Item 5

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CENTRE FOR HEALTH TECHNOLOGY EVALUATION
Technology Appraisals

Consultation on Batch 35 draft remits and draft scopes and summary of comments and discussions at scoping workshops

5.1	Aflibercept for treating diabetic macular oedema
5.2	Ipilimumab for the adjuvant treatment of completely resected stage IV or high risk stage III melanoma
5.3	Idelalisib for refractory indolent non-Hodgkin's lymphoma
5.4	Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation
5.5	Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism
5.6	Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

Provisional Title	**Aflibercept for treating diabetic macular oedema**		
Topic Selection ID Number	6810	**Wave / Round**	73
TA ID Number	717		
Manufacturer	Bayer Pharma		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of aflibercept within its licensed indication for treating diabetic macular oedema.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of aflibercept for treating diabetic macular oedema is appropriate. The proposed remit is appropriate. No changes are required. The population should be amended in line with the anticipated wording of the marketing authorisation and the population in the pivotal clinical trials to "people with visual impairment because of diabetic macular oedema". Attendees at the scoping workshop suggested that fluocinolone acetonide intravitreal implant and dexamethasone (appraisal due to begin in May 2014) should be included as comparators in the scope as "corticosteroids (including fluocinolone acetonide intravitreal implant and dexamethasone)". It was noted that these treatments are normally used in clinical practice later in the treatment pathway, however, it was noted that the marketing authorisation for aflibercept is likely to allow use during all lines of treatment; therefore they would be appropriate comparators after first-line use. The outcome "best corrected visual acuity" should be amended to "best corrected visual acuity (treated eye, non-treated eye and both eyes – with consideration given to whether it is the best, worst or equal performing eye)" Contrast sensitivity should be removed as an outcome because it was not included in the clinical trials for aflibercept and consultees did not consider that it is clinically meaningful.		
Population size	7% of people with diabetes have diabetic macular oedema, of whom approximately 39% have clinically significant disease (i.e. require treatment). This equates to approximately 62,000 – 70,000 people.		
Process (MTA/STA/HST)	STA		
Proposed changes to remit (in bold)	None		

Costing implications of remit change	No changes due to change in remit but population estimate updated to reflect more recent data used in TA301 fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy. Aflibercept is intended to be used as first line therapy for the treatment of visual impairment due to diabetic macular oedema (DMO). It is estimated that the number of people with diabetes who have visual impairment due to diabetic macular oedema is around 62,000 (TA301 fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy). The unit cost for this indication is not yet known; however for its current licensed indication the cost for a 4mg vial is £816. The indicated dose is 2mg however the number of injections and duration of treatment is not yet known. Assuming an eligible population of 62,000, the topic would be high cost if the incremental cost per person was around £240 which would include drug costs and administration. However, it is not known how many of the eligible population would use aflibercept. Offsetting savings are also anticipated due to a reduction in alternative treatments. The cost impact of the technology is therefore unknown, but has the potential to be high cost.
Timeliness statement	Assuming that the anticipated date of the marketing authorisation is the latest date that we are aware of and the expected referral date of this topic, issuing timely guidance for this technology will be possible.

Provisional Title	**Ipilimumab for the adjuvant treatment of completely resected stage IV or stage III high risk melanoma**		
Topic Selection ID Number	6154	**Wave / Round**	30
TA ID Number	721		
Manufacturer	Bristol-Myers Squibb		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of ipilimumab within its licensed indication for the adjuvant treatment of completely resected high risk stage III or IV melanoma.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of ipilimumab for the adjuvant treatment of completely resected high risk stage III or IV melanoma is appropriate. The proposed remit should be revised to reflect the population included in the key clinical trials as follows: 'To appraise the clinical and cost effectiveness of ipilimumab within its licensed indication for the adjuvant treatment of completely resected **stage IV or high risk stage III** melanoma'. The population should also be amended in line with the remit and clinical trials to 'Adults with completely resected stage IV or high risk stage III melanoma'. Consultees confirmed that adjuvant treatment following complete tumour resection is not routinely offered to patients in the UK. Instead, their condition is regularly monitored (observation) and treatment is only considered following disease recurrence. Consultees noted that high-dose interferon beta is licensed as an adjuvant treatment in the UK, but that it is only used by a small proportion of clinicians (around 5%) in the NHS. Therefore, it does not constitute established clinical practice and should not be included as a comparator. The comparator in the scope has been amended to only include 'observation (no treatment)'. Consultees agreed that the outcome measure 'response rate' should be removed from the scope, and 'disease-free survival' should be replaced with 'recurrence-free survival' to reflect the primary outcome in the pivotal trial.		
Population size	Based on the inclusion criteria for the population in the pivotal clinical trials for ipilimumab, it is estimated that there would be approximately 1000 people eligible for treatment with ipilimumab per year in England.		
Process (MTA/STA/HST)	STA		

Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of ipilimumab within its licensed indication for the adjuvant treatment of completely resected **stage IV or** high risk **stage III** melanoma.
Costing implications of remit change	No changes as a result of proposed change in remit; however the population estimate has been updated to be consistent with the data above. It is estimated the eligible population for this technology is around 1000 people per year. The treatment regimen and dosage are unclear at present. The cost of a 50mg/10ml vial is £3750. If treatment is provided at the same ipilimumab dose that is currently used for first or second line of melanoma (3mg/kg), the total cost for 32 doses in the first 24 weeks for a person weighing 80kg would be £577,500 [80*3*32 = 7680 mg / 50mg/vial ~ 154 vials = £3750*154 = £577,500]. And £198,750 for the rest of the 11 doses provided until a full period of 156 weeks of treatment; leading to a total of ~£776,250 over 3 years. At 10mg/kg (based on the dose from the clinical trials), the total cost could reach as much as £2.6million for one patient over 3 years. There are likely to be some savings on existing treatments but as a range of treatments may be used to manage malignant melanoma depending on the tumour stage and site, it is not possible to estimate what these would be or the level of potential savings. This topic has potential to be very high cost.
Timeliness statement	Assuming that the anticipated date of the marketing authorisation is the latest date that we are aware of and the expected referral date of this topic, issuing timely guidance for this technology will be possible.

Provisional Title	**Idelalisib for refractory indolent non-Hodgkin's lymphoma**		
Topic Selection ID Number	6882	**Wave / Round**	78
TA ID Number	723		
Manufacturer	Gilead Sciences		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of idelalisib within its licensed indication for refractory indolent non-Hodgkin's lymphoma.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of idelalisib for refractory indolent non-Hodgkin's lymphoma is appropriate. The proposed remit is appropriate. No changes are required. Consultees noted that the pivotal clinical trial only included patients whose disease is refractory to both rituximab and an alkylating agent. The manufacturer stated that it is expected that the marketing authorisation would reflect the trial population. Therefore, it was agreed that the population in the scope should reflect the patient population in the clinical trial, that is, "People with indolent non-Hodgkin's lymphoma that is refractory to rituximab and chemotherapy containing an alkylating agent". For the purpose of the appraisal, refractory will be defined in line with the clinical trial inclusion criteria to include "people whose disease has a lack of response while on treatment, or progresses within 6 months of completion of therapy". This definition is included in the "other considerations" section of the scope. Consultees noted that there is no standard of care for people with refractory indolent non-Hodgkin's lymphoma. Treatment depends on prior therapies and history of response. Once the disease is refractory to at least 2 lines of therapy including rituximab and chemotherapy, there are few options available that are likely to provide a durable treatment response. Consultees agreed that chemotherapy with or without rituximab is a suitable treatment option depending on which treatments the patient has received before and should be included as a comparator. For people in whom all other options have been exhausted or who are unable to receive further lines of active treatment with chemotherapy with or without rituximab, best supportive care was considered to be an appropriate comparator. Consultees noted that radioimmunotherapy is rarely used in UK clinical practice and it is not widely available, therefore, it has been removed as a comparator in the scope. It was agreed that the appropriate comparators for idelalisib are: "chemotherapy regimens with or without rituximab"; or in people for whom chemotherapy is unsuitable: "best supportive care".		

Population size	In 2010, 10,300 people were diagnosed with non-Hodgkin's lymphoma in England, of whom around 40% had indolent disease. There are no robust estimates of people with refractory indolent non-Hodgkin's lymphoma in England.
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	None
Costing implications of remit change	No changes as a result of change in remit. Using data from the costing template for TA243 (Follicular lymphoma – rituximab), it is estimated that the incidence of follicular lymphoma in England and Wales is 3.4 per 100,000 persons, around 1,900 cases per year in England. It is assumed that 85% (approximately 1,600) will have advanced (stage III and IV) disease, 94% (approximately 1,500) will be suitable for induction chemotherapy and 90% (approximately 1,300) will have a partial or complete response to induction therapy. The number of people refractory to these standard treatments and eligible to receive idelalisib is unknown. The cost of idelalisib is not yet known. The technology offers another treatment option; however the number of people who may switch from existing therapies cannot be estimated. Although this would provide offsetting savings from treatments avoided, the cost impact cannot be estimated.
Timeliness statement	Assuming that the anticipated date of the marketing authorisation is the latest date that we are aware of and the expected referral date of this topic, issuing timely guidance for this technology will be possible.

Provisional Title	**Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation**		
Topic Selection ID Number	5916	**Wave / Round**	23
TA ID Number	624		
Manufacturer	Daiichi Sankyo		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of edoxaban tosylate within its licensed indication for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation is appropriate. The proposed remit is appropriate. No changes are required. Consultees agreed that all of the comparators listed in the scope are appropriate. They noted that warfarin remains the primary comparator because there is limited uptake of the novel oral anticoagulants within the NHS. Consultees considered that it was redundant to specify that warfarin is only a comparator 'in people for whom warfarin is suitable' and suggested that this phrase be removed from the scope. The manufacturer stated that the pivotal trial pre-specified a subgroup of patients who had not previously been treated with warfarin. Clinical specialists advised that analyses for this subgroup would be useful to the NHS. Therefore, 'patients who have not previously been treated with warfarin' has been added to the scope as a possible subgroup for consideration if the evidence allows. In October 2014, there will be a review proposal to consider whether an MTA should be undertaken to update TA275, TA256 and TA249 (apixaban, rivaroxaban, and dabigatran) for this indication. During consultation, consultees considered that edoxaban should be appraised as an STA and not through the proposed MTA review to ensure timely guidance for edoxaban; to extend the choice of medication available to clinicians and patients; and to ensure fairness for all manufacturers of novel oral anticoagulants. There was agreement however that any future MTA of apixaban, rivaroxaban, and dabigatran should also include edoxaban (once the STA for edoxaban is complete).		
Population size	Approximately 430,000 people may be eligible for treatment with edoxaban in England.		
Process (MTA/STA/HST)	STA		

Proposed changes to remit (in bold)	None
Costing implications of remit change	Updated due to publication of TAs 275, 256 and 249: Figures taken from TA275 indicate that the eligible population for this technology is around 430,000 for England. Any cost impact will depend on the annual cost of edoxaban compared to warfarin and existing oral anticoagulant treatments appraised in TAs 275, 256 and 249. Since the unit cost of edoxaban is unknown, the cost impact cannot be estimated, but if it is similar in price to the other newer oral anticoagulants it is not expected that this technology will lead to a significant cost impact.
Timeliness statement	Assuming that the anticipated date of the marketing authorisation is the latest date that we are aware of and the expected referral date of this topic, issuing timely guidance for this technology will be possible.

Provisional Title	**Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism**		
Topic Selection ID Number	7030	**Wave / Round**	82
TA ID Number	726		
Manufacturer	Bristol-Myers Squibb and Pfizer		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of apixaban within its licensed indication for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism is appropriate. The proposed remit is appropriate. No changes are required. Edoxaban tosylate is also being considered for appraisal for this indication (see item 5.6). The scopes are consistent with each other. Consultees considered that aspirin should be included as a comparator for the long-term prevention of VTE. Although it is not included in current NICE guidance, attendees noted that recent evidence suggests that aspirin may be effective for long-term prevention, and in clinical practice some patients would take aspirin instead of another anticoagulant, due to patient preference, concomitant antiretrovirals or unsuitability of warfarin. Consultees acknowledged the ongoing appraisal of dabigatran for the same indication and suggested that it should also be included as a comparator given its similarly to apixaban. Consultees considered that 'No preventative treatment' should be included as a possible comparator in the long-term prevention phase; although this approach is becoming less common consultees agreed that it was plausible that there may be people who are currently not receiving long-term preventative treatment for whom apixaban could be considered. The comparators in the scope have been amended to reflect the comments from consultees as follows: • Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • Low molecular weight heparin or fondaparinux alone • Rivaroxaban • Dabigatran (subject to ongoing NICE technology appraisal) The appraisal should also consider initial treatment with one of the therapies listed above, followed by: • long-term preventative treatment with aspirin • no long-term preventative treatment		

	Consultees suggested that if the evidence allows and use is permitted by the marketing authorisation for apixaban, a subgroup analysis for people with cancer should be considered. In this subgroup, the appropriate comparators are the same as for the overall population (as listed above). Additional subgroup analyses suggested for inclusion are: • The analysis should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). • If evidence allows, subgroups will be considered by type of venous thromboembolism (pulmonary embolism or deep vein thrombosis).
Population size	The incidence of venous thromboembolism is approximately 1–2 per 1000 population, suggesting that about 50,000–100,000 people experience a venous thromboembolism each year in England.
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	None
Costing implications of remit change	Updated slightly to be consistent with population data above: The annual incidence of venous thromboembolic events is estimated at between 50,000 and 100,000 per year in England. The cost of apixaban per cycle is estimated at approximately £30; for people at further risk, a maintenance dose costing approximately £800 per annum may be prescribed. New anticoagulants have provided the opportunity for treatment to be given orally and for services to move away from secondary care (anticoagulation clinic) settings. Because there are a number of treatment options available and services are re-structuring, the likely uptake of apixaban cannot be estimated. Where people are able to switch treatments, there would be offsetting savings from these drugs avoided. Due to the comparability of cost of some of the other available drugs, it is anticipated that this topic has potential to be cost neutral.
Timeliness statement	Assuming that the anticipated date of the marketing authorisation is the latest date that we are aware of and the expected referral date of this topic, issuing timely guidance for this technology will be possible.

Provisional Title	**Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism**		
Topic Selection ID Number	5996	**Wave / Round**	25
TA ID Number	662		
Manufacturer	Daiichi Sankyo		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of edoxaban tosylate within its licensed indication for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism is appropriate. The proposed remit is appropriate. No changes are required. Apixaban is also being considered for appraisal for this indication (see item 5.5). The scopes are consistent with each other. Consultees considered that aspirin should be included as a comparator for the long-term prevention of VTE. Although it is not included in current NICE guidance, attendees noted that recent evidence suggests that aspirin may be effective for long-term prevention, and in clinical practice some patients would take aspirin instead of another anticoagulant, due to patient preference, concomitant antiretrovirals or unsuitability of warfarin. Consultees acknowledged the ongoing appraisal of dabigatran for the same indication and suggested that it should also be included as a comparator given its similarly to edoxaban tosylate. It was also noted that apixaban (for the same indication) is likely to be appraised before this topic, and therefore should also be considered as a comparator. Consultees considered that 'No preventative treatment' should be included as a possible comparator in the long-term prevention phase; although this approach is becoming less common consultees agreed that it was plausible that there may be people who are currently not receiving long-term preventative treatment for whom edoxaban tosylate could be considered. The comparators in the scope have been amended to reflect the comments from consultees as follows: • Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • Low molecular weight heparin or fondaparinux alone • Rivaroxaban • Dabigatran (subject to ongoing NICE technology		

	appraisal) • Apixaban (subject to proposed NICE technology appraisal) The appraisal should also consider initial treatment with one of the therapies listed above, followed by: • long-term preventative treatment with aspirin • no long-term preventative treatment Consultees suggested that if the evidence allows and use is permitted by the marketing authorisation for edoxaban tosylate, a subgroup analysis for people with cancer should be considered. The manufacturer expects the marketing authorisation will not make explicit reference to people with cancer, but agreed it was appropriate to consider this subgroup within an appraisal. In this subgroup, the appropriate comparators are the same as for the overall population (as listed above). Additional subgroup analyses for inclusion are: • The analysis should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). • If evidence allows, subgroups will be considered by type of venous thromboembolism (pulmonary embolism or deep vein thrombosis).
Population size	The incidence of venous thromboembolism is approximately 1–2 per 1000 population, suggesting that about 50,000–100,000 people experience a venous thromboembolism each year in England.
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	None
Costing implications of remit change	Updated to be consistent with population data above and more recent comparator information available: The annual incidence of venous thromboembolic events is estimated at between 50,000 and 100,000 per year in England. The cost of edoxaban tosylate per cycle is unknown but any cost impact will depend on the cost compared to current treatments including warfarin and other newer oral anticoagulants. Unlike warfarin, this therapy would not require anticoagulation monitoring and therefore some costs could be offset where warfarin is currently used, through avoiding anticoagulation monitoring and also the cost of strokes avoided. The cost impact cannot be estimated as the cost of the technology and uptake rate are not known.
Timeliness statement	Assuming that the anticipated date of the marketing authorisation is the latest date that we are aware of and the

	expected referral date of this topic, issuing timely guidance for this technology will be possible.