HSE Drugs Group – February 2023 Minutes

Meeting 2023.02: Tuesday 14th February 2023, 14.00 – 16.30

Via videoconference

1. Draft Minutes for Consideration

The minutes of the January 2023 meetings were considered and approved.

2. Confidentiality forms

It had previously been agreed that all members (including public servants) would sign confidentiality forms (once off action).

3. Matters arising / Update on Medicines considered at previous meeting

An update on items previously considered by the Drugs Group was provided. The positive recommendations for Olaparib (for metastatic castration-resistant prostate cancer) and Larotrectinib (for solid tumours with NTRK gene fusion) from the December 2022 meeting had been approved by the HSE EMT. The Group noted the referral of Larotrectinib to the HSE Medicines Management Programme for the progression of a managed access protocol to support reimbursement under the High Tech arrangements.

4. Declaration of Interests / Nil Interest

None declared

5. Medicines for Consideration

i. 22032 Risdiplam for 5q spinal muscular atrophy (SMA)

The Drugs Group considered Risdiplam (Evrysdi®) for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.

The totality of clinical and economic evidence for Risdiplam was comprehensively reviewed by the Drugs Group in December 2022. After an extensive discussion at the December 2022 meeting and on the basis of the value of the commercial offer submitted by Roche being applicable to a restricted population (Type I, II and III SMA <18 years), the Drugs Group were willing to progress a positive recommendation conditional on a Managed Access Protocol being put in place. This recommendation took into account reported cost-effectiveness versus relevant comparators (that are subject to confidential discounts) and the current limitations in the available evidence for efficacy when initiating targeted treatments in adults with SMA.

The applicant (Roche) responded by proposing a confidential discount of [redacted] for the restricted population (Type I, II and III SMA <18 years), which was presented to the Drugs Group at the February 2023 meeting.

The Drugs Group supported reimbursement on the [redacted] versus the most relevant comparator, which was considered to be Nusinersen and subject to a managed access protocol being put in place.

ii. 22036 Niraparib for 1L maintenance treatment of ovarian cancer

The Drugs Group considered Niraparib (Zejula®) as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or

primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. The Group reviewed the clinical and economic evidence in detail as well as the advice emanating from the National Cancer Control Programme Technology Review Committee (NCCP TRC). The key evidence informing this indication came from the pivotal PRIMA trial. In the intention-to-treat (ITT) population, at the primary efficacy analysis, median PFS was 13.8 months in individuals receiving Niraparib and 8.2 months in individuals receiving placebo (considered as a proxy for Routine Surveillance); ((HR) = 0.62 (95% CI 0.50 to 0.76; p<0.0001). In the interim analysis of Overall Survival (OS), data for median OS was very immature ((10.8%); HR = 0.70 (95% CI 0.44 to 1.11)). HRQoL scores indicated that overall Niraparib was not detrimental to HRQoL.

The Group acknowledged the substantial impact of the commercial offer on the cost-effectiveness estimates. The Drugs Group unanimously recommended reimbursement on the basis of the totality of the clinical and cost-effectiveness evidence submitted, noting that Niraparib [redacted] based on a willingness to pay threshold of €45,000/QALY (applicant and NCPE perspectives taken into account).

iii. 22037 Pembrolizumab for 1L MSI-H /dMMR colorectal cancer

The Drugs Group considered Pembrolizumab (Keytruda®) as monotherapy for the first line treatment of adults with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer. The Group reviewed the clinical and economic evidence in detail as well as the advice emanating from the National Cancer Control Programme Technology Review Committee (NCCP TRC). The key evidence informing this indication came from the KEYNOTE-177 trial. Pembrolizumab showed statistically significant and clinically meaningful improvement in PFS by BICR per RECIST 1.1 (final analysis; DCO 19 February 2020) compared to SOC, with HR 0.60 (95% CI 0.45, 0.80), p=0.0002. Median PFS was 16.5 (95%CI 5.4, 32.4) vs 8.2 (95% CI 6.1, 10.2) months. OS (interim analysis) was not statistically significant, although a trend toward a survival advantage for Pembrolizumab over SOC is noted: HR 0.77 (95% CI 0.54, 1.09), p=0.0694. It was acknowledged that the high crossover rate to immunotherapies from the SOC arm could be implicated in this observation. The Drugs Group unanimously recommended reimbursement under the ODMS for this indication, acknowledging that the proposed commercial offering resulted in cost effective ICERs ranging from [redacted] (applicant base case) to [redacted] (NCPE adjusted base case).

iv. 23001 Andexanet alfa for anticoagulation reversal

The Drugs Group considered Andexanet Alfa (Ondexxya®) 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. The group recognised that the lack of availability of an antidote for direct FXa inhibitors represents an unmet medical need and Andexanet Alfa is currently the only licensed reversal agent for FXa inhibitor anticoagulation (Apixaban or Rivaroxaban) in patients with life-threatening or uncontrolled bleeding.

The Group reviewed the clinical evidence from the pivotal Phase IIIb/IV ANNEXA-4 trial in patients with an acute major bleeding episode requiring urgent reversal of FXa anticoagulation. In Study ANNEXA-4, Andexanet Alfa was administered to 477 patients on FXa inhibitors, 419 of whom were on Apixaban and Rivaroxaban. The two co-primary endpoints were: a) percent change in anti-FXa activity from baseline to the nadir between five minutes after the end of the bolus until the end of the infusion, and; b) rate of good or excellent (compared to poor or none) haemostatic efficacy within 12 hours after infusion, as rated by an independent endpoint adjudication committee. The group noted a median (95% CI) decrease from baseline to nadir in anti-FXa activity for Apixaban of -93.3% (-94.2%,-92.5%); and Rivaroxaban; -94.1% (-95.1%; -93.0%) and that haemostatic efficacy was good or excellent in 79% of 169 patients taking Apixaban and in 80% of 127 patients taking Rivaroxaban. A key secondary endpoint was the percent change from baseline in anti-fXa activity by haemostatic efficacy

which demonstrated that the change in anti-FXa activity (surrogate) was not predictive for achievement of haemostatic efficacy.

The Drugs Group considered the uncertainties in the clinical and cost-effectiveness evidence, as reported by the National Centre for Pharmacoeconomics (NCPE). Given the unmet need for a licensed antidote in clinical practice (for what presents as an acute medical emergency) and the fact that more evidence is expected to be made available that would potentially reduce these uncertainties, the Drugs Group unanimously agreed to recommend reimbursement of Andexanet Alfa on an interim basis until the end of 2024 and subject to a [redacted] Andexanet Alfa received a conditional marketing authorisation from the EMA, with stipulations on the further supportive evidence to be submitted post-authorisation, which can also be used by the HSE in future appraisals of this medicine.

v. 23002 Nivolumab + Ipilimumab for mesothelioma

The Drugs Group considered Nivolumab (Opdivo®) in combination with Ipilimumab (Yervoy®) for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma. The Group reviewed the clinical and economic evidence in detail as well as the advice emanating from the National Cancer Control Programme Technology Review Committee (NCCP TRC). The Drugs Group noted that malignant pleural mesothelioma (MPM) is a rare and incurable disease with a poor prognosis. The Group reviewed the clinical evidence for the regulatory approval, which came from the CheckMate-743 phase III, open-label, randomised controlled trial. Nivolumab + Ipilimumab (n=303) was compared to standard of care (SoC) chemotherapy (n=302) in treatment naïve patients with unresectable MPM. At the pre-specified primary analysis of the intention to treat (ITT) population, treatment with Nivolumab+ Ipilimumab reduced the risk of all cause death by 26% compared with SoC chemotherapy (HR 0.74, 95% CI 0.61 to 0.89, p=0.002) at a minimum follow up of 22.1 months. Median overall survival (OS) was 18.1 months (95% CI 16.8 to 21.4) with Nivolumab + Ipilimumab vs 14.1 months (95% CI 12.4 to 16.2) with SoC chemotherapy. The Drugs Group acknowledged the [redacted] on the pricing proposed. On balance, having taken into account all the criteria it was required to consider, in particular the high level of unmet need, diminishing patient numbers (with peak incidence expected to have occurred in 2020) and the potential for substantial clinical benefits to be gained, especially for patients who elicit a durable response to this treatment, the Drugs Group in the majority recommended reimbursement of Nivolumab + Ipilimumab for this indication.

vi. 23003 Cenobamate for epilepsy

There was insufficient time for the Drugs Group to conclude deliberations on this application. This will be carried forward to the March 2023 meeting.

6. AOB

[redacted]

Appendix 1: Members Present on Microsoft Teams

Member	Title	Attendance
Prof. Áine Carroll	Chair, Medical Consultant	In attendance
Mr Shaun Flanagan	Primary Care Reimbursement Service (Assistant National Director)	In attendance
Ms Aoife Kirwan	Public Interest Member	Apologies received
Dr David Hanlon	National Clinical Advisor and Group Lead Primary Care (General Practitioner)	In attendance
Ms Patricia Heckmann for Professor Risteárd Ó Laoide	Chief Pharmacist, National Cancer Control Programme for National Director of the National Cancer Control Programme (Medical Consultant)	In attendance
Dr Philip Crowley	National Director for Quality Improvement (Medical Doctor)	In attendance*
Dr Valerie Walshe	Office of the Chief Financial Officer (Economist, PhD)	In attendance
Post Vacant	Office of Nursing & Midwifery Services (Director of Nursing)	n/a
Dr Roy Browne	Mental Health Division (Consultant Psychiatrist)	In attendance
Dr Cliona McGovern	Public Interest Member / Ethicist	In attendance
Mr Michael Power	Public Interest Member	In attendance
Dr Anne Dee	Specialist in Public Health Medicine	Apologies received
Post Vacant	Acute Operations Division (Assistant National Director)	n/a
Prof Ellen Crushell	Consultant in Inherited Metabolic Disorders	In attendance*
Dr Lisa Cogan	Consultant in Medicine for the Elderly, Medical Director, Royal Hospital Donnybrook	In attendance*

*parts of meeting and voting not attended

In attendance (non-voting):
Professor Michael Barry (NCPE)

Secretariat:
Ellen McGrath, Chief I Pharmacist, Head of CPU PCRS
Jennifer McCartan, Chief II Pharmacist, CPU PCRS
Mary Staunton, Chief II Pharmacist, CPU PCRS
Louise Walsh, Senior Pharmacist, CPU PCRS