NOVARTIS

AUTHORIZATION WITH CONDITIONS FOR PRJADENU™ TABLETS, A NEW FORMULATION OF DEFERASIROX

DEAR HEALTH CARE PROFESSIONAL LETTER

February 24, 2016

Dear Health Care Professional(s):

Novartis Pharmaceuticals Canada Inc. is pleased to announce that Health Canada has issued a Notice of Compliance with Conditions under the Notice of Compliance with Conditions (NOC/c) policy for JADENU™ (Deferasirox) 90 milligram (mg), 180 mg and 360 mg tablets for the management of chronic iron overload in patients with transfusion-dependent anemias aged 6 years or older and in patients aged 2 to 5 who cannot be adequately treated with deferoxamine.

JADENU™ has been issued marketing authorization with conditions for the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older.

JADENU™ is a once daily oral iron chelator. It contains the same active ingredient (deferasirox) as EXJADE®; however, it is a new formulation with a different dosing regimen and method of administration. EXJADE® and JADENU™ are indicated for the same patient populations. The two formulations (JADENU™ film-coated tablets and EXJADE® dispersible tablets) have a comparable extent of absorption (AUC) when administered as formulation-adjusted doses.

- JADENU™ film-coated tablets are a strength-adjusted formulation of deferasirox. At the same dose, JADENU™ film-coated tablets have a higher bioavailability compared to EXJADE® dispersible tablet.
- JADENU™ film-coated tablets are dosed and administered differently from EXJADE® dispersible tablets. The dose range is 7 to 28 mg/kg of patient body weight; dose modifications for safety or efficacy should be in steps of 3.5 or 7 milligram/kilogram (mg/kg).
- Patients converting from EXJADE® dispersible tablets to JADENU™ film-coated tablets require a 30% reduction in dose. A dose conversion table is included below.
- JADENU™ film-coated tablets are available in three strengths: 90 mg, 180 mg, and 360 mg. Both formulations are differentiated by name, tablet form, colour, size and packaging.
- To avoid dosing errors, it is important that prescriptions specify both the type of formulation (dispersible tablet or film-coated tablet) and the prescribed dose in mg/kg/day.

Health Canada has issued a marketing authorization with conditions under the NOC/c policy for JADENU™ to reflect the need for further follow-up to verify the clinical benefit. JADENU™ is of high quality and possesses an

acceptable safety profile based on the benefit/risk assessment. As part of its condition Novartis Pharmaceuticals Canada Inc. has undertaken to provide Health Canada with the final study report for Study CICL670A2411: A 5 year observational study (registry) of children aged 2 to < 6 years at enrollment with transfusional hemosiderosis treated with deferasirox.

Indications and Clinical Use:

Conditional marketing authorization has been issued for JADENU™ for the following indications:

- the management of chronic iron overload in patients with transfusion-dependent anemias aged six years or older;
- the management of chronic iron overload in patients with transfusion-dependent anemias aged two to five who cannot be adequately treated with deferoxamine.

These marketing authorizations are conditional, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorizations.

Other Uses of JADENU™:

JADENU™ has been issued non-conditional marketing authorization for the indication of:

- the treatment of chronic iron overload in patients with non-transfusion-dependent thalassemia syndromes aged 10 years and older.

Therapy with JADENU™ should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions.

Action and Clinical Pharmacology:

JADENU™ (deferasirox) is an orally active chelator that is highly selective for iron (as Fe^{3+}). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although its highest affinity is for iron, deferasirox has a significant affinity for aluminum. Deferasirox has very low affinity for zinc and copper, and there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

Contraindications

JADENU™ is contraindicated in patients with estimated creatinine clearance (ClCr) <60 mililitre/minute (mL/min) or serum creatinine >2 times the age-appropriate upper limit of normal (ULN).

JADENU™ is contraindicated in high-risk myelodysplastic syndrome (MDS) patients, any other MDS patient with a life expectancy < 1 year and patients with other hematological and non-hematological malignancies who are not expected to benefit from chelation therapy due to the rapid progression of their disease.

JADENU™ is contraindicated in patients with platelet counts < 50 x 10^9/Litre.

Serious Warnings and Precautions

Therapy with JADENU™ should be initiated and maintained by physicians experienced in the treatment of chronic iron overload due to blood transfusions.

Deferasirox is contraindicated in patients with moderate and severe renal impairment and has not been studied in patients with severe hepatic impairment.

The following are clinically significant adverse events:

- Acute renal failure
- Hepatic failure
- Gastrointestinal haemorrhage and perforations

Adverse Reactions

The most frequently occurring adverse events (all causalities) in the therapeutic trials of deferasirox were diarrhea, vomiting, nausea, headache, constipation, dyspepsia, abdominal pain, pyrexia, cough, proteinuria, increases in serum creatinine and transaminases, pruritis and skin rash. Gastrointestinal disorders, increases in serum creatinine and skin rash were dose related. Adverse events which most frequently led to dose interruption, dose adjustment, or discontinuation of therapy were skin rash, gastrointestinal disorders, infections, increased creatinine, and increased transaminases.

Drug Interactions

Caution should be exercised when JADENU™ is combined with substances metabolised through CYP3A4. The concomitant use of JADENU™ with potent UGT inducers (for example [e.g.] rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in JADENU™ efficacy.

Dosage and Administration

A new dosing regimen and method of administration must be applied when switching patients from EXJADE® dispersible tablets to JADENU™ film-coated tablets. To avoid dosing errors, it is important that prescriptions specify both the type of formulation (dispersible tablet or film-coated tablet) and the prescribed dose in mg/kg/day.

- JADENU™ film-coated tablets are a strength-adjusted formulation of deferasirox with higher bioavailability compared to dispersible tablets.
- The JADENU™ ovaloid, biconvex film-coated tablets are available in three strengths: 90 mg (light blue), 180 mg (medium blue), and 360 mg (dark blue).
- The JADENU™ film-coated tablet dose range is 7 to 28 mg/kg of patient body weight; with the dose calculated based on patient weight and rounded to the nearest whole tablet.
- The recommended initial daily dose of JADENU™ film-coated tablets is 14 mg/kg body weight (equivalent to EXJADE® dispersible tablets 20 mg/kg body weight).
- Dose modifications of JADENU™ for safety and efficacy should be in steps of 3.5 or 7 mg/kg body weight
- JADENU™ film-coated tablets should be swallowed whole with some water. For patients who are unable to swallow whole tablets, JADENU™ tablets may be crushed and administered by sprinkling the full dose on a soft food (e.g, yogurt or applesauce). Commercial crushers with serrated surfaces should be avoided for crushing a single 90 mg tablet. The dose should be immediately and completely consumed, and followed with a glass of water. The dose should not be stored for future use.
  The film-coated tablets should be taken on an empty stomach or with a light meal.
- When converting the patient's prescription to JADENU™ film-coated tablets, the dose of the film-coated tablets should be 30% lower than the dose of dispersible tablets, rounded to the nearest whole tablet.

Important differences between the EXJADE® dispersible tablets and JADENU™ film-coated tablets

To avoid dosing errors, it is important that prescriptions specify both the type of formulation (dispersible tablet or film-coated tablet) and the prescribed dose in mg/kg/day.

EXJADE® dispersible tablets	JADENU™ film-coated tablets
Strengths: 125 mg, 250 mg, 500 mg (round, white tablets)	Strengths: 90 mg, 180 mg, 360 mg (oval, blue tablets)
Dispersible tablets	Film-coated tablets
Must be taken on an empty stomach, at least 30 minutes before food	Should be taken on an empty stomach or with a light meal
Disperse tablets in water, orange juice, or apple juice. Dispersible tablets must not be chewed or swallowed whole.	Tablets can be swallowed whole with some water or crushed and administered by sprinkling onto soft food (e.g. yogurt or apple sauce).
Contains lactose	Does not contain lactose
	

Dose conversion between the dispersible tablets and the film-coated tablets

EXJADE® dispersible tablets	JADENU™ film-coated tablets
Dose range: 10-40 mg/kg; calculated and rounded to the nearest whole tablet size.	Dose range: 7-28 mg/kg; calculated and rounded to the nearest whole tablet size.
Dose adjustment: increments of 5-10 mg/kg	Dose adjustment: increments of 3.5-7 mg/kg
EXJADE® therapeutic dose range: 10 mg/kg 20 mg/kg 30 mg/kg 40 mg/kg (maximum recommended dose)	JADENU™ therapeutic dose range: 7 mg/kg 14 mg/kg 21 mg/kg 28 mg/kg (maximum recommended dose)
Calculated dose example for 50kg patient receiving EXJADE® 30 mg/kg: 30 mg/kg * 50 kg = 1500 mg/day Three (3) 500 mg tablets	Calculated dose example for 50kg patient receiving JADENU™ 21 mg/kg: 21 mg/kg * 50 kg = 1050 mg/day Three (3) 360 mg tablets

* For the complete prescribing information and information available for the patients/caregivers, please consult the JADENU™ Product Monograph. The Product Monograph can be found at: www.novartis.ca or should you have medical enquiries regarding JADENU™, contact our Medical Information Department at 1-800-363-8883.

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Reporting Suspected Side Effects
Canada Vigilance Program
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture
Address Locator: 0701C
Ottawa, Ontario
K1A 0K9
Telephone: 613-957-0337 or Fax: 613-957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Fax: 1-866-678-6789
Email: CanadaVigilance@hc-sc.gc.ca

The Adverse Reaction Reporting Form and the Adverse Reaction Guidelines can be found on the Health Canada website or in The Canadian Compendium of Pharmaceuticals and Specialties.

For other inquiries related to this communication, please contact Health Canada at:
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