Report Jakavi® - Ruxolitinib

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Ruxolitinib **Brand Name:** Jakavi **Originator/licensee:**Novartis Europharm Limited **Classification:** NI **ATC code:** L01EJ01 **Orphan Status:** **Eu:** No **Us:** Yes **Mechanism of action:** Ruxolitinib is a potent and selective inhibitor of JAK1 and JAK2, tyrosine kinases involved in cytokine signalling and hematopoiesis. Myeloproliferative neoplasms, such as myelofibrosis and polycythemia vera, are often characterized by aberrant activation of the JAK-STAT pathway, leading to abnormal blood cell counts and thrombotic complications. By inhibiting JAK1 and JAK2, ruxolitinib works to block the dysregulated cell signalling pathways and prevents abnormal blood cell proliferation [1].	**Authorized Indication:** **EMA:** Ruxolitinib is indicated for the treatment of pts aged 12 years and older with aGVHD or cGVHD who have inadequate response to corticosteroids or other systemic therapies [1]. **FDA**: Jakafi is indicated for treatment of:SR-aGVHD in adult and pediatric pts 12 years and older and for cGVHD after failure of one or two lines of systemic therapy in adult and pediatric pts 12 years and older [2]. **Route of administration:** os **Licensing status** **EU CHMP P.O. date:** 24/03/2022 **EU M.A. date:** **FDA M.A. date:** 24/05/2019 for acute GVHD and 22/09/2021 for chronic GVHD **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** Yes --- **ABBREVIATIONS:** **AE:** Adverse Event **aGVHD:** acute Graft-Versus-Host Disease **ASCT**: Allogeneic Stem-Cell Transplantation **cGVHD:** chronic Graft-Versus-Host Disease **CI:** Confidence Interval **ECP**: extracorporeal photopheresis **HCT**: Hematopoietic Stem Cell Transplantation **MSC**: mesenchymal stem cells **OR**: Overall Response, defined as the proportion of pts who had a complete response or partial response. **Pts**: patients **SAE**: Serious Adverse Event **SR**: Steroid-Refractory	**Summary of clinical EFFICACY:** **REACH 2 (NCT02913261)** is a randomized, open-label, phase 3 trial, that enrolled pts ≥12 years of age and recipients of ASCT with grade II to IV SR-aGVHD that involved the use of systemic immunosuppressive therapy. Pts (n=309) were randomly assigned in a 1:1 ratio to receive ruxolitinib 10 mg twice daily (n=154) or a control therapy (n=155)*. The primary endpoint was OR at day 28. OR was significantly higher in the ruxolitinib group than in the control group (62% vs 39%; odds ratio, 2.64; 95% CI, 1.65-4.22; p<0.001) [3]. **REACH 3 (NCT03112603)** is a randomized, open-label, phase 3 trial, that enrolled pts ≥12 years of age, had undergone ASCT, and had moderate to severe SR or –dependent cGVHD. Pts (n=329) were randomly assigned in a 1:1 ratio to receive ruxolitinib 10 mg twice daily (n=165) or a control therapy (n=164)**. The primary endpoint was OR at week 24. OR was higher with ruxolitinib than with control therapy (49,7% 25,6%; odds ratio, 2.99; 95% CI, 1.86-4.80; p<0.001)[4]. **Summary of clinical SAFETY:** **REACH 2**: the most common AEs in the Ruxolitinib group were thrombocytopenia (33% vs 18% in the control group), anemia (30% vs 28%) and cytomegalovirus infection (26% vs 21%). SAEs were reported in 38% and 34% of pts, respectively. AEs led to treatment discontinuation in 11% and 5% of pts, respectively. 47% in theruxolitinib group vs 51% in the control group had died by the data cut-off date. Most deaths were attributed to aGVHD (22% vs 25%) [3]. **REACH 3**: the most common AEs in the Ruxolitinib group were anemia (29% vs 13% in the control group), thrombocytopenia (21% vs 15%) and hypertension (16% vs 13%). SAEs were reported in 33% and 37% of pts, respectively. AEs led to treatment discontinuation in 16% and 7% of pts, respectively. At the data cut-off, 19% of pts in the ruxolitinib group vs 17% in the control group had died. Deaths were due primarily to complications caused by cGVHD or treatment (13% vs 8%) [4]. **Ongoing studies:** • ***For the same indication:***Yes (NCT04934670, NCT05121142, NCT04744116, NCT03491215, NCT05021276, etc.) • ***For other indications:***Yes **Discontinued studies (for the same indication):**No --- **References:** 1. https://www.ema.europa.eu/en/medicines/human/EPAR/jakavi 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202192s023lbl.pdf 3. Zeiser R., Von Bubnoff, N., et al.: Ruxolitinib for Glucocorticoid-RefractoryAcute Graft-versus-Host Disease. N Engl J Med 2020;382:1800-10. 4. Zeiser R., Polverelli N., et al.: Ruxolitinib for Glucocorticoid-RefractoryChronic Graft-versus-Host Disease. N Engl J Med 2021;385:228-38. 5. https://gallery.farmadati.it/ 6. https://www.ncbi.nlm.nih.gov/books/NBK538235/ 7. Malard F., Huang X.J., et al.: Treatment and unmet needs in steroid-refractory acute graft-versus-host disease. Leukemia (2020); 34:1229-1240. 8. Wolff D., Fatobene G., et al.: Steroid-refractory chronic graft-versus-host disease: treatment options and patient management. Bone Marrow Transplantation (2021); 56: 2079-2087. 9. https://adisinsight.springer.com/drugs/800026694 10. https://clinicaltrials.gov/ct2/results?cond=Graft+Vs+Host+Disease&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply	**Cost of therapy:** 56 tablets of Ruxolitinib 10 mg cost € 3.979,36 (ex-factory price) [5]. **Epidemiology:** aGVHD can occur in up to 50% of pts receiving HCT from a human leukocyte antigen-matched sibling. The occurrence is typically higher in unmatched donors. The incidence of cGVHD ranges from 6% to 80%. GVHD is considered one of the main causes of morbidity and mortality after HCT; more than 10% of pts will die from this complication [6]. --- **POSSIBLE PLACE IN THERAPY** There are no standard 2nd line treatments for SR-aGVHD and cGVHD. The options for SR-aGVHD therapy are: ECP, infliximab, etanercept, mechanistic target of rapamycin kinase inhibitors, mycophenolate mofetil, methotrexate, daclizumab, basiliximab, inolimomab[7]. Therapy options for 2nd line SR-GVHD are: ibrunitib, ECP, mycophenolate mofetil, rituximab, ruxolitinib, sirolimus, everolimus, imatinib, methotrexate, pentostatin, IL-2 therapy, pomalidomide, ixazomib, low-dose total lymphoid irradiation, MSC, thalidomide, alefacept, abatacept, tocilizumab, cyclophosphamide, baricitinib, belumosudil, axatilimab [8]. **OTHER INDICATIONS IN DEVELOPMENT** Cytokine release syndrome, Essential thrombocythaemia,SARS-CoV-2 acute respiratory disease [9]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** Yes (NCT04061876). **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION** Ibrutinib, Begelomab, Daclizumab, Itacitinib, Itolizumab [10]. *Service reorganization: No *Possible off label use: Yes

*The type of control therapy was chosen by the investigator from the following options: antithymocyte globulin, ECP, MSC, low-dose methotrexate, mycophenolate mofetil, everolimus or sirolimus, etanercept, or infliximab.

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** The type of control therapy was chosen by the investigator from the following options: ECP, low-dose methotrexate, mycophenolate mofetil, everolimus or sirolimus, infliximab, rituximab, pentostatin, imatinib, or ibrutinib.