Report IMBRUVICA® - Ibrutinib

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Ibrutinib **Brand Name:** Imbruvica **Originator/licensee:** Janssen-Cilag International N.V. **Classification:** NI **ATC code:** L01EL01 **Orphan Status:** **Eu:** No **Us:** / **Mechanism of action:** Ibrutinib works against cancerous B lymphocytes. It blocks an enzyme called Bruton's tyrosine kinase (Btk), which promotes survival of B lymphocytes and their migration to the organs where these cells normally divide. By blocking Btk, ibrutinib decreases survival and migration of B lymphocytes, thereby delaying cancer progression[1].	**Authorized Indication:** **EMA**: Ibrutinib in combination with R-CHOP alternating with R-DHAP (or R-DHAOx) without ibrutinib, followed by ibrutinib monotherapy, is indicated for the treatment of adults with previously untreated MCL who would be eligible for ASCT [1]. **FDA:** / **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 19/06/2025 **FDA M.A. date :** / **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** / --- **ABBREVIATIONS:** **AE**: Adverse Event **ASCT**: Autologous stem cell transplantation **BEAM/TEAM:** carmustine, thiotepa, etoposide, cytarabine, melphalan **CHMP**: Committee for Medicinal Products for Human Use **CI**: Confidential Interval **ECOG**: Eastern Cooperative Oncology Group **FFS**: Failure-free survival **HR**: Hazard Ratio **M.A.:** Marketing Authorization **MCL**: Mantle cell lymphoma **OS**: Oral administration **PFS**: Progression-Free Survival **P.O.**: Positive Opinion **PS**: Performance Status **Pts**: Patients **R-CHOP:** Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone **R-DHAOx**: Rituximab, dexamethasone, cytarabine, oxaliplatin **R-DHAP:** Rituximab, dexamethasone, cytarabine, cisplatin **R-ISS**: Revised International Staging System **SAE**: Serious adverse events **THAM**: Total body irradiation, cytarabine, melphalan **TRAE**: Treatment related AEs **WHO**: World Health Organization	**Summary of clinical EFFICACY:** **TRIANGLE (NCT02858258)** was an open-label, multicentre, randomised, three-arm, parallel-group, superiority, phase III trial to assess whether the addition of ibrutinib to standard immunochemotherapy regimen might improve outcomes in pts. with previously untreated MCL, who would be eligible for ASCT. Eligible pts. were aged 18-65 years with previously untreated MCL, stage II-IV, suitable for ASCT, with an ECOG PS ≤2 and ≥1 measurable lesion. Pts. (n=870) were randomly assigned in a 1:1:1 ratio to three treatment groups: • Immunochemotherapy with ASCT (group A; n=288); • Ibrutinib with immunochemotherapy with ASCT (group A+ I; n=292); • Ibrutinib plus immunochemotherapy without ASCT (group I; n=290). All three groups received induction immunochemotherapy consisting of six alternating cycles of R-CHOP and R-DHAP or R-DHAOx. All cycles had subsequent filgrastim support. ASCT was performed with THAM conditioning or BEAM/TEAM, on investigator's discretion. Ibrutinib was administered 560 mg orally on days 1-19 of the R-CHOP cycles. Pts. received two years of continuous oral ibrutinib 560 mg daily maintenance. In all three study groups, rituximab maintenance for three years could be added according to national guidelines. Randomization was stratified by study group and MCL international prognostic index risk factor. The primary outcome was investigator-assessed FFS in the ITT population. Failure-free survival was defined as time from randomisation to stable disease at end of induction immunochemotherapy, progressive disease, or death from any cause, whichever occurred first. After a median follow-up of 31 months, FFS at three years was 72% for group A and 88% for group A+I and 86% for group I (A vs A+I HR 0.52, 98.3% IC 0.00-0.78; p=0.0008; A vs I HR 1.77, 98.3% IC 0.00-3.76, p=0.9979) [2]. **Summary of clinical SAFETY:** AEs were assessed according to treatment period: induction, ASCT, and maintenance/follow-up. During Induction no relevant differences in grade 3–5 AEs were observed across groups. The most common grade 3–5 disorders were hematologic and lymphatic system disorders (71% of pts. in group A vs 76% of pts. in groups A+I and I combined. Grade 3–5 infections and infestations occurred in 9% (Group A) and 12% (Groups A+I and I combined). During ASCT, the frequencies of grade 3–5 adverse events were also similar between Group A and Group A+I. Hematologic and lymphatic system disorders remained the most common grade 3–5 AEs, reported in 59% of pts. in both groups undergoing ASCT. At 3 years, OS was 86% in Group A, 91% in Group A+I, and 92% in Group I. Causes of death included progressive lymphoma (6% in Group A, 1% in Group A+I, and 4% in Group I) and comorbidities (4% in Group A, 2% in Group A+I, and 2% in Group I) [2]. **Ongoing studies:** ● ***For the same indication:*** No ● ***For other indications:*** Yes **Discontinued studies (for the same indication):** No --- **References:** [1] https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica [2] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)00184-3/fulltext [3] https://gallery.farmadati.it/Home.aspx [4] https://www.ncbi.nlm.nih.gov/books/NBK536985/ [5] https://pmc.ncbi.nlm.nih.gov/articles/PMC3573424/ [6] https://onlinelibrary.wiley.com/doi/10.1111/bjh.19131	**Cost of therapy:** In Italy, 30 tablets of IMBRUVICA® 560 mg cost € 7,299.60 (ex-factory price) [3] . **Epidemiology:** MCL is a rare subtype of B-cell non-Hodgkin lymphoma with an annual incidence of one case per 200,000 people. MCL comprises around 5% of all non-Hodgkins lymphomas. MCL is more common in men (3 to 1), and the median age at diagnosis ranges from 60 to 70 years old[4]. --- **POSSIBLE PLACE IN THERAPY**: The choice of initial therapy for MCL depends on the pt's tolerance to aggressive treatments. Intense chemoimmunotherapy or chemotherapy followed by ASCT are preferred. For pts requiring less intensive therapies (e.g. pts. ineligible for aggressive therapy due to advanced age or comorbidities), other therapeutic options are available: cytotoxic treatment options include chlorambucil, CVP and attenuated CHOP or bendamustine, in combination with rituximab; non-cytotoxic approaches include ibrutinib, lenalidomide, bortezomib and rituximab monotherapy [5,6]. The addition of Ibrutinib to the current regimens could represent an opportunity for those pts. **OTHER INDICATIONS IN DEVELOPMENT:** Graft versus host disease (NCT03474679; NCT02959944); naïve follicular lymphoma (NCT02947347). **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**: - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION: -** *Service reorganization: No *Possible off label use: Yes

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