

Case study 5

Revolade and Treatment of Chronic ITP*

Summary

Need

- Idiopathic thrombocytopenic purpura (ITP) causes spontaneous bleeding and bruising of the skin in purple spots (called purpura).
- Chronic ITP occurs in less than 5 in every 10,000 people. Although difficult to be certain, chronic ITP is likely to affect between 3,000 to 9,500 adults in the England.

R&D

- Revolade is a man-made protein which stimulates platelet production.
- Revolade was developed in partnership between and Ligand Pharmaceuticals, illustrating the role of partnerships to bring a product from initial investigation through to market.

Regulatory Approval

- EMA approved Revolade in 2010.
- Revolade is also approved in Australia (in 2010), Canada (in 2011) but much faster in the US, in 2008, using an accelerated approval process.

Payer approval

- Revolade costs around £10,000 per patient per year, but it can be much higher, up to around £30,000 per patient per year.
- The opinions of agencies who consider clinical and cost effectiveness have differed:

NICE, in guidance available in 2010, does not recommend Revolade for people with chronic

immune ITP, because for most people with chronic ITP, eltrombopag does not provide enough benefit to justify its high cost. For people with long-standing chronic ITP that has not been controlled by other treatments, there is not enough evidence on how well Revolade works, or whether it works well enough to justify its cost. Some of the costs per QALY were extreme: £ millions per QALY and even those considered most likely were close to, or above, £100,000 per QALY.

SMC has given Revolade a restricted recommendation, focusing on those with most severe chronic ITP. This reflected their view that there could be a benefit for patients from its delivery (orally compared to injection for other treatments). The manufacturer also identified savings from the use of Revolade in comparison to other treatment. In this case, SMC reviewed cost savings estimated by the manufacture and no cost per QALYs

Both were relatively quick to provide guidance, with each producing guidance in the same year as marketing approval was given to Revolade, in 2010.

Other countries have taken a similar view to NICE: PBAC in Australia has not recommended reimbursement, similarly for CADTH in Canada. However the Province of Ontario is funding Revolade via their Exceptional Access Plan.

Prescription

The precise dosing of Revolade needs careful and expert consideration

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Introduction

Revolade (eltrombopag) is used in the treatment of chronic Idiopathic thrombocytopenic purpura (ITP) and is manufactured by GlaxoSmithKlein (GSK) (EMA, 2011a). It's also used for patients who have had their spleen removed and who do not respond to treatment with medicines such as corticosteroids or immunoglobulins (EMA, 2012g).

In chronic ITP the body reacts against platelets in the blood, adversely affecting the blood clotting process. In a healthy body, a hormone called thrombopoietin stimulates the production of platelets by attaching to certain receptors in the bone marrow. Revolade helps to mimic this action by attaching to and stimulating the same receptors as thrombopoietin, increasing production of platelets (EMA, 2012g).

Revolade was designated an 'orphan medicine' in 2007 (EMA, 2012g). It was approved by EMA in 2010 (EMA, 2012g).

Need

Chronic ITP occurs in less than 5 per 10,000 people (COMP and EMASS, 2011). It is difficult to determine precisely how many adults suffer from the condition, so estimates vary. The Platelet Disorder Support Association (PDSA) give the incidence of adult ITP as 3.3 per 100,000 adults/year (undated), with the prevalence as approximately 9.5 cases. That compares to estimates from NICE (2010c) of chronic ITP occurring in 23.6 per 100,000 adults (aged 18 years and over). The ITP Support Association (undated a) estimates that between 3,000 to 4,000 people have ITP at any one time in the UK, with no significant difference in prevalence on the basis of any particular racial or ethnic group. NICE estimates are higher: approximately 9,500 adults in England. Part of the challenge of estimating patient numbers is the absence of an established UK database (as at 2010) on the number of people affected by ITP (NICE, 2010c).

The precise reason people suffer from ITP is unknown (EMA, 2008). Those with chronic ITP can experience spontaneous bleeding and bruising of the skin in purple spots (called purpura) ITP can be classified as acute or chronic (long lasting), and can occur in both children and adults (EMA, 2008). There are different degrees of severity of the bruising experienced by patients. For example, it can range from small skin spots that occur after small injuries, to spontaneous blood losses (haemorrhages) from the nose, in the gut or in the brain (intracranial haemorrhage), which can be life threatening (EMA, 2008).

Treatment of ITP depends on the form of the disease (acute or chronic) and on the age of onset. Current treatment methods include surgery, consisting of spleen removal (splenectomy), or pharmacological treatment (medicines) (EMA, 2008). Since the spleen is the most important organ where platelets are removed from the blood, splenectomy is performed in order to limit the destruction of the platelets.

Several types of medicines have been approved for use in Europe for the treatment of ITP including Recombinant human soluble Fc-gamma receptor II b (EMA, 2008). There are also examples of recombinant megakariopoiesis stimulating proteins which could be used as treatments for ITP. These proteins are specifically engineered so that they attach to and stimulate the same receptors as thrombopoietin. One such example is Romiplostim (brand name Nplate) which is administered subcutaneously (The ITP Support Association, undated b) and regulates platelet production. Romiplostim has been authorised in Europe since 2009 for adult chronic ITP splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) and may also be as second line treatment for adult non-splenectomised patients where surgery is contra-indicated (EMA, 2011b).

Revolade is a man-made protein, and may act in a different way to other available medicines for ITP (EMA, 2012b).

Research and development

Revolades active ingredient, eltrombopag, was discovered as a result of research collaboration between GlaxoSmithKline (GSK) and Ligand Pharmaceuticals and developed by GSK (Ligand Pharmaceuticals Incorporated, 2010). Ligand Pharmaceuticals is a company which discovers and develops new drugs that address critical unmet medical needs of patients for a broad spectrum of diseases (Ligand Pharmaceuticals Incorporated, 2010).

Regulatory approval

EMA (2012) approved Revolade for chronic ITP in 2010. Approval was on the basis of improvements in platelet counts in two trials. Together these involved a total of 311 adults with chronic ITP. The patients had previously been treated but the

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treatments had not worked or the disease had come back. All of the patients had a platelet count of less than 30,000 per microlitre at the start of the studies (EMA, 2012g). Efficacy in the trials was measured on the basis of platelet counts.

In the first study, 59% of the patients who took Revolade (43 out of 73) had a platelet count of at least 50,000 per microlitre after six weeks, compared with 16% of those who took placebo (6 out of 37) (EMA, 2012g). In the second study, patients taking Revolade were around eight times more likely than those taking placebo to reach a platelet count of between 50,000 and 400,000 per microlitre during the six months of treatment (EMA, 2012g).

Revolate is also approved for use in chronic ITP for those who have an inadequate response or are intolerant to corticosteroids and immunoglobulins in Australia in 2010 (Australian Government, 2010b). Canada approved Revolade in 2011 (Health Canada, 2011).

In the US, Promacta (the US trade name) received initial FDA orphan drug designation in May 2008 and accelerated approval in November 2008 for chronic ITP (GSK, 2011). This Accelerated Approval program offers a pathway to gain provisional marketing approval for therapies that address unmet patient needs. Full approval of the therapy requires completion of post-marketing clinical trials and commitments that verify clinical benefit (GSK, 2011).

Payer approval

Revolade costs £55 per 50 mg tablet (2010 cost in UK). Eltrombopag is available in 28-tablet packs containing 25 mg tablets (£7,70) or 50 mg tablets (£1,540) (NICE, 2010c). The annual cost per patient is around £9,000 (NICE, 2010c). The costs will vary depending upon the individual requirements of people with chronic ITP (NICE, 2010c). The costs can reach £30,030 (SMC, 2010b).

Revolade has been subject consideration for both cost and clinical effectiveness by two key UK agencies: NICE and SMC. Based on our research on the latest guidance from these agencies:

- NICE does not recommend the use of Revolade in chronic ITP.
- SMC has recommended restricted use of Revolade in chronic ITP.

AWMSG (2012) indirectly does not recommend the use of Revolade because it has decided not to appraise given that NICE guidance was expected less than 12 months from projected receipt of submission to AWMSG (as at February 2010). NICE guidance supersedes AWMSG guidance in any case.

We look at each of these in more detail below.

NICE

NICE (2010a) does not recommend eltrombopag for people with chronic immune ITP . NICE (2010b) produced final guidance in 2010 (TA205). The Appraisal Committee concluded that for most people with chronic ITP, eltrombopag does not provide enough benefit to justify its high cost. For people with long-standing chronic ITP that has not been controlled by other treatments, there is not enough evidence on how well eltrombopag works, or whether it works well enough to justify its cost (NICE, 2010a).

The Appraisal Committee (AC) cited uncertainties in the clinical evidence base. For example, that the benefits of Revolade were based on a 26-week trial. In practice however, eltrombopag would not be discontinued after 26 weeks. The long-term effectiveness of eltrombopag for this chronic condition is uncertain (NICE, 2010).

They also noted the relative high costs per QALY of Revolade as an alternative to conventional watch and rescue management: from £77,496 to £545

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million (although £104,100 per QALY gained was considered most plausible) for the splenectomised population and £90,471 to £200million (although £116,800 per QALY gained was considered most plausible) for the non-splenectomised population (NICE, 2010a). These ranges were driven by costs, which could vary substantially. Even the most plausible estimates are much higher than usual ICERs considered cost effective (between £20,000 to £30,000 per QALY).

The AC also considered Revolade for those people with persistent bleeding. However the AC were concerned about applying the evidence from the general chronic ITP population to this subgroup. They also noted that the economic modelling presented by the manufacturer was not consistent with clinical practice for the management of ITP. The AC could not identify circumstances where Revolade could be considered a cost-effective use of NHS resources.

Although there is guidance for AC's to draw on which can allow some flexibility (through End of Life guidance) in the cost per QALY that is considered acceptable value for money, in this case these flexibilities did not apply (NICE, 2010a). The manufacturer did not offer a Patient Access Scheme either.

NICE intends to review their recommendation in June 2013 (NICE, 2010a).

SMC

SMC has recommended restricted use of Revolade in guidance published in 2010. Revolade is recommended in splenectomised patients with chronic ITP who are refractory to other treatments (such as corticosteroids, immunoglobulins). This essentially restricts use to those patients with severe ITP who are at high risk of bleeding. Revolade may also be considered as second-line treatment for adult non-splenectomised patients where surgery is contraindicated (SMC, undated b; SMC, undated a).

The manufacturers submission to SMC focused on bleeding events, rather than the primary clinical outcome of platelet response. Their analysis found, in comparison to Romiplostim (SMC, 2010b):

In the splenectomised population the manufacturer estimated savings of £12,641 and a Quality-Adjusted Life Year (QALY) gain of 0.039.

In the nonsplenectomised population the savings were estimated to be £2,094 and a QALY gain of 0.028.

These results are driven by both costs and benefits in comparison to Romiplostim, which costs between £25,064 – 75,192 per patient per year, vs £10,010 to 30030 for Revolade. Romiplostim is also delivered subcutaneously, whereas Revolade is taken orally.

There was uncertainty in the budget impact, with two scenarios presented by the manufacturer:

- Assuming the lower prevalence rate, there would be net savings of £237k in year 1 (24 patients) rising to £1.2million in year 5 (120 patients).
- Assuming the higher prevalence, there would be net savings of £589k in year 1 (60 patients) rising to £2.9million in year 5 (299 patients).
- These were underpinned by an assumption that market share would rise from 10% year 1 rising to 50% in year 5.

SMC noted that *“there were some weaknesses in the clinical evidence used to drive the economic analysis, the economic case was considered to be demonstrated as eltrombopag would offer an additional treatment option with the benefit of oral administration and, given the orphan status of the drug, greater uncertainty in the economic analysis could be accepted by SMC.”*

International funding

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) who determine reimbursement by the Pharmaceutical Benefits Scheme (PBS), have rejected listing of Revolade (Australian Government, 2010b). PBAC rejected the manufacturers submission for reimbursement on the basis of uncertain clinical effectiveness in comparison with romiplostim (Australian Government, 2010b).

In Canada, the Canadian Drug Expert Committee (CDEC), part of the Canadian Agency for Drugs and Technologies in Health (CADTH) has reviewed Revolade (CDEC, 2011). The committee is made up of drug evaluation experts and public members and provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans. However individual drug plans in Provinces across Canada make their own decision about whether or not to cover a drug (CDEC, 2011). In October 2011, CDEC recommended that eltrombopag olamine, should not be listed by Canada's publicly funded drug plans for the treatment of chronic ITP (CADTH, 2011). This decision was based upon the following three key factors (CDEC, 2011):

1. Three medical studies were reviewed by CDEC in order to make their decisions. All three studies focused on measuring blood platelet counts. The Committee considered blood platelet counts to be less important to patients than the number of bleeding events.
2. There was an absence of good-quality studies which compared eltrombopag with the various other treatments available for ITP.
3. The manufacturer's economic analysis suggested that Revolade is not cost effective compared with standard of care, either for patients who had their spleen removed or those who had not.

Individual Provinces have however provided funding. For example:

Ontario's Ministry of Health and Long-Term Care operate the Ontario Drugs Benefit Program (ODB). In special cases, the Exceptional Access Plan (EAP) covers most of the cost of approximately 850 prescription drug products that are not on the approved ODB. This includes cases where drugs on the ODB list have been tried and do not work; or, where an alternative drug is not available through ODB (Ontario Ministry of Health and Long Term Care, 2012a). Revolade is currently listed under the EAP with a standard approval duration of the initial 1 year (Ontario Ministry of Health and Long Term Care, 2012b).

The reimbursement criteria include (Ontario Ministry of Health and Long Term Care, 2012b):

- Requests for Revolade where the requesting physician has stated that the patient is not a candidate for splenectomy will be assessed on a case-by-case basis.
- The requesting physician must provide rationale for why a splenectomy cannot be considered, and where possible, to include a preoperative/surgical evaluation on the patient's surgical risks to splenectomy, to include consideration of risks of laparoscopic and open surgical interventions if these are available.
- This evaluation must come from a physician who is not the requesting physician.

Others have decided not to fund, for example, in British Columbia BC PharmaCare helps British Columbians with the cost of eligible prescription drugs and designated medical supplies. BC PharmaCare decided in May 2012, to give Revolade a 'non benefit' status (Ministry of Health Services, undated). Consequently, the online formulary database for PharmaCare states that eltrombopag is not covered by the PharmaCare program (British

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Columbia Ministry of Health Services, undated) . In Saskatchewan the Saskatchewan's Department of Health publish annually (with supplementary reports throughout the year) the Saskatchewan Formulary. This is a listing of the therapeutically effective drugs of proven high quality that have been approved for coverage under the Drug Plan (Government of Saskatchewan, 2012b). The list is compiled by the Minister of Health with the advice of the Drug Advisory Committee of Saskatchewan (DACS) and is then prepared, maintained and distributed by the Drug Plan and Extended Benefits Branch. In March 2012, Revolade was listed as a drug that had been reviewed and not approved for listing in the Saskatchewan Formulary (Government of Saskatchewan, 2012a).

Prescription

Prescription requires expertise in treating blood diseases. Prescription needs to consider ethnicity: An exception to this concerns those patients of East Asian descent (such as Japanese, Chinese, Taiwanese or Korean). In these cases the dosage should be half the normal dosage (25 mg once a day) (EMA, 2012g).

After treatment has started, the dose should be adjusted for each patient with the aim of keeping the level of platelets high enough to prevent bleeding (above 50,000 platelets per microlitre). The daily dose should not exceed 75 mg (EMA, 2012g).

Patients should not take any antacids, dairy products or mineral supplements for four hours before or four hours after taking Revolade (EMA, 2012g).