National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP Technology Review Committee (TRC)

Meeting Notes

Date of Meeting:	**September 3rd 2018 at 4.30pm**
Venue :	**Teleconference / NCCP Offices**
Assessment:	Pembrolizumab (Keytruda®) – NSCLC Blinatumomab (Blincyto®) – ALL Obinutuzumab (Gazyvaro®) – Follicular lymphoma Nivolumab (Opdivo®) - NSCLC

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CONTAINS COMMERCIALLY CONFIDENTIAL INFORMATION

Attendance:

Members present		
Ms. Patricia Heckmann	NCCP Chief Pharmacist **- Chair**	
Dr. Oscar Breathnach	Medical Oncologist Beaumont: ISMO nominee	By 'phone
Dr. Michael Fay	Consultant Haematologist: IHS representative	
Mr. Shaun Flanagan	Pharmacist: HSE Corporate Pharmaceutical Unit	By 'phone
Dr. Patricia Harrington	Head of Assessment, HTA Directorate: HIQA nominee	By 'phone
NCPE Representative	National Centre for Pharmacoeconomics (NCPE)	By 'phone
Dr. Deirdre Murray	NCCP Health Intelligence	By 'phone
Dr. Dearbhaile O'Donnell	Medical Oncologist St. James's: ISMO nominee	By 'phone
Dr. John Quinn	Consultant Haematologist: IHS representative	By 'phone
Dr. Cecily Quinn	Consultant Histopathologist St. Vincent's: Nominee Faculty of Pathology	By 'phone
Non-member invited specialists present		
None		
Apologies (members)		
Dr. Deirdre O'Mahony	Medical Oncologist Cork University Hospital: ISMO nominee	
Dr. Ray McDermott	Medical Oncologist AMNCH/Vincent's: ISMO nominee	
Dr. Eve O'Toole	Research Group Lead, NCCP	
Dr. Ronan Desmond	Consultant Haematologist: IHS representative	
Observers present		
Ms. AnneMarie DeFrein	Deputy Chief Pharmacist, NCCP	
Ms. Alma Hanevy	HSE Rare Diseases Programme	
XXXXXXXXXXXXX	Pharmacy Student, NCCP	

Item	Discussion	Actions
1	**Notes of previous meeting and matters arising**	
	The notes of the meeting on May 28th 2018 were agreed. In addition to the conflict of interest forms signed by all members previously, members were asked to raise any conflicts of interest that they had in relation to any drug for discussion prior to the commencement of the discussion of that item. No conflicts were raised during the meeting. It was noted by the Chair that Ms. Alma Hanevy was attending today's meeting as an observer to inform the establishment of a TRC for rare diseases as well as a pharmacy student who is on a training placement in the NCCP, Rory McLoughlin.	
2	**Drugs/Technologies for consideration**	
	Pembrolizumab (Keytruda®) *As monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving Pembrolizumab* O. Breathnach outlined the clinical guideline for this indication. Pembrolizumab is already approved for reimbursement in the first line indication for those patients expressing PD-L1 >50%. This is the secondline indication post first line chemotherapy for those patients expressing a lower PD-L1, .1%. Compared to chemotherapy, immunotherapy is superior. The toxicities are as expected for this drug. Some patients show long term remission. The NCPE representative outlined the NCPE assessment of the submitted indication, as above. The company's dossier was received in July 2017 and final data was submitted in March 2018. The authorised dose for this indication is 2mg/kg every three weeks by IV infusion. Treatment should be continued until disease progression or unacceptable toxicity. In clinically stable patients with initial evidence of disease progression, treatment should continue until disease progression is confirmed. Relative efficacy outcomes for the comparison with docetaxel were derived from the Keynote-010 study. This study was an open-label, multi-national, Phase III randomised controlled trial of 1033 patients with locally advanced or metastatic NSCLC, who had progressed after previous treatment. Patients were assigned to one of three arms on a 1:1:1 basis, pembrolizumab every 3 weeks at a dose of 10mg/kg or 2mg/kg, or docetaxel 75mg/m2 every three weeks. In the trial, treatment with pembrolizumab beyond progressive disease was permitted in the event of continuing clinical benefit, and treatment duration was capped at a maximum of 35 cycles (2 years continuous treatment). In the trial, pembrolizumab 2mg/kg was associated with an increase is overall survival (OS) compared to docetaxel in the patient population with TPS≥1%. The median OS with pembrolizumab was 10.4 months (95% CI 9.4, 11.9) compared to 8.5 months (95% CI 7.5, 9.8) with docetaxel. Pembrolizumab was not associated with a statistically significant increase in progression free survival (PFS). The overall response rate (ORR) was statistically significantly improved with pembrolizumab treatment, with an ORR of 18% seen in the pembrolizumab arm compared to 9.3% in the docetaxel arm. There were no clinically meaningful differences in quality of life between the two treatment arms.	

Similar numbers of adverse events (AEs) were reported in both arms, in 97.6% pembrolizumab patients and 96.1% docetaxel patients. There was a higher incidence of Grade 3-5 AEs in the docetaxel arm compared to pembrolizumab, 56% versus 46.6%. Similar numbers of serious AEs were reported in both arms, approximately 34%. Treatment discontinuation due to AEs was higher with docetaxel than pembrolizumab. Overall pembrolizumab was associated with improved safety.

For the cost-effectiveness analysis, the effectiveness inputs in the model were PFS and OS. Survival outcomes from Keynote-010 were extrapolated to the full time horizon of the model using parametric extrapolation. OS data was adjusted for treatment crossover. The applicant presented two separate sets of base case assumptions, which differed in the approach to survival extrapolation, but did not express a preference for which one should be used for decision making. Costs for drug acquisition and administration, hospital resource use, monitoring and follow up, management of AEs and terminal care costs were included. AEs which were of Grade ≥3 severity and occurred in ≥5% in either arm of Keynote-010 were included in the economic model, in addition to diarrhoea ≥Grade 2 and febrile neutropenia.
The stopping rule was included in the model, i.e. stop treatment at 2 years or 35 cycles. This isn't flagged in the license.
The NCPE implemented a number of changes to the model, resulting in a final ICER of €85,215/QALY (incremental costs €48,549, incremental QALYs 0.570) versus docetaxel. The NCPE consider that this ICER may be an underestimate as it does not incorporate the most recent treatment duration data, and assumes that treatment is discontinued at two years regardless of disease status. For the comparison with nivolumab, nivolumab was associated with lower costs and higher QALYs and so dominated pembrolizumab (incremental cost -€5,103, incremental QALYs 0.129).

In the applicant base case scenario considered most relevant by the NCPE, the ICER for pembrolizumab versus docetaxel was €81,518/QALY (incremental costs €50,037, incremental QALYs 0.614), and for pembrolizumab versus nivolumab was €31,318/QALY (incremental costs €2,003, incremental QALYs 0.064). The estimated annual cost of treatment per patient is €58,544.48 including VAT and rebate, assuming patients receive 9.73 cycles. The applicant estimates that 51 to 52 new patients will be eligible for treatment annually, while the NCPE consider that this figure could be closer to 70+ patients annually. The applicant estimates the 5-year gross budget impact to be approximately €14.76 million annually while the NCPE estimates yielded a projected gross budget impact of €21.68 million. The applicant estimates the 5-year net budget impact to be approximately €14.69 million, while the NCPE estimates €21.5 million.

Following assessment of the applicant's submission, the NCPE recommends that pembrolizumab (Keytruda®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments.

Members discussed the NCPE assessment and clinical guideline. It was noted that the dose of pembrolizumab has recently been changed to a flat 200mg dose every 3 weeks.

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P. Heckmann clarified that this is now the licensed dose and that the use of a lower dose is a clinical decision on reducing dose for a particular patient.

C Quinn flagged the requirements for testing and that the required resources need to be factored into the cost of associated tests. The NCPE

representative clarified that the cost of the test was included in the pharmacoeconomic assessement but not the resources. P. Heckmann noted that the Framework for Molceular testing was issued last week. There is a requirement for hospitals to use this to horizon scan and to consider impact through their service plan. NCCP input into service plan requests but needs to be flagged locally.

P. Heckmann summarised that this drug offers increased benefit but at increased cost due to the dose change, with good safety and tolerability. No benefit seen in PFS.
The group had concerns on the cost effectiveness due to the move to the flat dosing.

Having considered the NCPE assessment and the clinical guideline for the drug, it was unanimously agreed, to recommend this drug for approval to the HSE Drugs Group. (Decision No. TRC036)

Nivolumab (Opdivo®)
Nivolumab, as monotherapy for the treatment of adult patients with locally advanced or metastatic nonsquamous NSCLC, after prior chemotherapy in adults

O. Breathnach outlined the clinical guideline for the above indication. This is similar to the pembrolizumab as above but is second-line in the non-squamous NSCLC population. The dose in the study was a mg/kg dose but in the clinical guideline reflects the updated dosing posology of a flat dose, every 2 weeks. Nivolumab is well tolerated, standard inclusion and exclusion criteria, including reasonable performance status, no active infections, no prior PD-1 agents. The side effect management is outlined, most clinicians have experience of this drug.

P. Heckmann clarified that the original application for this was split into squamous and non-squamous NSCLC and they have been assessed separately but the lincesed indication has now been rationalised to one indication.

The NCPE representative outlined the NCPE's assessment of the above indication for nivolumab. In the submission, docetaxel was the comparator investigated. Relative efficacy outcomes for the comparison with docetaxel were derived from the CheckMate-057 study. This study was an open-label, multi-national, Phase III randomised controlled trial of 582 patients with locally advanced or metastatic non-squamous NSCLC, after failure of prior platinum doublet-based chemotherapy. Patients were assigned to one of two arms, nivolumab 3mg/kg every 2 weeks or docetaxel 75mg/m2 every three weeks. Treatment with nivolumab beyond progressive disease in the event of continuing clinical benefit was permitted; docetaxel treatment was continued until progressive disease or intolerable side-effects.
The study met its primary endpoint of overall survival (OS). Nivolumab was associated with a median OS of 12.2 months (95% CI 9.7, 15.5), compared to 9.4 months (95% CI 8.1, 10.7) with docetaxel treatment. The OS rate with nivolumab was 39% compared to 23% with docetaxel at 18 months. The OS rate at 24 months was 29% with nivolumab, compared to 16% with docetaxel. Docetaxel was associated with increased survival for the first seven months of the trial. Nivolumab was associated a median progression free survival (PFS) of 2.3 months (95% CI 2.2, 3.3) compared to 4.2 months (95% CI 3.5, 4.9) for docetaxel. The PFS rate at 12 months was higher for nivolumab than for docetaxel (18.5% versus 8.1%). At the 24 month data cut off, the PFS rate was 12% in patients treated with nivolumab, compared to 1% in docetaxel treated patients. There is considerable risk of bias in the PFS estimates given that they are investigator assessed, and due to the open-label nature of the trial. As with OS, the HRs submitted for PFS cannot be considered valid due to violation of the proportional hazards assumption. The survival curves crossed over so the assumption doesn't hold.

While crossover between treatment arms was not permitted during the trial

period, patients could receive further lines of treatment in the follow up period; no attempt is made to adjust the survival benefit for this, and thus the treatment effects attributed to nivolumab and docetaxel may not be the result of these interventions alone. Subgroup analysis suggests that a relative survival benefit with nivolumab is only seen in patients whose tumours express PD-L1. Overall the safety profile of nivolumab in non-squamous NSCLC is consistent with previous findings. There was a higher incidence of Grade 3-4 adverse events in the docetaxel arm of CheckMate 057 than in the nivolumab arm (67% versus 46%).

For the cost-effectiveness analysis, the key effectiveness inputs in the model were time to treatment discontinuation (TTD) and overall survival (OS). Inputs for the comparison of nivolumab and docetaxel were derived from CheckMate 057. Patient characteristics, dose intensity, utility measurements and adverse event frequency used in the model are derived from CheckMate 057. Patients in the ‘Progressive disease’ state are assumed to receive one third line treatment, based on the proportion of patients who received subsequent systemic therapy in Checkmate 057.
TTD and OS results from CheckMate 057 are extrapolated to the full time horizon of the model, using parametric and spline-based extrapolations. The NCPE had concerns over a number of assumptions employed in these extrapolations and the sensitivity analyses showed that they were a major source of uncertainty in the model. In particular the economic model predicted an implausible PFS benefit with nivolumab, much greater than that seen in the CheckMate 057 trial. In addition, survival extrapolation had to be modified to ensure that the TTD didn’t exceed the OS, and that the OS didn’t fall below the general population mortality; these modifications to prevent the implausible scenarios predicted by the model are indicative of flawed assumptions in the extrapolation of the trial data.
The NCPE applied a number of changes to the model, which produced an ICER of €202,393 (incremental costs €88,117, incremental QALYs 0.44). The NCPE believe that this ICER may overestimate the ICER, (since PFS and TTD could not be used to model state transitions) but believe that it is much closer to the true ICER than that generated by the company base case of €136,030/QALY (incremental costs €92,205, incremental QALYs 0.68).

The company estimate that 302 patients will be eligible for treatment annually, and predict market share of 43% in year 1, rising to 75% thereafter. The estimated cost per patient per treatment course is €50,425 (including VAT), assuming patients receive 12.6 doses of nivolumab. The gross cumulative drug impact of introducing nivolumab from 2017 to 2021 is approximately €57.1 million, assuming a market share of 75%. The net cumulative budget impact of the introduction of nivolumab from 2017 to 2021 is approximately €56.33 million.

Following review of the company submission, nivolumab is not considered to be cost-effective relative to docetaxel for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer in adults after prior chemotherapy, at a threshold of €45,000/QALY.

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P. Heckmann summarized that this is for all lung cancer patients in second line setting. There is an unmet need for this cohort that do not meet the criteria for PD-L1 in alternate options. Clinicians may still want to know the PD-L1 status for prognostic reasons.

There was some concern that the data to support this is not very good and is poorly modelled. There is a substantial budget impact to be considered.

	Taking into account the current unmet need in the patient population, it was agreed by majority, to recommend this drug for approval to the HSE Drugs Group. (Decision No. TRC039) **Blinatumomab (Blincyto®)** *Treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)* M. Fay outlined the clinical guideline for the above indication. The TOWER study was a phase 3 trial where patients were randomised to receive blinatumomab or high dose salvage chemotherapy. OS was significantly longer in the blinatumomab group than the chemotherapy group. The median OS was 7.7months in the blinatumomab group versus 4.0 months in the chemotherapy group. 24% of each group went on to allogeneic stem cell transplant. Inclusion and exclusion criteria were as expected, adults aged over 18. Testing required is as standard. Noted that hospitalisation is recommended for the 9 days of the first cycle and the first 2 days of the second cycles. Patients may receive 2 cycles, and up to 3 more but clinically is best to move forward to transplant. Toxicity is as expected in this type of treatment with significant neurological toxicity, tumour lysis and cytokine release syndrome. No side effect of particular worry with this drug. This is a hard population to treat. Ideally, clinicians would like these patients to move forward in terms of getting them to transplant. The cohort of patients here is no prior salvage looking to get to transplant. The chance of salvage in these patients is low and time dependent as the longer not in remission, the less likely to make transplant. There is a clear, significant need for them to get to transplant. These are small numbers of patients. The current options for salvage are poorly tolerated and ineffective so not very good. The NCPE representative outlined the NCPE's assessment of the above indication. The licensed treatment duration is for two cycles induction therapy and up to three cycles of consolidation therapy, based on the single arm MT103-211 study considered during the marketing authorisation process. The treatment duration in the Phase III randomised controlled trial (RCT) considered by the NCPE as part of the review process, the TOWER study, was longer than in the current marketing authorisation, allowing for up to four additional cycles to be administered (nine cycles in total). The TOWER study was as outlined above. The EMA requested specific risk minimisation measures to address the safety concerns regarding medication errors and neurologic events including the agreement of an educational program with the competent authority in each country, requiring physician, pharmacist and nurse educational material, patient/caregivers educational material and a patient alert card. For the cost-effectiveness analysis, the key effectiveness inputs in the model were OS, EFS and rate of CR/CRh*/CRi within 12 weeks of treatment initiation, all derived from the TOWER study. The NCPE implemented a number of changes to the cost-effectiveness model submitted by the company, resulting in an ICER of €472,215/QALY (incremental costs €104,693, incremental QALYs 0.22). At this ICER the probability of cost-effectiveness at a willingness to pay (WTP) threshold of €45,000/QALY was 0%. The gross budget impact is estimated at €6.92m and the net impact is €6.79m. These estimates are highly sensitive to treatment duration and are based on the assumption of only two cycles per eligible patient. The use of blinatumomab will be associated with cost offsets through reduced hospitalisation; the NCPE estimate the net cost offsets at approximately €1.37 million over 5 years. The NCPE assessment of blinatumomab has demonstrated evidence of benefit in overall survival (OS), although the size of the long-term OS gain is highly uncertain. There is a very low probability of cost effectiveness and a high probability that the ICER far exceeds the cost effectiveness threshold for existing treatments. The NCPE recommends that blinatumomab not be	

considered for reimbursement unless cost effectiveness can be improved relative to existing treatments.

Members discussed the NCPE assessment and clinical guideline. It was noted that the HTA expected 8-10 patients per year. It was felt that the transplant eligible cohort rather than the full licensed patient cohort benefit most. The NCPE representative clarified that the population considered in the HTA is reflective of the TOWER study.
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P. Heckmann summarized that there is a clear unmet need and a poor outcome for patients currently. The use of blinatumomab sees a doubling in complete remission to >33%. The HTA has an assumption of 2 cycles and
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Taking into account the *current unmet need* *in the patient population, it was* *unanimously* *agreed, to recommend this drug for approval to the HSE Drugs Group.* (Decision No. TRC037)

Obinutuzumab (Gazyvaro®)
ObinutuzumAB in combination with chemotherapy followed by obinutuzumab maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.

M. Fay outlined the clinical guideline for this indication. In a phase III, open label, multicentre, randomised clinical study (BO21223/GALLIUM), 1202 patients with previously untreated Grade 1-3a advanced (stage II bulky disease, stage III/IV) FL were evaluated. Patients with FL Grade 3b were excluded from the study. Patients were randomised to 1:1 to receive either obinutuzumab (n=601 patients) or rituximab (n=601 patients) in combination with chemotherapy (bendamustine, CHOP or CVP), followed by obinutuzumab or rituximab maintenance in patients achieving a complete or partial response. There is a trend towards improved progression free survival in the obinutuzumab versus the rituximab arm. The inclusion and exclusion criteria, the testing and the adverse events were all as expected and standard for this type of drug. Any grade 5 adverse events were mostly seen with Bendamustine.
The reviewer says that this is not a priority but not all haematologists are of this view. NICE have approved this for higher risk patients. PFS is the best correlate available to try maintain patients in remission for as long as possible. There may be a place for this in the high risk population.

The NCPE representative outlined the NCPE assessment of the submitted indication, as above.

Obinutuzumab is an orphan drug. The comparator used in the comparative analysis was rituximab in combination with chemotherapy (R-chemo) as an induction treatment, followed by rituximab maintenance /monotherapy. The evidence used to support efficacy was from the GALLIUM trial. GALLIUM is an open-label, international, multicentre, randomised, 2-arm, phase III trial to evaluate the efficacy and safety of O-chemo followed by obinutuzumab maintenance therapy for responders compared with R-chemo followed by rituximab maintenance therapy for responders, in previously-untreated patients with CD20-positive advanced B-cell indolent Non-Hodgkin's lymphoma (iNHL), including both FL and marginal zone lymphoma (MZL) patients, who had a life expectancy of greater than 12-months and an ECOG status of 0-2. The primary efficacy endpoint was progression-free survival as assessed by the investigator (PFS-INV) among patients with FL. Secondary efficacy endpoints included; PFS assessed by independent review

committee (PFS-IRC), overall survival (OS), overall response (OR), overall response rate (ORR) and safety outcomes.

The median time for PFS was not reached in either treatment arm. The hazard ratio for PFS-INV was 0.66 (95% CI 0.51, 0.85) and PFS-IRC was 0.68 (95% CI 0.54, 0.87) at the January 2016 clinical cut-off. Based on KM estimates, at the later September 2016 cut-off, 75.0% (95% CI 71.0, 78.5) of patients in the R-chemo arm and 81.5% (95% CI 77.9, 84.6) of patients in the O-chemo arm were progression-free at three years, based on investigator assessment. The median OS was not estimable in either treatment arm, HR=0.82 (95% CI 0.54, 1.22) at the September 2016 clinical cut-off. The NCPE review team has concerns regarding the immaturity of the survival data (PFS and OS), resulting in uncertainty in interpreting the effect of treatment with O-chemo on both PFS and OS. Adverse events and serious adverse events were generally less common during maintenance therapy than during the induction phase.

A cost-utility analysis comparing O-chemo followed by obinutuzumab maintenance therapy with R-chemo followed by rituximab maintenance therapy was submitted by the company. Costs in the model included, drug acquisition, drug administration and monitoring costs, health-state costs and costs of adverse events.
The exponential distribution was used to extrapolate PFS data beyond the observation period in the GALLIUM trial to inform treatment effectiveness in the model. Post-progression survival was analysed separately for patients who progressed before and after two years, using data from the GALLIUM trial for early progressors and the PRIMA trial of rituximab maintenance versus observation for late progressors. OS was calculated through the model based on the proportion of patients in the PFS and progressed disease states.

The base case incremental cost-effectiveness results indicate that O-chemo results in an additional 0.72 life-years, equating to 0.79 additional QALYs compared with R-chemo, at an additional cost of €42,209. This results in an ICER of €53,249 per QALY. Several changes were implemented in the model by the NCPE. Implementation of these changes resulted in increases in the ICER up to €95,606/QALY (incremental costs €43,809; incremental QALYs 0.458).

The list price of obinutuzumab is €3,479.37 per 1,000mg vial. The total treatment cost of obinutuzumab (excluding the companion chemotherapy cost) per patient after induction therapy and 2-years of maintenance, including all rebates and VAT, is estimated as €81,765 for patients receiving O-benda and €89,942 for patients receiving O-CHOP or O-CVP.

The Applicant estimated that the eligible population would increase from 37 patients in Year 1 increasing to 109 in Year 5. The projected gross budget impact including acquisition costs only for obinutuzumab (excluding the companion chemotherapy cost) was estimated as €1,845,440 (year 1), €3,950,077 (year 2), €6,289,379 (year 3), €7,969,654 (year 4) and €9,005,619 (year 5). This results in a cumulative gross budget impact of €29.1M over 5-years. The net budget impact was estimated to increase from €1.32 million in year 1 to €6.23 million in Year 5 (cumulative 5-year net budget impact €20.2 million).

The NCPE recommends that obinutuzumab (Gazyvaro®) for this indication should not be considered for reimbursement, unless cost-effectiveness can be improved relative to existing treatments.

S. Flanagan outlined that this drug is already approved in alternate indications XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXX. This work is to be considered with the NCPE.

The group members discussed that from a proposed clinical perspective, any proposed sub-population of high risk patients would further complicate the

	decision. NICE approved only those patients with FLIPI score of 2 or more but this is not the entire study population. The data available is a large study with better PFS. The clinicians would support approval in high risk patients. The group members decided that this would be for the clinicians to define. The group's recommendation is based on the data available. It was unanimously agreed, to recommend this drug for approval to the HSE Drugs Group. (Decision No. TRC038)	
3	**Update on other drugs in the reimbursement process**	
	P. Heckmann undertook to circulate, by e-mail, an update on the drugs that are in the reimbursement process.	
4	**Any other business / Next meeting**	
	There was no other business.	

The meeting concluded at 18.10.

Actions arising from meeting:

Ref.	Date of meeting	Details of action	Responsible	Update
18/05	03/09/18	Recommendations of the Group to be communicated to the HSE Drugs Group.	S. Flanagan (& NCCP letter to HSE Drugs Group chair)	
18/06	03/09/18	Update on drugs currently in reimbursement process to be circulated by e-mail.	P. Heckmann	