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

Bendamustine in combination with rituximab (MabThera®) for the treatment of previously untreated and relapsed indolent lymphomas

April 2017
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ONE WALES INTERIM COMMISSIONING DECISION

Bendamustine in combination with rituximab (MabThera®) for the treatment of previously untreated and relapsed indolent lymphomas

Date of advice: April 2017

The following Interim Pathways Commissioning Group (IPCG) recommendation has been endorsed by health board Chief Executives.

Bendamustine in combination with rituximab can be made available within NHS Wales for the treatment of previously untreated and relapsed follicular lymphoma, marginal zone lymphoma and Waldenstrom's macroglobulinaemia under the following circumstances:

- In the first-line setting, for use in fit patients with aggressive follicular lymphoma and marginal zone lymphoma as an alternative to rituximab plus cyclophosphamide, vincristine and prednisolone (R-CVP).
- In the relapsed setting, for use in patients with follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.
- For the treatment of Waldenstrom's macroglobulinaemia for first-line and relapsed disease in patients deemed unsuitable for anthracycline-based regimens and/or where other licensed and health technology appraisal-approved regimens are unsuitable.

Bendamustine in combination with rituximab is not a licensed regimen to treat these indications and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before these medicines are prescribed in combination.

The risks and benefits of the off-label use of bendamustine with rituximab for these indications should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

New safety alert
Following this recommendation, in May 2017 a letter was sent out to healthcare

professionals from Astellas in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA). The letter highlighted new safety information regarding a risk of increased mortality associated with use of bendamustine when used in non-approved combination treatments or outside approved indications. Fatal toxicities were mainly due to opportunistic infections. Prescribers should consult the safety information prior to prescribing. All suspected adverse drug reactions (ADRs) that are serious or result in harm should be reported to the MHRA via the Yellow Card Centre Wales.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

One Wales advice promotes consistency of access across NHS Wales.

KEY FINDINGS: This is an abbreviated summary of the evidence provided to IPCG

Report background
Bendamustine is available through NHS England's Cancer Drugs Fund for off-label use in the treatment of untreated and relapsed low grade lymphoma, in people for whom standard treatment is unsuitable. According to the Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication.

A cohort of patients has been identified through data from individual patient funding request (IPFR) panels and clinicians in Wales consider there is an unmet need within the service. This cohort includes: young and fit people with aggressive, untreated and relapsed follicular lymphoma and marginal zone lymphoma, and Waldenstrom's macroglobulinaemia for whom standard chemotherapy regimens are unsuitable. Based on this unmet need, this medicine combination was therefore considered suitable for assessment via the One Wales process.

Efficacy/Effectiveness
Data from two phase III studies showed that bendamustine plus rituximab is at least not inferior and may be superior to rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) or CVP (cyclophosphamide, vincristine and prednisolone) in the first-line treatment of stage III or IV indolent lymphoma and mantle cell lymphoma, as assessed by progression-free survival or complete response rate. However, in one study non-inferiority was not reached in the indolent non-Hodgkin's lymphoma group as a whole.

Data from a phase III study showed that bendamustine plus rituximab was more effective than fludarabine plus rituximab in treating relapsed indolent lymphomas, giving a longer progression-free survival and median overall survival.

Safety
Bendamustine plus rituximab is associated with high incidences of serious haematological toxicities, in common with other chemotherapy regimens used to treat indolent non-Hodgkin's lymphoma. The phase III studies showed that bendamustine plus rituximab has a safety profile that is distinct from those of the standard chemotherapy regimens, and has some favourable aspects. In the first-line treatment of indolent lymphomas bendamustine plus rituximab showed a generally lower incidence of neutropenia, leukopenia, alopecia and neuropathy than seen in patients treated with rituximab plus CHOP, with a higher incidence of skin reactions and drug sensitivity. A Cochrane review of bendamustine in treating indolent B cell lymphoid malignancies concluded that the risk of grade 3–4 adverse events was similar when bendamustine was compared with CHOP and fludarabine.

Patient factors
Health-related quality of life data showed that first-line treatment with bendamustine plus rituximab was associated with small improvements in functioning compared with standard therapy. No evidence was identified to assess the health-related quality of life in the relapsed setting.

Cost effectiveness
One study was identified assessing the cost-effectiveness of bendamustine plus rituximab and rituximab plus CHOP, and rituximab plus CVP from the UK NHS perspective. Treatment was in the first-line setting. The estimated incremental cost-effectiveness ratio of bendamustine plus rituximab compared to rituximab plus CHOP was £5,249 per quality-adjusted life-year for England and Wales, and £8,092 for bendamustine plus rituximab compared to rituximab plus CVP.

Budget impact
Using national incidence data, the number of patients eligible for treatment has been estimated at 77 patients per annum. This is associated with an annual cost of £44,044 based on bendamustine acquisition costs only because rituximab would be included in any alternative treatment regimens. Additional resource costs for one extra day of medicine administration per cycle for bendamustine will be dependent upon current service capacity. However some patients are already receiving this regimen through IPFR and local arrangements. Sixteen patients across three health boards have accessed this regimen over the last 12 months which would decrease the annual budget impact to £34,892. Accurate figures were not available for the remaining health boards. In addition, comparator regimens are similarly priced and therefore the true net cost is likely to be significantly lower than the above

estimates.

Welsh commercial access agreement
These medicines are currently not licensed for the indication under consideration (i.e. off-label). Therefore a commercial agreement cannot be offered by the relevant companies because the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine.

Impact on health and social care services
Using bendamustine plus rituximab to treat indolent lymphomas, including newly diagnosed and relapsed disease, is expected to have minimal impact on existing services.

Innovation and/or advantages
Bendamustine plus rituximab offers an anthracycline-free regimen for the treatment of indolent lymphomas. It therefore may be suitable for people who are unable to tolerate or who have a contraindication to an anthracycline-based regimen, or who may have reached the maximum cumulative dose of anthracycline at which the risk of chronic cardiotoxicity increases.