**New Medicine Review**

**Rituximab for the treatment of adults with idiopathic (immune) thrombocytopenic purpura (ITP)**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Rituximab (MabThera)</th>
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</thead>
<tbody>
<tr>
<td>Document status</td>
<td>Final</td>
</tr>
<tr>
<td>Date of last revision</td>
<td>16 July 2015</td>
</tr>
<tr>
<td>Proposed Sector of prescribing</td>
<td>Secondary care, Haematology</td>
</tr>
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</table>

**INTRODUCTION**

The Bedfordshire and Luton Joint Prescribing Committee (JPC) issued a set of recommendations on the use of rituximab for the treatment of adults with refractory idiopathic thrombocytopenia purpura (ITP) in January 2011. These recommendations were then superseded as the commissioning responsibility for the use of rituximab in this indication moved to NHSE.

As of 2015, The commissioning responsibility now lies with the Clinical Commissioning Groups (CCGs). NHSE had not issued any recommendations on the use of rituximab in ITP before the...
commissioning responsibility changed, hence a review of the place in therapy is required.

The National Institute for Health and Care Excellence (NICE) published an evidence summary on rituximab for the treatment of immune (idiopathic) thrombocytopenic purpura in October 2014. This was based on one meta-analysis and three subsequent studies (two randomised controlled trials and one retrospective cohort study). The information within this bulletin is primarily based on this NICE evidence summary.

Immune (idiopathic) thrombocytopenic purpura is an autoimmune condition characterised by increased platelet destruction and, in many cases, inadequate platelet production. The condition can result in low platelet counts and bleeding. In a blood test, a normal platelet count is between 150 and 400×10⁹ per litre. Bleeding does not usually occur until the platelet count is below 30×10⁹ per litre.

Immune thrombocytopenic purpura can be classified according to duration of the condition as newly diagnosed, persistent (lasting between 3 and 12 months) and chronic (lasting 12 months or more). In adults, the condition typically has a gradual onset with no preceding viral or other illness, and it is usually chronic. In children, the condition is normally short-lived and around two-thirds of children recover spontaneously within 6 months.

The UK incidence of adult immune thrombocytopenic purpura is estimated to be around 120 per year and 3000–3500 people are affected at any one time in England and Wales. In children, it is estimated that around 4 in every 100,000 develop immune thrombocytopenic purpura each year. People with the condition maybe asymptomatic or have symptoms including spontaneous bruising, mucosal bleeding and, in severe cases, gastrointestinal or intracranial bleeding.

An international working group report (Rodeghiero et al. 2009) states that the major goal of treatment for immune thrombocytopenic purpura is providing a safe platelet count that prevents major bleeding, rather than trying to correct the platelet count to normal levels. The report suggests that suitable primary end points in studies in immune thrombocytopenic purpura should include complete response (defined as a platelet count of at least 100×10⁹ per litre and the absence of bleeding) and response (defined as a platelet count of at least 30×10⁹ per litre and double that of baseline, and the absence of bleeding). Secondary outcomes suggested in the report include adverse events, need for rescue treatments, rates of splenectomy, bleeding scales, and health-related quality of life assessment.

For adults that need treatment, first-line options include corticosteroids, intravenous immunoglobulin and intravenous anti-D immunoglobulin (although specialist opinion suggests this is rarely used in the UK). Second-line options include azathioprine, ciclosporin, cyclophosphamide, danazol, dapsone, mycophenolate, rituximab, vinca alkaloids, and splenectomy. Newer therapies for immune thrombocytopenic purpura include the thrombopoietin receptor agonists eltrombopag and romiplostim.
Key points

- Rituximab is not licensed for treating immune thrombocytopenic purpura and so use for this indication is off-label. Although it is available as a solution for intravenous infusion and as a subcutaneous injection, only the former has been utilised in the studies included in the NICE evidence review.

- Most of the evidence for using rituximab in adults with immune thrombocytopenic purpura comes from observational studies, with no comparator arm. The pooled overall response to rituximab reported in a meta-analysis was 57% at one year (40% complete response) but there was a large variation in the response rates reported by individual studies (ranging from 0 to 100%). The populations in the included studies varied, as did the platelet count considered to represent an overall response or complete response. This, in addition to the moderate to high heterogeneity noted in the analyses, could have affected the results.

- The results of the RCTs discussed in the NICE evidence summary varied – one reported no statistically significant difference between rituximab and placebo for treatment failure, response rates, or quality of life (however limited by potential unblinding, small sample size and short duration) whereas the other reported benefit from the addition of rituximab to dexamethasone in terms of response at 6 months (however also small and unblinded; relevance to UK unclear as steroids are often used first-line whereas rituximab is usually a second-line treatment; plus prednisolone usually the steroid of choice).

- Due to the limitations of the individual studies and the heterogeneity reported in the meta-analysis, it is difficult to draw firm conclusions from the evidence on the efficacy of rituximab for the treatment of immune thrombocytopenic purpura.

- There are limited longer-term data on the use of rituximab in the treatment of immune thrombocytopenic purpura. Median follow-up in the studies included in the meta-analysis was 9 months (range 2.3 to 65 months) and the subsequent two RCTs and cohort study reported findings up to 12 months.

- Adverse effects highlighted in the evidence summary do not differ from those that have already been described in the Summary of Product Characteristics.

- Most studies used the standard dose of 375mg/m² BSA IV rituximab given weekly for four weeks. A single course (four doses) would be associated with drug costs of around £4900 (excluding VAT and assuming wastage). Some studies used a lower dose of rituximab (100mg weekly for four weeks); this would be associated with drug costs of around £700. There would be additional administration costs to consider alongside this, and further dosing of rituximab for relapses may increase costs.

- It is difficult to compare the cost of rituximab (usually given only as one course of treatment) with other second-line drug treatments for immune thrombocytopenic purpura (usually need to be given
The only other treatment for immune thrombocytopenic purpura that is a one-off treatment aimed at inducing long-term remission is splenectomy. By comparison, the cost to commissioners of an elective splenectomy is estimated to be in the range of £3252 to £4548, depending on the complexity of the procedure.

- In practice, rituximab is usually considered as a second-line option in the treatment of immune thrombocytopenic purpura. An international consensus report considers it as one of a number of second-line treatment options for adults; others include azathioprine, ciclosporin, cyclophosphamide, danazol, dapsone, mycophenolate, vinca alkaloids, and splenectomy. First-line options include corticosteroids, intravenous immunoglobulin and intravenous anti-D immunoglobulin (latter rarely used in the UK). Not all of these drug treatments are licensed for treating immune thrombocytopenic purpura in adults and most of the evidence for using these agents is from non-randomised or descriptive studies.

### The intervention

#### Mechanism of action

The effect of rituximab in immune thrombocytopenic purpura is thought to be related to B-cell depletion leading to inhibition of B-cell activities such as production of platelet autoantibodies\(^1\).

Rituximab has also been shown to up-regulate regulatory T cells (Auger et al. 2012)\(^3\).

### Licensed indication

Rituximab (MabThera) concentrate for solution for infusion is currently licensed for the treatment of adults with non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis\(^4\).

The use of rituximab for the treatment of immune (idiopathic) thrombocytopenic purpura is regarded as an "off-label" use.

### Formulation/Available Products

Rituximab is available as a solution for intravenous infusion, and as a subcutaneous injection. Studies included in the NICE evidence review used the intravenous formulation of rituximab, therefore only this formulation is reviewed in this summary\(^1,4\).

### Usual dosage

Usual dosage is 375mg/m\(^2\) weekly for 4 weeks, although there have been some reports describing fixed dose of 100mg per week for 4 weeks\(^1\).

### Treatment alternatives/place in therapy

There are currently no published British Committee of Standards in Haematology guidelines for the treatment of idiopathic thrombocytopenic purpura. Previous guidelines issued in 2003 have now been archived.

NICE TA 221 (April 2011) – Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura contains the following extracts:

- Clinicians in the UK treat people with ITP as needed with ‘rescue therapies’ (corticosteroids, intravenous immunoglobulins and platelet infusions) and thereafter, as needed, with ‘active treatments’ (rituximab, immunosuppressive agents including azathioprine, mycophenolate mofetil and ciclosporin, danazol, dapsone, and cytotoxic agents including cyclophosphamide and vinca alkaloids).
“The Committee noted that the pathway of care for ITP varies depending on the person's circumstances, and that no single standard treatment pathway is used in routine practice. The clinical specialists stated that clinicians increasingly prescribe rituximab as the first choice of active treatment; that azathioprine would be used for people whose condition is refractory to rituximab or who are intolerant of rituximab; that cyclophosphamide and ciclosporin were considered too toxic; and that people do not tolerate vinca alkaloids and danazol well and were considered unlikely to benefit from them.”

### Future alternatives

<table>
<thead>
<tr>
<th>National guidance</th>
<th>NICE TA 221 (April 2011) - Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NICE have recommended Romiplostim as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated), only if:</td>
</tr>
<tr>
<td></td>
<td>- their condition is refractory to standard active treatments and rescue therapies, or</td>
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<td></td>
<td>- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies and</td>
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<td></td>
<td>- if the manufacturer makes romiplostim available with the discount agreed in the patient access scheme.</td>
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</tbody>
</table>

**NICE TA 293 (July 2013) - Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (review of technology appraisal 205)**

NICE has recommended eltrombopag as an option for the treatment of adults with chronic immune (idiopathic) thrombocytopenic purpura, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated), only if:

- their condition is refractory to standard active treatments and rescue therapies, **or**
- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies **and**
- the manufacturer provides eltrombopag with the discount agreed in the patient access scheme.

**NICE has not issued any recommendation for the use of rituximab (MabThera) in patients with chronic immune (idiopathic) thrombocytopenic purpura.**

### Local Guidance

Prior to a move of the commissioning responsibility to NHSE, the Bedfordshire and Luton Joint Prescribing Committee (JPC) issued the following recommendation (agreed Jan 2011):

“to recommend the use of rituximab high dose (375mg/m²) and fixed
low dose (100mg) for refractory idiopathic thrombocytopenia purpura (ITP) third line use. Clinicians would be asked to collect audit data on benefits of treatment when using the high dose and fixed low dose regimens.”

**Evidence for use**

**Clinical evidence**

The evidence described below has been taken from the NICE evidence summary (Oct 2014). This discusses the findings of a meta-analysis, two RCTs and one retrospective cohort study looking at the use of rituximab for the treatment of idiopathic thrombocytopenia purpura in adults.¹

The systematic review and meta-analysis investigated using rituximab before splenectomy in adults with primary immune thrombocytopenic purpura.² The review included 19 studies (n=368) in adults who had immune thrombocytopenic purpura and were receiving rituximab before splenectomy. Only 4 of the included studies were randomised. The remaining studies were prospective and retrospective observational studies with no comparator arm. Consequently no comparisons of rituximab with other treatments were made in the review. Participants in the included studies differed in the duration of their immune thrombocytopenic purpura, their age, sex and previous treatments they had received. Most studies used rituximab at a dosage of 375 mg/m² body surface area weekly for 4 weeks, 1 study used dose escalation from 35 to 375 mg/m², and 3 studies used different schedules (1−4 cycles). Two studies used a lower fixed dose of 100 mg weekly for 4 weeks.

Overall response rate and complete response rate after treatment with rituximab were reported in the primary assessment. Overall response was defined as a platelet count of greater than $50 \times 10^9$ per litre. The definition of complete response varied in the included studies and was considered as either a platelet count of greater than $100 \times 10^9$ per litre, or greater than $150 \times 10^9$ per litre. Overall response and complete response at 1 year, response time, mean platelet count at response, and duration of response were also reported. Median follow-up was 9 months (range 2.3 to 65 months). Pooled overall response rate was 57% (n=368, 95% confidence interval [CI] 48 to 65%) after rituximab treatment (time point ‘after’ not further defined), and 57% (n=157, 95% CI 35 to 76%) at 1 year after rituximab treatment. However there was a large variation in the reported overall response rates in the individual studies (16−100% after rituximab, and 33−85% at 1 year after rituximab treatment). Heterogeneity was moderate or high in all analyses, except for the analysis including only studies that provided individual data, which had no heterogeneity.

Pooled complete response rate was 41.5% (n=346, 95% CI 33 to 50%) after rituximab treatment (time point ‘after’ not further defined), and 40% (n=108, 95% CI 31 to 49%) at 1 year after rituximab treatment. However, there was a large variation in the reported complete response rates in the individual studies (0−86% after rituximab, and 0−48.4% at 1 year after rituximab treatment). Again, heterogeneity was moderate or high in all analyses, except for the analysis including only studies that provided individual data, which had no heterogeneity. Mean time to response was 6.34 weeks (n=36, 95% CI 2.83 to 9.85 weeks). The mean platelet count increased to $200 \times 10^9$ per litre (n=54, 95% CI 129
to 271x10⁹ per litre), and the median duration of response was 49 weeks (n=36, 95% CI 17 to 60 weeks).

Arnold et al. (2012) reported a pilot double-blind, placebo-controlled randomised trial of adjuvant rituximab or placebo in 60 adults (median age 40 years) with newly diagnosed or relapsed primary immune thrombocytopenic purpura who had not received a splenectomy, and who had a platelet count of less than 30x10⁹ per litre (median baseline platelet count 15x10⁹ per litre)⁸. Participants were randomised in a 1:1 ratio to iv rituximab 375 mg/m² body surface area (n=33) or saline placebo (n=27) once weekly, for 4 weeks. Allocation was concealed. Participants also received standard treatment for up to 8 weeks with 1 or more of: corticosteroids; intravenous immunoglobulin; intravenous anti-D immunoglobulin; romiplostim; or platelet transfusions. One participant in each group withdrew consent after randomisation, before receiving any study treatment. The primary outcome was treatment failure, defined as the composite of any of: platelet count below 50x10⁹ per litre; significant bleeding or administration of rescue treatment because of severe thrombocytopenia; bleeding; or a planned invasive procedure. Significant bleeding was defined as bleeding of grade 2 severity, where grade 0=no bleeding, grade 1=mild bleeding, and grade 2=marked bleeding) from any site that occurred since the last study visit. Secondary outcomes included quality of life, complete response rate (defined as a platelet count of at least 100x10⁹ per litre) and overall response rate (defined as a platelet count of at least 30x10⁹ per litre with doubling from baseline) and without rescue treatment at 6 months. For the primary composite outcome of treatment failure, there was no statistically significant difference between the rituximab and placebo groups (65.6% of people in the rituximab group compared with 80.8% people in the placebo group; relative risk [RR] 0.81, 95% CI 0.59 to 1.11).

At 6 months, there was no statistically significant difference between the groups for complete response rate (53.1% in the rituximab group and 46.2% in the placebo group; RR 1.15, 95% CI 0.68 to 1.95) and overall response rate (62.5% in the rituximab group and 73.1% in the placebo group; RR 0.86, 95% CI 0.60 to 1.22). No statistically significant treatment effect for change in quality of life summary scores was found (p=0.45 for physical domains; p=0.32 for mental domains).

Two serious adverse events (serum sickness and accidental fall) were reported in the rituximab group, and 1 serious adverse event (adrenal haemorrhage) was reported in the placebo group. Infusion reactions were more common with rituximab than with placebo (20 reactions reported in the rituximab group, compared with 10 in the placebo group).

Gudbrandsdottir et al. (2013) reported an open-label RCT of rituximab plus dexamethasone, compared with dexamethasone alone, in 137 adults (median age 51 years in the rituximab plus dexamethasone group, and 58 years in the dexamethasone alone group) with newly diagnosed primary immune thrombocytopenic purpura who had not received a splenectomy, and who had a platelet count of 25x10⁹ per litre or less, or 50x10⁹ per litre or less and concomitant bleeding symptoms⁹. Participants were randomised 1:1 to a combination of rituximab 375 mg/m² body surface area once weekly for 4 weeks plus dexamethasone 40 mg daily for 4 days (n=63) or to the same dosage of
Dexamethasone alone (n=74). A protocol amendment allowed 'non-responders' in both arms to repeat dexamethasone treatment every 1 to 4 weeks for a total of 6 cycles. The method of randomisation was not described in enough detail to determine if allocation was concealed. The primary outcome was sustained partial (defined as a platelet count of at least $50 \times 10^9$ per litre) or complete (defined as a platelet count of at least $100 \times 10^9$ per litre) response at 6 months' follow-up. Secondary outcomes included time to relapse, time to rescue treatment, and rates of splenectomy.

In an intention-to-treat analysis (total number of participants not reported; included participants that had died or withdrawn from the study because of adverse events), the proportion of people whose condition achieved a sustained partial or complete response at 6 months' follow-up (the primary outcome) was 57% in the rituximab plus dexamethasone group, compared with 35% in the dexamethasone monotherapy group (p=0.01). At 12 months' follow-up, sustained partial or complete response was achieved in 53% of people in the rituximab plus dexamethasone group, compared with 33% of people in the dexamethasone monotherapy group (p<0.05). There was a statistically significantly longer time to rescue treatment in the rituximab plus dexamethasone group compared with the dexamethasone monotherapy group (p=0.007). In people who had initially achieved a partial or complete response, median time-to-rescue treatment was 7.4 months in the dexamethasone monotherapy group, and was not reached in the rituximab plus dexamethasone group after 48 months of follow-up. There was no difference between the groups in number of people who had a splenectomy (6/62 [10%] people in the rituximab plus dexamethasone group compared with 5/71 [7%] in the dexamethasone monotherapy group, p=0.8).

The most common adverse events reported in either group were fatigue, dizziness, headache, epigastritis and anxiety. Muscle or joint pain, and fever were statistically significantly more common in the rituximab plus dexamethasone group, whereas anxiety was more common in the dexamethasone monotherapy group (all comparisons p<0.05). There were statistically significantly more serious adverse events in the rituximab plus dexamethasone group, compared with the dexamethasone monotherapy group (16 events [including 1 death], compared with 9 events [including 3 deaths] respectively, p=0.04). One person in the rituximab plus dexamethasone group and 2 people in the dexamethasone monotherapy group withdrew from the study because of adverse events.

A retrospective cohort study (Moulis et al. 2013) compared rituximab 375 mg/m$^2$ body surface area weekly for 4 weeks with splenectomy for treating primary immune thrombocytopenic purpura in 105 adults$^{10}$. Rituximab was mainly used to treat persistent immune thrombocytopenic purpura (lasting from 3 to 12 months), whereas splenectomy was mainly used to treat chronic immune thrombocytopenic purpura (lasting more than 12 months). People treated with rituximab were older and had more comorbidities than people treated with splenectomy. The primary outcome was a composite of death from bleeding or infection, and hospitalisation for bleeding or infection. Secondary outcomes included overall mortality, mortality from bleeding, hospitalisation for bleeding, hospitalisation for infection, response and complete response rate at 3 and 12 months, loss of
response and loss of complete response. Mean follow-up was 8.4±4.7 years in the splenectomy group and 3.0±1.9 years in the rituximab group. The primary composite outcome occurred in 14/43 (32.6%) people in the rituximab group, and 11/62 (17.7%) people in the splenectomy group. After adjusting for propensity score, there was no difference between the groups for the primary outcome (p=0.7), overall mortality, or hospitalisation for bleeding (p values not reported). Response rate (defined as a platelet count of at least $30 \times 10^9$ per litre and the absence of bleeding and absence of other treatments for immune thrombocytopenic purpura) was statistically significantly greater in the splenectomy group than in the rituximab group at 3 months (91.4% compared with 69.8% respectively, $p=0.005$) and 12 months (87.9% compared with 59.0% respectively, $p=0.001$).

Complete response rate (defined as a platelet count of at least $100 \times 10^9$ per litre and the absence of bleeding and absence of other treatments for immune thrombocytopenic purpura) was also statistically significantly greater in the splenectomy group than in the rituximab group at 3 months (82.8% compared with 39.5% respectively, $p<0.0001$) and 12 months (81.0% compared with 35.9% respectively, $p<0.0001$). Maintenance of response and complete response was statistically significantly higher in the splenectomy group compared with the rituximab group (adjusted $p<0.0001$ for both comparisons).

Seven people in the rituximab group were hospitalised for infection (5 people with pneumonia, 1 with staphylococcus septicaemia, and 1 with hepatitis E virus infection), compared with 6 people in the splenectomy group (2 with septicaemia and 4 with enterobacteria infections). The authors report that there was no significant difference between the groups in hospitalisations for infection; however no statistical analysis was reported.

**Evidence following publication of the NICE evidence summary**

Subsequent to this evidence summary from NICE, a prospective registry report by Khellaf et. al (2014) has described the use of rituximab in 245 patients with ITP with a view to evaluating safety. A total of 173 patients received rituximab 375mg/m$^2$ weekly for 4 weeks, whilst 72 patients received 2 fixed 1g infusions 2 weeks apart – the choice of regimen was based on physician preference, and not patient characteristics. Overall, 38 patients showed minor intolerance to rituximab infusions; infusions had to be stopped for only 3 patients. Seven showed infection (11 cases), with an incidence of 2.3 infections/100 patient-years. Three patients died of infection 12 to 14 months after rituximab infusions, but the role of rituximab was questionable. In total, 152 patients (61%) showed an overall initial response (platelet count $\geq 30 \times 10^9$/L and $\geq 2 \times$ baseline value). At a median follow-up of 24 months, 96 patients (39%) showed a lasting response.

**Safety**

For full details of cautions, contraindications and side effects please refer to the Summary of Product Characteristics.

Serious infections, including fatalities, can occur during rituximab therapy, and rituximab is contraindicated in people with an active, severe infection, and in people who are severely immunocompromised.

Very rare cases of fatal progressive multifocal leukoencephalopathy
have been reported after use of rituximab and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition.

Adverse effects highlighted in the evidence summary do not differ from those that have already been described in the Summary of Product Characteristics.

<table>
<thead>
<tr>
<th>Costs</th>
<th>Rituximab (Single treatment course)</th>
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<tbody>
<tr>
<td>Tariff status</td>
<td>100mg/10ml = £175 and 500mg/50ml = £873.15 (MIMS July 201514);</td>
</tr>
<tr>
<td>Activity costs</td>
<td>• Standard dose of 375mg/m²;</td>
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<tr>
<td></td>
<td>Based on the average body surface area of 1.86m² as stated by NICE, £4890 for 4 doses administered at weekly intervals for 4 weeks</td>
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<tr>
<td></td>
<td>• Lower dose 100mg weekly = £175 per dose = £700 for 4 doses in 1 month</td>
</tr>
<tr>
<td>Licensed treatments administered on a continual basis:</td>
<td></td>
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<tr>
<td>Romiplostim</td>
<td>250mcg = £482 (MIMS July 201514)</td>
</tr>
<tr>
<td></td>
<td>Based on an average weight of 80kg as used by NICE, £150 to £1500 once weekly, or £600 to £6000 for 4 weeks</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>28x25mg= £770; 28x50mg tablets = £1540 (MIMS July 201514); 50mg/day to 75mg/day = £1540 to £2310 28 days</td>
</tr>
<tr>
<td></td>
<td>Dose: initial 50mg/d adjusted according to platelet count, up to maximum 75mg/d= £1540- £2310 per month</td>
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<tr>
<td>N.B.</td>
<td>Doses are for general comparison and do not imply therapeutic equivalence</td>
</tr>
<tr>
<td>Cost effectiveness</td>
<td>No published data identified.</td>
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<tr>
<td>(if available)</td>
<td>According to the NICE evidence summary, comparing the cost of rituximab to other second-line drug treatment is difficult because it is usually given as only 1 course of treatment and is intended to induce long-term remission, whilst other second-line treatments usually need to be given continuously. The only other treatment that is a one-off treatment aimed at inducing long-term remission is splenectomy. By comparison, the cost to commissioners of an elective splenectomy is estimated to be in the range of £3252 to 4548 depending on the complexity of the procedure.</td>
</tr>
<tr>
<td>Potential number of patients in Bedfordshire and Luton Impact per 100,000 population</td>
<td>Exact number of patients within the Bedfordfordshire and Luton population is unknown.</td>
</tr>
<tr>
<td>Affordability considerations</td>
<td>The UK incidence of adult immune thrombocytopenic purpura is estimated to be around 120 per year and 3000 -3500 people are affected at any one time in England and Wales.</td>
</tr>
</tbody>
</table>
**Decision from other bodies**

None identified.

NICE - New evidence summary available, but as rituximab is not licensed for ITP, NICE will not undertake a technology appraisal.

SMC – Not considered.

AWMSG - not considered.

**Comments sought from**

**CCGs**

Hertfordshire Medicines Management Committee (HMMC)

www.hertsvalleysccg.nhs.uk

HMMC recommend use in line with previous JPC policy.

Cambridgeshire and Peterborough Joint Prescribing Group (CPJPG) www.cambsphn.nhs.uk/CJPG.aspx

Group Prior Approval available. Funded in the following clinical circumstances:

- refractory to standard active treatments and rescue therapies OR
- have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies
- undergoing a planned surgery with known co-morbidity of severe ITP requiring a short treatment course to bring platelets up to a safe level prior to surgery

Milton Keynes Prescribing Advisory Group (MKPAG)

www.formularymk.nhs.uk

Rituximab should be available for such patients, at the lowest clinically effective dose. As evidence does not clearly indicate the best position of rituximab in the patient care pathways, it is essential that the use of rituximab for these indications is monitored together with patient outcomes.

Northamptonshire Prescribing Advisory Group (NPAG)

www.corbyccg.nhs.uk

None found.

**Evidence strengths and limitations**

Most of the evidence for using rituximab in adults with immune thrombocytopenic purpura comes from observational studies, with no comparator arm. The populations in the included studies varied, as did the platelet count considered to represent an overall response or complete response, and the place of rituximab in the treatment pathway. The RCTs discussed in this evidence summary were in relatively small numbers of people and had other limitations such as being open-label, or participants being able to guess treatment allocation.

In the RCT by Gudbrandsdottir et al. (2013), the corticosteroid used in the study was dexamethasone. Specialist opinion suggests that prednisolone is the most widely used corticosteroid for treating immune thrombocytopenic purpura in the UK. Therefore the relevance of these findings to UK practice is unclear.
Consult Summary of Prescribing Characteristics for full prescribing detail.

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

References:

4. MabThera SPC (rituximab); Date of revision = 23 May 2014
12. Romiplostim SPC (Nplate with reconstitution pack); Date of revision = December 2013
13. Eltrombopag SPC (Revolade); Date of revision = 5 May 2015
## Appendix 1 - Search Strategy

### 1. NICE

### 2. EMBASE and Medline

<table>
<thead>
<tr>
<th></th>
<th>EMBASE</th>
<th>Medline</th>
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<td>*IDIOPATHIC THROMBOCYTOPENIC PURPURA/</td>
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### 3. UpToDate

### 4. BNF

### 5. Electronic medicines compendium

### 6. eMims

### 7. MICROMEDEX
### Treatment assessed (July 2015): 
**Rituximab (MabThera) for the treatment of adults with idiopathic (immune) thrombocytopenic purpura (ITP)**

The Committee concluded that there was not a clear evidence base to favour any one approach in the treatment of ITP and therefore the recommendations should adopt a pragmatic approach and allow clinician discretion of whether to use rituximab as a second line or third line agent.

**JPC Recommendation:**
- Steroids and intravenous immunoglobulin remain the first line treatments for ITP.
- Second line treatment choices include rituximab, eltrombopag or romiplostim. Clinicians can use their clinical discretion when choosing the most appropriate second line treatment option for individual patients.

#### 1) Clinical Effectiveness

Most of the evidence for using rituximab in adults with immune thrombocytopenic purpura comes from observational studies, with no comparator arm. The populations in the included studies varied, as did the platelet count considered to represent an overall response or complete response. The RCTs discussed in this evidence summary had a number of limitations, including small numbers of participants.

A systematic review of mainly observational studies (n=368) suggests that rituximab can increase platelet levels in adults with immune thrombocytopenic purpura; although response rates varied significantly between individual studies. No comparisons with other treatments were made.

An RCT (n=137) suggests that rituximab plus dexamethasone may be better than dexamethasone alone for achieving a sustained response in terms of increased platelet levels in adults with newly diagnosed primary immune thrombocytopenic purpura.

Another RCT (n=60) shows that rituximab is no better than placebo for preventing treatment failure in adults with immune thrombocytopenic purpura once standard treatment was stopped.

A retrospective cohort study (n=105) suggests that there is no difference between rituximab and splenectomy for the composite outcome of death from, or hospitalisation for, bleeding or infection in adults with immune thrombocytopenic purpura.

#### 2) Cost Effectiveness

No published data identified.

#### 3) Equity

No issues identified.

#### 4) Needs of the community

Exact number of patients within the Bedfordshire and Luton population is unknown.

The UK incidence of adult immune thrombocytopenic purpura is estimated to be around...
120 per year and 3000 -3500 people are affected at any one time in England and Wales.

5) Need for healthcare (incorporates patient choice and exceptional need)
Clinicians in the UK treat people with ITP as needed with 'rescue therapies' (corticosteroids, intravenous immunoglobulins and platelet infusions) and thereafter, as needed, with 'active treatments' (rituximab, immunosuppressive agents including azathioprine, mycophenolate mofetil and ciclosporin, danazol, dapsone, and cytotoxic agents including cyclophosphamide and vinca alkaloids).

The Committee noted that the pathway of care for ITP varies depending on the person’s circumstances, and that no single standard treatment pathway is used in routine practice. The clinical specialists stated that clinicians increasingly prescribe rituximab as the first choice of active treatment; that azathioprine would be used for people whose condition is refractory to rituximab or who are intolerant of rituximab; that cyclophosphamide and ciclosporin were considered too toxic; and that people do not tolerate vinca alkaloids and danazol well and were considered unlikely to benefit from them.”

6) Policy drivers
No formal guidance identified.

7) Disinvestment
The only other treatment that is a one-off treatment aimed at inducing long-term remission is splenectomy. By comparison, the cost to commissioners of an elective splenectomy is estimated to be in the range of £3252 to 4548 depending on the complexity of the procedure.

The JPC agreed the following sections within the PCT Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.