NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CENTRE FOR HEALTH TECHNOLOGY EVALUATION
Technology Appraisals

Consultation on Batch 37b draft remits and draft scopes and summary of comments and discussions at scoping workshops

	Batch 37b
5.2	Bortezomib for previously untreated mantle cell lymphoma
5.3	Idelalisib for relapsed chronic lymphocytic leukaemia
5.4	Ibrutinib for relapsed chronic lymphocytic leukaemia
5.5	Nintedanib for treating idiopathic pulmonary fibrosis
5.6	Liposomal cisplatin in combination with chemotherapy for treating inoperable advanced non small cell lung cancer
5.7	Liposomal cisplatin in combination with gemcitabine for previously untreated locally advanced or metastatic pancreatic cancer
5.8	Vorapaxar for the secondary prevention of atherothrombotic events after myocardial infarction

Provisional Title	Bortezomib for previously untreated mantle cell lymphoma		
Topic Selection ID Number	6386	**Wave / Round**	R45
TA ID Number	724		
Manufacturer	Janssen		
Anticipated licensing information	**CONFIDENTIAL INFORMATION REMOVED** Anticipated marketing authorisation: VELCADE in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma		
Draft remit	To appraise the clinical and cost effectiveness of bortezomib within its licensed indication for treating previously untreated mantle cell lymphoma.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of bortezomib for previously untreated mantle cell lymphoma is appropriate The proposed remit is appropriate. No changes are required The attendees at the scoping workshop understood that the license includes potential use of bortezomib in patients who could have a stem cell transplant but would not receive it for reasons unrelated to their condition, as well as use in patients that who are not eligible for a stem cell transplant on clinical grounds. Attendees at the scoping workshop concluded that it would be reasonable to appraise bortezomib in people who are not going to have a stem cell transplant, irrespective of whether or not they are eligible for transplant. Stem cell transplantation would therefore not be an appropriate comparator to include. Although it is anticipated that the marketing authorisation will not be restricted to people for whom stem cell transplants (SCT) are unsuitable, clinicians advised that you would not consider bortezomib fŷor those who could and would opt for a SCT and therefore it was appropriate to define the population and comparators accordingly The comparator 'bendamustine plus rituximab' has been amended to 'bendamustine plus rituximab (with or without cytarabine)' • There is no gold standard regimen for mantle cell lymphoma and therefore there are several comparators in the scope. • Adding cytarabine to the bendamustine and rituximab combination is used in clinical practice, although less often than the dual combination, and it appears to be effective • The most commonly used regimens are R-CHOP and bendamustine plus rituximab		
Population size	Approx. 220 patients per year. • 500 diagnosed with MCL per year in England • ~66% treated with chemotherapy • Of which ~ 66% would not have a stem cell transplant		

Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	No changes proposed
Costing implications of remit change	Updated to use population given above (previously not estimated): It is estimated that around 220 people per year would be eligible to use this technology. The estimated cost of 7 cycles of treatment is around £21,000 per person for bortezomib. The technology is to be administered in combination with rituximab, cyclophosphamide, doxorubicin and prednisolone. There is no current standard regime of treatment and so current treatment costs and those of any offsetting savings will vary per person. From the information provided, the cost impact cannot currently be estimated, but given the relatively small population is unlikely 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	Idelalisib for relapsed chronic lymphocytic leukaemia		
Topic Selection ID Number	6846	**Wave / Round**	R76
TA ID Number	**764**		
Manufacturer	Gilead Sciences		
Anticipated licensing information	Since the scope was developed, and since the workshop, a positive opinion has been received that is different to the anticipated marketing authorisation on which the scope and workshop were based. Several changes have therefore been made to the scope **CONFIDENTIAL INFORMATION REMOVED** <u>CHMP positive opinion (shortly after the workshop):</u> Idelalisib is indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia: • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. The company explained that the CHMP positive opinion included the 'treatment-naïve' population because of a "lack of effective therapeutic options available for high risk patients who are unlikely to benefit from chemoimmunotherapy". "The regulators were therefore willing to consider a much lower level of evidence than would normally be required". **CONFIDENTIAL INFORMATION REMOVED** 2 phase III trials have just started of idelalisib combination therapy in previously untreated CLL (expected completion: June 2016 and September 2018). **CONFIDENTIAL INFORMATION REMOVED** The company considered that, "within the current estimated timelines for the proposed STA of idelalisib, it would be more appropriate **<u>not</u>** to include the first-line high-risk (17p/TP53) patients" **CONFIDENTIAL INFORMATION REMOVED**		
Draft remit	To appraise the clinical and cost effectiveness of idelalisib within its licensed indication for treating relapsed chronic lymphocytic leukaemia.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of idelalisib for relapsed chronic lymphocytic leukaemia is appropriate. The proposed remit should be revised to reflect the changes to the anticipated marketing authorisation. The following changes are suggested: To appraise the clinical and cost effectiveness of idelalisib within its licensed indication for chronic lymphocytic leukaemia <u>Intervention</u>		

	To include idelalisib in combination with rituximab <u>Population</u> **Draft scope:** People with relapsed chronic lymphocytic leukaemia, for whom cytotoxic therapies are not suitable. **Amend to:** • Adults with CLL who have received at least one therapy • Adults with untreated CLL associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable <u>Comparators</u> **Draft scope:** bendamustine (with or without rituximab), chlorambucil (with or without rituximab), best supportive care **Additions/changes (previously treated):** • corticosteroids (with or without rituximab) • ofatumumab • best supportive care (including but not limited to, regular monitoring, blood transfusions, infection control and psychological support) • FCR (for those for whom cytotoxic therapies are appropriate) **Suggested comparators for previously untreated population:** • alemtuzumab • ofatumumab in combination with bendamustine or chlorambucil (subject to ongoing NICE technology appraisal) • best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support) <u>Outcomes</u> No changes <u>Other considerations (previously treated)</u> • To include 'presence or absence of 17p deletion' ○ Idelalisib is equally effective with or without the deletion but other treatments are less effective for those with deletion 17q. The differential effectiveness is therefore expected to be different for this population.
Population size	<u>Previously treated: less than 2000 a year</u> • Approx. 2800 new diagnoses in England/year. • 67% need treatment • Proportion relapsed unknown • The 5-year survival rates for all stages of CLL are 44% and 52% for men and women respectively. <u>Previously untreated (17p/TP53): 230-690 a year</u> • Approx. 5-10% have 'high-risk' disease (17p/TP53). • Median survival of 2 to 3 years.

Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of idelalisib within its licensed indication for chronic lymphocytic leukaemia
Costing implications of remit change	Updated for change in remit and clarified populations: Idelalisib is intended to be used in combination with rituximab for people with previously treated CLL and for people with previously untreated CLL with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable. The exact population for each is unknown but is estimated to be less than 1900 for the first group and up to 700 for the second group. The cost of idelalisib is not yet known. The cost of rituximab is approximately £10,000 per regimen. As rituximab is already a treatment option for people with CLL, for those people already choosing this drug, only the cost of idelalisib will be incremental, and as rituximab is delivered intravenously, it is not anticipated that there would be additional administration costs. Other treatment options exist, and if there is a switch from them, there will be offsetting savings. Since there are a variety of current treatment options and the unit cost of idelalisib is unknown, the cost impact for this technology cannot be calculated, but it has potential to be a high cost topic.
Timeliness statement	**CONFIDENTIAL INFORMATION REMOVED**issuing timely guidance for this technology will not be possible.

Provisional Title	**Ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia and small lymphocytic lymphoma**		
Topic Selection ID Number	7021	**Wave / Round**	R81
TA ID Number	749		
Manufacturer	Janssen		
Anticipated licensing information	The scope was developed based on the anticipated marketing authorization. However, before the workshop Janssen informed NICE that the MA may include an additional population. A positive CHMP opinion has now been received which does include this population, but the wording is different to that of the anticipated MA, and the update provided by Janssen. Several changes have therefore been made to the scope <u>Anticipated marketing authorisation</u> (on which the scope and scoping workshop were based): Ibrutinib is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) or for patients with CLL/SLL for whom purine analogue‑based therapy or for whom chemo-immunotherapy may not be appropriate <u>Update from the company prior to the workshop</u> The anticipated marketing authorisation would also include first line treatment for those for whom purine analogue‑based therapy was not appropriate including those with deletion 17p or TP53 mutation <u>CHMP positive opinion (shortly after the workshop):</u> Ibrutinib is indicated for adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. The company highlighted that the data supporting the high-risk, treatment-naive population was from a small phase 1B/2 clinical trial (n=38), and that a phase 3 study for this first-line population is underway, expected to report in Q4 2015. The company proposed that this population is considered **<u>separately at a later date</u>** when more data becomes available. **<u>Key differences to original anticipated marketing authorisation (used for scope):</u>** • Licence uses term ‘received at least one prior therapy’ rather than relapsed or refractory • License does not include SLL • License does not specify that the previously treated population was for whom ‘purine analogue‑based therapy or for whom chemo-immunotherapy may not be appropriate’ • Licence includes additional population (1st line treatment for 17p/TP53)		

Draft remit	**Draft scope:** To appraise the clinical and cost effectiveness of ibrutinib within its licensed indication for treating relapsed or refractory chronic lymphocytic leukaemia and small lymphocytic leukaemia.
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of ibrutinib for treating relapsed or refractory chronic lymphocytic leukaemia and small lymphocytic lymphoma is appropriate. The proposed remit should be revised to reflect the changes to the anticipated marketing authorisation. The following changes are suggested: To appraise the clinical and cost effectiveness of ibrutinib within its licensed indication for chronic lymphocytic leukaemia <u>Population</u> **Draft scope:** People with relapsed or refractory chronic lymphocytic leukaemia or small lymphocytic leukaemia, for whom cytotoxic therapies are not suitable **Amend to:** • Adults with chronic lymphocytic leukaemia (CLL) who have received at least one therapy • Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable <u>Comparators</u> **Draft scope:** bendamustine (with or without rituximab), chlorambucil (with or without rituximab), best supportive care **Additions/changes (previously treated):** • corticosteroids (with or without rituximab) • ofatumumab • best supportive care (including but not limited to, regular monitoring, blood transfusions, infection control and psychological support) • FCR (for those for whom cytotoxic therapies are appropriate) **Suggested comparators for previously untreated population:** • alemtuzumab • ofatumumab in combination with bendamustine or chlorambucil (subject to ongoing NICE technology appraisal) • best supportive care (including but not limited to regular monitoring, blood transfusions, infection control and psychological support) <u>Outcomes</u> No changes

Population size	<u>Previously treated: less than 2000 a year</u> • Approx. 2800 new diagnoses in England/year. • 67% need treatment • Proportion relapsed unknown • The 5-year survival rates for all stages of CLL are 44% and 52% for men and women respectively. <u>Previously untreated (17p/TP53): 230-690 a year</u> • Approx. 5-10% have 'high-risk' disease (17p/TP53). • Median survival of 2 to 3 years.
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of ibrutinib within its licensed indication for chronic lymphocytic leukaemia
Costing implications of remit change	Updated for change in remit and clarified populations: Ibrutinib is intended to be used for people with previously treated CLL and for people with previously untreated CLL with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable. The exact population for each is unknown but is estimated to be less than 1900 for the first group and up to 700 for the second group. The cost of ibrutinib is not yet known. Other treatment options exist, and if there is a switch from them, there will be offsetting savings. Since there are a variety of current treatment options and the unit cost of ibrutinib is unknown, the cost impact for this technology cannot be calculated, but it has potential to be a high cost topic.
Timeliness statement	**CONFIDENTIAL INFORMATION REMOVED** issuing timely guidance for this technology will not be possible.

Provisional Title	Nintedanib for treating idiopathic pulmonary fibrosis		
Topic Selection ID Number	6820	**Wave / Round**	R75
TA ID Number	752		
Manufacturer	Boehringer Ingelheim		
Anticipated licensing information	**CONFIDENTIAL INFORMATION REMOVED**		
Draft remit	To appraise the clinical and cost effectiveness of nintedanib within its licensed indication for treating idiopathic pulmonary fibrosis		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of nintedanib for treating idiopathic pulmonary fibrosis is appropriate, Consultees at the scoping workshop agreed that the remit in the draft scope is appropriate. Consultees agreed that no changes to the PICO table were required. Following the scoping workshop, comments were received from stakeholders taking part in the review proposal for TA282 pirfenidone for idiopathic pulmonary fibrosis. Following consultation, stakeholders indicated that a review of pirfenidone for this indication is required and suggested that this could be a MTA of pirfenidone and nintedanib for idiopathic pulmonary fibrosis. After further consideration this topic will be processed as a STA in order to ensure timely guidance for nintedanib.		
Population size	IPF is rare. The incidence of IPF is approximately 8 to 9 per 100,000 person-years		
Process (MTA/STA/HST)	STA		
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of nintedanib within its licensed indication for treating idiopathic pulmonary fibrosis		
Costing implications of remit change	No changes to original costing comments: Idiopathic pulmonary fibrosis (IPF) is the most common and severe form of idiopathic interstitial pneumonia. NICE costing template for TA282 (Idiopathic pulmonary fibrosis – pirfenidone) estimates that there are around 12,600 people with IPF in England. Nintedanib is intended to be used as first line therapy for the treatment of mild to moderate IPF. If licensed, it would offer another treatment		

	option for people with IPF who currently have limited effective therapeutic options. The number of people with mild to moderate stage disease isn't known. The cost of nintedanib is not yet known but assuming all 12,600 people were eligible, in order for it to be high cost, the incremental cost per person would need to be around £1,200 per year. One of its comparators pirfenidone has an annual cost of around £22,246 before a patient access scheme (PAS) reduction. There is a possibility that the manufacturer could price match pirfenidone if there isn't any significant incremental benefit. Although much is variable, it is considered that this topic has potential to be low cost if there is price matching.
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	Liposomal cisplatin in combination with chemotherapy for treating inoperable advanced non-small cell lung cancer		
Topic Selection ID Number	6508	**Wave / Round**	R41
TA ID Number	657		
Manufacturer	Regulon AE		
Anticipated licensing information	**CONFIDENTIAL INFORMATION REMOVED**		
Draft remit	To appraise the clinical and cost effectiveness of liposomal cisplatin in combination with chemotherapy within its licensed indication for inoperable advanced non-small cell lung cancer		
Main points from consultation	The Institute is of the opinion that an appraisal of liposomal cisplatin in combination with chemotherapy for treating inoperable advanced non-small cell lung is appropriate. The Institute recommends that the proposed remit is appropriate and no changes are required to the scope. A scoping workshop for this topic was scheduled, but was cancelled after the manufacturer indicated that they were not attending and few other groups responded. The comments on the scope from the manufacturer generally agreed with the remit and scope.		
Population size	Approximately 3600 to 5100 people depending on the marketing authorisation		
Process (MTA/STA/HST)	STA		
Proposed changes to remit (in bold)	No changes proposed		
Costing implications of remit change	Updated to reflect uncertainty about potential cost impact: There were around 34,000 new diagnoses of lung cancer in England in 2010, of which around 85% (29,000) are estimated to be non-small cell lung cancer (NSCLC). It is estimated that around 30% (8600) are non-squamous and that around 78% (6700) have advanced disease (stage III or IV). Around 30% (2000) are treated with chemotherapy. The eligible population is therefore estimated to be around 2000 people. The cost of liposomal cisplatin for this indication has not yet been determined and the duration of treatment is unknown. Based on the cost of tablets for current licensed indications, if every eligible patient were to switch to liposomal cisplatin, the technology would be high cost if the incremental cost was around £7,500 per patient per year. Since the number of people who may switch to this technology is unknown, 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	Liposomal cisplatin in combination with gemcitabine for previously untreated locally advanced or metastatic pancreatic cancer		
Topic Selection ID Number	6315	**Wave / Round**	R41
TA ID Number	658		
Manufacturer	Regulon AE		
Anticipated licensing information	**CONFIDENTIAL INFORMATION REMOVED**		
Draft remit	To appraise the clinical and cost effectiveness of liposomal cisplatin in combination with gemcitabine within its licensed indication for previously untreated locally advanced or metastatic pancreatic cancer.		
Main points from consultation	Following the consultation exercise, the Institute is of the opinion that an appraisal of liposomal cisplatin in combination with gemcitabine for previously untreated locally advanced or metastatic pancreatic cancer is appropriate. The Institute recommends that the proposed remit is appropriate and no changes are required to the scope. Only 2 consultees submitted comments during the consultation on the draft scope for this appraisal, Pancreatic Cancer UK submitted comments agreeing with the draft remit and with the comparators. The manufacturer did not submit any comments nor indicate that it would attend the scoping workshop. As a result of this lack of engagement the scoping workshop was cancelled.		
Population size	In 2010, there were 7058 new diagnoses of pancreatic cancer in England. It is estimated that around 10–20% are suitable for resectable surgery and that the remaining 80–90% (n = 5650–6350) would be eligible for treatment with this drug.		
Process (MTA/STA/HST)	STA		
Proposed changes to remit (in bold)	No changes proposed		
Costing implications of remit change	Updated to reflect population data provided above: In 2010, there were 7058 new diagnoses of pancreatic cancer in England. It is estimated that around 10–20% are suitable for resectable surgery and that the remaining 80–90% (5650–6350) would be eligible for treatment with this drug. The cost of liposomal cisplatin is not yet known. It is expected to be used as a first line treatment for patients with pancreatic cancer however the number of people who would switch from current treatment options is unknown. As the eligible population is sizable, it is considered that there is potential for this topic 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	**Vorapaxar for the secondary prevention of atherothrombotic events after myocardial infarction**		
Topic Selection ID Number	4866	**Wave / Round**	W27
TA ID Number	616		
Manufacturer	Merck Sharpe and Dohme		
Anticipated licensing information	**CONFIDENTIAL INFORMATION REMOVED**		
Draft remit	To appraise the clinical and cost effectiveness of vorapaxar within its licensed indication for the prevention of atherothrombotic events in people who have prior myocardial infarction.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of vorapaxar for the prevention of atherothrombotic events after myocardial infarction is appropriate. The clinical trial (TRA 2P-TIMI 50) upon which the regulatory submission is based included patients who had a history of atherosclerosis, which was defined as: • a spontaneous myocardial infarction (MI) or ischemic stroke within the previous 2 weeks to 12 months or • peripheral vascular disease (PVD) associated with a history of intermittent claudication in conjunction with either an ankle–brachial index of less than 0.85 or previous revascularization for limb ischemia The trial enrolled a total of 26,449 patients of which approximately 66% had prior MI, 18% prior stroke and 14% PVD. In January 2011, after completion of enrolment and a median of 24 months of follow-up, the data and safety monitoring board reported an excess of intracranial haemorrhage in patients with a history of stroke in the vorapaxar group and recommended discontinuation of the drug in all patients with previous stroke, including those with a new stroke during the trial. The manufacturer has confirmed that the marketing authorisation will exclude patients with prior stroke. At the time of the scoping workshop there was uncertainty about whether the population with PVD would be included in the marketing authorisation. **CONFIDENTIAL INFORMATION REMOVED**If an appraisal were to be referred for PVD, the proposed remit is not appropriate and should be amended to: To appraise the clinical and cost effectiveness of vorapaxar within its licensed indication for reducing atherothrombotic events in people who have had a prior myocardial infarction or have peripheral vascular disease. PVD was not included in the initial scope consultation exercise because the remit covered only those people who have had a prior myocardial infarction. At the scoping workshop attendees noted that in the clinical trial vorapaxar had shown benefit in		

	people with PVD. NICE recommends that if PVD is included in any appraisal a further scope consultation is considered. **CONFIDENTIAL INFORMATION REMOVED**
Population size	There are 80,000 hospital admissions for myocardial infarction per year in England. In addition, 577,000 people in England have peripheral vascular disease with symptoms of intermittent claudication, but a smaller number of these patients are considered to have severe disease or be more likely to develop critical limb ischaemia.
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of vorapaxar within its licensed indication ~~**for the prevention of**~~ **for reducing** atherothrombotic events in people who have **had a** prior myocardial infarction **or have peripheral vascular disease.**
Costing implications of remit change	Costing comments updated to reflect changes in remit: Vorapaxar is intended as a second line treatment in the prevention of thrombotic cardiovascular events to reduce atherothrombotic events in people who have had a prior myocardial infarction or have peripheral vascular disease The potential population may be over 650,000 but it is unclear how many of these would be eligible for treatment. At present the cost of the technology is unknown but since it is additional to existing treatments it is possible the overall impact may be high cost. However, there may be offsetting costs where patients avoid subsequent non-fatal cardiovascular events.
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.