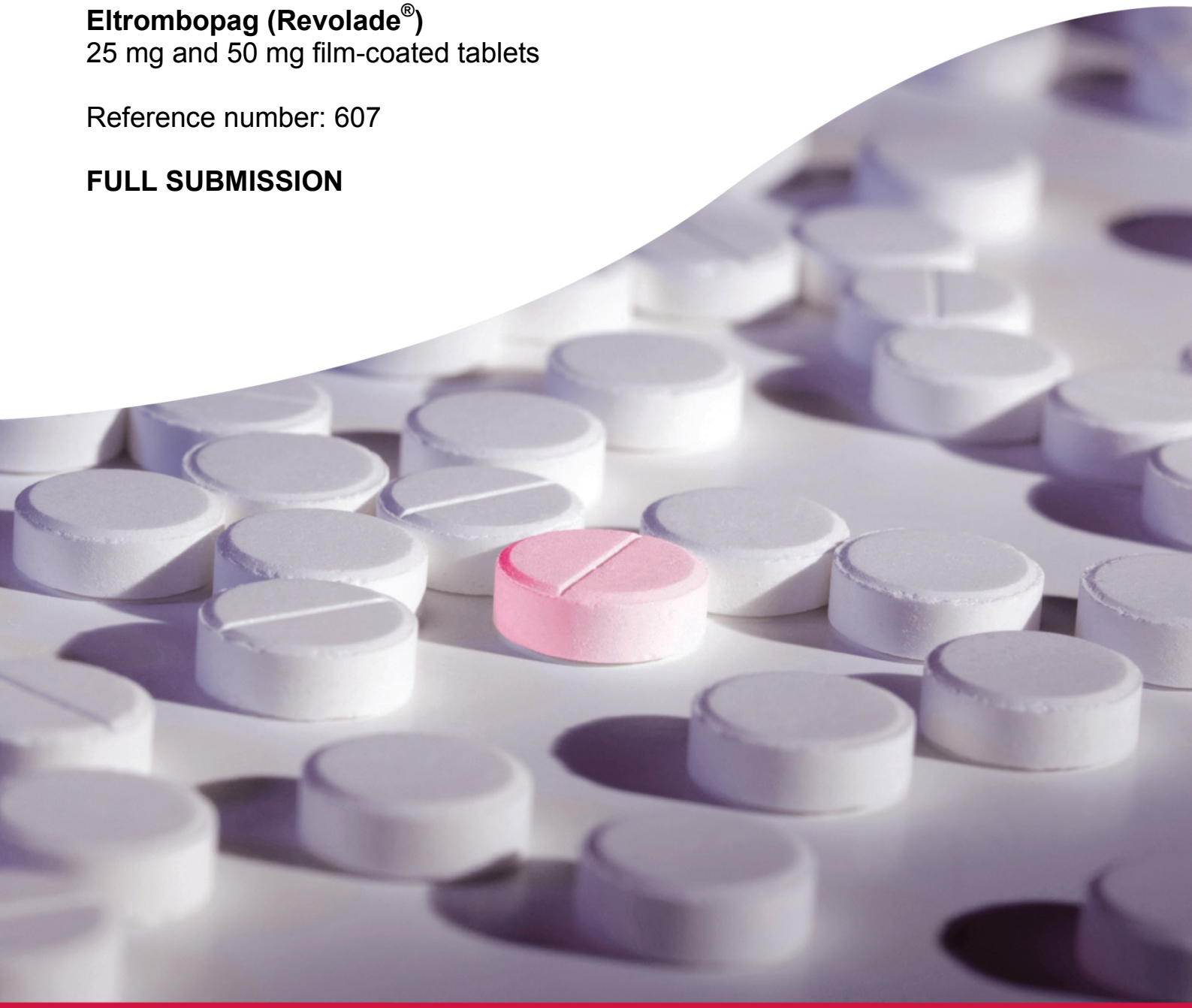
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Eltrombopag (Revolade®)
25 mg and 50 mg film-coated tablets

Reference number: 607

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Eltrombopag (as olamine) (Revolade®) 25 mg and 50 mg film-coated tablets

This assessment report is based on evidence submitted by GlaxoSmithKline Limited on 14 February 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Eltrombopag (Revolade®) is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy[2].
Dosing	Prior to commencing antiviral therapy (AVT) the lowest dose of eltrombopag is used to achieve a sufficiently high platelet count to allow AVT to commence. Eltrombopag is initiated at a dose of 25 mg once daily. The dose should be adjusted, as necessary in increments of 25 mg every 2 weeks to achieve the target platelet count required to initiate AVT. Platelet counts should be monitored every week prior to starting AVT. During AVT, adjust the dose of eltrombopag as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding. Monitor platelet counts weekly during AVT until a stable platelet count is achieved, normally around 50,000–75,000/microlitre. Dose reductions on the daily dose by 25 mg should be considered if the platelet counts exceed the required target. The effect of any dose adjustments should be assessed after two weeks. Refer to the Summary of Product Characteristics (SPC) for further details[2].
Marketing authorisation date	19 September 2013[2] (licensed for the treatment of chronic immune [idiopathic] thrombocytopenic purpura on 11 March 2010)[2].

2.0 DECISION CONTEXT

2.1 Background

Chronic hepatitis C virus (HCV) infection can cause liver cirrhosis, liver cancer and lead to the need for liver transplantation[3,4]. In 2006 the estimated number of people in Wales with chronic HCV infection was 12,000 (0.4% of the population)[5]. HCV is categorised into six genotypes with genotypes 1 and 3 accounting for 90% of infected patients in Wales[3]. Thrombocytopenia is a common complication of chronic liver disease associated with HCV infection and correlates with disease severity and portal hypertension[6]. Liver cirrhosis and thrombocytopenia occur in approximately 20% of HCV infected patients and in the absence of antiviral therapy (AVT) this leads to liver decompensation, liver cancer and death[4]. AVT with pegylated interferon alfa (P-IFN) and ribavirin (RBV) further reduces platelet counts through bone marrow suppression[7].

The aim of treating HCV infected patients with AVT is to achieve a sustained virological response (SVR); defined as an undetectable serum HCV RNA[3] which leads to a 4–10 fold decrease in mortality and a 2–4 fold decrease in the incidence of decompensated liver disease[4]. The National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) recommends AVT as a combination

of P-IFN and RBV for patients infected with all HCV genotypes with the addition of a protease inhibitor as triple therapy in patients with HCV genotype 1[3,8–10]. The dose of P-IFN should be reduced or discontinued in patients with low platelet counts[4,11,12]. Currently patients with chronic HCV infection and thrombocytopenia are treated with either no AVT or with a reduced dose of antiviral medicine, however this is associated with a reduced likelihood of achieving a SVR[4]. P-IFN dose reductions are particularly detrimental to achieving SVR in chronic HCV patients with cirrhosis/advanced fibrosis who constitute the group at highest risk of HCV-related complications, including death[13].

Eltrombopag is a thrombopoietin receptor agonist, which induces proliferation and differentiation of megakaryocytes from bone marrow progenitor cells to increase platelet counts[4]. Thrombocytopenia limits initiation and dose of P-IFN and RBV therapy[6]. Eltrombopag enables AVT in patients who would otherwise receive either no treatment or reduced doses of AVT[1]. Eltrombopag is the first medicine licensed for this indication.

2.2 Comparators

- Best Standard of Care

2.3 Guidance and related advice

- European Association for the Study of the Liver. Clinical practice guidelines: management of hepatitis C virus infection (2014)[14].
- SIGN guidance 133. Management of hepatitis C (2013)[8].
- Danish F and Yasmin S. The role of eltrombopag in the management of hepatitis C virus-related thrombocytopenia (2013)[15].
- NICE. Technology appraisal 200: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (2010)[3].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submitted evidence from two phase III clinical studies, for the use of eltrombopag in patients with HCV infection and thrombocytopenia (ENABLE 1 and ENABLE 2)[1,6]. In addition the company referred to a supportive study of eltrombopag for thrombocytopenia in patients with cirrhosis associated with HCV, however, this will not be discussed further as this was a smaller phase II study[1,16].

3.1 ENABLE 1 and ENABLE 2 studies

The company submitted evidence from two double-blind, randomised, multicentre phase III clinical studies in adults, ENABLE 1 (N = 716) and ENABLE 2 (N = 805)[1,4,6]. The studies comprised two phases: an open-label phase lasting 2–9 weeks, in which all patients received eltrombopag and a double blind placebo-controlled phase lasting 24 weeks (for patients with HCV genotypes 2 and 3) or 48 weeks (for patients with HCV genotypes 1, 4 and 6). Patients received either eltrombopag or placebo together with the AVT provided using a combination of P-IFN and RBV. Patients were followed up at 24 weeks after completion of AVT. Patients included in the studies had platelet counts < 75,000/microlitre and haemoglobin concentrations ≥ 11.0 g/decilitre for men and ≥ 10.0 g/decilitre for women. The design of the studies was the same except that P-IFN alfa-2a was used in ENABLE 1 and P-IFN alfa-2b was used in ENABLE 2 and the RBV doses differed. Patients continued in the open-label phase until the platelet count, measured at two weekly intervals was sufficient to commence AVT, ≥ 90,000/microlitre for ENABLE 1 or ≥ 100,000 /microlitre for ENABLE 2. Patients were stratified at randomisation to the AVT phase by HCV genotype, (2 and 3 versus 1, 4 and 6), baseline platelet counts (< 50,000 versus ≥ 50,000/microlitre) and baseline HCV-RNA level (< 800,000 versus ≥ 800,000 IU/ml). An initial daily dose of 25 mg of eltrombopag was increased if necessary, in increments of 25 mg every two weeks to a

maximum of 100 mg daily and patients not achieving the required platelet count after nine weeks did not enter the double-blind phase of the studies. No dose adjustment was required for patients of East Asian origin. Patients achieving the required platelet count were randomised 1:2 to receive either placebo plus AVT (n = 232 [ENABLE 1], n = 253 [ENABLE 2]) or eltrombopag plus AVT (n = 450 [ENABLE 1], n = 506 [ENABLE2]) in the double-blind phase. Post randomisation patients received either P-IFN alfa-2a 180 microgram once weekly together with RBV 800–1,200 mg daily (ENABLE 1) or P-IFN alfa-2b 1.5 microgram/kg once weekly with RBV 800–1,400 mg daily (ENABLE 2)[6]. Dose adjustment of eltrombopag and placebo were permitted to maintain platelet counts at a level sufficient to enable the continuation of AVT, with a maximum permitted dose of 100 mg daily (P-IFN doses were reduced if the platelet count < 50,000/microlitre in adults and permanently discontinued if the platelet count < 25,000/microlitre[11,12]).

The primary endpoint was the number of patients who achieved SVR, determined as the percentage of patients with undetectable HCV RNA both at the end of the double blind placebo-controlled phase and all subsequent visits through to 24 weeks following AVT treatment. SVR, a result of AVT, is a surrogate endpoint as the aim of eltrombopag is to either enable initiation of AVT or to help avoid dose reductions/withdrawals of P-IFN due to thrombocytopenia. Results for the primary endpoint are given in Table 1.

Table 1. Number of patients who achieved SVR for ENABLE 1 and ENABLE 2[6].

Treatment	n	SVR	Adjusted % difference (95% CI)	p-value
ENABLE 1				
Placebo	232	33 (14%)	-	
Eltrombopag	450	104 (23%)	7.9 (2.4–13.4)	0.0064
ENABLE 2				
Placebo	253	32 (13%)	-	
Eltrombopag	506	97 (19%)	6.0 (1.2–10.9)	0.0202
CI: confidence interval; n: intent-to-treat population, patients randomised to receive AVT.				

Pooled results for the primary endpoint showed similar differences between placebo and eltrombopag arms for the stratified subgroups of HCV genotype, baseline platelet counts and baseline HCV-RNA level. Secondary endpoints included the proportion of patients initiating AVT and the number of patients requiring AVT dose reductions. The number of patients randomised to initiate AVT was 682 of 715 (95%) in ENABLE 1 and 759 of 805 (94%) in ENABLE 2. Patients in the eltrombopag treatment arms in the combined ENABLE studies required less AVT dose reduction than those who received placebo which was statistically significant ($p < 0.0001$)[1,4]. SF-36 scores, a measure of health related quality of life (HRQoL) were collected for patients in both ENABLE studies. SF-36 scores were reduced during AVT but use of eltrombopag did not further reduce HRQoL[1].

3.2 Comparative safety

Pooled data from the double blind phases of the ENABLE 1 and 2 studies showed that serious adverse events (SAEs) occurred in 72 of the 484 (15%) patients treated with placebo and in 189 of 955 (20%) of patients receiving eltrombopag[1,4]. The number of patients deaths in the studies was 10 (2%) in the placebo arm and 29 (3%) in the eltrombopag arm. Adverse events (AEs) leading to study withdrawal, occurred for 16 patients (3%) in the placebo arm (21 events) and for 34 patients (4%) in the eltrombopag arm (61 events). Eleven deaths were considered by the investigator to be related to one of the investigational products (either eltrombopag/placebo or P-IFN/RBV) with five deaths attributed to AVT, five attributed to all investigational

products and one attributed to eltrombopag[4]. Eltrombopag was associated with an increased risk of thromboembolic events (TEEs). There were 34 events in 31 eltrombopag-treated patients (3%) and five events in five placebo-treated patients (1%). Portal vein thrombosis was the most common TEE in both treatment groups[2]. Although the majority of patients experiencing a TEE made complete recoveries, one patient in each treatment arm died as a result of TEEs. The number of patients with AEs associated with hepatic decompensation (such as ascites, hepatocellular cancer and hepatic encephalopathy) were 35 (7%) in the placebo arm versus 125 (13%) in the eltrombopag arm[4]. In patients with low albumin levels (≤ 35 g/L) or model for end stage liver disease (MELD) score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease[2]. The rates of development of new cataracts and progression of pre-existing cataracts were greater in patients receiving eltrombopag (74 of 955 [8%]) versus those receiving placebo (24 of 484 [5%])[1,4,6].

3.3 AWTTC critique

- Eltrombopag is the first medicine licensed for this indication and the Committee for Medicinal Products for Human Use (CHMP) observed that the ENABLE studies show that generally eltrombopag causes platelet counts to increase within one week of commencing treatment[4]. Eltrombopag allowed AVT in more than 95% of patients whose baseline platelet counts would have made them ineligible or marginal candidates for P-IFN therapy[6]. The primary endpoint data shows SVR increases of 9% in ENABLE 1 and 6% in ENABLE 2 for eltrombopag versus placebo. The rate of antiviral dose reductions in patients receiving eltrombopag during AVT was 40% less than in those receiving placebo. Adherence to AVT was higher in eltrombopag treated patients, and was shown to be related to a higher probability of achieving SVR[4].
- The Scientific Advisory Group on HIV/Viral Diseases (SAG) agreed that the effect of eltrombopag, though modest, represents an appreciable benefit in the treatment of patients with thrombocytopenia, HCV infection and compensated liver disease; in particular the medicine could assist patients in need of P-IFN based therapy who are currently prevented from initiating AVT due to thrombocytopenia[4].
- CHMP found that the use of eltrombopag was associated with an increase in fatal AEs, increased risk of thromboembolic events and hepatic decompensation. Although patients with poorer prognosis MELD score ≥ 10 [see Glossary] or albumin < 35 g/litre) were at greater risk, they were also those most in need of SVR[4].
- Best standard of care would be patients receiving either no or reduced AVT, however regulatory requirements meant that the patients in the placebo arm of the ENABLE studies received eltrombopag in the open-label phase to allow them to initiate AVT which does not reflect clinical practice[6].
- The standard of care for treatment of chronic HCV genotype 1 has progressed to triple therapy with P-IFN/RBV and protease inhibitors, such as boceprevir or telaprevir which were not licensed at the time of the ENABLE studies and were not used in AVT[4]. The use of eltrombopag with the triple therapy combination is therefore not recommended[2,4]. The SAG recommended further studies be conducted to determine the safety and efficacy of eltrombopag used in conjunction with triple therapy[4].
- In the ENABLE studies patients were only permitted to enter the AVT phase once their platelet level had reached ≥ 90,000 /microlitre or ≥ 100,000 /microlitre which is in line with the Summary of Product Characteristics (SPC) for P-IFN[11,12] but is contrary to the SPC for eltrombopag, which advises platelet counts > 75,000/microlitre should be avoided[2]. However it is reported that some clinicians believe that P-IFN therapy may be initiated below the recommended minima[1]. The SPC for eltrombopag states that during AVT, platelet count should be maintained around 50,000–75,000/microlitre[2].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of eltrombopag plus dual AVT (P-IFN plus RBV) versus standard care in adults with chronic HCV infection who have thrombocytopenia[1]. Standard care is considered to comprise either reduced doses of AVT or best supportive care without AVT. Two main patient groups have been modelled: those with a baseline platelet count < 75,000/microlitre (total population) and a sub-population (40%) with a baseline platelet count < 50,000/microlitre. The model consists of a short term phase based on a decision tree, and a longer term phase based on a Markov health state model.

In the short term phase, the eltrombopag arm is modelled using SVR rates obtained from pooled patient-level data from the ENABLE 1 and 2 studies. Data from a minority of patients with decompensated liver disease prior to randomisation in the ENABLE studies are excluded. Eltrombopag is used initially to elevate platelet counts to the thresholds defined in the ENABLE 1 and 2 studies for initiation of AVT, and then to maintain platelet counts for up to 48 weeks of AVT. As patients in the control (placebo) arms also received initial eltrombopag therapy to elevate platelet counts to the same thresholds, these data alone were not considered appropriate to use to model the standard care arm. Therefore, the company has modelled SVR rates for the standard care arm by reference to a published study Hepatitis Antiviral Long-term Treatment Against Cirrhosis (HALT-C), identified via a systematic literature search, that reported rates of SVR based on cumulative doses of P-IFN alfa-2a received[13]. In the base case analysis, relative risks of SVR estimated from HALT-C are applied to the SVR rates observed in the control (placebo) arms of the ENABLE 1 and 2 studies, to adjust the observed rates of SVR downwards. The company also explores an alternative approach in which the relative risks of SVR are applied to the SVR rates observed in the eltrombopag arms. Patients not achieving an early virological response (EVR) at 12 weeks are assumed to stop AVT within 1 month in the base case analysis. An alternative scenario, in which only 23% of patients not achieving EVR stop AVT (as per the ENABLE 1 and 2 studies), is also explored.

In the longer term phase, patients with chronic HCV progress annually through fibrosis states towards decompensated cirrhosis (incorporating ascites, hepatic encephalopathy and variceal bleeding), hepatocellular carcinoma, liver transplant, and death, based on SVR status determined in the short term phase. The rates of progression through the different health states are based on rates reported in the literature[17–19]; those with SVR move through the model at reduced rates compared to those who failed to achieve SVR in the short-term phase[20].

Utility values for weighting health states in the short term phase of the model are derived from SF-36 data collected at five time points in the ENABLE 1 and 2 studies, which have been mapped to the SF-36 Dimensions (SF-6D) instrument. For the longer-term phase of the model, utility values were obtained from a previous Health Technology Assessment of AVT in patients with mild HCV[17].

A Department of Health PAS has been agreed for eltrombopag, and all analyses employ a confidential discount on the eltrombopag list price. The maintenance dose of eltrombopag in the model is assumed to be 50 mg daily (as the mean dose of 64 mg daily observed in the ENABLE studies was the dose required to maintain the study-specified platelet counts, which were considered to be higher than the platelet counts likely to be required in practice[1]). Treatment duration is that observed in the

pooled ENABLE studies. AVT costs (P-IFN plus RBV) are also based on the doses and durations observed in the ENABLE studies, assuming a mean patient weight of 79 kg. Other costs include monitoring and haematology test costs assumed for eltrombopag. The costs of ongoing AVT monitoring and long-term HCV management and the different modelled health states, are based on those assumed in previous analyses of HCV AVT, inflated to 2011 values[17]. The costs of managing AEs of eltrombopag (thromboembolic events and development of cataracts) have been included. The time horizon of the base case analyses is 50 years (lifetime), with costs and outcomes discounted at 3.5%.

4.1.2 Results

[Commercial in confidence data removed].

The results of the base case analyses, assuming a PAS-agreed confidential discount on the list price of eltrombopag, are presented in Table 2.

In both populations, eltrombopag generated a gain of 0.51 quality-adjusted life-years (QALYs).

Table 2. Base case CUA results and probabilistic sensitivity analyses[1].

	Total population baseline platelet counts < 75,000/microlitre		Subgroup baseline platelet counts < 50,000/microlitre	
	Eltrombopag	**Standard of care**	**Eltrombopag**	**Standard of care**
Total costs	*	£49,634	*	£49,807
Total QALYs	7.15	6.64	6.93	6.42
ICER	*		*	
Probability ICER < £20,000/QALY gained	*		*	
Probability ICER < £30,000/QALY gained	*		*	

*Commercial in confidence figures removed.

ICER = Incremental cost effectiveness ratio (incremental cost per QALY gained) for eltrombopag versus. standard of care

[Commercial in confidence data removed].

A wide range of other sensitivity and scenario analyses has been conducted. Table 3 summarises the key analyses and plausibility considerations for the total population. Results in the subgroup with baseline platelet counts < 50,000/microlitre were generally similar.

Table 3. Key sensitivity/scenario analyses in the total population.

Scenario description	Scenario details	Incremental cost per QALY	Plausibility considerations
Base case		*	The base case analysis is in effect a blended analysis of two distinct and clinically identifiable groups that could be separated: those with genotype 1 HCV and those with other genotype HCV. It is not clear that this is appropriate given that these are distinct and clinically identifiable groups in which the cost effectiveness of eltrombopag is plausibly significantly different. See separate analyses below.
Relative risk for suboptimal /optimal SoC: range = 0.4 to 0.8	As base case but with relative risk for suboptimal SoC/optimal SoC as 0.4 to 0.8. Estimated SoC SVR = 4.8% to 10.1%.	*	Demonstrates sensitivity of analyses to assumed SVR rates. Important given range of uncertainties in data used to model standard of care arm.
Relative risk for suboptimal /optimal SoC = 0.8 in order to estimate the relative efficacy of SoC as 0.51 of that of the intervention arm	As base case but with RR for suboptimal SoC applied to the eltrombopag arm of the ENABLE trial, rather than the placebo arm. Estimated SoC SVR = 10.6%.	*	Demonstrates the sensitivity of the base case analyses to assumptions used to generate SVR for the SoC arm. This approach to generate SVR for the SoC arm would seem to be at least as plausible as the approach adopted for the base case analysis.
Eltrombopag average daily dose as per clinical study	As base case but with dose of eltrombopag of 64 mg/day.	*	Study results driving model are still based on the mean average dose, so assuming lower daily dose in base case model acts to reduce the assumed costs of eltrombopag.
No progression with SVR with CC and full progression with DC	As base case but with 'no progression' selected for compensated cirrhosis and 'full progression' selected for decompensated cirrhosis.	*	Unclear how plausible this is. Company notes expert opinion was that reduced progression was more plausible.
EVR stopping rule as per clinical study	As base case but with EVR stopping rule as per clinical study - mixed clinical practice (approx 23% failed to achieve EVR at 12 weeks stopped AVT within 1 month).	*	Given relatively small change in ICER this assumption alone is not a significant driver of the model.
Duration of eltrombopag during AVT - 75%	As base case but with duration of eltrombopag 75% of AVT.	*	Possible that clinicians would stop eltrombopag earlier than AVT? [Commercial in confidence data removed].

Scenario description	Scenario details	Incremental cost per QALY	Plausibility considerations
Genotype 1 subgroup with triple therapy including a protease inhibitor (PI)	As base case but for genotype 1 patients only and including a PI in addition to P-IFN/RBV. An uplift of 67% is applied to the SVR rate in the eltrombopag arm (SVR = 24.9%). No uplift in SVR is applied to the SoC arm (SVR = 4.1%).	*	There are no efficacy and safety data for eltrombopag in triple AVT setting in patients with genotype 1. Company notes this is an exploratory analysis. It is unclear why only patients taking eltrombopag would benefit from the addition of PI, and not the standard of care arm. [Commercial in confidence data removed]. Highlights the uncertainty associated with the lack of data in this key subgroup of patients.
Genotype 2/3 subgroup with dual therapy	As original base case but for genotype 2/3 patients only and incorporating dual AVT.	*	Would seem to be plausible, although the limitations of the base case analyses still exist.
*Commercial in confidence figures removed. SoC: standard of care; CC: compensated cirrhosis; DC: decompensated cirrhosis.			

4.1.3 AWTTC critique

[Commercial in confidence data removed].

However, there are significant uncertainties in the clinical data available to use in the economic model, which may not reflect the use of eltrombopag or SoC in practice. The approach to derive data for the SoC arm of the model may underestimate the incremental costs per QALY gained in the base case analyses. Further, the base case analysis reflects two distinct, identifiable patient groups: those with genotype 1 HCV and those without. The cost effectiveness of eltrombopag may plausibly differ significantly between these two groups, as demonstrated by exploratory scenario analyses.

Strengths of the economic evidence include:

- The company has conducted systematic literature reviews to inform its approach to modelling and identify parameter values. The modelled pathway appears to be appropriate.
- A wide range of sensitivity and scenario analyses has been conducted to explore some of the key assumptions used in the model.
- A key subgroup analysis has been conducted in those with baseline platelet counts < 50,000/microlitre.

Limitations of the economic evidence include:

- There are significant uncertainties in the efficacy data used to model eltrombopag and standard care:
    - The platelet count thresholds required for P-IFN initiation and dose reduction/discontinuation that were mandated in the ENABLE studies may bias the results in favour of eltrombopag.
    - All patients in the studies were treated with dual AVT, including the 60% of patients with genotype 1 HCV infection who would currently routinely be treated with triple antiviral therapy[6]. The efficacy and safety of eltrombopag in patients with genotype 1 HCV receiving triple antiviral therapy have not been established.
    - The HALT-C study data, used to adjust the ENABLE data to estimate SVR rates for standard of care, recruited patients with genotype 1 HCV infection. This population had mean baseline platelet counts generally

higher than in the ENABLE study population, and were previous non-responders to standard interferon therapy with or without ribavirin[13].

- In the base case analysis, the relative risks of SVR derived from the HALT-C study were, somewhat counter intuitively, applied to the control (placebo) arms of the ENABLE studies, rather than to the eltrombopag arms, to estimate SVR rates for standard care. [Commercial in confidence data removed]. This approach to generate SVR for the SoC arm would seem to be at least as plausible as the approach adopted for the base case analysis.
- The base case analysis of the total population reflects two distinct, identifiable patient groups: those with genotype 1 HCV and those without. There appears to be greater uncertainty in cost-effectiveness in the subgroup with genotype 1 HCV, and the limited, exploratory analyses provided by the company suggest that eltrombopag is less cost effective in that patient group. It is unclear that a blended analysis of these two distinct, identifiable groups, between which there is a plausible difference in cost effectiveness, is appropriate.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any fully published cost effectiveness analyses of eltrombopag in this indication relevant to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Public Health Wales data published in 2013, the prevalence of diagnosed HCV in Wales is reported as around 12,000[5]. Of these, 3.44% (413 patients) are crudely estimated to receive antiviral therapy each year, based on Public Health England figures for the UK[21]. [Commercial in confidence data removed]. In the absence of Welsh incidence data, incident cases are estimated based on Scottish data extrapolated to Wales. [Commercial in confidence data removed]. Eltrombopag is expected to prolong AVT. Based on pooled ENABLE study data, 36% of patients with genotype 1 did not show an EVR by 12 weeks and so discontinued AVT at that time[1].

5.1.2 Results

[Commercial in confidence data removed].

Table 4. Company estimates of net cost implications (including PAS for eltrombopag)

	Total population baseline platelet counts < 75,000/microlitre	Subgroup: baseline platelet counts < 50,000/microlitre
Number of eligible patients	*	*
Uptake (%)	*	*
Treated patients	*	*
Net costs		
Administration and monitoring	£7,159	£3,932
Secondary & tertiary care: Eltrombopag costs	*	*
Secondary & tertiary care: Antiviral therapy costs	£292,618	£170,250
Secondary & tertiary care: PI treatment for genotype 1 patients only (assumed 46% of total population)	£414,379	£240,788
Overall net cost	*	*
*Commercial in confidence figures removed.		

No sensitivity analyses have been conducted.

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the number of eligible patients in Wales, relying on Scottish and English data where necessary.
- A number of assumptions are made in terms of eligible patient numbers and uptake figures, which are subject to uncertainty, as in all budget impact exercises.
- The above estimates are based on the Department of Health PAS-agreed discount price of eltrombopag.

5.2 Comparative unit costs

As eltrombopag is the only treatment currently available for thrombocytopenia in HCV infected adults there are no relevant comparators. The required dose and duration of treatment depend on individual platelet count response and the infecting HCV genotype[2]. The licensed dose range is 25 -100 mg daily, although 86% of patients in the ENABLE studies required 25 - 50 mg daily and the majority achieved target platelet counts within 4 weeks[6]. [Commercial in confidence data removed].

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, eltrombopag (Revolade®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration. The company anticipate that eltrombopag (Revolade®) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission identified, ENABLE-ALL, an open-label extension study using eltrombopag in 27 patients who had previously participated in the ENABLE 1 and

2 studies and had developed thrombocytopenia within the first 12 weeks of antiviral treatment. The majority of the patients were from the placebo arms of the ENABLE studies and had completed 24 weeks of follow-up assessment. ENABLE-ALL completed in June 2013 and data analysis is ongoing[1,23].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 24 February 2014.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Model for end stage liver disease (MELD)[24]
A scoring system used for assessing the severity of chronic liver disease; the score depends on the serum bilirubin and serum creatinine levels.

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