AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: rituximab for the treatment of myasthenia gravis: reassessment to include first-line use **(OW12)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
March 2023

Key findings

Licence status
Rituximab is not licensed for treating myasthenia gravis (MG); its use for this indication is off-label.

Clinical evidence
A double-blind, randomised, placebo-controlled study investigated the efficacy and safety of rituximab as an add-on to standard of care in new-onset MG and found that first-line treatment can reduce MG manifestations and reduce the need for rescue medicine. A retrospective cohort study compared the efficacy of rituximab in new-onset vs refractory disease and found that in the new-onset group remission was achieved quicker and fewer rescue therapies were required.

Safety
The short-to medium-term safety of rituximab was found to be in line with previous literature, no new safety signals emerged with the use of rituximab in new-onset generalised MG compared with its use in other indications.

Patient factors
The proposed new regimen is a 500 mg dose of rituximab by intravenous infusion, repeated 6-monthly, according to response. This is a lower dose than has been recommended for refractory disease.

Cost effectiveness
No cost-effectiveness analyses have been undertaken for this indication.

Budget impact
The addition of rituximab to steroid treatment as a first-line treatment for generalised MG is estimated to cost [commercial in confidence figure removed] in Year 1 to [commercial in confidence figure removed] in Year 3. There may be associated cost savings in relation to reducing steroid-related complications, readmission rates and rescue therapy use with treatments such as immunoglobulins or plasma exchange. A scenario analysis has explored the potential for cost savings in Year 1.

Impact on health and social care services
Slight increased use of existing services associated with administering the infusion as a day case with a potential reduction in in-patient bed use for rescue therapies.

Innovation and/or advantages
Rituximab as a first-line treatment represents a potential improvement in patient outcomes compared to current therapy. Emerging evidence and clinical expert opinion suggest this treatment may improve time to symptom control, reduce the use of long-term steroids and reduce the need for rescue treatments.

Background

Rituximab is available through a One Wales interim decision as an off-label fourth-line or later treatment of refractory myasthenia gravis (MG) in adults[1]. A recently published trial suggests that rituximab may be of benefit as a first-line immunosuppressive treatment and at a lower dose than is currently recommended in the guidance for refractory disease[2].

Clinicians in Wales are supportive of using rituximab earlier in the treatment pathway and consider there is an unmet need based on currently available treatment strategies. Rituximab was therefore considered suitable for assessment though the One Wales Medicines process.

Target group

The indication under consideration in this reassessment is rituximab for use as a low dose first-line immunosuppressive treatment for newly diagnosed, antibody positive, generalised myasthenia gravis in adults.

Marketing authorisation date: Not applicable, off-label

Rituximab is not licensed to treat MG; its use in this indication is off-label.

Dosing information

The current One Wales guidance for the treatment of refractory MG recommends a dose of 1,000 mg of rituximab followed by a second 1,000 mg dose two weeks later administered by intravenous infusion. Repeat courses may be given at up to six monthly intervals.

The pivotal evidence supporting the use of rituximab as a first-line treatment (RINOMAX clinical trial) uses a single 500 mg dose administered by intravenous infusion[2]. Clinical experts indicate that patients may require a second dose at 6 months and some patients may need to continue treatment on a 6-monthly basis to maintain symptom control.

Clinical background

MG is an autoimmune disorder of the neuromuscular junction[3]. In MG, antibodies targeting components of the neuromuscular junction, such as acetylcholine receptors (AChR) and muscle-specific kinase (MuSK) receptors located at the post-synaptic muscle membrane, are generated and disrupt normal communication between neurons and skeletal muscles[3]. Without proper neuronal-muscle communication, muscle weakness results and is characterised by a range of symptoms, depending on which muscle groups are affected[3]. MG muscle weakness is aggravated after

activity and improved after rest. The muscle groups affected include those responsible for eye and eyelid movement (which can be affected early), facial expression, chewing, talking, swallowing, breathing control, neck extension and limb movements[4]. Myasthenic crisis may be experienced by approximately 15–20% of people where exacerbation of symptoms is so severe as to necessitate the use of mechanical ventilation and acute treatment with intravenous immunoglobulin (IVIg) or plasma exchange.[4,5].

MG is a heterogeneous condition and the variations in clinical presentation and autoantibody presence allow MG to be categorised into subtypes which both guides the therapeutic approach and informs individual prognosis[3,4,6]. Muscle weakness confined to the ocular muscles defines the less severe ocular form of MG (15% of people) and if this presentation remains stable for 2–3 years, it is unlikely that the disease will become more generalised[3,7]. The more generalised form of MG may also affect bulbar and proximal skeletal muscles. Antibodies to AChR are present in 85% of all people with MG[6,8]. The remainder of people either have antibodies targeting MuSK receptors (7.5% of people), antibodies targeting other components of the neuromuscular junction (for example lipoprotein receptor-related protein 4 [1–2%]) or are seronegative[6].

The prognosis for people with MG is generally good in relation to quality of life, muscle strength and functional abilities[3]. However, the onset of improvement varies greatly from days to months, and some patients have a significant burden of disease[5]. The goals of therapy are symptomatic improvement followed by full or nearly full pharmacological remission (the absence of MG symptoms and signs while receiving therapy)[3]. Myasthenic exacerbations or relapse can occur due to stressors such as infection, surgery and pregnancy, however myasthenic crisis can sometimes be averted with early intervention[5,6].

Incidence/prevalence

Annual incidence of MG is 0.3 to 2.8 new cases per 100,000 people with a mean of 1 new case per 100,000 people[9]. There is some variability in the literature and so this is a broad approximation. Annual incidence is rising but this can be partially attributed to improvements in diagnosis, an aging population and a longer lifespan[10,11]. In Wales this incidence rate equates to 31 (range 9-87) new cases of MG per year[6,12]. In terms of prevalence, there is approximately 15 people in 100,000 who have MG[13].

Clinical experts estimate between 40-50 new patients per year in Wales will be eligible for this treatment, which is slightly higher than the mean incidence rate would predict.

Current treatment options and relevant guidance

The Association of British Neurologists' management guidelines for MG published in 2015 recommend first-line treatment with oral pyridostigmine, followed by oral prednisolone for those people not achieving a satisfactory response[14]. A thymectomy would be considered as first-line treatment for those with AChR antibody positive (AChR+) generalised MG and who are aged under 45 years, ideally carried out within two years of disease onset. For people who do not achieve remission on corticosteroids, or who have significant side effects, an oral immunosuppressant such as azathioprine is recommended. If azathioprine has failed or the patient cannot tolerate it, a second-line immunosuppressive drug such as mycophenolate mofetil,

methotrexate, ciclosporin or rituximab may be used[14]. Clinical expert opinion suggests that mycophenolate mofetil may be used more frequently now in place of azathioprine. None of these immunosuppressive therapies are licensed to treat MG.

International consensus guidance for management of MG published in 2018 and updated in 2020 details treatments for MG that remains refractory after the use of standard immunosuppressive medicines[15]. These include plasma exchange or IVIg infusion, cyclophosphamide and rituximab which are listed as second-line immunosuppressant options. As the effects of plasma exchange or IVIg infusion typically last for a short time they should be combined with other treatments such as other immunosuppressive drugs[14,16].

Eculizumab is a monoclonal IgG2/4K antibody that binds to and inhibits the cleavage of the C5 protein. It is currently licensed for use to treat MG but was not recommended by NICE due to a terminated appraisal[17].

NICE currently have two medicine appraisals scheduled for MG, efgartigimod alfa[18] (expected publication date October 2023) and ravulizumab[19] (expected publication 26 July 2023). Efgartigimod alfa (Vyvgart®) is a human Immunoglobulin G1 antibody fragment engineered for increased affinity to the neonatal Fc Receptor[20]. It is currently available through the Early Access to Medicine Scheme (EAMS) for AChR+ generalised MG, including patients with refractory generalised MG who have failed, not tolerated or are ineligible for licensed treatment[20]. Ravulizumab (Ultomiris®) is a monoclonal antibody IgG2/4K and is licensed as an add-on to standard therapy for patients with generalised MG who are AChR+[21].

Expert clinical opinion sought by AWTTC has suggested rituximab could be used as a first-line treatment for newly diagnosed antibody positive MG with steroids. This is based on emerging evidence suggesting the efficacy of rituximab at this point in the treatment pathway. It is proposed that subsequent treatment options will then be guided by the severity of the disease, more mild disease may follow the traditional approach of using azathioprine and mycophenolate. More severe disease will follow the treatment pathway for refractory disease.

Guidance and related advice:

- NHS England Clinical Commissioning Policy (2018). Rituximab biosimilar for the treatment of myasthenia gravis (adults)[7]
- British Medical Journal Best Practice Guidelines: Myasthenia gravis (2022)[5]
- Myasthenia Gravis Foundation of America. International consensus guidance for management of myasthenia gravis (2020)[15]
- Myasthenia gravis: Association of British Neurologists' management guidelines (2015)[14]
- One Wales interim decision: Rituximab for refractory myasthenia gravis (last reviewed 2021)[1]

Summary of evidence on clinical effectiveness

A literature search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC), together with a submission provided by the manufacturer, identified one randomised, double-blind, placebo-controlled study and one retrospective cohort study. These studies are briefly described below.

Efficacy

The RINOMAX clinical trial was a double-blind, randomised, placebo-controlled study to investigate the efficacy and safety of rituximab as an add-on to standard of care in patients with new-onset generalised MG[2]. Eligible patients were 18 years or older with a Quantitative Myasthenia Gravis (QMG) score of 6 or more (QMG is a 13 item scale each item is scored from 0 (no impairment) to 3 (severe impairment) total score ranges from 0-39) and a Myasthenia Gravis Foundation of America (MGFA) classification of II to III (mild to moderate weakness) and symptom onset within the previous twelve months (people who had ocular symptoms for longer than 12 months were also potentially eligible provided the duration of their generalised symptoms was shorter). Patients were excluded from the study if they had MGFA I (ocular only) or IV (severe weakness), had received a prior thymectomy or had a suspected thymoma based on radiology findings. Participants were randomised to either the rituximab group (n=25) or the placebo group (n=22). The majority of patients (n=20) were AChR+ and 2 patients were also MuSK negative. Rituximab was administered as a single 500 mg intravenous infusion at baseline. Prednisolone use was allowed, tapered down to 10 mg/day by study week 8, and was not to exceed 40 mg/day throughout. Treatment with intravenous immunoglobulins or plasma exchange within the first eight weeks was not considered rescue treatment. A requirement for a prednisolone dose exceeding 40 mg/day or other immunomodulatory treatments after eight weeks was classified as rescue treatment.

Assessments were performed at baseline, and at 16, 24, 36 and 48 weeks, and efficacy was evaluated using QMG, Myasthenia Gravis Activity of Daily Life (MG-ADL), and Myasthenia Gravis Quality of Life (MG-QoL) scores. The primary outcome measured was a QMG score of 4 or less at week 16, prednisolone 10 mg/day or less and no rescue treatment. The primary outcome was met by 71% of the rituximab group, and 29% of the placebo group (probability ratio, 2.48, 95% confidence interval (CI),1.20-5.11; p = 0.007). There was no difference between the rituximab arm and the placebo arm in terms of the predefined secondary endpoints: change in QMG, MG-ADL and MG-QoL. Fewer patients in the rituximab group required rescue treatment compared with placebo (1 of 25 [4%] in the rituximab group vs 8 of 22 [36%] in the placebo group). Additionally, no patients in the rituximab group required hospitalisation for MG exacerbations, compared to three in the placebo group, one of whom required invasive ventilation.

A 2020 cohort study assessed whether the response to rituximab differed with new-onset vs refractory disease[22].The main outcome was time to remission defined as a QMG score less than or equal to 2. Data was collected prospectively from 72 patients, of whom 24 had received rituximab within 12 months of disease onset, and 48 received rituximab at a later point, 34 of whom had previously had an inadequate response to at least one immunosuppressant. Patients with the MuSK form of myasthenia gravis were excluded. For the first intravenous infusion of rituximab, three patients received 1000 mg, 57 received 500 mg and 12 received 100 mg based on differing protocols used. Subsequent intravenous infusions were given at a dose of 500 mg for all but three patients who received 100 mg. The mean observation time following rituximab initiation was 15 months in the new-onset group and 23 months in therapy-refractory cases. Median time to remission was shorter for the new-onset group vs refractory group (7 vs 16 months; hazard ratio [HR], 2.53; 95% CI, 1.26-5.07; P = 0.009 after adjustment for age, sex, and disease severity), and fewer rescue therapies were required for the new-onset group during the first 24 months.

Data was also collected on a control cohort of MG patients treated with conventional immunotherapies. Patients with new-onset MG receiving rituximab therapy (n=24) went into clinical remission significantly faster than patients in the control group (n=26) receiving conventional immunotherapies (7 vs 11 months: HR, 2.97; 95% CI, 1.43-6.18; P =0.004 after adjustment).

Safety

Adverse events associated with rituximab, reported in ≥ 1 in 10 people, include bacterial and viral infections, neutropenia, leukopenia and thrombocytopenia, infusion related reactions, nausea, pruritis, fever, headache and decreased immunoglobulin G levels[23]. Cases of hepatitis B reactivation have been reported in people receiving rituximab; screening should be performed in all people prior to treatment[23]. A drug safety alert was issued in 2014 following cases of progressive multifocal leukoencephalopathy (PML), this is listed as a very rare adverse event in the Summary of Product Characteristics[24]. The risk of PML may be increased with increased use of immunosuppressive drugs[25].

In the RINOMAX trial there was a higher occurrence of adverse events in the rituximab arm compared to placebo (81 vs 44), although the number of severe adverse events was similar (6 vs 4)[2]. One patient in the rituximab arm died of a pre-existing heart condition, and two patients in the placebo arm recovered from events defined as life-threatening (cardiac arrest in the context of an MG exacerbation and septicaemia, respectively).

The safety of rituximab for use in MG has been reported for a previous One Wales recommendation (2019)[1]. No safety issues effecting the recommendation were identified in any of the subsequent reviews. There were no new safety concerns reported with rituximab in the RINOMAX trial or the Brauner cohort study[2,22].

Discussion

- The RINOMAX trial results suggest rituximab can reduce MG manifestations and reduces the need for rescue medicine in the AChR+ form of MG when rituximab is used as a first-line agent, however patient numbers were small and there is a lack of longer term follow up.
- As the RINOMAX clinical trial included mainly patients with AChR+ MG, there is a lack of clinical evidence for using low dose rituximab first-line for patients with MuSK+ MG. There is evidence in the refractory setting that MuSK+ MG responds favourably to rituximab treatment and patients often do better than those with AChR+ disease[26,27]. This view is supported by clinicians in Wales. BEATMG a placebo-controlled randomised study of rituximab in refractory AChR+ MG did not reach its clinical endpoint[28]. However, results have been mixed, with evidence of benefit for this sub group of patients[29].
- In the RINOMAX study there were differences between the two treatment arms at baseline. The placebo group were generally younger (mean 10 years), had higher AChR titers (70.7 vs 25.1 nmol/L) and a higher proportion were classified as MGFA III (65% vs 47%), indicating more severe disease. More patients in the rituximab group had late-onset disease. The effect of these differences at baseline on outcomes is unclear.
- The current recommended dosing regimen for fourth-line use of rituximab is 1000 mg administered by intravenous infusion, followed by a second 1000 mg

dose two weeks later. Repeat courses can be given in six-month cycles. The RINOMAX trial utilised a single 500 mg intravenous infusion. There is currently a lack of evidence supporting the use of the lower 500 mg dose in refractory MG patients.

- According to guidelines, most patients require years of treatment with immunosuppressants such as azathioprine, with the aim to establish a minimally effective dose[5]. This can expose patients to side-effects over long periods. Using a 500 mg dose of rituximab with a steroid as first-line therapy may reduce the need for long term immunosuppressant treatment, although there is a lack of longer-term data to support this assumption.

Cost-effectiveness evidence

No studies on the cost-effectiveness of rituximab were identified for this indication.

In a recent international study undertaken in adults (n=841), the impact of MG on HRQoL from the perspective of the patient was collected using a mobile application[30]. General and disease-specific patient-reported outcome measurements included: EuroQol 5 Domains Health Related Quality of Life Questionnaire (EQ-5D-5L), MG-ADL, MG-QoL, Hospital Anxiety and Depression Scale (HADS) and Health Utilities Index III (HUI3). Patients were categorised by their self-assessed MGFA class. MGFA class was a strong predictor of all aspects of HRQoL, more severe disease was associated with a greater impact on QoL. The domains in which patients with MG most frequently mentioned problems were usual activities, anxiety and depression, tiredness, breathing and vision. The mean total MG-ADL Score, a measure of daily function, was higher (worse) for patients with a higher MGFA (more severe disease). Mean baseline EQ-5D-5L utility was also associated with MGFA classes and was 0.817, 0.766, 0.648 and 0.530 for MGFA class I–IV. Due to the method of data collection, older patients and those with severe visual difficulties or poor dexterity were under represented in the study.

In a 2015 HRQoL update study in MG patients from Norway and the Netherlands[31], current treatment with non-steroid immunosuppressive drugs affected physical composite scores (PCS) negatively independent of disease activity (p-value <0.05 when adjusted for age, sex and disease activity). Prednisolone alone did not lower the PCS, but did so in combination with other immunosuppressive medicines (p = 0.002)[31]. The authors concluded that despite an increase in immunotherapy choices since the last population study conducted in 2001 there was no associated improvement in quality of life for MG patients.

The RINOMAX clinical trial analysed MG-QoL scores as a secondary endpoint, measuring at baseline and at week 16 of treatment. There was a trend in favour of the rituximab group over placebo in improving QoL; rituximab arm −9.2, placebo arm −7.0 p= 0.47 95% CI −2.2 (−8.2 to 3.8) but this was not statistically significant[2].

Budget impact

The dosing regimen for the considered indication of rituximab is a 500 mg intravenous infusion. This may be repeated at 6-monthly intervals. The confidential NHS Wales contract price (excluding VAT) for a 10 mg/ml 50 ml vial is [commercial in confidence text removed]. Clinical experts have estimated between 40-50 new patients will start treatment each year, for simplification this higher figure has been

used in the budget impact. Steroid costs have not been included in the calculation as the rituximab is an add-on therapy. Two scenarios have been included, one assuming all patients receive a second dose of intravenous rituximab 500 mg at 6 months (table 2a) and one assuming that 25% of patients receive a second dose of intravenous rituximab 500 mg (table 2b). In both scenarios, patient numbers are assumed to fall by 50% at the third and then the fourth dose and all patients still requiring treatment after the fourth dose are assumed to require ongoing 6-monthly treatment.

Table 1: Estimated annual cost for 500 mg intravenous rituximab per patient in Wales

	Medicine acquisition cost	Administration costs	Total annual cost per patient†	Cost per patient over 3 years
Rituximab (single 500 mg infusion)	¶¶	£527 initial infusion* £471 repeat infusions**	¶¶	¶¶
2020-2021 National Schedule of Reference Costs: *Deliver Simple Parenteral Chemotherapy at first attendance (HRG code SB12Z); **Deliver Subsequent Elements of a Chemotherapy Cycle (HRG code SB15Z) Prices are confidential NHS Wales contract listings (including VAT) †Patients may require up to two doses annually ¶¶ commercial in confidence figure removed				

Table 2a: Total estimated annual costs for rituximab assuming 100% of patients require repeated dose after 6 months, 50% at 12 months, 50% at 18 months and 100% beyond

	Year 1	Year 2	Year 3
Number of new patients treated with rituximab	50	50	50
Number of patients receiving repeated doses at 6 months onwards	50	88	114
Total annual costs for rituximab	¶¶	¶¶	¶¶
Assumes 100% of patients require a second dose at 6 months; of these 50% receive a third dose at 12 months; of these 50% receive a fourth dose 18 months; all of patients who receive rituximab at 18 months are assumed to continue to receive rituximab every six months in Year 3 (doses five and six). ¶¶ commercial in confidence figure removed			

Table 2b: Total estimated annual costs for rituximab based on 25% of patients receiving a repeated dose after 6 months, 50% at 12 months, 50% at 18 months and 100% beyond

	Year 1	Year 2	Year 3
Number of new patients treated with rituximab	50	50	50
Number of patients receiving repeated doses at 6 months onwards	13	24	32
Total annual costs for rituximab	¶¶	¶¶	¶¶
Assumes 25% of patients require a second dose at 6 months; of these 50% receive a third dose at 12 months; of these 50% receive a fourth dose 18 months; all of patients who receive rituximab at 18 months are assumed to continue to receive rituximab every six months in Year 3 (doses five and six). ¶¶ commercial in confidence figure removed			

Estimated costs indicate treatment with rituximab would be associated with a total increased annual spend of [commercial in confidence figure removed] in Year 1 to [commercial in confidence figure removed] in Year 3 when compared to steroid use alone.

Budget impact issues

- The budget impact has not considered incidence, treatment discontinuation or mortality rates.
- Additional costs of any rescue treatments patients may require have not been included in the calculation. In the RINOMAX trial rescue treatments were more frequently used for patients in the placebo group (8 [36%]) vs the rituximab group (1 [4%]). Treatments used in the placebo group included high-dose steroids (5), plasmapheresis (1), IVIg (6) and rituximab or tocilizumab (5). The patients in the rituximab group received high-dose steroids as a rescue treatment. Three patients in the placebo group experienced MG exacerbations that required hospitalisation (one requiring invasive ventilation) compared with none in the rituximab group. These associated offset costs will have an impact on the overall budget impact. The NHS reference cost for plasmapheresis treatment for a course of 5 exchanges would be £663.02; one cycle of IVIg (2 g/kg administered over 5 days) based on the NHS Wales contract price is [commercial in confidence figure removed]. A hospital stay including an intensive care unit (ITU) stay would be between £17,515.01 and £18,081.01, depending on whether this includes an emergency visit to A&E. A scenario analysis (see appendix 1) has been undertaken whereby the rate of hospitalisations and use of rescue treatments have been applied based on those in the RINOMAX study to a population receiving rituximab compared with steroid alone. The results suggest that if the study reflects actual response rates, rituximab could be cost saving in Year 1. However, this does not take in to account any associated side effects or monitoring requirements. Overall there is limited evidence to support this assumed benefit and benefits

have not been modelled after Year 1 due to a lack of longer-term data in the study.
- Screening, monitoring and adverse event costs are also excluded from the budget impact.
- The primary endpoint of the RINOMAX study was minimal disease manifestation, part of which required that the prednisolone dose was 10 mg per day or less. A reduced use of steroids may result in a reduction in the adverse events associated with steroid use, however any potential benefit of reduced steroid use has not been considered in the budget impact analysis.

Additional factors

Prescribing unlicensed medicines

Rituximab is not licensed to treat this indication and is therefore prescribed 'off label'. Providers should consult relevant guidelines in prescribing unlicensed medicines before any off-label medicines are prescribed.

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Appendix 1

Table 3: Total estimated annual costs for rituximab and rescue treatment compared with standard care and rescue treatment assuming 100% of patients require repeated dose of rituximab after 6 months

	rituximab + steroid	steroid alone
Number of new patients treated with rituximab	50	50
Total annual costs for rituximab	¶¶	
Number of cases receiving high dose steroid rescue treatment in Year 1	2	11
Total cost of high dose steroid rescue treatment	£35.42	£194.83
Number of cases receiving rituximab rescue treatment in Year 1	0	11
Total cost of rituximab rescue treatment	£0	£6,087.40
Number of cases receiving IVIg rescue treatment in Year 1	0	14
Total cost of IVIg rescue treatment	£0	¶¶
Number of cases receiving plasmapheresis rescue treatment in Year 1	0	2
Total cost of plasmapheresis rescue treatment	£0	£1,326.04
Number of cases requiring ITU admission (via A&E) in Year 1	0	1
Total cost of ITU (via A&E) admission in Year 1	£0	£18,081.01
Number of cases requiring ITU admission (via ward) in Year 1	0	1
Total cost of ITU (via ward) admission in Year 1	£0	£17,515.01
Total treatment costs including rescue therapy	¶¶	¶¶

High dose steroid costs assume at least two weeks on 60 mg/day, then weaned down to maintenance dose, using BNF costs.
Rituximab costs assume 1 dose of 500 mg using contract costs.
IVIg based on 2 g/kg (76.9 kg patient), rounded down to 15 vials administered over 5 days using SB14Z and SB15Z national reference costs and NHS Wales contract price for IVIg infusion (10g).
Plasmapheresis assuming 5 treatments using 2-9 costs from national reference.
ITU (A&E) stay includes ambulance, A&E visit, 1 week (one organ affected) on ITU, more than 2 days inpatient stay, using national reference costs.
ITU (ward) stay includes 1 week (one organ affected) on ITU, more than 2 days inpatient stay, using national reference costs.
¶¶ commercial in confidence figure removed