NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CENTRE FOR HEALTH TECHNOLOGY EVALUATION
Technology Appraisals

Consultation on Batch 30 and Batch 31 draft remits and draft scopes and summary of comments and discussions at scoping workshops

	Batch 30
5.1	Paclitaxel as albumin-bound nanoparticles for the first-line treatment of metastatic melanoma
	Batch 31
5.2	ChondroCelect for repairing articular cartilage defects
5.3	Empagliflozin combination therapy for treating type 2 diabetes
5.4	Everolimus in combination with trastuzumab and vinorelbine for treating locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane
5.5	Nalmefene for reducing alcohol consumption in people with alcohol dependence
5.6	Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia
5.7	Pazopanib for maintenance treatment of epithelial ovarian, fallopian and peritoneal cancer
5.8	Sofosbuvir for treating chronic hepatitis C
5.9	Tolvaptan for treating autosomal dominant polycystic kidney disease

Provisional Title	Paclitaxel as albumin-bound nanoparticles for the first-line treatment of metastatic melanoma		
Topic Selection ID Number	5962	**Wave / Round**	R23
TA ID Number	570		
Manufacturer	Celgene		
Anticipated licensing information	*****Confidential information removed*****		
Draft remit	To appraise the clinical and cost effectiveness of nanoparticle albumin bound paclitaxel within its licensed indication for the first-line treatment of metastatic malignant melanoma.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of paclitaxel as albumin-bound nanoparticles for the first-line treatment of metastatic melanoma is appropriate. The Institute recommends that the proposed remit is not appropriate. The scoping workshop attendees stated that the terms metastatic and malignant are equivalent and that the term 'malignant' could be removed from the remit and scope. The wording of the technology name should also be updated to reflect the name specified in the BNF 'paclitaxel as albumin-bound nanoparticles'. The use of some treatments in metastatic melanoma is dependent on BRAF mutation status. Paclitaxel as albumin-bound nanoparticles could be a relevant treatment option for people with metastatic melanoma irrespective of BRAF mutation status. The manufacturer also indicated that it is in the process of exploring the role of SPARC (serum protein acidic and rich in cysteine) as a biomarker for the effectiveness of paclitaxel as albumin-bound nanoparticles.		
Population size	There were 10,656 new diagnoses of malignant melanoma and 1825 related deaths in England in 2010.		
Process (MTA/STA)	STA		
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of **paclitaxel as albumin-bound nanoparticles** within its licensed indication for the first-line treatment of metastatic melanoma		
Costing implications of remit change	The scoping workshop attendees considered the terms 'metastatic' and 'malignant' to be equivalent. As a result the change in the remit should have no significant impact. No changes proposed.		
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	ChondroCelect for repairing articular cartilage defects		
Topic Selection ID Number	3394	**Wave / Round**	R69
TA ID Number	686		
Manufacturers	TiGeni		
Anticipated licensing information	*****Confidential information removed*****		
Draft remit	To appraise the clinical and cost effectiveness of ChondroCelect within its licensed indication for repairing articular cartilage defects of the knee.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of ChondroCelect and matrix-applied chondrocyte implantation for repairing articular cartilage defects is appropriate. The Institute recommends that the proposed remit is not appropriate. The remit should be changed to reflect the marketing authorisation specifying that the technologies are used for used for repairing symptomatic articular cartilage defects of the knee. Attendees stated that there are three types of autologous chondrocyte implantation currently available: ChondroCelect, matrix-applied chondrocyte implantation (MACI) and 'traditional' autologous chondrocyte implantation. Attendees considered that it was appropriate to consider MACI in any appraisal of ChondroCelect. Further attendees stated that 'traditional' autologous chondrocyte implantation may be used to treat smaller lesions in some UK hospital laboratories that provide cultured chondrocytes for such procedures under hospital exemption from the European ATMP regulation (ATMP regulations mean that cell-based therapies must obtain a marketing authorisation). Attendees discussed the related existing NICE guidance technology appraisal No.89 'The use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints' Workshop attendees noted that because of the recent implementation of the ATMP regulations, some products considered as part of TA89 are no longer available. Two products (ChondroCelect and MACI) now have a marketing authorisation for use in similar populations. The inclusion of two products as interventions in the appraisal and the potential to include relevant components of TA89 should be indicated in the remit. The title of the appraisal will be updated to be: Autologous chondrocyte implantation for repairing articular cartilage defects		
Process	MTA with consideration of incorporating a review of TA89 if		

(MTA/STA)	appropriate
Population size	Approximately 10,000 with cartilage defects requiring treatment but the number eligible for treatment such as ChondroCelect is likely to be much less. Clinical specialists during consultation suggested 200-500 per year would be suitable for ACI
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness of **autologous chondrocyte implantation** within **the applicable** licensed indications for repairing **symptomatic** articular cartilage defects of the knee **(to include a review of technology appraisal 89 if appropriate)**.
Costing implications of remit change	The costing comments were based on approximately 10,000 cartilage defects requiring treatment within the UK annually. It is assumed that those who seek treatment are symptomatic, so the addition of the word 'symptomatic' to the remit has no effect on the estimates. The costing comments estimated around 880 cases are eligible for treatment with ChondroCelect. This was based on the manufacturer suggesting between 9-12% of the 10,000 cases requiring treatment within the UK to be suitable, which was then adjusted down to reflect the population of just England. Using manufacturer's estimates for ChondroCelect and those of the clinical specialists for ACI would give a midpoint eligible population of around 600 people.
Timeliness statement	Noting that ChondroCelect and Matrix-applied chondrocyte implantation are now licensed, issuing timely guidance for this topic will not be possible.

Provisional Title	Empagliflozin combination therapy for treating type 2 diabetes		
Topic Selection ID Number	5953	**Wave / Round**	R34
TA ID Number	641		
Manufacturer	Boehringer Ingelheim / Lilly		
Anticipated licensing information	*****Confidential information removed*****		
Draft remit	To appraise the clinical and cost effectiveness of empagliflozin within its licensed indication for treating type 2 diabetes.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of empagliflozin for treating type 2 diabetes is appropriate. The Institute recommends that the proposed remit is appropriate. The draft scope included empagliflozin monotherapy as an intervention and its use was discussed at the scoping workshop. The manufacturer confirmed that it was seeking a monotherapy licence, in people for whom metformin was considered inappropriate. Clinicians at the workshop did not consider that empagliflozin would be used as a monotherapy given the current treatment options available, and recommended that the appraisal need not consider empagliflozin as a monotherapy treatment. It was recommended that the scope of the appraisal should focus on combination therapy.		
Process (MTA/STA)	STA		
Population size	In the appraisal of dapagliflozin for the same indication it was estimated that approximately 2 million people with type 2 diabetes are suitable for oral anti-diabetic drugs.		
Proposed changes to remit (in bold)	No changes proposed		
Costing implications of remit change	No changes proposed		
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	Everolimus in combination with trastuzumab and vinorelbine for treating locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane		
Topic Selection ID Number	5981	**Wave / Round**	R25
TA ID Number	643		
Manufacturer	Novartis		
Anticipated licensing information	*****Confidential information removed*****		
Draft remit	To appraise the clinical and cost effectiveness of everolimus in combination with trastuzumab and vinorelbine within its licensed indication for treating locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of everolimus in combination with trastuzumab and vinorelbine for treating locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane is not appropriate. The clinical trial for everolimus (BOLERO-3) included a subgroup of people whose disease had progressed within 12 months of receiving trastuzumab in the adjuvant setting. Therefore, depending on the wording of the marketing authorisation, everolimus could be used as a first line metastatic treatment for some people. However, for the majority of people everolimus would be used as a subsequent treatment after trastuzumab in the metastatic setting. Clinical specialists and professional groups who were approached to take part in the workshop indicated that the clinical trial data show an increase in progression free survival of approximately 1 month for everolimus in combination with trastuzumab and vinorelbine compared with trastuzumab and vinorelbine alone. No differences in overall survival, quality of life or response rates have been reported. Specialists considered that, it was unlikely to be used widely and did not attend the workshop. Information provided by the cancer drugs fund following the workshop indicated no clinical interest in using everolimus in this indication and that NICE guidance may not add value. A referral is not sought for this appraisal.		
Process (MTA/STA)	A referral is not sought		
Population size	In the appraisal of lapatinib in combination with capecitabine (that is use after trastuzumab in the metastatic setting), it was estimated that approximately 2000 people would be suitable for		

	treatment. The size of the population for everolimus would be slightly larger because of the inclusion of the subgroup of people whose disease progresses within 12 months of treatment with trastuzumab in the adjuvant setting.
Proposed changes to remit (in bold)	A referral is not sought
Costing implications of remit change	The original costing comments estimated that around 4300 people present with or progress to HER2 positive locally advanced or metastic disease each year. There is now a revised eligible population of at least and possibly slightly larger than 2000 people based on the appraisal of lapatinib in combination with capecitabine who have been treated with trastuzumab in the metastatic setting. The exact position in the pathway based on the marketing authorisation and hence the population cannot yet be defined accurately. Due to the high cost of everolimus, it is still considered that there is potential for the topic to be high cost if the technology is recommended.
Timeliness statement	N/A – A referral is not sought

Provisional Title	Nalmefene for reducing alcohol consumption in people with alcohol dependence		
Topic Selection ID Number	5113	**Wave / Round**	R45
TA ID Number	660		
Manufacturer	Lundbeck		
Anticipated licensing information	Nalmefene has a UK marketing authorisation for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification. It should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption. Marketing authorisation was received February 2013		
Draft remit	To appraise the clinical and cost effectiveness of nalmefene within its licensed indication for reducing alcohol consumption in people with alcohol dependence.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of nalmefene for reducing alcohol consumption in people with alcohol dependence is appropriate. The marketing authorisation for nalmefene states that people have alcohol dependence without physical withdrawal symptoms. The manufacturer clarified that in the clinical trials patients were all alcohol dependent and were also assessed on the Clinical Institute Withdrawal Assessment for Alcohol scale of the likelihood of them having physical withdrawal symptoms when stopping alcohol consumption. People who scored over 10 as having a moderate risk of withdrawal symptoms were excluded from the trial, hence the specification in the marketing authorisation of alcohol dependence with no physical withdrawal symptoms. It was agreed that the population in the marketing authorisation most closely reflected those people defined in NICE clinical guideline CG115 as having mild alcohol dependence. For people with mild alcohol dependence it was agreed that moderation of alcohol consumption was an appropriate treatment goal. It was discussed whether naltrexone, acamprosate or disulfiram should be included as comparators in the scope. • Attendees indicated that naltrexone could be used off label to reduce alcohol consumption for people with mild dependence. However, the manufacturer considered that this wasn't an established treatment. • There was agreement that disulfiram would not be used in mild alcohol dependence because of the risks of adverse events associated with treatment. • It is noted that the marketing authorisation for acamprosate states "treatment should only be initiated after weaning therapy, once the patient is abstinent from alcohol". It was agreed that the comparators in the scope should be		

	amended to include naltrexone in combination with psychological support for certain people who have mild alcohol dependence as well as psychological support alone. It was agreed that treating alcohol dependence results in costs and benefits to other government departments and that the remit should be amended to request the Department of Health allow a wider perspective to be taken into account, including: • Home Office – social and criminal issues (including domestic violence and prison issues) • Department of Education – the social effects of alcohol dependence of adults on children • Department of Transport – the effects of driving while under the influence of alcohol Comments received from consultation stated that in April 2013 elements of the commissioning and funding of alcohol addiction services moved to the responsibility of Local Authorities public health function. GPs may be requested to prescribe under shared care arrangements and any associated costs with shared care monitoring should be in the economic model. Representatives of local authorities should be included as a stakeholder in the appraisal.
Process (MTA/STA)	STA
Population size	The costing tool for NICE CG115 estimates that in England over a million people age 16 years or over have mild alcohol dependence, but a much smaller proportion currently receive treatment. Approximately 100,000 people are provided with evidence based specialist treatment each year and 15% of these have mild alcohol dependence.
Proposed changes to remit (in bold)	To appraise the clinical and cost effectiveness **(allowing adoption of a wider perspective than the NHS and PSS)** of nalmefene within its licensed indication for reducing alcohol consumption in people with alcohol dependence.
Costing implications of remit change	No changes proposed
Timeliness statement	Noting that nalmefene is now licensed, issuing timely guidance on this topic will not be possible.

Provisional Title	Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia		
Topic Selection ID Number	5993	**Wave / Round**	R25
TA ID Number	642		
Manufacturer	GlaxoSmithKline		
Anticipated licensing information	*****Confidential information removed*****		
Draft remit	To appraise the clinical and cost effectiveness of ofatumumab within its licensed indication for previously untreated 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 chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia is appropriate. The Institute recommends that the proposed remit is appropriate. The draft scope specified the use of ofatumumab in combination with chlorambucil. However, the manufacturer noted that the licence for ofatumumab may include ofatumumab in combination with any alkylator-based regimen (for example chlorambucil, bendamustine and cyclophosphamide). The manufacturer noted that cyclophosphamide would be given in combination with both fludarabine and ofatumumab. Clinical attendees stated that the combination of ofatumumab, cyclophosphamide and fludarabine would be unlikely to replace the combination of rituximab, cyclophosphamide and fludarabine because the latter has shown a survival advantage, and there are no proposed studies comparing rituximab with ofatumumab. Therefore clinicians perceived no value in appraising the combination of ofatumumab, cyclophosphamide and fludarabine. It was considered that the place of ofatumumab in clinical practice would be in combination with either bendamustine or chlorambucil in people for whom fludarabine treatment was not appropriate. It was noted that this population was the focus of the clinical trials. Consultees noted that the comparators for this appraisal: chlorambucil and bendamustine are often used in combination with rituximab. Although this is not consistent with NICE recommendations (TA174: “rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of chronic lymphocytic leukaemia”), these combinations are often funded through the cancer drugs fund as well as routine local commissioning arrangements. It was estimated that approximately half of patients who receive chlorambucil or bendamustine also receive rituximab		

	(amounting to more than 25% of all first-line CLL patients), although this is variable across the country. The comparators were amended to include chlorambucil and bendamustine both with and without rituximab. Attendees at the scoping workshop discussed whether an appraisal of ofatumumab could be combined in an MTA with an appraisal of obinutuzumab (batch 32 ***CONFIDENTIAL***) which will be used in a similar position in clinical practice. The value of guidance covering all treatment options was welcomed, but the need for timely guidance was also underlined. It was agreed that this would proceed as an STA
Process (MTA/STA)	STA
Population size	2,800 patients diagnosed with CLL per year, approx. 50% unsuitable for FCR = 1,400 patients
Proposed changes to remit (in bold)	No changes proposed
Costing implications of remit change	No changes proposed
Timeliness statement	STA - 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. ***Confidential information removed***

Provisional Title	Pazopanib for maintenance treatment of epithelial ovarian, fallopian and peritoneal cancer		
Topic Selection ID Number	5402	**Wave / Round**	R16
TA ID Number	545		
Manufacturer	GlaxoSmithKline		
Anticipated licensing information	*****Confidential information removed*****		
Draft remit	To appraise the clinical and cost effectiveness of pazopanib within its licensed indication for maintenance treatment of epithelial ovarian, fallopian and peritoneal cancer in patients whose disease has not progressed after first line therapy		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of pazopanib for maintenance treatment of epithelial ovarian, fallopian and peritoneal cancer is appropriate. The Institute recommends that the proposed remit is appropriate. In the draft scope the comparator was specified as none. However, it was noted that patients in clinical practice would be followed up after first-line chemotherapy and therefore routine surveillance should be incorporated into the comparator description. The scoping workshop attendees also discussed whether bevacizumab could be an appropriate comparator because it may be given off label at a dose of 7.5 mg/kg (half the licensed dose). Scoping workshop attendees noted that the use of bevacizumab may not be entirely comparable with pazopanib because of the differences in treatment regimens between bevacizumab (licensed for maintenance therapy following induction therapy with bevacizumab) and pazopanib (licensed for maintenance therapy only). It was also noted that patients who are receiving bevacizumab may show a higher risk profile compared to those patients in the inclusion and exclusion criteria of the main clinical trials for pazopanib. On balance it was agreed that bevacizumab was an appropriate comparator.		
Process (MTA/STA)	STA		
Population size	In 2010, around 7000 new cases of ovarian cancer were diagnosed and there were approximately 4300 deaths from ovarian cancer		
Proposed changes to remit (in bold)	No changes proposed		
Costing implications of remit change	The original costing was based on 2008 incidence rates for ovarian cancer.		

	Using 2010 figures, it's suggested that the wording is changed to: *"*It is estimated that approximately 7,000 women will present with ovarian cancer each year, of whom the majority present in stages II to IV. Of the 75% who receive chemotherapy, around a quarter (1300) do not respond and may be eligible for treatment with Pazopanib. If it is priced the same as for its use for Renal Cell Carcinoma, the cost per patient would be around £27,000. There is therefore potential for this topic to be high cost with a total incremental cost of around £35 million*"*.
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	Sofosbuvir for treating chronic hepatitis C		
Topic Selection ID Number	6885	**Wave / Round**	R49
TA ID Number	654		
Manufacturer	Gilead		
Anticipated licensing information	***Confidential information removed***		
Draft remit	To appraise the clinical and cost effectiveness of sofosbuvir within its licensed indication 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 sofosbuvir for treating chronic hepatitis C is appropriate. The Institute recommends that the proposed remit is appropriate. The draft scope stated that the intervention was sofosbuvir in combination with ribavirin (with or without peginterferon). However, it was clarified that the treatments with which sofosbuvir will be combined will differ depending on genotype, and that the comparators for the genotypes also differ. Attendees at the scoping workshop discussed whether the MTA or STA process was the most appropriate for considering sofosbuvir in hepatitis C. New treatments will be available shortly after sofosbuvir and there is also a decision pending on whether to review the TA 200 guidance (Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C' Review Proposal Date July 2013).The workshop conveyed a strong opinion that timely guidance was important in hepatitis C. Therefore it was agreed that the STA process was more appropriate than the MTA process. Attendees at the workshop discussed whether sofosbuvir for chronic hepatitis C should be appraised through 1 or 2 STAs, given the number of populations and treatment regimens. Attendees at the workshop expressed concerns about equity if the 2 STAs were not done in parallel, as the recommendations could be released at different times. To ensure timely guidance and the production of recommendations for all populations at the same time point it was agreed that the appraisal would be completed as a 1 STA.		
Process (MTA/STA)	STA		
Population size	2012 estimates: 216,000. Attendees at the scoping workshop commented that it was difficult to establish prevalence because of under diagnosis and stated that the 2012 estimate was likely to be an underestimate.		

Proposed changes to remit (in bold)	No changes proposed
Costing implications of remit change	At topic selection stage, the population was hepatitis C genotype 1 – a small subgroup of those presented here, so the new population of at least 216,000 of cases of hepatitis C is more appropriate. Of these, 80% or approximately 175,000 would be classified as having 'chronic' hepatitis C (TA202 – Peginterferon alpha and ribavirin for the treatment of chronic hepatitis C, 2010). Despite the unknowns, due to the large potential population it is considered that the topic has potential to be high cost.
Timeliness statement	Assuming that the anticipated date of the marketing authorisation is the latest date that we are aware of and the expected referral date of this topic, issuing timely guidance for this technology will be possible.

Provisional Title	Tolvaptan for treating autosomal dominant polycystic kidney disease		
Topic Selection ID Number	6034	**Wave / round**	R34
TA ID Number	652		
Manufacturer	Otsuka Pharmaceuticals		
Anticipated licensing information	*****Confidential information removed*****		
Draft remit	To appraise the clinical and cost effectiveness of tolvaptan within its licensed indication for treating autosomal dominant polycystic kidney disease.		
Main points from consultation	Following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of tolvaptan for treating autosomal dominant polycystic kidney disease is appropriate. The Institute recommends that the proposed remit is appropriate. Stakeholders stated that there is currently no other treatment available that will alter the course of disease progression for people with ADPKD. The attendees noted that although everolimus has in the past been used off-label for the treatment of ADPKD it is no longer used because it is has a negative impact on renal function. Attendees at the scoping workshop attendees agreed that standard of treatment depended on symptoms but include monitoring of renal function and cardiovascular risk assessment (including blood pressure monitoring). Symptomatic management of ADPKD included pain relief and management of cyst and urinary tract infections.		
Process (MTA/STA)	STA		
Population size	At the workshop, the PKD charity indicated that the population of people with autosomal dominant and autosomal recessive PKD is in the region of 70,000. The target population number for tolvaptan will be smaller than this because it only includes autosomal dominant disease.		
Proposed changes to remit (in bold)	No changes proposed		
Costing implications of remit change	No changes proposed		
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.		