National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Obeticholic acid for treating primary biliary cirrhosis ID785

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	Yes: there is only one licenced therapy for PBC at present and at the same time a large unmet need from patients for those failing on this therapy.	Comment noted.
	Intercept Pharmaceuticals	Yes, it is appropriate that NICE reviews obeticholic acid (OCA) for primary biliary cirrhosis (PBC). Though rare, PBC is a serious, life-threatening, cholestatic liver disease. Left untreated, PBC progresses to hepatic fibrosis, cirrhosis, and hepatic decompensation ending in either liver transplant or death. Recent data has demonstrated the need for reassessment of treatment goals to focus on lowering of the biochemical markers, ALP and bilirubin which result in the extension of time to liver transplant-free survival. Key supportive information is provided below: 1) Liver disease is the fifth greatest cause of death in the UK, and the only	Comments noted.

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		one of the five leading causes of mortality that is rising. This is in contrast to the rest of Europe, where deaths from liver disease are decreasing (APPHG, 2014). 2) The incidence and prevalence of PBC in the UK is one of the highest in the world at 5.8 and 39.2 per 100,000 respectively (Boonstra, 2012). 3) The UK-PBC consortium is funded by MRC and NIHR as PBC represents an area of specific unmet medical need in the UK. One of the goals of the UK-PBC consortium is "to identify better treatments" for people with PBC. 4) In the UK, there were 630 liver transplants performed in 2013/2014. At least 7% were for PBC (NHS Blood and Transplant Report, 2014), almost certainly an underrepresentation. Overall, the number of patients waiting for liver transplant has steadily increased since 2007/8 and recent data found that PBC patients on the transplant waiting list were more likely to die before transplant compared to patients with other liver diseases [Mohamed, 2015). Even after transplant 43% of patients will have a recurrence of PBC (Charatcharoenwitthaya 2007). 5) The only approved pharmacologic treatment for PBC, licensed in the UK in 1996, is ursodeoxycholic acid (UDCA). In randomised placebo controlled trials, UDCA improves biomarkers of PBC progression, including ALP and bilirubin, resulting in delayed histological progression and increased liver transplant-free survival (Poupon, 1997; Corpechot, 2008). 6) Epidemiologic studies have shown that the majority of UDCA-treated patients could further reduce their risk of liver transplant and death by incremental reductions in ALP and bilirubin. 7) Importantly, PBC patients able to achieve normal ALP and bilirubin have rates of liver transplant and mortality no greater than age and gender matched controls (Corpechot, 2005; ter Borg, 2006; Pares, 2006). The relationship between achieved ALP and bilirubin, and liver transplant-free survival, has been independently confirmed in two large cohorts in the [redacted] and worldwide (Lammers, 2014).	

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		8) [redacted] In the UK, the increase in liver-related mortality, the growing waiting list for liver transplant and the higher prevalence of PBC, coupled with the compelling evidence that incremental lowering of ALP/bilirubin improves transplant-free survival, all argue for the prioritisation of this review by NICE and the recommendation for a new treatment option for patients living with PBC.	
Wording	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	Yes	Comment noted.
	Intercept Pharmaceuticals	No. It is our understanding that in the coming months there will be an announcement that primary biliary cirrhosis (PBC) will be renamed “primary biliary cholangitis” in order to differentiate the condition from cirrhosis, which has negative associations. We would ask that NICE reflects this change in terminology at the earliest point in the appraisal so that when the guidance is issued there is no confusion with the renamed condition.	Comment noted. The wording of the remit is based on the expected wording of the marketing authorisation for obeticholic acid which currently states primary biliary cirrhosis.

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			Obeticholic acid will be appraised within the boundaries of its marketing authorisation.
Timing Issues	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	Urgent: PBC is a rare disease with a significant burden of mortality and morbidity, affecting adults across all ages. There is only one licenced therapy and no new therapies have come to the market in more than 15 years. The group of patients who benefit potentially most from new therapies are patients with PBC diagnosed young (often under the age of 50) who fail therapy with ursodeoxycholic acid and have a high risk of progression to death, unless saved by liver transplantation (a scarce and expensive resource).	Comment noted. NICE aims to schedule technology appraisals into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to issue guidance within 6 months of a technology receiving its marketing authorisation in the UK.
	Intercept Pharmaceuticals	This appraisal is urgent relative to others under consideration. The FDA has fast tracked OCA review recognising the urgency of improving care for patients with this rare disease. This is an important step towards a clear objective of improving transplant-free survival for patients. As the majority of patients have a sub-optimal response to UDCA, the lack of an effective add on treatment leaves them at risk of disease progression. Patients who have significantly raised ALP, that are starting to see an increase in bilirubin above the upper limit of normal, are at significant risk of progressing towards the need for transplant. The progression of these patients can be sudden and is one of the reasons that patients can die whilst awaiting transplant and transplantation is not curative. As the first therapeutic option being presented to NICE in 20 years for this rare, but serious condition, we believe the need is urgent and OCA in PBC requires a priority	Comment noted. NICE aims to schedule technology appraisals into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to issue guidance within 6 months of a technology receiving its marketing authorisation in the UK.

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		review.	
Additional comments on the draft remit	Intercept Pharmaceuticals	References: Liver disease: Today's complacency, tomorrow's catastrophe. The All-Party Parliamentary Hepatology Group (APPHG) Inquiry into Improving Outcomes in Liver Disease (March 2014) Boonstra K et al. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: A systematic review. Journal of Hepatology 2012; 56: 1181–1188 [redacted] Charatcharoenwitthaya P et al: Long-Term Survival and Impact of Ursodeoxycholic Acid Treatment for Recurrent Primary Biliary Cirrhosis After Liver Transplantation. Liver Transplantation 13:1236-1245, 2007 Corpechot C et al. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology 2005;128:297–303. Corpechot C et al. Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008 Sep;48(3):871-7. Lammers WJ et al. Levels of Alkaline Phosphatase and Bilirubin Are Surrogate End Points of Outcomes of Patients with Primary Biliary Cirrhosis: An International Follow-up Study. Gastroenterology. 2014 Aug 23;147(6):1338–49. Mohamed K et al. Patients with Primary Biliary Cirrhosis Have the Highest Wait-List Mortality: Poster presented Digestive Disease Week Annual Meeting 2015 NHS Blood and Transplant. Annual report on liver transplantation. Report for 2013/2014 (1 April 2004 – 31 March 2014). Published September 2014 Pares A et al. Excellent long-term survival in patients with primary biliary	References noted.

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		cirrhosis and biochemical response to ursodeoxycholic acid. Gastroenterology 2006;130: 715–720. Poupon, RE et al. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 1997; 113(3): 884-890. ter Borg PC et al. Prognosis of ursodeoxycholic acid-treated patients with primary biliary cirrhosis. Results of a 10-yr cohort study involving 297 patients. Am J Gastroenterol 2006;101:2044–2050.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	Broadly ok but lacks precision and could benefit of expert review and revision	Comment noted. The background section of the scope is only intended to provide a brief description of the condition and current treatment options. A detailed description of these aspects will be included in the company's evidence submission and will be considered during the appraisal.
	British Association for	1."Symptomatic Treatment of pruritus –cholestyramine and antihistamines" This statement is incorrect, antihistamines are ineffective and are not used; it	Comments noted. The background section in

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	the Study of the Liver	should read “Symptomatic treatment of pruritus- bile acid sequestrants such as cholestyramine,rifampicin and the opioid antagonist naltrexone” 2.”Liver Transplantation is the only treatment that improve prognosis in patients with PBC” This statement is incorrect, as the 50-60% of patients who respond to ursodeoxycholic acid have a normal life span. It should read “Liver transplantation is the only treatment that can improve prognosis in patients with endstage liver disease ie with decompensated liver disease. The 50-60% of PBC patients who respond to ursodeoxycholic acid have a normal life span.”	the scope has been updated accordingly.
	Intercept Pharmaceuticals	Please note that it is anticipated that primary biliary cirrhosis will be renamed primary biliary cholangitis in the near future. We believe that the prevalence of inadequate response to UDCA is inaccurate and based on more recent evidence from the [redacted]. The NICE document states: “*The estimated proportion of people whose disease have an inadequate response to ursodeoxycholic acid ranges between 15 and 40%*.[1,3]” The supporting citations are: 1. Horizon Scanning Centre (2013) Obeticholic acid for primary biliary cirrhosis – second line 3. PBC Foundation http://www.pbcfoundation.org.uk/Home/CMSPageView/531. Accessed April 2015 The only statement on the PBC Foundation website concerning UDCA responsiveness is:	Comments noted. Obeticholic acid will be appraised within the boundaries of its marketing authorisation. The epidemiological data included in the background section in the scope have been updated. The UK-PBC website states that in the UK, 80% of patients respond to ursodeoxycholic acid and have normal or near-normal life expectancy.

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		"*However, there is a figure (still to be agreed but approximately 15%) for whom UDCA doesn't work fully*." There is no citation for this statement, and the statement itself indicates that there is no agreement on this number. We do not believe there is a scientific justification to support the 15% UDCA inadequate response rate. The Horizon Scanning document is a secondary reference. The primary reference for inadequate response cited in this document is: Parés A et al. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. Gastroenterology 2006;130(3):715-720. The statement in this article supporting a 40% inadequate response rate is: "*In the current study, most of the patients did respond to UDCA with a marked decrease or even normalisation in serum alkaline phosphatase activity, but a relevant number of patients (almost 40%) did not exhibit a good biochemical response, which is associated with lower long-term survival than responders*." p 719. While Pares et al, 2006 is an excellent study, it has limited applicability. It was published nearly a decade ago and there have been significant advances since that time. The study involved 192 patients treated at a tertiary care centre in France, and 40 patients who were enrolled in a UDCA clinical trial. Thus we believe it may have significant limitations in terms of generalisability to UK PBC patients in the general population. Fortunately, [redacted] This replicates the	

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		observation reported in Lammers 2014. We disagree that "*Treatment for PBC aims to alleviate symptoms and slow disease progression*". We believe the goal of PBC treatment is to increase transplant free survival. Data have shown that patients treated with UDCA who achieve ALP and bilirubin levels ≤ ULN have liver transplant and mortality rates equivalent to healthy gender and age matched controls (Corpechot, 2005; ter Borg, 2006; Pares, 2006). [redacted] Therefore, any patient with ALP and/or bilirubin ≥ ULN would benefit from additional reduction. While we recognise that historically some physicians have used immunosuppressants to treat PBC, immunosuppressants are not licensed for PBC in the UK and there is no evidence for their efficacy. Both AASLD (2009) and EASL (2009) guidelines do not recommend the use of immunosuppressants. This should be clarified in the background information.	Comment noted. Following the scoping workshop, references to immunosuppressive therapies have been removed from the scope as it was noted these are not considered established clinical practice in the NHS for treating primary biliary cirrhosis.

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The technology/ intervention	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	No: implies human derived; it is a drug that is synthesised, that is a derivative of chenodeoxycholic acid that has farnesoid x receptor agonist activity.	Comment noted. The technology section in the scope has been amended.
	British Association for the Study of the Liver	1. recommend adding "The mode of action of obeticholic acid is as an activator of the nuclear receptor FXR, which favourably alters the composition of bile" It should be made clear that obeticholic acid will only be indicated for the minority of patients who do not respond to ursodeoxycholic acid after 12 months of therapy. The trials on obeticholic acid have been carried out in this select group of patients	Comments noted. The technology section of the scope is only intended to provide a brief description of the technology. A detailed description of the technology will be included in the company's evidence submission and will be considered during the appraisal. Obeticholic acid will be appraised within the boundaries of its marketing authorisation.
	Intercept Pharmaceuticals	No. OCA represents the first innovation in the treatment of PBC in around 20 years. OCA is a selective farnesoid X receptor (FXR) agonist and modified bile acid.	Comments noted. The technology section in the scope has been

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		FXR controls bile acid homeostasis in cholestatic liver diseases, thereby protecting the liver and delaying progression of fibrosis and cirrhosis. FXR is also a key regulator of inflammatory, fibrotic, and metabolic pathways. The endogenous bile acid chenodeoxycholic acid (CDCA) is the natural ligand for FXR. OCA is approximately 100-fold more potent at the FXR than CDCA and this FXR activation is an important mechanistic feature differentiating OCA from the structurally related endogenous bile acids CDCA and UDCA. The regulation of bile acid homeostasis primarily underlies the therapeutic rationale for FXR agonists in PBC. OCA's unique combination of decreased bile acid synthesis and increased transport of bile acids out of the hepatocyte serves to combat the toxic burden of hepatic bile acid accumulation in cholestasis and thus lowering of ALP and bilirubin. Intercept recommend that the description for OCA should be revised to describe its unique mode of action i.e. hepatoprotective, modified bile acid with potent and selective FXR mediated effects.	amended. The technology section of the scope is only intended to provide a brief description of the technology. A detailed description of the technology will be included in the company's evidence submission and will be considered during the appraisal.
Population	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	Yes	Comment noted. Following the scoping workshop, the population in the scope has been updated to "People with primary biliary cirrhosis whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid" to reflect the expected wording of the

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			marketing authorisation.
	Intercept Pharmaceuticals	Yes, the population is defined appropriately.	Comment noted. Following the scoping workshop, the population in the scope has been updated to "People with primary biliary cirrhosis whose disease has an inadequate response to, or who are unable to tolerate, ursodeoxycholic acid" to reflect the expected wording of the marketing authorisation.
Comparators	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	Ursodeoxycholic acid is the only comparator. I don't understand the comment on immunosuppression.	Comment noted. Following the scoping workshop the comparators list has been updated and immunosuppressive therapies have been removed.
	Intercept Pharmaceuticals	We wish to take the opportunity to clarify that OCA is not a first line therapy. OCA will be used in addition to UDCA in patients who have an inadequate response to UDCA, defined as an achieved ALP and/or bilirubin > ULN.	Comment noted. Following the scoping workshop the comparators list has

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		Therefore the comparator in UDCA inadequately responding patients will be UDCA plus OCA versus UDCA plus no additional treatment. UDCA is not a comparator in patients who achieve an adequate response, or a comparator as first line therapy. For adult patients who are unable to tolerate UDCA we propose that no treatment is the comparator to OCA. Immunosuppressants should not be considered as comparators as they are not standard /established clinical practice in the UK. Both AASLD (2009) and EASL (2009) guidelines do not recommend the use of immunosuppressants as there is no evidence that that are effective.	been updated and immunosuppressive therapies have been removed.
Outcomes	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	Most- should specify liver biochemistry, markers of liver fibrosis Jaundice is a sign not a symptom	Comments noted. Following the scoping workshop, the outcome measure “liver function” has been defined as “liver function based on markers of liver biochemistry” and jaundice has been removed from the list of symptoms.
	Intercept Pharmaceuticals	The outcomes listed in the remit are clearly important for the pharmacoeconomic evaluation of OCA. We would like to expand the	Comments noted. Following the scoping

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		outcomes to include: • Liver function/damage, as measured by ALP and total bilirubin • PBC-related events, including (but not limited to) ascites, varicies and hepatic cell carcinoma • Time to liver transplant • Mortality • Symptoms, including pruritus, fatigue, jaundice and abdominal pain • Health-related quality of life • Adverse effects of treatment • Changes in high-density lipoprotein metabolism Patients should be treated early in disease, when ALP and bilirubin levels first exceed ULN, and patients should be treated to the lowest levels possible to avoid liver transplant and premature death. [redacted]	workshop the outcome measures have been updated to: • mortality • liver function based on markers of liver biochemistry • symptoms, including pruritus, fatigue and abdominal pain • time to liver transplantation • primary biliary cirrhosis related events, including ascites, varices, encephalopathy and hepatic cell carcinoma • adverse effects of treatment • health-related quality of life.

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Economic analysis	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	This needs to acknowledge that PBC is a rare disease that is slowly progressive and that the economic impact is related to quality and quantity of life.	Comment noted.
	Intercept Pharmaceuticals	As PBC is a chronic, progressive disease usually diagnosed in the fourth and fifth decades of life, a lifetime horizon is appropriate.	Comment noted.
Equality and Diversity	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	The rare nature of disease means that it is essential that patients with PBC have the same opportunity to receive new therapy, despite the fact that the rare nature of disease, and slow natural history hinders absolute trials of survival.	Comment noted. Please see the Equality Impact Assessment form.
	Intercept Pharmaceuticals	PBC disproportionately affects women versus men with a nearly tenfold higher incidence in women. Therefore facilitating access to OCA for women in a disease with currently no medical treatment options beyond UDCA would be of significant benefit. In addition, as recognised in the NHS Mandate, *"Too many people die too soon from illnesses that can be prevented or treated. From cancer, liver and lung disease…England's rates of premature mortality are worse than those in many other European countries".* The introduction of more effective treatments for PBC that would	Comment noted. Please see the Equality Impact Assessment form.

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		disproportionately benefit women would reduce the under 75 mortality rate in liver disease as outlined in the aims of the NHS mandate.	
Innovation	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	Yes: this is the first rationally designed FXR agonist to be close to use in man. There is huge opportunity to improve the quality and quantity of life of patients with PBC, and ultimately other chronic inflammatory liver diseases. There has been a long scientific history of in vitro and in vivo studies of the the FXR axis, and intervention with OCA. There is now a large body of human interventional data arising.	Comment noted. Consultees are encouraged to describe the innovative nature of the technology in their evidence submissions. The Committee will consider this information during the appraisal process.
	Intercept Pharmaceuticals	OCA is the first innovative medicine in PBC, an area of significant unmet need, in nearly 20 years. Based on the mechanisms of action of OCA (i.e. hepatoprotective, modified bile acid with potent and selective FXR mediated effects), OCA offers a unique therapeutic modality to a significant number of patients with an inadequate response to or poor tolerance of UDCA. OCA provides incremental ALP and bilirubin lowering in patients taking UDCA, and has been shown to be effective in patients with sub-optimal responses to UDCA and/ or unable to tolerate UDCA. In addition, clinical trials have shown that patients on UDCA may lose bilirubin control over time, while those on OCA maintain response out to 4 years based on registrational trial data.	Comment noted. Consultees are encouraged to describe the innovative nature of the technology in their evidence submissions. The Committee will consider this information during the appraisal process.
Other considerations	British Society of Gastroenterology/ University of	No	Comment noted.

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	Birmingham (endorsed by Royal College of Physicians)		
NICE Pathways	Intercept Pharmaceuticals	*Where do you consider obeticholic acid will fit into the existing NICE pathway, Liver conditions?* Within the existing NICE pathway, “Liver Conditions”, OCA is likely to best fit under cirrhosis. PBC is currently captured as one of the conditions for the guideline on the assessment and management of cirrhosis that NICE is developing (expected publication date May 2016). However as noted above under the “Wording” section of the draft remit the name PBC is soon going to change to Primary Biliary Cholangitis. Therefore in future this condition may need to be positioned into a new part of the NICE pathway and not under cirrhosis.	Comment noted.
Questions for consultation	British Society of Gastroenterology/ University of Birmingham (endorsed by Royal College of Physicians)	Nil specific except to recognise the clinical urgency of offering patients new therapies in PBC.	Comment noted.
	British Association for the Study of the Liver	1. The scope should also include the possible role of fibrates which are currently in clinical trial. The pilot studies show benefit in PBC patients refractory to Urso.	Comment noted. Following the scoping workshop, fibrates have been included as a

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			relevant comparator for obeticholic acid.
	Intercept Pharmaceuticals	*Have all relevant comparators been included in the scope? Which treatments are considered to be established clinical practice in the NHS for primary biliary cirrhosis?* There are no other relevant comparators other than those described by Intercept in the comparator section above. *Are there any subgroups of people in whom obeticholic acid alone or in combination with ursodeoxycholic acid is expected to be more clinically effective and cost effective or other groups that should be examined separately?* Intercept is of the opinion that there are no subgroups of people in whom OCA alone or in combination with UDCA is more clinically effective. *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.* Intercept agrees that OCA should be appraised through the STA process.	Comments noted.
Additional comments on the draft scope	Intercept Pharmaceuticals	References: [redacted]C orpechot C, et al. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology	References noted.

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		2005;128:297–303. EASL. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. Journal of hepatology. 2009;51(2):237-67. [redacted] Lindor KD et al. Primary biliary cirrhosis: AASLD Practice Guidelines. Hepatology. 2009 Jul;50(1):291-308. Pares A et al. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology. 2006 Mar; 130(3):715-20. ter Borg PC et al. Prognosis of ursodeoxycholic acid-treated patients with primary biliary cirrhosis. Results of a 10-yr cohort study involving 297 patients. Am J Gastroenterol 2006;101:2044–2050.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health