AWMSG Secretariat Assessment Report – Limited submission

Eltrombopag (Revolade®) 25 mg, 50 mg film coated tablets and 25 mg powder for oral suspension

Company: Novartis Pharmaceuticals UK Ltd

Licensed indication under consideration:
Eltrombopag (Revolade®) is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year to < 18 years who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)

Marketing authorisation date: 4 April 2016

Comparator(s)

Off-label use of rituximab (budget impact only)

Limited submission details

AWMSG limited submission criteria were met as this is a minor licence extension for use in patients from the age of 1 year to less than 18 years old.

Clinical effectiveness

- The key evidence supporting the clinical effectiveness of eltrombopag is derived from two randomised, double-blind, placebo-controlled studies (PETIT2 and PETIT). Both studies investigated the efficacy, safety and tolerability of eltrombopag as an add-on therapy to standard treatment in paediatric patients (ages 1 to < 18 years) with previously treated chronic ITP; with PETIT2 considered the pivotal study and PETIT as the supporting dose-finding study.
- Ninety-two subjects were enrolled in the 13week randomised period (eltrombopag [n = 63]: placebo [n = 29]). Twenty-eight (97%) patients receiving placebo and 59 (94%) eltrombopag, entered the open-label, second stage; the eltrombopag-only period. The majority of subjects (78%) received two or more prior therapies, with corticosteroids, immunoglobulins, and rituximab being the most common.
- A statistically greater proportion of patients receiving eltrombopag in the PETIT2 study achieved a sustained platelet response (≥ 50 x 10^9/L in the absence of rescue) for at least six of eight weeks (75% of study duration) between weeks 5 to 12 of the randomised period (39.7%) compared with those receiving placebo (3.4%). Overall, data provided are indicative of a clinical benefit for the paediatric population with chronic ITP following treatment with eltrombopag. The data obtained support that the effect of eltrombopag is in line with that in the adult population, eltrombopag achieves an increase in the platelet count to a level considered enough to control the risk of bleeding.
- The main uncertainty highlighted by Committee for Medicinal Products for Human Use (CHMP) concerned the relevance of the results with regards to what extent the effect is maintained in the long term. In PETIT2, of the 26 subjects who responded in the randomised period, 50% responded for 20 of 24 weeks in the open-label eltrombopag period. Overall, 75% of the subjects responded for at least 18 of 24

weeks.

- Overall, incidence of bleeding was decreased whilst on eltrombopag; suggesting fluctuations in platelet count may not be associated with an increased risk of bleeding.
- CHMP acknowledge that since the target platelet count will be decided in clinical practice by the patient's individual bleeding risk and the current Summary of Product Characteristics recommends continuous monitoring and dose adjustments based on platelet counts, these are appropriate risk reduction measures to avoid under or over-treatment.
- The safety profile in the paediatric population appears similar to that in adults, although there seems to be higher incidence of some adverse events such as upper respiratory tract infections and neutropenia in the paediatric population. However, due to the limited number of patients and the lack of long-term follow up data, CHMP have highlighted the need to follow the Risk Management Plan.
- The doses needed for children were broadly similar to those needed for adults. Increased liver enzyme concentrations led to drug discontinuation for 5 of 92 patients and were most frequent in East Asian patients; the abnormal liver test results resolved after patients stopped taking eltrombopag. In their submission the applicant company acknowledge that liver function tests and eye examinations might be necessary, particularly when eltrombopag is used in combination with steroids.

Budget impact

- Based on the information provided by a clinical expert in Wales, the company estimate [commercial in confidence data removed] patients would be eligible to be prescribed eltrombopag per annum, with an actual uptake of eltrombopag among the paediatric population in Wales of 10% in year 1, rising by 10% each year to Year 5. Therefore, [commercial in confidence data removed] paediatric patients are estimated to receive eltrombopag in Year 1, increasing to [commercial in confidence data removed] patients by Year 5.
- The company suggest that these patients would currently be offered rituximab therapy (100 mg weekly for 4 weeks [1 course]), or in rare cases, splenectomy. If approved for use in Wales, eltrombopag would be considered at this second-line stage of treatment, in replacement of rituximab.
- The budget impact therefore of treating paediatric patients with eltrompobag (at an average dose of 50 mg daily) in comparison to one course of intravenous rituximab ranges from [commercial in confidence data removed] in Year 1 to [commercial in confidence data removed] in Year 5 based on a Patient Access Scheme (PAS) price considered with NICE technology appraisal 293.
- There are several assumptions which have been highlighted in the company submission which have not been incorporated in to the calculations. For example, no estimation has been made of the numbers of patients who reach 18 years of age during their treatment; dose reductions or discontinuation of treatment have not been included; also no hospital administration costs have been included for rituximab (giving sets, saline etc.).

Additional information

- Eltrompobag 25 mg and 50 mg tablets have been licensed for use in adults with

chronic ITP since March 2011.

- A UK ITP registry has been set up in order to try and address the lack of data relating to the incidence and prevalence of paediatric ITP. It is a multi-centre study designed to collect prospective data on all new cases of childhood ITP.
- AWTTC is of the opinion that, if recommended, eltrombopag is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.
- The company do not anticipate that eltrombopag will be supplied by a home healthcare provider.
- Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily.
- It should be noted that the 25 mg powder for oral suspension will not be available until later in 2016.

Evidence search

Date of evidence search: 13 June 2016
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Eltrombopag (Revolade®) 25 mg,50 mg film coated tablets and 25 mg powder for oral suspension. Reference number: 2692. September 2016.