Pharmacotherapeutic report, summary

Ruxolitinib (Jakavi®) for the indication 'symptomatic treatment of myelofibrosis'

Recommendation by CVZ dated 22-4-2013, based on Evaluation by the WAR (Scientific Advisory Committee)

The WAR has drawn up a pharmacotherapeutic report for the medicine ruxolitinib (Jakavi®) tablets. Its therapeutic value was determined via comparison with placebo and the best available therapy (BAT) then currently available.

They reached the following conclusions: ruxolitinib has an added value in comparison with placebo or BAT in the treatment of the disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post-essential-thrombocythaemia myelofibrosis.

Medicine. Jakavi®. Tablets with 5 mg, 15 mg or 20 mg ruxolitinib.
Registered indication. "The treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis."
Posology. The recommended starting dose is based on the platelet count: 5 mg ruxolitinib twice daily for patients with 50,000/mm^3 to 100,000/mm^3 blood platelets; 15 mg twice daily if the number of blood platelets is between 100,000/mm^3 and 200,000/mm^3 and 20 mg twice daily if the number of blood platelets is >200,000/mm^3. If efficacy is insufficient and neutrophil counts are adequate, the dose may be increased by a maximum of 5 mg twice daily. The maximum dose is 25 mg twice daily.
Mechanism of action. A selective inhibitor of the Janus Associated Kinases JAK1 and JAK2. JAKs mediate the signalling of a number of cytokins and growth factors that are important for the haematopoiesis and immune function. Myelofibrosis is a myeloproliferative neoplasm known to be associated with dysregulated JAK1 and JAK2 signalling. Blocking the JAK-STAT signalling can reduce the genesis of deviant blood cells, the splenomegaly and the symptoms of the disease.
Specific details. Jakavi® (ruxolitinib) is a registered orphan drug.

Summary of the therapeutic value

Intended effects. The effects of ruxolitinib in treating the symptoms of myelofibrosis were studied in 2 direct comparative studies of patients in a risk category of intermediate-2 or high-risk (IPPS≥ 2).
- After 48 weeks' treatment, a significant reduction in the spleen volume (a spleen reduction of at least 35%) was measured in 28% of the patients in the ruxolitinib group and 0% in the control group with best available therapy (p<0.001). This effect was also seen in the study in which ruxolitinib was compared with placebo (32 weeks follow-up; 41.9% in the ruxolitinib group versus 0.7% in the placebo group; p<0.0001).
- The total symptom score (TSS), measured using the MFSAF, is more favourable for the ruxolitinib group that the placebo group.

After 24 weeks 45.9% of the patients in the intervention group had ≥50% decrease in TSS, while the percentage in the placebo group was 5.3 ($p<0.001$). The measured symptoms include stomach complaints (e.g., due to spleen enlargement) and night sweats (constitutional symptom). Haematological abnormalities, such as anaemia or thrombocytopenia, were not included in this symptom score.

- An improved quality of life was measured. The group treated with ruxolitinib scored better in the EORTC QLQ-C30 and the FACT-lym questionnaires.
- Treatment with ruxolitinib does not result in any survival advantage. No significant difference in survival could be demonstrated between the two groups.

Unintended effects. The adverse drug reactions reported most frequently in the clinical studies were thrombocytopenia and anaemia. In view of the working mechanism of ruxolitinib, cytopenia is to be expected as a side effect. These side effects can be managed by dose adjustment or by a transfusion.

Experience. Experience with ruxolitinib is limited, while ample experience has been gained with most of the comparative treatments (best available therapies).

Applicability. Ruxolitinib is not recommended for children, during pregnancy or breast-feeding. The dose of ruxolitinib should be reduced for patients with severe renal failure or liver function disorders. Interaction can occur between ruxolitinib and strong CYP3A4 inhibitors. Theoretically, interaction is also possible between ruxolitinib and haematopoietic growth factors.

Ease of use. Ruxolitinib is administered orally.

Final conclusion regarding therapeutic value.

Ruxolitinib has an added therapeutic value in comparison with placebo or best available medicinal therapy for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, secondary myelofibrosis after polycythaemia vera, or secondary myelofibrosis after essential thrombocythaemia and a risk category of intermediate-2 or high-risk (IPSS≥2).

Verwijderd: For further information, please contact: PCheung@cvz.nl; warcg@cvz.nl¶

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Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.