NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CENTRE FOR HEALTH TECHNOLOGY EVALUATION
Technology Appraisals and Highly Specialised Technologies

Consultation on Batch 42a draft remits and draft scopes and summary of comments and discussions at scoping workshops

Item number	ID	Topic
5.1	763	Dexamethasone intravitreal implant and sirolimus intravitreal injection for treating non-infectious posterior segment uveitis
5.2	814	Eltrombopag for treating severe aplastic anaemia following insufficient response to immunosuppressive therapy
5.3	700	Methylnaltrexone bromide for treating opioid-induced constipation
5.4	786	Lumacaftor in combination with ivacaftor for treating cystic fibrosis homozygous for the F508del mutation
5.5	829	Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts
5.6	817	Idelalisib in combination with ofatumumab for chronic lymphocytic leukaemia
5.7	844	Aflibercept for treating visual impairment due to macular oedema secondary to branch retinal vein occlusion

Provisional Title	**Dexamethasone intravitreal implant and sirolimus intravitreal injection for treating non-infectious posterior segment uveitis**		
Topic Selection ID Number	6649	**Wave / Round**	R64
TA ID Number	763		
Company	Allergan - Dexamethasone intravitreal implant Santen – Sirolimus intravitreal injection		
Anticipated licensing information	**Dexamethasone intravitreal implant:** • OZURDEX is indicated for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. • Marketing authorisation granted in 2010 **Sirolimus intravitreal injection:** ***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of dexamethasone intravitreal implant and sirolimus within their marketing authorisations for treating chronic non-infectious posterior segment uveitis.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of dexamethasone intravitreal implant and sirolimus intravitreal injection is appropriate. There was mixed reaction from the consultees and scoping workshop attendees regarding the value of appraising these treatments. Given the concerns that the results of economic modelling would be extremely uncertain due to small patient numbers (8% -10% of the overall uveitis population) and limited evidence and the uncertain treatment pathway, it is considered that a Technology Appraisal will add value. <u>Remit:</u> Scoping workshop attendees stated that the definition of 'chronic' was uncertain and subject to misinterpretation. ***CONFIDENTIAL INFORMATION REMOVED*** Workshop attendees indicated that dexamethasone and sirolimus could be used at multiple points in the treatment pathway; therefore restricting the remit to 'chronic disease' could potentially exclude relevant patient subgroups. It is proposed that the remit should exclude reference to chronicity. <u>Comparators:</u> Consultees and workshop attendees stated that there is no defined treatment pathway for uveitis and also that normal prescribing practice is unknown. However they considered that most of the comparators in the draft scope were appropriate, but that TNF-alpha inhibitors should be removed as there are no clinical trial data to support their use in uveitis. <u>Process:</u> Some consultees expressed concerns that an MTA may be difficult due to the differences in the treatments, trials and patient groups. However, it was noted that an MTA would be more relevant than an STA, and that recommendations		

	could be tailored to different subgroups. At the decision point 4 meeting, it was agreed that this topic should proceed as an MTA.
Population size	Between 1500 and 5000 people are diagnosed with non-infectious posterior segment uveitis each year in England (based on data from 2010). Only a minority may receive the dexamethasone implant and sirolimus injection as a first line treatment. It is more likely that the technologies will be used later, in about 40% of people whose posterior segment uveitis has not responded to standard systemic treatments.
Process (MTA/STA/HST)	MTA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of dexamethasone intravitreal implant and sirolimus **intravitreal injection** within their marketing authorisations for treating ~~**chronic**~~ non-infectious posterior segment uveitis.
Costing implications of remit change	The annual number of people with non-infectious posterior segment uveitis equates is estimated to be to between 1500 and 5000. The cost of intravitreal sirolimus is unknown. It is intended to be administered by intravitreal injection every 2 months and would offer another treatment option for this patient group. The annual drug cost for treatment with intravitreal dexamethasone implant is £5,220 (6 x implant cost of £870). Annual administration costs (assuming 6 injections per year) are estimated to be around £2,100 based on day case procedures. (£347, Combined day case/ordinary elective spell tariff 2015/16 Minor Vitreous retinal procedures BZ23Z) or around £650 based on outpatient procedures (£107, Outpatient tariff 2015/16 Minor Vitreous retinal procedures BZ23Z).
Timeliness statement	Given that the marketing authorisation has already been received for the dexamethasone intravitreal implant, issuing timely guidance will not be possible. As this topic will progress as a MTA, issuing timely guidance on the use of sirolimus intravitreal injection will also not be possible.

Provisional Title	**Eltrombopag for treating severe aplastic anaemia following insufficient response to immunosuppressive therapy**		
Topic Selection ID Number	7507	**Wave / Round**	R118
TA ID Number	814		
Company	Novartis		
Anticipated licensing information	**CHMP positive opinion received July 23, 2015:** Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation. **Marketing authorisation:** ***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of eltrombopag within its marketing authorisation for treating severe aplastic anaemia following insufficient response to immunosuppressive therapy.		
Main points from consultation	The company stated that it is not appropriate to refer this topic to NICE because of the limited evidence base (phase II, non comparative trials) and very small patient population. However, other consultees indicated that there was high unmet need in this patient population and an appraisal would be useful. At the decision point 4 meeting, it was decided that an appraisal would be valuable and the topic should proceed as an STA. Remit: Workshop attendees agreed that the remit should specify 'very severe aplastic anaemia' in addition to 'severe' disease. This is because the clinical trials included people with severe and very severe anaemia, and the company confirmed that treating very severe disease is expected to be within the marketing authorisation for eltrombopag. However, the wording of the CHMP opinion does not specify 'very severe'; therefore, this change will not be made to the remit. The NICE technical team noted that very severe disease could still be covered within the marketing authorisation, and therefore would be covered by the remit. It was also decided that 'insufficient response to immunosuppressive therapy' stated in the remit should be changed to 'refractory to immunosuppressive therapy, so as not to mistake it for relapsed disease. Attendees noted that all patients in the trial had refractory disease and that in some patients the disease had first relapsed and then became refractory to immunosuppressive therapies. Comparators: Scoping workshop attendees stated that apart from best supportive care, a range of other treatment options are available and should be included in the scope. These		

	include: • Bone marrow transplantation with a matched unrelated donor • Further immunosuppressive therapy including alemtuzumab • Oxymethalone The CHMP positive opinion specifies 'refractory to prior immunosppresive therapy' and 'unsuitable for haematopoietic stem cell transplantation'; therefore immunosuppressive therapies and bone marrow transplant would not be appropriate comparators.
Population size	The incidence of aplastic anaemia in Europe is estimated at 2 cases per 1 million people. The company estimated that about 120 - 180 people in the UK will be eligible for eltrombopag. This is based on the assumption that 84% of patients have severe or very severe disease, the proportion of those patients with disease that is refractory to immunosuppressive therapy; and also taking into account the prevalent population.
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of eltrombopag within its marketing authorisation for treating severe aplastic anaemia **refractory** to immunosuppressive therapy.
Costing implications of remit change	It is estimated there is approximately 2 cases of aplastic anaemia per million population each year. It is unclear how many people would need second line treatment however it is estimated that the eligible population would be 150 people (range 120-180 people) in the first year following launch. This may reduce in subsequent years to around 30 people per year. Eltrombopag is administered daily at 25mg for 2 weeks, increasing by 25mg every 2 weeks to a maximum of 100mg for up to 8 weeks. The current cost of eltrombopag for other indications is £770 per 28 tab pack 25mg and £1,540 per 28 tab pack 50mg, therefore the maximum cost per cycle would be approximately £2,500 per person.
Timeliness statement	Assuming the marketing authorisation is ***CONFIDENTIAL INFORMATION REMOVED*** and the expected referral date of this topic, issuing timely guidance for this technology will not be possible.

Provisional Title	**Methylnaltrexone bromide for treating opioid-induced constipation**		
Topic Selection ID Number	6658	**Wave / Round**	R118
TA ID Number	ID 700		
Manufacturer	TMC Pharma Services Ltd		
Anticipated licensing information	Marketing authorisation: Extended indication granted May 27, 2015. Wording of marketing authorisation: For the treatment of opioid-induced constipation (OIC) when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older.		
Draft remit	To appraise the clinical and cost effectiveness of methylnaltrexone bromide within its marketing authorisation for treating opioid-induced constipation.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of methylnaltrexone bromide for treating opioid-induced constipation is appropriate. The proposed remit is considered appropriate. No changes are required. <u>Population</u> Scoping workshop attendees agreed that the population in the scope should be amended to be in line with marketing authorisation that has now been granted and changed to: Adults with opioid-induced constipation who have not responded sufficiently to laxative therapy. <u>Comparators</u> The attendees agreed that the comparators are appropriate but that oxycodone with naloxone could only be a comparator for adults who are already receiving oxycodone therefore the comparator section has been amended to state this. At the Decision Problem 4 meeting it was agreed that given the marketing authorisation oral laxatives were not an appropriate comparator. <u>Outcomes</u> The attendees agreed that the outcomes defined in the scope were appropriate and clinically relevant. However, they noted that there were additional relevant outcome measures that should be included in the scope. These were: time to first bowel action after intervention (as this was the primary outcome of the clinical trials); use of rescue medication or interventions; and response rate (to be in line with the naloxegol scope). It was also agreed to state after adverse effects of treatment '(for example, pain from reversal of opioid induced analgesia)'.		
Population size	The population with opioid-induced constipation is unknown. The scoping workshop attendees noted that many patients receiving opioids will have opioid-induced constipation. In England in 2010 there were over 17 million prescriptions for opioid items and therefore concluded that the population size is expected to be large. The population likely to be eligible to		

	receive methylnaltrexone bromide could not easily be estimated from available routine published sources.
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	None.
Costing implications of remit change	It is not possible to identify the eligible population from published sources. The cost for average of 4 months treatment with methylnaltrexone is £1,284. In practice, it may be prescribed for a longer period where treatment is successful. As a result the actual cost can vary depending on local practice. Comparator treatments are less expensive – naloxegol (£671.60 annual cost), naloxone-oxycodone (£1,103 annual cost) and bisacodyl (£13 annual cost). It should be noted that the alternative treatments are orally administered, while methylnaltrexone bromide can be administered either orally or via subcutaneous injection, and administration by the latter route could incur additional costs, such as through training people to self-administer, or administration for those incapable of self-administration.
Timeliness statement	Considering that this technology already has a marketing authorisation, issuing timely guidance for this technology will not be possible.

Provisional Title	**Lumacaftor in combination with ivacaftor for treating cystic fibrosis homozygous for the F508del mutation [ID786]**		
Topic Selection ID Number	7259	**Wave / Round**	R99
TA ID Number	786		
Manufacturer	Vertex		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of lumacaftor in combination with ivacaftor within its marketing authorisation for treating cystic fibrosis in people who are homozygous for the F508del mutation.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of lumacaftor in combination with ivacaftor for treating cystic fibrosis homozygous for the F508del mutation is appropriate. The proposed remit is appropriate. No change required. <u>Comparators</u> Scoping workshop attendees agreed that 'oral, nebulised and intravenous antibiotics' should be added to the description of established clinical management. <u>Outcomes</u> Attendees agreed that there were some additional outcome measures that should be added to the scope: • pulmonary exacerbations (are important to patients and are associated with long-term health, survival, quality of life, care costs and hospital admissions); and • need for hospital admissions and other treatments (can significantly affect the quality of life of people with cystic fibrosis, and should be included as an outcome). <u>Additional issues</u> It was stated at the workshop that the patient population is a very active and close-knit community. People with F508del cystic fibrosis are aware of (and supportive of) the developments with ivacaftor for other mutations.). People also highlighted that there is a perception that the commissioning of ivacaftor by NHS England for the 500 people with cystic fibrosis who have the G551D mutation may have set a precedent. Points were also raised with respect to the potential unfairness that different populations within the CF community are treated differently. NHS England explained that they had advised the company that commissioning policy decisions should not be taken as setting precedent for future policy decisions. This condition is a lifelong genetic disease, and attendees at the workshop highlighted that it had many of the features of conditions evaluated through the HST evaluation. Concerns were raised with regard to the emphasis of Technology Appraisals on ICERs and the ICER threshold.		

Population size	Approximately 4000
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	None
Costing implications of remit change	There are approximately 8,400 people with cystic fibrosis in England. Of these around 52% (4,400) have an F508 mutation and would be eligible for treatment with lumacaftor and ivacaftor. Currently there are no therapies available that target the F508del-CFTR mutation. The cost of lumacaftor is not yet 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.

Provisional Title	**Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts**		
Topic Selection ID Number	ID7519	**Wave/Round**	R122
TA ID Number	ID829		
Manufacturer	Celgene		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of azacitidine within its marketing authorisation for treating acute myeloid leukaemia with more than 30% bone marrow blasts and when haematopoietic stem cell transplantation is not suitable.		
Main points from consultation	Remit In line with the entry criteria of the clinical trial the MA is may specify an age cut-off of '65 years or more'. However clinical specialists stated that this age cut-off in the trial design was arbitrary and in clinical practice treatment is based on performance status rather than age. Also considering the equalities legislation, it was agreed that an age restriction does not need to be specified in the remit or the scope but it was noted that NICE guidance is issued in line with the MA. It was noted that the expected MA does not include ineligibility for stem cell transplantation. However, it was an inclusion criteria in trials and is also a specification in the MA for azacitidine for for adults with AML with 20-30% blasts and multi-lineage dysplasia. Clinical specialists stated that treatment decisions depend on performance status and some patients who may be thought of being ineligible for stem cell transplant before chemotherapy may become eligible once the disease is in remission. It was agreed that the remit should be kept broad. Population: the population should be amended to reflect the proposed remit: 'Adults with acute myeloid leukaemia with bone marrow blasts more than 30%' Comparators Decitabine is not a relevant comparator as it is not routinely used in practice, not funded by the Cancer Drugs Fund and its appraisal by NICE was terminated (TA270). Including low dose chemotherapy (hydroxycarbamide, mercaptopurine, etoposide) as part of best supportive care (BSC) is not accurate. . Mercaptopurine and etoposide are not used routinely and instead, intermittent low dose chemotherapy with hydroxycarbamide may be offered as part of BSC. BSC in the scope should be defined as blood product replacement, antibiotics, antifungals and intermittent low dose chemotherapy with hydroxycarbamide.		

	The company suggested a single comparator 'conventional care regimen' defined as a weighted average of intensive chemotherapy, low dose cytarabine and best supportive care, noting this was used in TA218. However, it was noted that the 3 regimens are used differently based on performance status and co-morbidities and it would not be appropriate to include them as a single comparator. It was also noted that in TA218 the Committee noted the significant methodological limitations of this approach. Outcomes: progression-free survival data was not collected in the trials. Instead, event free survival data was collected but stakeholders noted that components of 'event' are not clearly defined and included patients lost to follow-up. However, 'time to disease progression' was a component of the composite outcome 'events' and could be examined separately and should be included in the scope in place of progression-free survival. Subgroups: azacitidine has been shown to be particularly effective in 3 a priori subgroups in the trial - women, people with pre-existing myelodysplastic syndrome, and people with adverse-risk cytogenetics. Attendees agreed that subgroups on the basis of gender cannot be specified in the scope but the other 2 subgroups should be included.
Population size	Around 1900 patients per year
Process (MTA/STA)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of azacitidine within its marketing authorisation for treating acute myeloid leukaemia with more than 30% bone marrow blasts. ~~**and when haematopoietic stem cell transplantation is not suitable.**~~
Costing implications of remit change	Acute myeloid leukaemia affects approximately 2,250 people each year in England. Of these about 1,900 would be aged 65 years or older, and those eligible for treatment under this indication are the subset of this group who have >30% bone marrow blasts. The cost of azacitidine is £4,494 per person per cycle of treatment, with up to 6 cycles per person. Therefore the total annual drug cost is estimated at £26,964. As azacitidine is an additional first line treatment option the costs will be offset by other first-line treatments avoided. One cycle of current alternative treatments cost around £3770 (based on TA218), leading to a likely incremental cost of £720 per cycle. This would be an incremental cost of around £4320 per person across 6 cycles. Where it is used instead of standard chemotherapy treatments, there may be savings on administering the drug due to fewer outpatient attendances.
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 in combination with ofatumumab for chronic lymphocytic leukaemia**		
Topic Selection ID Number	ID7212	**Wave/Round**	R95
TA ID Number	ID817		
Manufacturer	Gilead Sciences		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of idelalisib in combination with ofatumumab within its marketing authorisation for previously treated chronic lymphocytic leukaemia.		
Main points from consultation	<u>Referral</u> Stakeholders suggested that in clinical practice, idelalisib–ofatumumab is unlikely to be prescribed based on current use of ofatumumab and initial trial results show idelalisib in combination with ofatumumab to be less efficacious (and more expensive) than idelalisib in combination with rituximab, which is currently undergoing appraisal. However, it was noted that a small number of people who cannot tolerate rituximab may benefit from a different idelalisib combination. A referral is considered appropriate. <u>Remit:</u> In line with the MA received for the idelalisib–rituximab, the MA may include first-line treatment in patients with 17p deletion or TP53 mutation. The remit should therefore be broadened to allow for this. <u>Population:</u> the population should reflect the broader suggested remit. The scope should therefore also include: 'Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for whom chemo-immunotherapy is not suitable' <u>Comparators</u> The comparators should be updated to reflect the treatment-naïve population in line with the idelalisib–rituximab scope: include bendamustine with or without rituximab, chlorambucil with or without rituximab, ofatumumab in combination with chlorambucil (in line with TA344), obinutuzumab in combination with chlorambucil (in line with TA343), and best supportive care. It was agreed that alemtuzumab should not be included because its MA has been withdrawn and it is not used in practice. For the previously treated population, it was agreed that rituximab monotherapy, ofatumumab monotherapy and high dose corticosteroids with or without rituximab are not routinely used in clinical practice and should not be included in the scope.		

	Subgroups: in addition to a subgroup by the presence or absence of 17p deletion, a subgroup by the presence or absence of TP53 mutation should be added to the scope because testing for the TP53 mutation is increasingly being carried out and a fairly significant number of patients have a genetic abnormality, and ideally these patients should be identified to make the right treatment decisions. It was also noted that recent national guidelines recommend testing for TP53 mutation before each new treatment.
Population size	Previously treated group – 363 eligible patients. About 5–10% of people diagnosed with CLL have 17p deletion or TP53 mutation. Taking an average value of 7.5%, 203 patients are expected to be eligible for treatment in the treatment-naïve patient group with CLL associated with 17p deletion or TP53 mutation. Total eligible population – 566.
Process (MTA/STA)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of idelalisib in combination with ofatumumab within its marketing authorisation for **~~previously treated~~** chronic lymphocytic leukaemia.
Costing implications of remit change	Approximately 2,700 new cases of chronic lymphocytic leukaemia (CLL) were registered in England 2011. Of these approximately 67% (1,800) need treatment, and will either be refractory, or will relapse at some stage. It is estimated that around 570 people will be eligible for treatment with idelalisib in combination with ofatumumab. Current comparator treatments include rituximab, fludarabine and cyclophosphamide (FCR) combination treatment which costs £13,089 per course of treatment. The cost of idelalisib is not yet known. Ofatumumab is already marketed for a different indication and based on that market price; the associated treatment cost per patient, based on 12 intravenous treatments, would be £22,300. Assuming the price of ofatumumab is the same for this indication, additional drug costs of approximately £9,200 would be incurred where it is used instead of FCR before the cost of idelalisib is added. It is not known how many people will switch treatments. Expert opinion suggests there may be an additional cost burden due to the requirement for frequent visits to hospital for the prescription of the drug and it's monitoring.
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.

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Provisional Title	**Aflibercept for treating visual impairment due to macular oedema secondary to branch retinal vein occlusion**		
Topic Selection ID Number	ID7631	**Wave/Round**	R129
TA ID Number	ID844		
Manufacturer	Bayer		
Anticipated licensing information	Marketing Authorisation granted in February 2015 for this licence extension of "treatment of adults with visual impairment due to macular oedema secondary to branch retinal vein occlusion".		
Draft remit	To appraise the clinical and cost effectiveness of aflibercept within its marketing authorisation for treating visual impairment due to macular oedema secondary to branch retinal vein occlusion		
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 visual impairment due to macular oedema secondary to branch retinal vein occlusion is appropriate. The proposed remit is appropriate. No changes required. <u>Comparators</u>: The meeting heard that laser is no longer being used as a first line treatment (except as a rescue treatment) and that in practice, ranibizumab or dexamethasone are being used. Therefore laser photocoagulation should be removed from the scope. Bevacizumab is not as widely used as ranibizumab, but clinical experts confirmed that some centres are using it. It was also acknowledged that it has been included as a comparator in all scopes in this disease area and therefore it should remain a comparator. <u>Subgroups</u>: The relevance of a subgroup based on the presence or absence of ischaemia was questioned, since the levels of ischaemia in BRVO are quite low (approximately 25% of people with BRVO have ischaemia). It was suggested that this subgroup should be removed from the scope.		
Population size	Estimated annual incidence circa 13000		
Process (MTA/STA)	STA		
Proposed changes to remit (in bold)	N/A		
Costing implications of remit change	The estimated number of people potentially eligible to receive aflibercept each year is around 13000. As aflibercept is an additional treatment option the number of people treated will be a subset of this group, and the costs will be offset by savings from other treatments avoided. Aflibercept can avoid future damage to vision in the long-term, and avoids the need for interventional procedures, and so is anticipated to have a large		

	market share for this indication. The annual cost of the drug per person for 9 injections (including intravitreal administration costs) is £8,577.
Timeliness statement	Considering that this technology already has a marketing authorisation, issuing timely guidance for this technology will not be possible.