NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CENTRE FOR HEALTH TECHNOLOGY EVALUATION
Technology Appraisals

Consultation on Batch 44b draft remits and draft scopes and summary of comments and discussions at scoping workshops

ID	Topic
842	Grazoprevir–elbasvir for treating chronic hepatitis C
777	Ofatumumab in combination with chemotherapy for treating relapsed chronic lymphocytic leukaemia
863	Pegaspargase for treating acute lymphoblastic leukaemia
870	Eluxadoline for treating irritable bowel syndrome with diarrhoea
872	Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids
857	Lutetium-177 for treating unresectable, somatostatin receptor-positive gastroentero-pancreatic neuroendocrine tumours
778	Nanoliposomal irinotecan for treating pancreatic cancer after prior treatment with gemcitabine

Provisional Title	**Grazoprevir–elbasvir for treating chronic hepatitis C**		
Topic Selection ID Number	7414	**Wave / Round**	R113
TA ID Number	842		
Manufacturer	Merck Sharp & Dohme		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of grazoprevir–elbasvir within its marketing authorisation for treating chronic hepatitis C.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of grazoprevir–elbasvir for treating chronic hepatitis C is appropriate. The proposed remit is appropriate.. No changes to the scopes were requested by stakeholders and no issues for change were raised at the scoping workshop		
Population size	Potentially over 100,000 people in England may be eligible for treatment with grazoprevir–elbasvir. The true prevalence of HCV infection is difficult to establish and likely to be underestimated because many people do not have symptoms. More than half of people with chronic hepatitis C are unaware of their infection. There are 6 major genotypes and several subtypes of HCV; the prevalence of each varies geographically. Recent estimates (2012) suggest that around 160,000 people are chronically infected with HCV in England, and that approximately 90% of these people are infected with genotype 1 or genotype 3.		
Process (MTA/STA/HST)	STA		
Proposed changes to remit (in bold)	None		
Costing implications of remit change	Grazoprevir–elbasvir is a fixed-dose combination tablet (FDT) and is intended to be used alone or as part of a combination antiviral treatment regimen for chronic HCV infection (genotypes 1, 3, 4, and 6) in treatment naïve patients or those with prior treatment failure. Around 167,000 people in England have chronic hepatitis C, of whom an estimated 50% (87,000) have been diagnosed, of which around 25,000 are under care. 94% have genotypes 1, 3, 4 or 6. Therefore it is anticipated that around 23,500 people may be eligible for grazoprevir–elbasvir. There are a number of established treatment options for this population, so the uptake for this FDT is uncertain, but depending on the price there may be costs or savings where it is used in place of an alternative treatment. It is a self-administered oral drug so there is potential for administration savings as well. The cost of alternative treatment options varies. The 12 weekly cost of common first-line treatment peginterferon alfa-2a is around £1,500, but some treatment options can be up		

	to £70,000. As there are a number of treatment options available and the number of people who would switch treatments to FDT 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	**Ofatumumab in combination with chemotherapy for treating relapsed chronic lymphocytic leukaemia**		
Topic Selection ID Number	7134	**Wave / Round**	R88
TA ID Number	777		
Manufacturer	Novartis		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of ofatumumab within its marketing authorisation in combination with chemotherapy 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 ofatumumab in combination with chemotherapy for treating relapsed chronic lymphocytic leukaemia is appropriate. The proposed remit is appropriate. No changes are required. However the company has indicated that if this appraisal is referred they will not make a submission (no reason given). If referred the following changes are suggested: <u>Population</u> The intervention should be changed to ofatumumab in combination with fludarabine and cyclophosphamide because this is in line with the pivotal trial. <u>Comparators</u> The list of comparators should be amended to remove bendamustine with or without rituximab (as bendamustine is no longer funded via the CDF) and rituximab monotherapy (as it is not used in clinical practice in England). <u>Subgroup</u> Include people with a 17p deletion and/ or TP53 mutation.		
Population size	Approximately 1809 people in England (67% of the 2700 incident cases of CLL that need treatment) would be eligible for treatment with ofatumumab in combination with fludarabine and cyclophosphamide.		
Process (MTA/STA/HST)	STA		
Proposed changes to remit (in bold)	None		
Costing implications of remit change	There are approximately 2,300 people diagnosed with chronic lymphocytic leukaemia (CLL) each year in England. Of these approximately 67% (1,500) need treatment, and either don't respond, or relapse. Current comparator treatments include rituximab which costs £9,954 per course of 6 cycles. While the		

	cost of ofatumumab for this indication is not yet known, for other current indication the cost is £11,466 for 6 cycles. Assuming the cost of ofatumumab is the same as for the current indication, additional drug costs of £1,500 would be incurred where it is used instead of rituximab. Expert opinion suggests it would also be likely to increase the costs associated with treating adverse events. It is not known how many will switch.
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	**Pegaspargase for treating acute lymphoblastic leukaemia**		
Topic Selection ID Number	7704	**Wave / Round**	R135
TA ID Number	863		
Manufacturer	Baxalta		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of pegaspargase within its marketing authorisation for treating acute lymphoblastic leukaemia.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of pegaspargase for treating acute lymphoblastic leukaemia is appropriate. Clinical experts at the workshop who were involved in the key trials noted that pegaspargase (polyethylene glycol conjugate of Escherichia coli derived l- asparaginase), though unlicensed, had been an essential component of the established clinical management for ALL in the UK for more than a decade. It is an essential component of almost all multi agent chemotherapy regimens used in induction and consolidation phase of the treatment. The workshop attendees agreed that a NICE appraisal of pegaspargase may not be appropriate. Although pegaspargase has been used outside of its marketing authorisation for a decade, considering that it is a cancer medicine, an appraisal of the clinical and cost effectiveness of treatment is still of value to the NHS therefore the Institute is of the opinion that an appraisal is appropriate. The proposed remit is appropriate. No changes are required. No further points were raised during consultation.		
Population size	Approximately 500-550 people in England would be eligible for treatment with pegaspargase. This estimate is based on 536 people being diagnosed in England in 2011, almost all of whom are eligible for this treatment.		
Process (MTA/STA/HST)	STA		
Proposed changes to remit (in bold)	None		
Costing implications of remit change	529 people were diagnosed with acute lymphoblastic leukaemia (ALL) in England during 2012. The proportion of people that would be eligible for treatment with pegaspargase each year is not known but it is anticipated that almost all people diagnosed with ALL would be eligible. Pegaspargase is not currently licensed in the UK for the treatment of ALL and cost information is not available. It would represent an additional treatment option and therefore it is anticipated that there would be savings from treatments avoided.		
Timeliness	Assuming that the anticipated date of the marketing		

statement	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	**Eluxadoline for treating irritable bowel syndrome with diarrhoea**		
Topic Selection ID Number	7521	**Wave / Round**	R122
TA ID Number	870		
Manufacturer	Furiex Pharmaceuticals, a subsidiary of Actavis plc		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of eluxadoline within its marketing authorisation for treating irritable bowel syndrome with diarrhoea (IBS-D)		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of eluxadoline for treating IBS-D is appropriate. The proposed remit is appropriate. No changes are required. <u>Population</u> The population was changed to include people with IBS-D "when response to non-pharmacological interventions (such as dietary and lifestyle advice) are inadequate" because this was the population most likely to be treated with eluxadoline. <u>Comparators</u> There was a difference in opinion in the place of eluxadoline in the treatment pathway. The company thought it would be used as an extra step after inadequate response to antispasmodic and antimotility agents and before referral to secondary care for further investigations. The clinical experts considered that it would be used mainly in secondary care after further investigations (to rule out other conditions) alongside tricyclic antidepressants. They also noted that SSRI's are rarely used for the treatment of IBS-D. The relevant comparators may be different depending on whether eluxadoline is used in primary or secondary care. The comparators in the scope have therefore been kept broad to include antispasmodic and antimotility agents and tricyclic antidepressants. <u>Outcomes</u> Faecal incontinence and the composite response of daily pain and stool consistency (used in the trials) have been added to the scope.		
Population size	The incidence of IBS in England in over 15 year olds is 11% (4.84 million). Of these 30% (1.45 million) will have IBS-D and it is estimated that 50% people (725,720) with IBS-D will seek treatment and be diagnosed with IBS-D. The clinical expert at the workshop advised that the majority of IBS-D will be resolved with dietary control (FODMAP diet) and approximately 10-15% (72,000 to 109,000) of people who have inadequate response to pharmacological (antispasmodic or antimotility) agents would be eligible for treatment with		

	eluxadoline.
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	None
Costing implications of remit change	The cost of the drug is unknown. Eluxadoline is intended for use as a first-line treatment option and is administered orally. The cost of a comparator treatment is £1.74 or £2.15 for a 30 tab pack. Eluxadoline represents an additional treatment option and therefore the costs of current treatment would at least partially offset the 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	**Reslizumab for treating asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids**		
Topic Selection ID Number	7717	**Wave / Round**	R138
TA ID Number	872		
Manufacturer	Teva Pharmaceuticals		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of reslizumab within its marketing authorisation for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of reslizumab for treating eosinophilic asthma inadequately controlled by inhaled corticosteroids is appropriate. Remit The proposed remit is not appropriate and should be amended as follows 'To appraise the clinical and cost effectiveness of reslizumab within its marketing authorisation for treating asthma with **elevated blood eosinophils** inadequately controlled by inhaled corticosteroids' in line with the expected wording of the marketing authorisation. The company also noted that the wording 'asthma with elevated eosinophils' is more appropriate because 'eosinophilic asthma' is not a disease or condition itself and thus, it might be a confusing term. Population The population has been amended to '**adults** with asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids' because the expected MA will be restricted to adults and there is limited data in the 12-18 year age group. Comparators The consultees noted an overlap between the populations with severe allergic asthma (omalizumab) and asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids, but that the extent of this is uncertain.		
Population size	The difficult asthma registry states that around 5.4 million people are treated for asthma and approximately 5-10% of would have difficult to treat asthma which would equate to **270,000 – 540,000** people. The scoping workshop report for mepolizumab for treating severe eosinophilic asthma states that "severe difficult to control asthma has an estimated prevalence of 140 patients/million population. In England with a population of 53.9 million approximately **7546** people with severe difficult to control asthma.		
Process (MTA/STA/HST)	STA		

Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of reslizumab within its marketing authorisation for treating ~~eosinophilic~~ asthma **with elevated blood eosinophils** inadequately controlled by inhaled corticosteroids.
Costing implications of remit change	Reslizumab is administered by intravenous infusion (IV) and requires 13 doses over a year. Drug administration costs for a year are estimated to be £1,400 (2015/16 Tariff - Outpatient procedures for respiratory medicine). It is anticipated that people are likely to have to attend specialist treatment centres for IV administration, and that additional staff training may be required. There may be savings from decreased use of emergency services if the drug is effective. The cost of a non-elective hospital spell for asthma ranges from £573 to £3,062 (2015/16 Tariff) depending on the level of treatment needed.
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	Lutetium-177 for treating unresectable, somatostatin receptor-positive gastroentero-pancreatic neuroendocrine tumours		
Topic Selection ID Number	7277	**Wave / Round**	R104
TA ID Number	857		
Manufacturer	Advanced Accelerator Applications (Imaging Equipment)		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED*** Lutetium-177 DOTATATE was removed from the CDF on the 4th November. It was on the CDF for : • Advanced pancreatic NETs, progressed or symptoms not controlled, despite or not suitable for other systemic therapy • Other advanced NETs, progressed or symptoms not controlled following prior somastatin analogue		
Draft remit	To appraise the clinical and cost effectiveness of lutetium-177 within its marketing authorisation for treating unresectable, somatostatin receptor-positive gastroentero-pancreatic neuroendocrine tumours.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of lutetium-177 DOTATATE for treating somatostatin receptor positive gastroentero-pancreatic neuroendocrine tumours is <u>appropriate.</u> The proposed remit is not appropriate and should be amended. The description of lutetium177 is incorrect as lutetium-177 is not itself a radiolabelled analogue of somatostatin. It should be referred to as lutetium-177 DOTATATE. Attendees at the scoping workshop agreed that the population specified in the PICO table in the draft scope was not appropriate. They agreed that the population should be broadened to include people 'with disease progression' (that is the population should include people with or without disease progression), thereby making the population in the scope consistent with the population covered by the remit. The rationale for broadening the population in the PICO table was as follows • The main clinical trial supporting the registration of lutetium-177 DOTATATE, the NETTER study, included only patients with midgut NETs who mainly had progressed disease. A phase I/II trial, which included patients with gastrointestinal or pancreatic NETs (both with or without disease progression), was also being included in the marketing authorisation application and therefore will potentially allow a broader indication, albeit with limited data for the population with pancreatic NETs or 'without progressed disease'. • Attendees agreed that based on the proposed marketing authorisation for lutetium-117 DOTATATE and the clinical evidence on which it will be based, it could be used as a treatment option for pancreatic NETS (both non-progressed and progressed) and gastroentero NETs (both non-progressed and progressed). However, they acknowledged that it would most likely be used as a treatment option for		

	people with progressed gastroentero NETs as it was in this population where there was the most unmet need and the most evidence on the clinical effectiveness of lutetium-177 DOTATATE (that is from the NETTER-1 trial). Attendees at the scoping workshop agreed that an appraisal of lutetium-177 DOTATATE for people with gastroentero-pancreatic NETs with or without disease progression should proceed through the STA process. *At the Decision Point 4 meeting, attendees agreed that a remit should be sought for an STA of lutetium-177 DOTATATE for unresectable, somatostatin receptor-positive gastroentero-pancreatic neuroendocrine tumours without disease progression. Attendees also confirmed the decision made at the DP4 meeting for Batch 43 (23 September 2015), that lutetium-177 DOTATATE should be included in the MTA for unresectable or metastatic neuroendocrine tumours with disease progression along with everolimus, lanreotide and sunitinib.*
Population size	Approximately 2000 people in England would be eligible for treatment with lutetium-177 DOTATATE. The clinicians at the scoping workshop stated that incidence was 3 to 3.5 per 100,000 people per year for gastrointestinal NETs, and 0.7 per 100,000 for pancreatic NETs. Based on an England population of 53,000,000, the number of people with gastrointestinal NETs would be between 1590 and 1855, and approximately 370 people with pancreatic NETs. There was no further information on the breakdown of people with progressed and non-progressed disease. The clinical experts at the scoping workshop stated that since many NETs are slow-growing or of uncertain malignant potential, with even malignant NETs associated with prolonged survival, the prevalence of NETs is relatively high. The clinical experts estimated that median survival is about 5 years for pancreatic NETs and 6 years for gastrointestinal NETS, meaning that prevalence of gastrointestinal NETs is much higher (approximately 3 times more than for pancreatic NETs).
Process (MTA/STA/HST)	STA
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of lutetium-177 **DOTATATE** within its marketing authorisation for treating unresectable, somatostatin receptor-positive gastroentero-pancreatic neuroendocrine tumours **without disease progression.**
Costing implications of remit change	The number of people eligible to receive treatment with lutetium-177 DOTATATE cannot be estimated with certainty but may be around 2,000, depending on the number of people with inoperable tumours. The cost of the drug is expected to be around £12,000 per administration with up to 4 administrations

	per person (total cost of up to £48,000 per person). There would also be tariff costs for administration of IV chemotherapy. The cost of treatment would represent additional costs to the NHS. NHS England is the commissioner for this topic.
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	Nanoliposomal irinotecan for treating pancreatic cancer after prior treatment with gemcitabine		
Topic Selection ID Number	6509	**Wave / Round**	R53
TA ID Number	778		
Manufacturer	Baxalta		
Anticipated licensing information	***CONFIDENTIAL INFORMATION REMOVED***		
Draft remit	To appraise the clinical and cost effectiveness of nanoliposomal irinotecan within its marketing authorisation for treating pancreatic cancer after prior treatment with gemcitabine.		
Main points from consultation	Following the consultation exercise and a teleconference with consultees, the Institute is of the opinion that an appraisal of nanoliposomal irinotecan for treating metastatic adenocarcinoma of the pancreas therapy is appropriate. However, consultees requested that the remit be amended to include people who have received gemcitabine in combination with other therapies, not only those who have received gemcitabine monotherapy. It was also suggested that the remit should specify metastatic adenocarcinoma, in line with the expected marketing authorisation. Consultees were keen for NICE to appraise this technology in view of the lack of existing treatment options for this patient group. Consultees did not think it appropriate to compare this technology with irinotecan. Irinotecan monotherapy is not used for treating this disease at this position in the pathway. All consultees were in agreement that the treatments that are in routine use in clinical practice are oxaliplatin in combination with either fluorouracil or capecitabine, or a fluoropyrimidine alone. The comparators in the scope have been changed accordingly.		
Population size	Approximately 1300 people in England would be eligible for treatment with nanoliposomal irinotecan. This estimate is based on a prevalent population of around 8000, of whom 90% will have unresectable disease at diagnosis. Of these, 60% will have metastatic adenocarcinoma. Of these, 60% will receive gemcitabine based therapy as their initial chemotherapy. On progression of disease, around 50% will be considered for further chemotherapy.		
Process (MTA/STA/HST)	STA		
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of nanoliposomal irinotecan within its marketing authorisation for treating ~~pancreatic cancer~~ **metastatic adenocarcinoma of the pancreas** after prior treatment with gemcitabine**-based treatments**.		
Costing	Approximately 1300 people in England would be eligible for		

implications of remit change	treatment with nanoliposomal irinotecan. This estimate is based on a prevalent population of around 8000, of whom 90% will have unresectable disease at diagnosis. Of these, 60% will have metastatic adenocarcinoma. Of these, 60% will receive gemcitabine based therapy as their initial chemotherapy. On progression of disease, around 50% will be considered for further chemotherapy. The cost of nanolipsomal irinotecan is currently unknown. It will provide an alternative treatment option for this patient group and so there will be offsetting savings from current treatments avoided. Although the number that would switch to this treatment option is unknown.
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.