for example, if the toxicity had not settled after one cycle, a second would be given. If there is clear deterioration despite infliximab, the team would not wait for three doses before considering switching to vedolizumab as six weeks would be too long. The team have typically seen a fast, convincing response of toxicity to infliximab. The clinical expert, Valerie Harris, added that reviews of blood and faecal calprotectin would also give an indication of response, which alongside clinical symptom progression, would guide the consultant's treatment decisions.

Members asked whether three doses of vedolizumab was sufficient. The patient organisation representative stated that, although experience limited to date, one dose of vedolizumab is usually sufficient with additional doses rarely used. If refractory to infliximab, a one-off dose of vedolizumab is usually sufficient to resolve toxicity.

The Chair invited discussion on cost-effectiveness. Members highlighted the difference in price between infliximab and vedolizumab but acknowledged the difficulty in making any judgment about cost without cost-effectiveness evidence. The Chair reminded members that each medicine stands on its own merit. The health economist reminded members that, without cost-effectiveness evidence, only assumptions can be made with a risk of bias. There was discussion around the downstream effects of using vedolizumab and the relative efficacy of vedolizumab compared with infliximab based on the comparative data provided in the evidence submission.

The Chair invited discussion on budget impact and asked whether there was any difference in administration costs between infliximab and vedolizumab. AWTTC indicated that these costs are the same for both medicines. There was a discussion around how costs are currently met for vedolizumab and current usage. Members asked for clarification on patient numbers for vedolizumab. AWTTC stated that vedolizumab patient numbers included both those with toxicity refractory to infliximab and also those for whom infliximab is unsuitable.

The Chair invited discussion on the patient and public perspective. The lay representative highlighted that the arguments for vedolizumab were similar to

those for infliximab and included equity concerns, standardisation aiding patient clarity, easing clinician access to the treatments, avoiding surgery and enabling patients to return home quicker. The patient organisation representative stated the critical importance of being able to treat immunotherapy toxicity quickly. In the instance that the toxicity is refractory to steroids, the quicker that a second line treatment can be given, the more efficacious it can be. Members queried whether the South East Wales service covered all immunotherapy toxicities or just enterocolitis, as significant issues with pneumonitis were being found elsewhere. The clinical expert, Dr Joanita Ocen, confirmed that the service is comprehensive and covers all toxicities.

The clinical experts and the patient organisation representative left the meeting and members were invited to vote. The OWMAG recommendation for health board Chief Executives was agreed:

Date of advice: Monday 28 November

Using the agreed starting and stopping criteria, infliximab can be made available within NHS Wales for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids. Infliximab should be prescribed on the basis of lowest acquisition cost.

Date of advice: Monday 28 November

Using the agreed starting and stopping criteria, vedolizumab (Entyvio®) can be made available within NHS Wales for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and infliximab, or when infliximab is unsuitable.

7. AOB

Gail informed members that there are three full assessments and one review for the December OWMAG meeting.