August 2019

IMPORTANT PRESCRIBING INFORMATION ABOUT ONCASPAR®(pegaspargase)

Dear Healthcare Professional,

As you may be aware, Servier, a privately-held company governed by a non-profit foundation, has recently acquired ONCASPAR (pegaspargase) from Shire plc. We're pleased to announce that the regulatory transfer is now complete.

We would also like to underline changes in the prescribing information recently approved by the FDA. These changes impact numerous sections of the prescribing information and this letter specifically emphasizes the following points that refer to the safety of the patient.

- Dosage and Administration, Recommended Dosage
- Dosage and Administration, Dose Modifications
- Contraindications

Other sections have also been modified, to comply with the latest format and to include a revised discussion of additional clinical data. Please refer to the full prescribing information provided with this letter.

Dosage and Administration:

Recommended Dose

For patients >21 years the dose has been reduced to 2,000 International Units(IU)/m^2, intramuscularly or intravenously no more frequently than every 14 days. This change was based on studies supporting the adjustment of the dose to 2,000 IU/m^2 to decrease adverse reactions while maintaining sufficient efficacy in the adult population.

The product information reads now as follows:

Patients ≤21 years of age

The recommended dose of ONCASPAR for patients up to and including 21 years of age is 2,500 International Units/m^2 intramuscularly or intravenously no more frequently than every 14 days.

Patients >21 years of age

The recommended dose for adult patients more than 21 years of age is 2000 International Units/m^2 intramuscularly or intravenously no more frequently than every 14 days.

Dose Modifications

This section has been added to provide recommendations on:

- Patient monitoring: monitor the patient at least weekly until recovery from the cycle therapy with bilirubin, transaminases, glucose and clinical examinations.
- If an adverse reaction occurs, the treatment should be modified as follows:

Adverse Reaction	Severity*	Action
Infusion Reaction/ Hypersensitivity Reaction	Grade 1	• Reduce the infusion rate by 50%
	Grade 2	• Interrupt the infusion of ONCASPAR • Treat the symptoms • When symptoms resolve, resume the infusion and reduce the infusion rate by 50%
	Grade 3 to 4	• Discontinue ONCASPAR permanently

Hemorrhage	Grade 3 to 4	• Hold ONCASPAR. • Evaluate for coagulopathy and consider clotting factor replacement as needed. • Resume ONCASPAR with the next scheduled dose if bleeding is controlled.
Pancreatitis	Grades 3 to 4	• Hold ONCASPAR for elevations in lipase or amylase >3 x ULN until enzyme levels stabilize or are declining • Discontinue ONCASPAR permanently if clinical pancreatitis is confirmed.
Thromboembolism	Uncomplicated deep vein thrombosis	• Hold ONCASPAR. • Treat with appropriate antithrombotic therapy • Upon resolution of symptoms consider resuming ONCASPAR, while continuing antithrombotic therapy.
	Severe or life-threatening thrombosis	• Discontinue ONCASPAR permanently. • Treat with appropriate antithrombotic therapy.
Hepatotoxicity	Total bilirubin more than 3 times to no more than 10 times the upper limit of normal	• Hold ONCASPAR until total bilirubin is ≤ 1.5 times the upper limit of normal
	Total bilirubin more than 10 times the upper limit of normal	• Discontinue ONCASPAR and do not make up for missed doses
*Grade 1 is mild, grade 2 is moderate, grade 3 is severe, and grade 4 is life-threatening		

Contraindications
ONCAPAR is now also contraindicated in case of severe hepatic impairment. Please refer to the full prescribing information for all the contraindications.

Reporting Adverse Events
Heath care providers and patients are encouraged to report adverse events in patients taking ONCASPAR to Servier at 1-857-895-4853 or pharmacovigilance-US@servier.com. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.
If you have any questions about the information contained in this letter or the safe and effective use of ONCASPAR, you may also contact Servier at customerservice@servier.com or at 1-800-807-6124.
This letter is not intended as a complete description of the benefits and risks related to the use of ONCASPAR. **Please refer to the attached full prescribing information**.

Sincerely,

Raffaele Baffa

Raffaele Baffa, M.D., Ph.D.
Chief Medical Officer
Servier Pharmaceuticals LLC