NOVARTIS

CINC424, RUXOLITINIB, JAKAVI ®

Ruxolitinib Managed Access Program (MAP) for patients diagnosed with COVID19 and have severe/very severe lung disease

Guidance and information package

This guidance will be sent to each Treating Physician in response to his/her independent request for Ruxolitinib. It should be used as a guidance document for the treatment and monitoring of patients on MAP to ensure adherence to the Novartis safety standards.

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1 Treatment guidance

The purpose of this document is to provide the patient's Treating Physician with all useful known product information to administer ruxolitinib to eligible patients diagnosed with COVID-19 and have severe pneumonia. The patient's Treating Physician must comply with all local health authority regulations before moving forward with a request for a Novartis drug.

The requesting Treating Physician submitted a request for access for a drug in Novartis which was reviewed and approved by the medical team experienced with the drug.

Please refer to the latest Investigator's Brochure (IB) and/or approved product information for overview of drug including non-clinical and clinical experience, risk and benefits, including the following:

- **Currently there is no clinical experience with ruxolitinib in the treatment of severe pneumonia.**
- **Serious Infections Warning: Ruxolitinib is associated with an increased incidence of serious infections. Therefore, patients should be monitored carefully for signs and symptoms of infections during and after treatment with ruxolitinib.**
- **Physicians should exercise caution when administering ruxolitinib to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to severe infections**.

Novartis will continue to provide any new safety information to the Treating Physicians as they emerge. Careful benefit/risk evaluation should be conducted when considering the use of ruxolitinib for unapproved indications, and the access to ruxolitinib will be provided unless experience in COVID-19 patients reveals an unacceptable safety risk.

2 Patient eligibility

2.1 MAP-specific criteria

The following criteria must be fulfilled for the provision of Managed Access:

- An independent unsolicited request should be received from the Treating Physician, Health Authorities, Institutions or Governments;
- The patient to be treated has a COVID-19-related serious or life-threatening disease including CRS;
- There is a potential patient benefit to justify the potential risk of the treatment use, and the potential risk is not unreasonable in the context of the disease or condition to be treated;
- Such access provision as described above is allowed as per local laws and regulations.

2.2 Inclusion criteria

Patients eligible for inclusion in this Treatment Plan have to meet **all** of the following criteria:
Patients eligible for inclusion in this Treatment Plan have to meet **all** of the following criteria:
Written patient informed consent must be obtained **prior to** start of treatment.

1. Patients aged ≥ 6 years

2. Patients clinically diagnosed with SARS-CoV-2 infection, either through positive serum antibodies (IgM or IgG); or by PCR; or by other approved diagnostic methodology. Patients with presumptive diagnosis of COVID-19 (other respiratory causes ruled out and SARS-CoV-2 test pending) may be included.

3. Adult and adolescent patients (≥12years), who meet one of the below criteria

- Respiratory frequency ≥ 30/min
- Oxygen saturation ≤ 93% on room air (FiO2=0.21)
- Arterial oxygen partial pressure (PaO2)/ fraction of inspired oxygen (FiO2) < 300mmHg (1mmHg=0.133kPa) (corrective formulation should be used for higher altitude regions (over 1000m).

  AND

- Patients with lung imaging showing pulmonary infiltrates (chest X-ray or CT scan)

Pediatric patients (≥6-<12 years) who meet one of the below criteria (where appropriate):

- Shortness of breath
- Oxygen saturation <92% on room air (Fi)2=0.21)
- Labored breathing (e.g. wheezing, flaring of nostrils, three concave sign), cyanosis, intermittent apnea.
- Lethargy or convulsions
- Refusal to eat or difficulty with feeding; signs of dehydration

2.3 Exclusion criteria

Patients eligible for this Treatment Plan must not meet **any** of the following criteria:

1. History of hypersensitivity to any drugs or metabolites of similar chemical classes as ruxolitinib

2. Presence of severely impaired renal function defined by serum creatinine > 2 mg/dL (>176.8 µmol/L), or have estimated creatinine clearance < 30 ml/min measured or calculated by Cockcroft Gault equation or calculated by the updated bedside Schwartz equation.

3. Pregnant or nursing (lactating) women.

4. Patients who are NOT able to understand and to comply with treatment instructions and requirements unless health care proxy is able to provide consent.

3 Dosing information

Currently there is no clinical experience with ruxolitinib in the treatment of severe pneumonia, which is not an approved indication.

Route of administration for ruxolitinib is oral.
Patients are recommended to be dosed as follows:

- For patients ≥ 6 - <12 years, dosing is 5 mg QD (once daily)
- For patients ≥ 12 years, dosing is 5 mg BID
- Ruxolitinib will be administered orally once daily/twice per day at the assigned doses based on age group, given as 5-mg tablets. Dosing can be provided without regards to food.
- Recommended duration of treatment is 7 days followed by clinical/radiological evaluation. Treatment could be extended up to 28 days if clinically indicated and the benefits of treatment outweigh the risks.

3.1 Dose modifications

Dose reductions or interruptions for worsening cytopenias attributed to ruxolitinib are permitted in order to allow the patient to continue on the study treatment. Dose adjustments for different ranges of cytopenias are described below.

Neutropenia

Grade 3 (ANC < 750 - 500/mm3):

For patients≥ 12 years, reduce dose to 2.5mg BD, monitor ANC daily until resolved to ≤Grade 2, then resume initial dose level.

For patients ≥ 6 - <12 years, reduce dose to 2.5 mg QD, monitor ANC daily until resolved to ≤Grade 2, then resume initial dose level.

Grade 4 (ANC < 500/mm3): Hold dose, monitor ANC daily until resolved to ≤ Grade 3, then resume with 50% of the dose level. If resolves to ≤ Grade 2, can resume initial dose level.

Thrombocytopenia (transfusion support should be provided as clinically indicated)

For platelet counts < 20,000 mm3: Hold dose until resolved to ≥ 20,000/mm3, then resume at a reduced dose level. If counts are stable, dose may be cautiously re-escalated.

Dose reductions or interruptions for non-hematologic toxicity are permitted in order to allow the patient to continue on the study treatment. Dose adjustments for different ranges of non-hematologic toxicity are described below. The objective of the dose adjustment rules is to optimize treatment response for each individual patient while avoiding significant non-hematologic toxicities.

Other adverse events

Recommendation for Grade 1 or 2: maintain dose level

Grade 3 Recommendation: Reduce dose level 50% until resolved to ≤ Grade 2
Grade 4 Recommendation: Hold dose and then discontinue from study treatment

3.2 Concomitant medications

Use of oral, injected or implanted hormonal methods of contraception are allowed while on ruxolitinib.

All medications and significant non-drug therapies (including herbal/natural medications) administered during treatment should be noted in the patient's record.

The patient must be told to notify the Treating Physician about any new medications he/she takes after the start of ruxolitinib.

3.2.1 Permitted concomitant therapy requiring caution and/or action (if applicable)

Patients may receive: anti-emetics, calcineurin inhibitors, azole fungal prophylaxis, broad spectrum antibiotics (either semi-synthetic penicillin or third generation cephalosporin with vancomycin, gentamycin or equivalent), acyclovir prophylaxis, G-CSF, steroid pre-meds prior to RBC/platelet transfusions, narcotics, and sedatives; however warrant close monitoring of potential drug-drug interaction effects of these concurrent drugs.

Ruxolitinib dose adjustments may be required, particularly in patients treated with CYP450 modulators. Upon initiation of a strong CYP3A4 inhibitor or a dual CYP3A4/CYP2C9 inhibitor including fluconazole up to a dose of 200 mg, the dose of ruxolitinib may be reduced (e.g. by 50%), and more frequent monitoring of hematology parameters and clinical signs and symptoms of ruxolitinib related adverse events is recommended.

The patient and the treating physician should be aware of potential signs of overdose of the concomitant medications and in the event of suspected study drug related toxicity; administration of ruxolitinib should be dose reduced or held according to the treating physician's judgement.

For additional information, please refer to the IB or approved label.

3.2.2 Prohibited concomitant therapy

The following medications are prohibited until treatment discontinuation:

- Concomitant use of another JAK inhibitor
- Any investigational medication
- Aspirin in doses exceeding 150 mg per day is prohibited

Please refer to the IB or approved label for additional information.

3.3 Patient discontinuation

The patient may voluntarily withdraw from treatment for any reason, at any time.

The Treating Physician should discontinue treatment for the patient and/or withdraw the patient from treatment if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

The patient may continue treatment until patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the Treating Physician or withdrawal of consent.

4 Product supply

Product must be received by designated personnel at the treating site, handled and stored safely and properly, and kept in a secured location to which only the Treating Physician and designated site personnel have access. Upon receipt, product should be stored according to the instructions specified in the IB or approved label.

In order to ensure adequate supply, distribute only the required amount for each patient. Do not reserve a full package of ruxolitinib for each patient.

Upon patient discharge, if patient still requires ruxolitinib therapy; dispense only the amount that is required to complete their treatment course.

4.1 Re-supply

In order to receive additional product for the patient, the Treating Physician must submit a MAP Patient Re-Supply/Follow-up Form. Before receiving product, the Treating Physician will review and confirm:

- Patient is deriving continued benefit from treatment and;
- All Adverse Events have been reported as per local laws/regulations and;
- All relevant local approvals have been obtained as required.

The Treating Physician must also submit a MAP Patient Re-Supply/Follow-up Form to inform Novartis of patient discontinuation.

4.2 Disposal and destruction

Destruction of product should follow local laws/regulation. The leftover medication may be directly destroyed at the site or be sent to a local 3rd party within the country with the proper qualifications to perform this task.

5 Recommended patient monitoring parameters / assessments

- Physical Examination with vital signs, height and weight.
- Electrocardiogram (ECG): a standard 12 lead ECG with QTc Interval report.
- Pregnancy Test: Before initiation of ruxolitinib a serum pregnancy test should be performed.
- Hematology including hemoglobin, hematocrit, total WBC count with differential, and platelet count.
- Chemistries including urea or BUN, creatinine, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), calcium, lipase, amylase, potassium, magnesium, and phosphorus.

- Concomitant Medications. Educate patients on the importance of reporting all medications including over-the counter medications. Educate on medications that should be avoided explaining the potential for interaction.
- Adverse events should be monitored continuously from the time of consent including the need for non-invasive or mechanical ventilation with tracheal intubation.

5.1 Recommended assessments

Patients with COVID19 and have severe/very severe disease on ruxolitinib should be monitored daily.

5.1.1 Patient medical and medication history

Relevant medical history on each patient should be provided to Novartis for review prior to inclusion of a patient in the IPR MAP.

Assessment of latent infections (including CMV, EBV, HHV-6, HBV, HCV, BK and tuberculosis) should be made and if present, patients should be monitored closely for reactivation.

5.1.2 Safety and tolerability assessments

Patient informed consent should be collected at baseline.

For women of child-bearing potential serum pregnancy test is recommended before initiation of ruxolitinib

6 Data management

Patients will be treated according to the approved treatment plan. The above mentioned proposed visit schedule is recommended. In line with local regulation some minimal data can be collected in order to increase the data of this population in clinical practice to increase knowledge on this restrict setting.

6.1 Type of data to be collected

The type of data to be collected should be:

1. Medical history
2. Treatment duration
3. Outcome at 7,14 and 28 days
4. Hospitalization duration

6.2 How will data be collected

The physician or assigned personnel should complete a data collection tool that will be provided to the physician.

7.2.1 Database management

The data will be collected through specific forms and will be kept confidential and managed under the applicable laws and regulations. The data collected will be analyzed and could be published by Novartis.

7 Safety reporting requirements

Reporting safety information to the local Health Authority and/or to EC/IRB must follow local regulatory requirements. Reporting of safety information to Novartis must follow the provisions of the MAP Agreement Letter, using the Novartis Adverse Event forms for Managed Access and be done to the respective Novartis Local Patient Safety Department. Details on reporting of safety information are described in section 7.1.

7.1 Adverse event reporting

Treating Physician acknowledges that it is his/her responsibility to report to Novartis Local Patient Safety Department (address below) any relevant information about the safety of the Product, including, but not limited to (a) any Serious Adverse Events (SAEs), and (b) any additional safety reports submitted to the local Health Authority and Ethics Committee / IRB according to the applicable local laws and regulations.

Such safety reporting shall be made to the Novartis Local Patient Safety Department (email: [add local safety mailbox (es)], fax number(s): [add local safety fax number(s)]; online via PSI: https://www.report.novartis.com/)

8 Patient informed consent

The patient informed consent must be obtained in accordance with local regulatory requirements.

- Patient (or parent/legal guardian, if a minor) must give a written, signed and dated informed consent prior to ruxolitinib administration.

- However, if a person needs emergency treatment with ruxolitinib to save their life, and they are incapacitated (i.e. unconscious). The reasons why treatment was necessary should be fully explained to the patient once they have recovered.

9 Ethical considerations and administrative procedures

9.1 Regulatory and ethical compliance

This guidance is designed and should be implemented and reported in accordance with applicable local regulations including European Directive 2001/83/EC, Regulation (EC) No 726/2004 and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

9.2 IRB/IEC/REB

The Treatment Guidance and the proposed informed consent form should be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before treatment start. Confirmation of approval by the IRB/IEC/REB and Informed Consent must be given to Novartis using the Treating Physician Attestation Form. Please follow local laws/regulations as applicable.