CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761166Orig1s000

<u>RISK ASSESSMENT and RISK MITIGATION REVIEW(S)</u>

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761166
PDUFA Goal Date	November 13, 2021
OSE RCM #	2020-502; 2020-505
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	November 8, 2021
Subject	Review to determine if a REMS is necessary
Established Name	ropeginterferon alfa-2b-njft
Trade Name	Besremi
Name of Applicant	PharmaEssentia Corporation
Therapeutic Class	type I interferons
Formulation(s)	500 mcg/1.0 mL in a single-dose pre-filled syringe
Dosing Regimen	The recommended starting dosage for single-agent therapy is 100 mcg by subcutaneous injection every two weeks. _{(b) (4)}

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EXECUTIVE SUMMARY

This review provides additional analysis beyond what was included in the Division of Risk Management's (DRM) deferral memo, dated March 8, 2021, to evaluate whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) ropeginterferon alfa-2b-njft (Besremi) is necessary to ensure the benefits outweigh its risks. PharmaEssentia Corporation resubmitted Biologic Licensing Application (BLA) 761166 for ropeginterferon alfa-2b-njft with the proposed indication for the treatment of polycythemia vera (PV) in adults without symptomatic splenomegaly after receiving a Complete Response (CR) letter on March 12, 2021, due to the deficiencies in human factors validation. The serious risks associated with the use of ropeginterferon alfa-2b-njft are depression and suicide, decreased peripheral blood counts, hepatotoxicity, cardiovascular disorders, hypersensitivity reactions, rash, endocrine disorders, renal toxicity, ophthalmologic disorders, dental and periodontal disorders and driving and operating machinery. The Applicant did not submit a REMS with this application but proposed describing these risks in the Prescribing Information as follows: Warnings and Precautions, as well as in the Patient Counseling Information. The Agency informed the Applicant at the Post Mid-cycle meeting that the adverse event profile suggests similar findings to other drugs in the class and therefore warnings and precautions (including Boxed Warning) in labeling and the Medication Guide for ropeginterferon would be similar to those for FDA approved interferons.

The Division of Risk Management (DRM) and the Division of Nonmalignant Hematology (DNH) have determined that if approved, a REMS is not necessary to ensure the benefits of ropeginterferon alfa-2b-njft outweigh its risks. PV is a rare myeloproliferative neoplasm which is marked by an increase in red blood cell mass which can lead to thromboembolic events and cardiovascular disease. Patient with PV are also at risk for myelofibrosis, acute myeloid leukemia and myelodysplastic syndromes. Treatment and palliation of PV is generally risk-stratified and consists of mainly phlebotomy, aspirin, cytoreductive agents and interferon alpha formulations.

Ropeginterferon alfa-2b-njft appeared efficacious in its primary outcome of complete hematologic response (CHR). Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of ropeginterferon alfa-2b-njft for the treatment of PV in adults without symptomatic splenomegaly. The most concerning adverse reactions observed with the use of ropeginterferon alfa-2b-njft are depression and suicide, decreased peripheral blood counts, hepatotoxicity, cardiovascular disorders, hypersensitivity reactions, rash, endocrine disorders, renal toxicity, ophthalmologic disorders, dental and periodontal disorders and driving and operating machinery. Similar to other interferons, labeling will include the risk of neuropsychiatric, autoimmune, ischemic, and infectious disorders as a Boxed Warning, and none of these products require REMS at this time. If approved, labeling, including information in Warnings and Precautions, Patient Counseling Information, and the Medication Guide will be used to communicate the safety issues and management of toxicities associated with ropeginterferon alfa-2b-njft.

1 Introduction

This review provides additional analysis beyond what was included in the DRM deferral memo, dated March 8, 2021[1], to evaluate whether a REMS for the new molecular entity (NME) ropeginterferon alfa-2b-njft (Besremi) is necessary to ensure the benefits outweigh its risks. PharmaEssentia Corporation resubmitted a Biologic Licensing Application (BLA) 761166 for ropeginterferon alfa-2b-njft with the proposed indication[2] for the treatment of PV in adults without symptomatic splenomegaly after

receiving a Complete Response (CR) letter on March 12, 2021, due to the deficiencies in human factors validation[1,3,4,5]. The Applicant did not submit a REMS with this application but proposed describing these risks in the Prescribing Information as follows: Warnings and Precautions, as well as in the Patient Counseling Information.

2   Background

2.1   PRODUCT INFORMATION

Ropeginterferon alfa-2b-njft is an NME BLA type 351(a) pathway application.[a] It is an interferon alfa-2b analog. Ropeginterferon alfa-2b-njft belongs to the class of type I interferons which exhibit their cellular effects by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signaling cascade through the activation of kinases, in particular Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs and exhibit various cellular effects. The actions involved in the therapeutic effects of interferon alfa in PV are uncertain. Interferon alfa may have direct effects on hematopoietic stem cell proliferation and differentiation and is able to decrease the mutated JAK2V617F allele burden in patients with polycythemia vera.[2] Ropeginterferon alfa-2b-njft will be supplied as 500 mcg/1.0 mL in a single-dose pre-filled syringe. The recommended starting dosage for single-agent therapy is 100 mcg by subcutaneous injection every two weeks. Gradually increase the dose by 50 mcg every two weeks (to a maximum dose of 500 mcg every two weeks) until the hematological parameters are stabilized (hematocrit <45%, platelets <400 x 10^9/L, and leukocytes <10 x 10^9/L).[b]   (b) (4)

                    . Gradually increase the dose by 50 mcg every two weeks   (b) (4)
                                             until the hematological parameters are stabilized (hematocrit <45%, platelets <400 x 10^9/L, and leukocytes <10 x 10^9/L) and to a maximum dose of 500 mcg every two weeks. Ropeginterferon alfa-2b-njft was granted orphan drug designation on April 2, 2012. Ropeginterferon alfa-2b-njft was authorized for marketing in the European Union on February 2019 as monotherapy in adults for the treatment of PV without symptomatic splenomegaly.

2.2   REGULATORY HISTORY

The following is a summary of the regulatory history for ropeginterferon alfa-2b-njft (BLA 761166) relevant to this review:

- 04/02/2012: Orphan Drug designation granted.

- 06/18/2014 Investigation New Drug IND 119047 submission for Pegylated-proline interferon alpha-2b solution for injection (P1101) received.

- 04/13/2020: BLA 761166 submission for ropeginterferon alfa-2b-njft with the proposed indication for the treatment of PV in adults without symptomatic splenomegaly, received.

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[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 09/22/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the adverse event profile suggests similar findings to other drugs in the class and therefore warnings and precautions (including Boxed Warning) in labeling for ropeginterferon would be similar to those for FDA approved interferons, and based on the currently available data, there were no safety issues that require a REMS for ropeginterferon alfa-2b-njft.

- 03/12/2021: The Sponsor was issued a Complete Response letter until the sponsor can adequately address the issue related to the deficiencies in human factors validation.[3,4,5]

- 05/13/2021: Application resubmitted to the Agency.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

PV is currently classified by the World Health Organization (WHO) classification system under the major category of myeloproliferative neoplasms (MPN).[6] The Philadelphia chromosome-negative MPN include primary myelofibrosis (PMF), PV, and essential thrombocythemia (ET).[7] PV is a rare myeloproliferative neoplasm marked by an increase in red blood cell mass. Criteria for disease include elevated hemoglobin/hematocrit values of >16.5 g/dL/49% for males and >16 g/dL/48% for females and the presence of a Jak2 mutation, with bone marrow morphological changes differentiating it from other myeloproliferative disorders. Clinical features include splenomegaly, constitutional symptoms, symptoms of hyperviscosity, leukocytosis, thrombocytosis, microvascular symptoms, thrombotic and bleeding complications, and risk of leukemic transformation or myelofibrosis.[6] The estimated number of new cases of PV is estimated at 44 to 57 per 100,000 individuals in the United States with a preponderance in men for unknown reasons.[8,c] Thromboembolic events and cardiovascular disease are the most prevalent complications in patients with PV compared with other myeloproliferative disorders and are the major cause of morbidity and mortality in this population.[9] Patients with PV generally live for many years though they may exhibit profound decreases in quality of life and life expectancy due to symptoms, thrombotic complications and progression to more severe diseases such as myelofibrosis, acute myeloid leukemia, myelodysplastic syndromes.[10,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment and palliation of PV is generally risk-stratified and consists of mainly phlebotomy, aspirin, and cytoreductive agents.[6] Low-risk individuals are defined as < 60 years of age with no history of thrombotic complications. Low-risk patients can be initially managed with low-dose aspirin, phlebotomy and monitoring per National Comprehensive Cancer Network (NCCN) guidelines. Patients should be monitored for disease progression and symptoms regularly and those that experience the symptoms

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

such as new thrombosis or disease-related major bleeding event, persistent need for phlebotomy and decreased tolerance of phlebotomy, splenomegaly, thrombocytosis, leukocytosis, disease-related symptoms including pruritus, night sweats and fatigue may be candidates for cytoreductive therapy. Patients that exhibit these symptoms as well as high-risk patients, or those over 60 years of age with a history of thrombotic complications, should be additionally initiated on cytoreductive therapy consisting of hydroxyurea or interferons.[7] If a patient cannot tolerate cytoreductive therapy or symptoms recur or increase or failing both hydroxyurea and interferon therapy, a new agent is recommended by participating in clinical trial or ruxolitinib[11] and busulfan as alternatives.

Cytoreductive therapy is chosen with consideration of various patient and drug-related factors. Hydroxyurea is often used first line due to it's long term safety and efficacy data, ease of administration and low cost.[10,12] Adverse events associated with hydroxyurea include myelosuppression, secondary malignancies, vascular toxicities and teratogenicity among others.[13] A significant number of patients are either intolerant of hydroxyurea because of hematologic or nonhematologic toxicity or resistant because of a lack of effective cytoreduction treatment with hydroxyurea.[14] Although busulfan can be effective in treating PV that is resistant to hydroxyurea or interferon, it is associated with a significant rate of transformation to AML, and the sequential use of busulfan and HU has been reported to significantly increase the risk of secondary malignancies. Therefore busulfan is not recommended as a main treatment option[7] and use is limited due to it's adverse effects of myelosuppression, pulmonary toxicity, and gastrointestinal toxicity among others with higher serum concentrations, and more prominently, an increased risk of secondary malignancies.[6,15] Ruxolitinib was more recently incorporated into treatment algorithms and is currently the only recommended drug with an FDA approved indication of treatment of PV a in adults who have had an inadequate response to or are intolerant of hydroxyurea.[11] It's use is mainly limited by adverse effects of myelosuppression, increased incidences of infection, and lipid derangement.[7]

Interferon alpha formulations are the interferons recommended in PV and may be used first line in younger patients (<40 years old) and those that may become pregnant.[7] Interferon alfa-2b, peginterferon alfa-2a, and peginterferon alfa-2b are the interferon alpha therapies currently marketed and all share a boxed warning of the potential to cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.[16,17,18] Interferon alpha therapies are given subcutaneously, intramuscularly, intravenously and intralesionally depending on the formulation and differ in dosing and duration of response. Non-pegylated interferons are generally dosed multiple times per week while pegylated interferons are dosed once weekly. The development of pegylated interferons represented a major advancement in improving the pharmacokinetics (PK) of interferons. Conjugation of PEG to interferon causes a reduction in the elimination of the molecule and hence a prolongation of the plasma half-life. Compared to administration three times per week for unmodified interferon alfa, peginterferons allow administration once per week and avoid large fluctuating serum concentrations, resulting in increased tolerance and efficacy.[19,20] The therapy with pegylated interferons has been associated with toxicities including flu-like symptoms, depression, hepatotoxicity, and autoimmune syndromes.[21] Therefore, new alternative modalities of medical treatment with improved long-term safety and efficacy are still needed beyond the existing medical therapies to enable move convenient treatment schedule.

4 Benefit Assessment

The efficacy of ropeginterferon alfa-2b-njft was evaluated in the PEGINVERA study, a prospective, multicenter, single-arm study of 90.5-month duration included adult patients (n=51) with PV. The mean age at baseline was 59 years, 16% of subjects were newly diagnosed; 84% had a known median disease duration of 2.2 years. One-third (33%) of patients were undergoing treatment with hydroxyurea (HU) upon study entry. Median spleen size was 13.2 cm. In stage I, the maximum tolerated dose (MTD) was determined to be 540 mcg and in stage II, an intra-patient dose escalation began at 150 mcg, or 100 mcg if titrating from HU, or at the highest dose achieved in those patients enrolled during stage I. Titration with ropeginterferon alfa-2b-njft occurred every two-weeks at doses of 225 mcg, 300 mcg, 400 mcg and 450 mcg with dose escalation stopping when hematological parameters were stabilized. For patients transitioning from another cytoreductive therapy, the dose was reduced over the first twelve weeks of treatment to avoid toxicity. At a median time of 21.5-months, twenty-eight eligible patients in PEGINVERA study increased the dosing interval to once every 4-weeks. The median duration of treatment exposure was sixty-one months and 53% of patients completed at least sixty months of treatment. Thirty-six patients completed one year of treatment with eleven patients discontinuing after one year of treatment mainly due to treatment emergent adverse events. The mean dose of ropeginterferon alfa-2b-njft was 236.6 mcg (± 110) during the treatment period.[2]

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for ropeginterferon alfa-2b-njft. The efficacy of ropeginterferon alfa-2b-njft was evaluated by complete hematological response (CHR); defined as hematocrit <45% without phlebotomy [at least 2 months since last phlebotomy], platelets ≤400 x 10^9/L and leukocytes ≤10 x 10^9/L, normal spleen size (longitudinal diameter ≤ 12 cm for females and ≤ 13cm for males) and absence of thromboembolic events. The overall CHR rate in the treated population during the treatment period was 60.8% (31/51) (95% CI: 46.1, 74.2). The median duration of response was 14.3 months (95% CI: 5.5, 30.1).

Among the patients in the treated population who achieved a CHR, the median time to response was 7.8 months of treatment with ropeginterferon alfa-2b-njft and the median time on treatment required to achieve any hematological response was 10 weeks. It required 1.2 years for 50% of patients (HU-naïve) to achieve CHR and 1.4 years for 50% of patients with prior HU use to achieve CHR. With the exclusion of normal spleen size and thrombosis, a CHR (CHR based on objective laboratory parameters only) was achieved among 80.4% of patients (41/51) (95% CI: 66.9, 90.2). The median duration of response is 20.75 months (95% CI: 13, 43.8).[2,e]

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were ongoing with the applicant. The following section is a summary of relevant safety information to date for ropeginterferon alfa-2b-njft.

The safety of ropeginterferon alfa-2b-njft was evaluated in the PEGINVERA trial (see Section 4: Benefit Assessment). Patients received ropeginterferon alfa-2b-njft at a at a starting dose of 150 mcg

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[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

subcutaneously every two weeks (escalated gradually based on disease response and tolerability to a maximum of 540 mcg). Among the 51 patients receiving ropeginterferon alfa-2b-njft, 71% (36/51) were exposed for 12 months or longer and 63% (32/51) were exposed for three years or longer, and 53 % (16/51) were exposed for greater than five years.[2]

The most common adverse reaction occurring at > 10% were influenza-like illness (21%), fatigue (24%), pyrexia (14%), arthralgia (31%), myalgia (18%), nausea (14%), headache (14%), dizziness (10%), leukopenia (18%), thrombocytopenia (12%), alopecia (12%), insomnia/sleep disturbances (10%), depression (10%), decreased appetite 10%), liver enzyme elevations (16%), thyroid reaction and lab abnormalities.[2]

Deaths

There were 4 deaths reported in PROUD PV/CONTINUATION-PV studies, which was a randomized, open-label, multicenter, controlled, parallel arm, phase III study. Two were in the ropeginterferon alfa-2b-njft arm (one was due glioblastoma and the other was unknown) and 2 in the HU arm (one patient died of acute Leukemia/sepsis after 2 years of treatment, and the 2nd death was a sudden death. The clinical reviewer noted that the unknown and sudden death in both arms were not associated with their assigned treatment arm.[22]

Serious Adverse Events (SAE)

Serious adverse reactions in $\geq$ 1% of patients who received ropeginterferon alfa-2b-njft included acute stress disorder (2%), anti-thyroid antibody positive (2%), antinuclear antibody increased (2%), arthralgia (2%), atrial fibrillation (2%), depression (4%), fatigue (2%), influenza like illness (2%), pyrexia (2%) and transaminases increased (2%). No thrombotic adverse reactions were observed over the study duration. Adverse reactions requiring permanent discontinuation in > 1% of patients who received ropeginterferon alfa-2b-njft included depression (2%) and arthralgia (1%).[2]

If approved, labeling will include the following risks in the Warnings and Precautions section:

5.1   DEPRESSION AND SUICIDE

^{(b) (4)} (n=178) seventeen cases of depression, depressive symptoms, depressed mood, listlessness occurred. Serious neuropsychiatric reactions have been observed in 3% of patients treated with ropeginterferon alfa-2b-njft during the clinical development program. Of these seventeen cases, 3.4% of the patients recovered and 2.8% stopped ropeginterferon alfa-2b-njft treatment. Other CNS effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products.[2]

Similar to other interferon such as peginterferon alfa-2b (Pegintron)[23], labeling will include the risk of depression and suicide as a Boxed Warning. Ropeginterferon alfa-2b-njft is contraindicated in patients with history of severe psychiatric disorders, particularly severe depression, suicidal ideation or suicide attempt. Labeling recommends to monitor for any symptoms of psychiatric disorders and therapeutic management should be considered by the treating physician if such symptoms emerge, and it is recommended to discontinue ropeginterferon alfa-2b-njft, if psychiatric symptoms worsen.

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5.2 DECREASED PERIPHERAL BLOOD COUNTS

[blacked out] (b) (4) interferon alfa [blacked out] (b) (4) -treated patients experienced the decrease in peripheral blood counts, particularly, thrombocytopenia or leukopenia. Thrombocytopenia of grade 3 or greater was reported in 2% of ropeginterferon alfa-2b-njft-treated patients. Anemia of grade 3 or greater occurred in 1% of ropeginterferon alfa-2b-njft -treated patients. Leukopenia of grade 3 or greater occurred in 2% of ropeginterferon alfa-2b-njft-treated patients. Labeling recommends monitoring complete blood counts at baseline, as required during titration and every 3-6 months during the maintenance phase.[2]

Other adverse events that ropeginterferon alfa-2b-njft has in common with currently approved interferons such as peginterferon alfa-2b (Pegintron)[23], will likely be communicated in the Warnings and Precautions section of the ropeginterferon alfa-2b-njft label as well. These adverse events include: hepatotoxicity, cardiovascular disorders, hypersensitivity reactions, rash, endocrine disorders, renal toxicity, ophthalmologic disorders, dental and periodontal disorders and driving and operating machinery. Similar to other interferons, labeling will include the risk of neuropsychiatric, autoimmune, ischemic, and infectious disorders as a Boxed Warning. Similar to other interferon such as interferon beta-1a (Rebif)[24], labeling for ropeginterferon alfa-2b-njft will likely be included the monitoring and dosage modifications for toxicities to address the safety issues with ropeginterferon alfa-2b-njft in the Dosage and Administration section of the label.[2]

6 Expected Postmarket Use

According to the currently proposed indication, if approved, orally administered ropeginterferon alfa-2b-njft will be used in both inpatient and outpatient settings and the likely prescribers will be hematologists, who are involved in the management and treatment of PV.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for ropeginterferon alfa-2b-njft beyond routine pharmacovigilance and labeling. The Agency informed the Applicant at the post mid-cycle meeting that the adverse event profile suggests similar findings to other drugs in the class and therefore warnings and precautions (including the Boxed Warning) and the Medication Guide in labeling for ropeginterferon would be similar to those for FDA approved interferons. Similar to peginterferon alfa-2b (Pegintron)[2323], the applicant proposed a PI that includes Warnings and Precautions to address the risks of depression and suicide, decreased peripheral blood counts, hepatotoxicity, cardiovascular disorders, hypersensitivity reactions, rash, endocrine disorders, renal toxicity, ophthalmologic disorders, dental and periodontal disorders and driving and operating machinery. There were no new AEs in the clinical trial setting that hematologists were not already familiar with. It is expected that hematologists familiar with the management of these toxicities will be the likely prescribers of ropeginterferon alfa-2b-njft.

8 Discussion of Need for a REMS

Ropeginterferon alfa-2b-njft is a monopegylated interferon, with the proposed indication for the treatment of PV in adults without symptomatic splenomegaly.[2] When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for ropeginterferon alfa-2b-njft, this

reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

PV is a rare myeloproliferative neoplasm. Thromboembolic events and cardiovascular disease are the most prevalent complications in patients with PV compared with other myeloproliferative disorders and are the major cause of morbidity and mortality in this population. Patients with PV generally live for many years though they may exhibit profound decreases in quality of life and life expectancy due to symptoms, thrombotic complications and progression to more severe diseases such as myelofibrosis, acute myeloid leukemia, myelodysplastic syndromes. Treatment and palliation of PV is generally risk-stratified and consists of mainly phlebotomy, aspirin, cytoreductive agents and interferon alpha formulations. The long-term use of HU in young patients includes a mutagenic and carcinogenic risk and is a major impediment to the use of HU. The therapy with interferons has been associated with toxicities including flu-like symptoms, depression, hepatotoxicity, and autoimmune syndromes. Therefore, the availability of an alternative agent is of significant clinical importance to patients with PV.

Ropeginterferon alfa-2b-njft appeared efficacious in its primary outcome of CHR. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of ropeginterferon alfa-2b-njft for the treatment of PV in adults without symptomatic splenomegaly, and its risks can be communicated and managed through labeling.[2,2222] The following risks and adverse reactions are observed with the use of ropeginterferon alfa 2bnjft and include: depression and suicide, decreased peripheral blood counts, hepatotoxicity, cardiovascular disorders, hypersensitivity reactions, rash, endocrine disorders, renal toxicity, ophthalmologic disorders, dental and periodontal disorders and driving and operating machinery. At the time of this review, labeling negotiations were still ongoing with the Applicant; however, similar to other interferons, labeling will include the risks of neuropsychiatric, autoimmune, ischemic, and infectious disorders as a Boxed Warning, and none of these products require REMS at this time. If approved, these risks will be communicated in the label in the following sections: Dosage and Administration, Contraindications, Warnings and Precautions, and Patient Counseling Information and a Medication Guide will be required. These communications of these risks are similar to other interferons that are currently FDA approved. The likely prescribers for ropeginterferon alfa-2b-njft will be hematologists who are involved in the management and treatment of PV. The risks identified in the draft label are risks that these providers have likely encountered in their practice experience and can manage without additional risk mitigation measures.

DRM and DNH have determined that if approved, a REMS is not necessary to ensure the benefits of ropeginterferon alfa-2b-njft outweigh its risks.

9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of ropeginterferon alfa-2b-njft. The management of the risks associated with ropeginterferon alfa-2b-njft treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

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/s/

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Team Leader	Naomi Boston, Pharm.D.
Deputy Director	Doris Auth, Pharm.D.
Review Completion Date	March 8, 2021
Subject	Defer comment on DRM evaluation of the need for a REMS for ropeginterferon alfa-2b-njft
Established Name	ropeginterferon alfa-2b-njft
Trade Name	Besremi
Name of Applicant	PharmaEssentia Corporation
Therapeutic Class	type I interferons
Formulation(s)	500 mcg/1.0 mL in a single-dose pre-filled syringe
Dosing Regimen	The recommended starting dosage for single-agent therapy is 100 mcg by subcutaneous injection every two weeks. [(b) (4)]

1

This memo is to defer the Division of Risk Management (DRM) review of the need for a risk evaluation and mitigation strategy (REMS) for ropeginterferon alfa-2b-njft, BLA 761166.

On April 13, 2020, the Applicant submitted BLA 761166, which included draft labeling but did not include a REMS.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewer has made the following recommendation for regulatory action based on the submission:

> *Based on the results of the human factors (HF) validation study data, root cause analysis, and participants' subjective feedback, the proposed product design and user interface does not support safe and effective use of Besremi (ropeginterferon alfa-2b-njft) injection. We recommend that you implement our HF protocol recommendations prior to commencing your HF validation study, consider additional design modifications and labeling changes, and submit the results of another human factor validation study to demonstrate that the product can be used safely and effectively.*[1,2,3]

Please refer to Dr. Stephanie DeGraw's review for a detailed review of identified issues and recommendations.[1]

Therefore, an evaluation of the need for REMS for ropeginterferon alfa-2b-njft will be undertaken by DRM after the Applicant addresses the deficiencies in the CR letter. Please send DRM a new consult request at such time. This memo serves to close the existing consult request to DRM for ropeginterferon alfa-2b-njft under BLA 761166.

References

[1] DeGraw S. Division of Medication Error Prevention and Analysis (DMEPA) review on human factors (HF) for ropeginterferon alfa-2b-njft, BLA 761166, dated February 26, 2021. [Reference ID: 4752998]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed March 1, 2021.

[2] Human factors validation study protocol – Advice for ropeginterferon alfa-2b-njft, BLA 761166, dated February 26, 2021. [Reference ID: 4753686]. Available from: Food and Drug Administration (FDA), Document Archiving, reporting, and regulatory Tracking System (DARRTS). Accessed March 1, 2021.

[3] BLA 761166 Complete Resposne Letter – Draft, dated March 3, 2021.

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/s/

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