ITEM 5

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

CENTRE FOR HEALTH TECHNOLOGY EVALUATION
Technology Appraisals

Consultation on Batch 22 draft remits and draft scopes and Summary of comments and discussions at scoping workshops

	Batch 22 topics
5.1	Bortezomib for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation and for consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma
5.2	Canakinumab for the treatment of systemic juvenile idiopathic arthritis
5.3	Mipomersen for the prevention of cardiovascular events due to homozygous and severe heterozygous familial hypercholesterolaemia
5.4	Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome
5.5	Tofacitinib for the treatment of moderate to severe active rheumatoid arthritis
5.6	Zonisamide monotherapy for the treatment of partial onset seizures in epilepsy
5.7	Bendamustine in combination with rituximab for the treatment mantle cell lymphoma *A formal referral recommendation for this topic was deferred from Batch 15*
5.8	Loxapine inhalation for the treatment of acute agitation and disturbed behaviours associated with schizophrenia or bipolar disorder *A formal referral recommendation for this topic was deferred from Batch 19*

Provisional Title	Bortezomib for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation and for consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma
Topic Selection ID Number	5435
Wave	R15
Anticipated licensing information	*Confidential*
Draft remit	To appraise the clinical and cost effectiveness of bortezomib as induction treatment for people with newly diagnosed multiple myeloma and as consolidation therapy after autologous stem cell transplantation for people with multiple myeloma.
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of the clinical and cost effectiveness of bortezomib as induction treatment for people with newly diagnosed multiple myeloma and as consolidation therapy after autologous stem cell transplantation for people with multiple myeloma is appropriate. The manufacturer confirmed that they will be initially seeking a marketing authorisation for the induction regimen. A regulatory submission for the consolidation indication will be submitted at a later date (date still to be determined). In light of these regulatory timings, the proposed remit is not appropriate. It is recommended that the remit is split into two and the wording amended as follows: a) To appraise the clinical and cost effectiveness of bortezomib within its licensed indication for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation for the treatment of multiple myeloma. b) To appraise the clinical and cost effectiveness of bortezomib within its licensed indication for consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma.
Process (MTA/STA)	Two separate STAs (one for each indication) to allow appraisal timings to be aligned with regulatory schedule for each indication.
Proposed changes to remit (in bold)	Induction and consolidation indications should have separate remits as follows: a) To appraise the clinical and cost effectiveness of bortezomib within its licensed indication for induction therapy **prior to high dose chemotherapy and autologous stem cell transplantation** for the treatment of multiple myeloma. b) To appraise the clinical and cost effectiveness of bortezomib within its licensed indication for consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma.
Costing	The change in remit defines two separate scenarios; one for

implications of remit change	induction and one for consolidation. The two scenarios are now treated separately for cost impacts. <u>Induction Therapy</u> 4026 new cases of multiple myeloma were registered in England in 2009. Of these, approximately 1600 patients are eligible for high dose therapy (HDT) and autologous stem cell transplant (ASCT) including patients between the ages of 65-70 who are considered on an individual basis. Patients suitable for HDT and ASCT would receive induction therapy. The briefing note states that the cost of bortezomib for this indication has not yet been determined nor has the number of cycles and doses for induction treatment. However, assuming the drug cost is the same as for other licensed indications and that it is given as 3, 21 day cycles as the trial data in the briefing note, the cost impact could be around £15million. This topic has potential to be 'high cost'. <u>Consolidation Therapy</u> 4026 new cases of multiple myeloma were registered in England in 2009. Of these, approximately 1600 patients are eligible for high dose therapy (HDT) and autologous stem cell transplant (ASCT) including patients between the ages of 65-70 who are considered on an individual basis. Patients suitable for HDT and ASCT may also receive induction therapy and it is assumed that all would be eligible for consolidation treatment. The briefing note states that the cost of bortezomib for this indication has not yet been determined however it states that the manufacturer estimates the consolidation treatment to cost around £12,000 per patient. This suggests the cost will be the same as for other licensed indications. Assuming the cost per patient to be as stated, the cost impact could be around £20million. This topic has potential to be 'high cost'.
Timeliness statement	Assuming that the anticipated date of the marketing authorisation for the induction therapy indication 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. If NICE are given appropriate notice of the anticipated date of the marketing authorisation for the consolidation therapy indication, issuing timely guidance will be possible.

Provisional Title	Canakinumab for the treatment of systemic juvenile idiopathic arthritis
Topic Selection ID Number	4832
Wave	26
Anticipated licensing information	*Confidential*
Draft remit	To appraise the clinical and cost effectiveness of canakinumab within its licensed indication for the treatment of systemic juvenile idiopathic arthritis.
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of canakinumab for the treatment of systemic juvenile idiopathic arthritis is appropriate. There are approximately 800 people aged up to 19 years with systemic juvenile idiopathic arthritis (sJIA) in the UK. Consultees considered an appraisal of canakinumab for the treatment of systemic juvenile idiopathic arthritis (sJIA) to be worthwhile given the increasing importance of biologic therapy in the management of this condition. This appraisal will consider patients with sJIA aged 2 years and older. Consultees emphasised that an upper age limit should not be imposed, to ensure that the population is in line with the anticipated marketing authorisation. No changes to the draft remit are proposed.
Process (MTA/STA)	STA
Proposed changes to remit (in bold)	None
Costing implications of remit change	No change to 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	Mipomersen for the prevention of cardiovascular events due to homozygous and severe heterozygous familial hypercholesterolaemia
Topic Selection ID Number	5197
Wave	28
Anticipated licensing information	*Confidential*
Draft remit	To appraise the clinical and cost effectiveness of mipomersen, within its licensed indication for the prevention of cardiovascular events in people with homozygous or severe heterozygous familial hypercholesterolemia.
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of mipomersen for the prevention of cardiovascular events due to homozygous and severe heterozygous familial hypercholesterolaemia is appropriate. The manufacturer considers that mipomersen should be considered by the Advisory Group on National Specialized Service (AGNSS) and therefore the topic should not be referred to NICE. The NICE topic selection team contacted AGNSS prior to the scope consultation and were advised that because the technology will be used for a subpopulation of hypercholesterolaemia, it did not meet AGNSS's criteria for inclusion in their work programme and therefore they would not be considering it. During the scoping workshop, the manufacturer disagreed that mipomersen does not meet AGNSS's criteria. The attendees considered that mipomersen would only be used for patients with severe He-FH and Ho-FH, which constitutes between 300 - 500 patients across England and Wales. It was noted that this number would reflect the population who are currently receiving (or need) LDL apheresis. The company, however, has estimated the prevalence of severe HeFH to be 1 in 15,000 of the UK population (calculated by NHSC as approximately 3,650 patients in England and Wales). Consultees highlighted the difficulties that many patients experience when trying to access LDL apheresis in England and Wales. They considered that an appraisal of mipomersen may improve patient access to treatment and reduce the postcode lottery problems currently impacting on this population. The Institute considers it only appropriate to appraise mipomersen if the final marketing authorisation includes patients with severe heterozygous familial hypercholesterolaemia.
Process (MTA/STA)	STA.

Proposed changes to remit (in bold)	None
Costing implications of remit change	No change to 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	Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome
Topic Selection ID Number	5452
Wave	R15
Anticipated licensing information	*Confidential*
Draft remit	To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment of acute coronary syndrome.
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of rivaroxaban for the treatment of acute coronary syndrome is appropriate. During consultation the manufacturer indicated that the proposed remit is not in line with the expected license for rivaroxaban. The anticipated indication will be for secondary prevention, rather than acute treatment of ACS. It was suggested that the remit should not be limited to the prevention of atherothrombotic events but should include the prevention of all possible adverse outcomes associated with ACS. It was also suggested that the remit should clarify that rivaroxaban is to be used after the acute management of ACS (that is, for patients who have been stabilised using initial management strategies, including possible revascularisation, after hospital admission for ACS). In light of comments received during consultation, the proposed remit should be changed to: “to appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome”. Similarly, the title of the appraisal and scope should be changed to: “Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome”.
Process (MTA/STA)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the **prevention of adverse outcomes in patients after the acute management** of acute coronary syndrome.

Costing implications of remit change	The change in remit now indicates that this technology is to be used after the acute management of an acute coronary syndrome. This is potentially a small change to the population considered in the original costing comments. The estimated annual number of people who require treatment for acute coronary syndromes is around 240,000 people. The drug is to be used as an add-on therapy to existing treatments after the acute management. It is not known what proportion of people will be eligible for the treatment after their acute phase of treatment therefore it is considered that it may be up to 240,000 people per year. The cost of rivaroxaban for this indication is unknown. The cost range provided by the manufacturer is £100 - £1000 per patient per year; the mid-point cost is £550. A comparator treatment costs around £460 per patient per year. There may be reduced outpatient attendances or other adverse events as the therapy does not require dose adjustment or routine coagulation monitoring. This topic has cost pressure associated with it although it has potential to be low incremental 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	Tofacitinib for the treatment of moderate to severe active rheumatoid arthritis
Topic Selection ID Number	4692
Wave	27
Anticipated licensing information	*Confidential*
Draft remit	To appraise the clinical and cost effectiveness of tofacitinib within its licensed indication for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs.
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of tofacitinib for the treatment of moderate to severe active rheumatoid arthritis is appropriate. It is suggested that the remit is changed to: To appraise the clinical and cost effectiveness of tofacitinib within its licensed indication for the treatment of rheumatoid arthritis after the failure of disease modifying anti-rheumatic drugs. [It is anticipated that the marketing authorisation will not restrict the use to after conventional DMARDs, and therefore use after failure of biological DMARDs is also expected]. The population and comparators will also need to be amended to reflect the possible use of tofacitinib after conventional DMARDs and after biological DMARDs **Population 1**: Adults with moderate to severe active rheumatoid arthritis whose disease has had an inadequate response to, or who are intolerant to, conventional non-biological DMARDs only: **Comparators for population 1**: Management strategies involving DMARDs without tofacitinib including: – Biological DMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab) – Conventional non-biological DMARDs (for example sulfasalazine, leflunomide) **Population 2**: Adults with moderate to severe active rheumatoid arthritis whose disease has had an inadequate response to, or who are intolerant to, conventional non-biological DMARDs and biological DMARDs: **Comparators for population 2**: Management strategies involving DMARDs without tofacitinib including: – Biological DMARDs (rituximab, adalimumab, etanercept, infliximab, golimumab, abatacept, tocilizumab) – Conventional non-biological DMARDs (for example sulfasalazine, leflunomide) Consultees highlighted the advantage of appraising all treatments for rheumatoid arthritis in one appraisal. It was

	noted that a review of TA186 (Certolizumab pegol for the treatment of rheumatoid arthritis), TA130 (Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis) and TA225 (Golimumab for the treatment of rheumatoid arthritis after the failure of disease modifying anti-rheumatic drugs) has been scheduled in the work programme and will begin in August 2012. It was noted that this review will only consider treatments directly after the failure of conventional DMARDs, and therefore would only cover part of the anticipated marketing authorisation for tofacitinib (that is, would not consider tofacitinib after failure of biological DMARDs), if this topic was also included in the review. In addition, including tofacitinib within the review would not provide the opportunity to issue timely guidance; therefore it was considered that an STA would be the most appropriate process to consider this topic.
Process (MTA/STA)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of tofacitinib within its licensed indication for the treatment of rheumatoid arthritis after the failure of ~~**conventional**~~ disease modifying anti-rheumatic drugs.
Costing implications of remit change	The change in remit now indicates that this technology is to be used after the failure of both biologics and conventional non-biologic drugs. This is potentially a change to the population considered in the original costing comments. Tofacitinib is intended as a second line treatment after the failure of DMARDs (biological and conventional non-biological) for patients with moderate to severe disease. The number of people with moderate to severe disease is 35,000 patients. The eligible population will be a subset for whom DMARDs (biological and conventional non-biological) have failed. At present the cost is unknown. However, there may be offsetting costs where patients switch from other therapies, typically pharmacological. Despite the unknowns, this topic is considered to be low 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	Zonisamide monotherapy for the treatment of partial onset seizures in epilepsy
Topic Selection ID Number	5454
Wave	R15
Anticipated licensing information	*Confidential*
Draft remit	To appraise the clinical and cost effectiveness of zonisamide monotherapy within its licensed indication for the treatment of partial onset seizures in epilepsy.
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of zonisamide monotherapy for the treatment of partial onset seizures in epilepsy is not appropriate. Two consultees provided written comments in response to the scope consultation (manufacturer and a patient group). The patient group considered that an appraisal should be undertaken to ensure that patients have access to zonisamide monotherapy. The manufacturer and clinical experts present at the workshop commented that referring this topic to NICE for appraisal would not represent an effective use of NICE resources as there are many well established, generic drugs available as monotherapies for the treatment of partial onset seizures and the number of patients who would be treated with zonisamide monotherapy would be very low. Clinicians considered that most people on monotherapy will respond to one of the five drugs recommended in the NICE clinical guideline, and in accordance with the guideline people only try two of the five drugs before moving to adjunctive treatment (people are not therefore cycling through lots of different monotherapies). In addition, clinicians commented that the evidence for the use of zonisamide as monotherapy was considered poor, and insufficient to appraise it adequately or to support its use as a monotherapy in routine clinical practice. Clinicians noted that there were other epilepsy drugs with monotherapy licences, which were not used in clinical practice. Therefore, even if zonisamide gains a licence as monotherapy, it would not necessarily be used in clinical practice. In general, there is a strong view that an appraisal would not add value to the NHS.
Process (MTA/STA)	N/A – referral not sought
Proposed changes to remit (in bold)	N/A – referral not sought
Costing implications of	N/A – referral not sought

remit change	
Timeliness statement	N/A – referral not sought

Provisional Title	Bendamustine in combination with rituximab for the first line treatment of mantle cell lymphoma
Topic Selection ID Number	4900
Wave	Deferred from Batch 15, Wave 26
Anticipated licensing information	*Confidential*
Draft remit	N/A
Main points from consultation	As part of Batch 15, NICE scoped the proposed topic; Bendamustine in combination with rituximab for the first-line treatment of low-grade non-Hodgkin's lymphoma. This was subsequently formally referred onto the appraisal work programme (STA is due to commence late 2012). . During the scoping phase, the manufacturer confirmed that the indication was expected to include mantle cell lymphoma in addition to advanced indolent non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma and mantle cell lymphoma have different clinical courses and comparators. Therefore it was recommended that these conditions are considered as separate appraisals. At the time of the Batch 15 DP4 meeting, it was agreed that the decision to refer an appraisal for mantle cell lymphoma was to be deferred while further clarification on the specific intention of the marketing authorisation is requested from the manufacturer. Following this, the TA Planning and Operations team have been liaising with the manufacturer. The manufacturer has confirmed that a submission was presented to the regulatory body in late February 2012 with the anticipated MA wording of: *Confidential* Referral for the following additional remit should now be sought: 'To appraise the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indicated for the first-line treatment of mantle cell lymphoma'. Approximately 5% of people diagnosed with NHL have mantle cell lymphoma, which equates to approximately ~530 patients in England and Wales (based on 2008 statistics).
Process (MTA/STA)	STA
Proposed changes to remit (in bold)	**To appraise the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indicated for the first-line treatment of mantle cell lymphoma**.
Costing implications of remit change	Given the small number of patients affected by the disease (~500 people per year), this topic is unlikely to be high cost unless the drug incremental cost per patient is more than

	£30,000 per person and assuming that all patients switch to the new technology.
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	Loxapine inhalation for treatment of acute agitation and disturbed behaviours in people with schizophrenia or bipolar disorder
Topic Selection ID Number	4940
Wave	Deferred from Batch 19, Wave 27
Anticipated licensing information	*Confidential* In October 2011, the Company established a commercial partnership for loxapine with Grupo Ferrer International.
Draft remit	To appraise the clinical and cost effectiveness of loxapine inhalation within its licensed indication for the treatment of acute agitation in people with schizophrenia or bipolar disorder.
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of loxapine inhalation for the treatment of acute agitation and disturbed behaviours associated with schizophrenia or bipolar disorder is appropriate. The proposed remit is not appropriate and should be amended in line with the anticipated wording of the marketing authorisation "for the treatment of acute agitation and disturbed behaviours in people with schizophrenia or bipolar disorder". The proposed change to the remit is not expected to significantly affect the population size. Consultees considered that an appraisal of loxapine inhalation will be challenging as there is very little evidence available. However, they acknowledged that an STA would offer the timeliest guidance. Correspondence received from a clinical psychiatrist and two former members of the Mental Health Consideration panel after the scoping workshop confirms that they consider that a technology appraisal of loxapine would be the most suitable approach to ensuring that loxapine is not used for unsuitable groups (such as agitated patients with dementia or delirium, adults with learning difficulties or children and adolescents with behavioural disturbances). In addition, they expressed concerns that the novel route of administration may make loxapine more attractive to prescribers, leading to a potential risk of prescribing creep, and the drug being used outside its evidence base for agitation not related to psychosis. Therefore, a technology appraisal (rather than including loxapine in an update of NICE clinical guideline 25 on the short-term management of disturbed/violent behaviour) would help address this.
Process (MTA/STA)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of loxapine inhalation for the treatment of acute agitation **and disturbed behaviours** in people with schizophrenia or bipolar disorder.

Costing implications of remit change	Loxapine inhalation is to be used to treat agitation associated with schizophrenia and bipolar disorder. The medication is taken via a breath actuated hand held inhaler acts as a tranquiliser. The potential population for the treatment is around 185,000 patients, although it is uncertain how many patients will have an episode of agitation or how often it will occur. The cost of the drug is not yet known. It is to be used as a substitute for current therapies. There may therefore be offsetting cost opportunities from other drugs avoided.
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.