ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8.

1. NAME OF THE MEDICINAL PRODUCT

Imreplys 250 microgram powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 mcg sargramostim*.
After reconstitution each mL contains 250 mcg sargramostim.

*Sargramostim is a human granulocyte-macrophage colony-stimulating growth factor (GM-CSF) produced by recombinant DNA technology in a yeast (*S. cerevisiae*) expression system.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

Lyophilised, white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imreplys is indicated for treatment of patients of all ages acutely exposed to myelosuppressive doses of radiation with Haematopoietic Sub-syndrome of Acute Radiation Syndrome (H-ARS).

Imreplys should be used in accordance with official radiological/nuclear emergency recommendations.

4.2 Posology and method of administration

Treatment with Imreplys should be started as soon as possible in any adult, adolescent, child, or infant who has been acutely exposed to myelosuppressive doses (greater than 2 gray [Gy]) of radiation with suspected H-ARS based on clinical signs and symptoms or confirmed H-ARS based on laboratory tests. If possible, a baseline complete blood count (CBC) with differential should be obtained.

If possible, estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical features and laboratory findings such as lymphocyte depletion kinetics.

Treatment should not be withheld if H-ARS is suspected or diagnosed even if the absorbed radiation dose is estimated as lower than 2 Gy. Imreplys should not be delayed if a CBC is not readily available or absorbed radiation dose cannot be estimated.

<u>Posology</u>

Imreplys should be administered once daily as a subcutaneous injection and dosing is based on body weight as follows:

- 7 micrograms/kg in children and adolescents weighing greater than 40 kg and in adults
- 10 micrograms/kg in children and adolescents weighing 15 kg to 40 kg
- 12 micrograms/kg in neonates, infants or children weighing less than 15 kg

See *Treatment Response* for guidance regarding Imreplys duration of treatment.

Dose modification

For grade 3 or 4 adverse reactions (see section 4.8), Imreplys dose should be reduced to 50%, or interrupted until the adverse reaction abates and then resumed at 50% of the dose. Other measures to manage the adverse reaction should be instituted and continued as necessary. If a grade 3 or 4 adverse reaction persists or recurs following dose adjustment/resumption, Imreplys should be permanently discontinued.

For grade 1 or 2 adverse reactions (see section 4.8), sargramostim should be continued with close patient monitoring and management of the adverse reaction.

Special populations

Elderly

No dose adjustment is required in elderly individuals ≥ 65 years of age.

Treatment response

A baseline CBC with differential and then serial CBCs should be obtained approximately every third day (when possible) until the absolute neutrophil count (ANC) remains greater than 1 000/mm^3 for 3 consecutive CBCs. After the first achievement of ANC greater than 1 000/mm^3, then serial CBCs should be collected daily (when possible) to avoid unnecessary treatment and minimise any risk of leucocytosis (see section 4.4). The start or continuation of administration of Imreplys should not be delayed if a CBC is not available.

Administration of Imreplys should continue until the ANC remains greater than 1 000/mm^3 for 3 consecutive CBCs or exceeds 10 000/mm^3 after a radiation-induced nadir. If CBCs are not available or in absence of treatment response, Imreplys may be discontinued after 23 consecutive days of dosing.

Method of administration

Imreplys should be administered subcutaneously in the abdomen, thigh, or upper arm.

Imreplys may be self-administered or administered by a caregiver.

Imreplys must be reconstituted in 1 mL of water for injections. Instructions for the preparation and administration of the reconstituted Imreplys powder are given in the package leaflet, section 3, "How to use Imreplys".

4.3 Contraindications

History of serious hypersensitivity reactions, including anaphylaxis, to human GM-CSF or yeast derived products, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Imreplys may be used in conjunction with other supportive care to treat H-ARS.

Given that the mechanism of radiation toxicity begins at the time of exposure, treatment with Imreplys should start as soon as possible after radiation exposure. However, efficacy studies for sargramostim when administered earlier than 24 hours after exposure to myelosuppressive doses of radiation, have not been conducted in a large animal model of total body irradiation-induced H-ARS.

Hypersensitivity and anaphylaxis

Hypersensitivity reactions, including anaphylactic reactions, have been reported with sargramostim. Sargramostim treatment should be discontinued in those who have experienced anaphylaxis after a prior dose of sargramostim.

Haemodynamic oedema, effusions and fluid overload

Oedema, capillary leak syndrome, and pleural and/or pericardial effusion have been reported in patients after sargramostim administration in haematological conditions.

In patients with pre-existing pleural and pericardial effusions, administration of sargramostim may aggravate fluid retention. Fluid retention associated with or worsened by sargramostim has been reversible after interruption or dose reduction of sargramostim with or without diuretic therapy.

Imreplys should be used with caution in patients with pre-existing fluid retention, pulmonary infiltrates, or congestive heart failure. Body weight and hydration status should be carefully monitored during sargramostim administration.

Supraventricular arrhythmias

Supraventricular arrhythmia has been reported in uncontrolled studies during sargramostim administration in haematological conditions, particularly in patients with a previous history of cardiac arrhythmia. These arrhythmias have been reversible after discontinuation of treatment. Imreplys should be used with caution in patients with pre-existing cardiac disease. A physician or other health care professional should be consulted if any new or worsening arrhythmia is observed.

Potential effect on malignant cells

Sargramostim is a growth factor that stimulates normal myeloid precursors. However, the possibility that sargramostim can act as a growth factor for any tumour type, particularly myeloid malignancies, cannot be excluded. Patients with pre-existing, or a history of, cancer should be treated with Imreplys as soon as possible following radiation exposure due to the life-threatening nature of the exposure and consult an oncologist as soon as practical.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Treatment with sargramostim in persons who have not been exposed to myelosuppressive doses of radiation may induce neutralising anti-drug antibodies which may be related to duration of exposure to sargramostim.

Risk of leucocytosis

White blood cell (WBC) counts of ≥ 50 000/mm^3 were observed in patients receiving sargramostim for haematological conditions. Following discontinuation of sargramostim treatment, leucocytosis has resolved within 3 to 7 days. If WBC counts exceed ≥ 50 000/mm^3 in any patient, Imreplys should be discontinued immediately.

Limitations of effectiveness

The effectiveness of sargramostim may be limited in immunocompromised patients and those with underlying conditions affecting bone marrow function. Patients with pre-existing bone marrow suppression, such as those with haematologic malignancies, autoimmune disorders, or those undergoing chemotherapy/radiation therapy, may exhibit a suboptimal response to sargramostim due to reduced progenitor cell reserves or impaired haematopoiesis. Additionally, there is uncertainty regarding the efficacy of sargramostim in individuals acutely exposed to high-dose radiation exceeding 7.3 Gy (see section 5.1, nonclinical efficacy). High-dose radiation exposure can cause irreversible bone marrow failure, limiting the potential benefit of Imreplys in promoting haematopoietic recovery.

4.5 Interaction with other medicinal products and other forms of interaction

Limited data are available on drug-drug interactions. Patients receiving both sargramostim and medicinal products that induce leucocytosis (e.g., corticosteroids, other colony-stimulating factors, lithium) may have an increased risk of leucocytosis (see section 4.4).

4.6 Fertility, pregnancy and lactation

Acute exposure to myelosuppressive doses of radiation has per se a toxic effect on fertility and embryo/foetal development. This should be considered for clinical judgement on the use of Imreplys in pregnant and/or lactating women.

Pregnancy

There are no or limited data on the use of sargramostim in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Imreplys can be used in pregnant women with H-ARS if clinically needed.

Breast-feeding

It is unknown whether sargramostim/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded.

Breast-feeding may be considered during treatment with Imreplys, keeping in mind that the newborns may also need treatment

Fertility

There is no data available on sargramostim and human fertility. Studies in rabbits have shown adverse effects on female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Imreplys has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of sargramostim was evaluated using all available sources, including clinical studies in adults and children across various indications, healthy human volunteer studies, solicited and unsolicited reports, and literature-reported events.

Summary of the safety profile

The most serious adverse drug reactions (ADR) that occurred during sargramostim treatment were:

- Serious hypersensitivity reactions including anaphylaxis
- Haemodynamic oedema, effusions and fluid overload
- Supraventricular arrhythmias

The most common ADRs observed in haematological cancer patients treated with intravenously administered sargramostim are: fever (without infection; up to 95%), diarrhoea (up to 88%), vomiting (up to 84%), skin reactions (up to 77%), rash (up to 70%), asthenia (up to 69%), metabolic laboratory abnormalities (up to 58%), malaise (up to 58%), high glucose (up to 49%), abdominal pain (up to 38%), weight loss (up to 37%), low albumin (up to 36%), pruritis (up to 23%), GI haemorrhage (up to 27%), chills (up to 25%), pharyngitis (up to 23%), bone pain (up to 21%), chest pain (up to 15%), hypomagnesaemia (up to 15%), haematemesis (up to 13%), arthralgia (joint pain; up to 11%), anxiety (up to 11%), eye haemorrhage (up to 11%). In some subjects, the underlying diseases may have contributed to the occurrence of those ADRs.

Tabulated list of adverse reactions

The tabulated ADRs table is based on 5 clinical studies in 182 patients with haematological cancers where WBC are affected similarly to what occurs during acute exposure to myelosuppressive doses of radiation. In these studies, sargramostim was administered intravenously.

The adverse reactions are listed by MedDRA system organ class and categories of frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Table 1: Adverse reactions reported in adults and children with haematological cancers treated with intravenous sargramostim in controlled clinical studies

System Organ Class (MedDRA)	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**
Nervous system disorders	Anxiety				
Eye disorders	Eye haemorrhage				
Vascular disorders		Vasodilation			
Respiratory, thoracic and mediastinal disorders	Pharyngitis				
Gastrointestinal disorders	Abdominal pain				
	Diarrhoea				
	Gastrointestinal haemorrhage				
	Haematemesis				
	Vomiting				
Skin and subcutaneous tissue disorders	Pruritis				
	Rash				
	Skin reactions				
	Bone pain				

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Very rare
Musculoskeletal and connective tissue disorders	Arthralgia				
General disorders and administration site conditions	Asthenia				
	Chest pain				
	Chills				
	Fever (no infection)				
	Malaise				
	Weight loss				
Investigations	High glucose				
	Low albumin				
	Hypomagnesaemia				
	Metabolic function test abnormalities NOS				

Paediatric population

A total of 332 paediatric subjects were treated with intravenous sargramostim in 15 clinical studies in haematological conditions, premature neonates and Crohn's disease of which 5 were controlled, 190 patients were 0-1 month of age, 6 patients were > 1 month to < 2 years of age, 1 patient was < 1 year of age (not otherwise specified), 86 patients were 2 to < 12 years of age, and 49 patients were 12 to < 18 years of age. The overall safety profile was similar to that seen in adults.

Adverse drug reactions reported with subcutaneous administration of sargramostim

Additional ADRs have been observed in clinical studies in healthy adult volunteers and children with Crohn's disease, where the majority of patients were administered sargramostim via the subcutaneous route. From these studies, in addition to Table 1, ADRs include injection site reactions (up to 91%), headache (up to 50%) back pain, (up to 47%), nausea (up to 23%), abdominal cramps (up to 17%), dyspnoea (up to 12%), and general body pain (up to 13%).

Solicited, unsolicited, and literature-reported events in patients treated with sargramostim (across various routes of administration)

The most common ADRs were pyrexia, injection site reaction, dyspnoea, nausea, chest pain, vomiting, diarrhoea, chills, rash, hypotension, abdominal pain, febrile neutropenia, sepsis, pneumonia, dizziness, and syncope.

Serious hypersensitivity reactions including anaphylaxis, haemodynamic oedema, effusions and fluid overload and supraventricular arrhythmias have been reported with the use of sargramostim in various health conditions.

No overall differences in safety profile are observed between reports from adult and paediatric populations.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Doses up to 100 mcg/kg/day (4 000 mcg/m^2/day or about 16 times the recommended dose) were administered to 4 patients with solid tumours in a Phase 1 uncontrolled study by continuous intravenous infusion for 7 to 18 days. Increases in WBC up to 200 000 cells/mm^3 were observed.

Dyspnoea, malaise, nausea, fever, rash, tachycardia, respiratory disorder, thrombocytopenia, headache, and chills were reported and were reversible after discontinuation of sargramostim.

In case of overdose, discontinue Imreplys therapy and monitor the patient for WBC increase and respiratory symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Colony-stimulating factors, ATC code: L03AA09

Mechanism of action

Sargramostim is a recombinant human GM-CSF. The binding to GM-CSF receptors expressed on the surface of target cells (haematopoietic progenitors and mature immune cells), initiates an intracellular signalling cascade which induces the cellular responses (i.e., division, maturation, activation). GM-CSF is a multilineage factor and, in addition to dose-dependent effects on the myelomonocytic lineage, it can promote the proliferation and maturation of megakaryocytic and erythroid progenitors.

Non-clinical efficacy

Efficacy studies of sargramostim for the H-ARS indication could not be conducted in humans because the conduct of such studies is contrary to generally accepted principals of medical ethics and field studies after accidental or deliberate exposure to life-threatening doses of ionising radiation are not feasible. Therefore, 3 adequate and well-controlled studies (i.e., randomised, blinded, placebo-controlled) were conducted in a well-characterised Rhesus monkey model of total body irradiation (TBI)-induced H-ARS.

These studies provided minimal supportive care, mimicking the limited resource environment following a radiological and/or nuclear mass casualty incident. No whole blood, blood products, or individualised antibiotics were provided.

In all studies, Rhesus monkeys were administered with 7 mcg/kg as a single daily subcutaneous injection, which is the clinical recommended dose for adults exposed to myelosuppressive doses of radiation (see section 4.2).

The primary evidence of efficacy of sargramostim is summarised in Tables below.

Table 2: Randomised, blinded, placebo-controlled study in Rhesus monkey (Study 1)

Design	Randomised, blinded, placebo-controlled efficacy study conducted in Rhesus monkey
Number of animals	108 Non-Human Primates (NHP, 54 male, 54 female). Animals exposed to 6.55 Gy (36 male:36 female) or 7.13 Gy (18 male:18 female)
Randomisation	NHPs randomised to receive sargramostim (7 mcg/kg/day) or placebo (water for injections). Treatment began 48 ± 1 hours post-TBI and continued daily until ANC ≥ 1 000 cells/μL for 3 consecutive days or ANC ≥ 10 000 cells/μL
Radiation dose	6.55 and 7.13 Gy
Primary endpoint	60-day survival post-radiation
Results	
Primary endpoint results (6.55 Gy TBI)	Sargramostim significantly increased 60-day survival: 28/36 (77.8%) survived compared to 15/36 (41.7%) in the control group (p=0.0018, Fisher's exact one-sided)
Primary endpoint results (7.13 Gy TBI)	Sargramostim improved 60-day survival: 11/18 (61.1%) survived compared to 3/18 (16.7%) in the control group (p=0.0076, Fisher's exact one-sided)
Secondary endpoint results	Sargramostim improved recovery rates of leukocytes, neutrophils and platelets at both radiation doses (6.55 and 7.13 Gy). A reduction in incidence of bacterial infections was also noted.
Mean duration of exposure to Imreplys	17.6 days (range 12 to 23) [6.55 Gy group] 16.8 days (range 12 to 23*) [7.13 Gy group]

Abbreviations: ANC: absolute neutrophil count; NHP: non-human primate; TBI: total body irradiation
*Study report Table 32 lists range of duration as 12 to 24, however 1 day was missed on day 16 for the animal that received treatment days 2-25.

Table 3: Time to recovery for neutrophils (ANC) and platelets, and incidence of infection in Rhesus monkey (Study 1)

Study 1	**TBI Dose**	**Sargramostim (N=36)**	**Vehicle control (N=36)**	**Statistical significance (log-rank test)**
Time to recovery (days), median days (95% CI)				
ANC ≥ 500/μL	6.55 Gy	17 (16, 18)	19 (18, 20)	p<0.0001
ANC ≥ 1 000/μL		18 (17, 18)	20 (19, 20)	p<0.0001
Platelet count ≥ 20 000/μL		16 (NE, NE)	18 (18, NE)	p=0.0008
ANC ≥ 500/μL	7.13 Gy	17 (16, 18)	19 (19, 20)	p=0.2076
ANC ≥ 1 000/μL		17 (17, 18)	19 (18, 20)	p=0.0206
Platelet count ≥ 20 000/μL		16 (15, 17)	20 (17, NE)	p=0.0002
Incidence of infection				
Incidence % of bacterial infection (95% CI)	6.55 Gy	32 (27, 38)	63 (58, 69)	p<0.0001
Incidence % of positive haemoculture	6.55 Gy	18%	45%	NA

Abbreviations: ANC: absolute neutrophil count; CI: confidence interval; NE: not estimated

Table 4: Randomised, placebo-controlled efficacy study in the Rhesus monkey model of TBI-induced H-ARS (Study 2)

Design	Efficacy study, specifically the survival benefit and delayed response (expectant haematopoietic recovery response) of sargramostim 60 days following lethal TBI at the LD50/60 dose with minimal supportive care (antibiotics and fluids) in Rhesus monkey
Number of animals	105 male NHPs randomised into 3 groups (n=35 per group)
Treatment	Daily until ANC count ≥ 1 000 cells/µL
Radiation dose	6.80 Gy TBI
Primary endpoint	60-day survival
Results	
60-day survival 24-hours 48-hours	Number of sargramostim-treated NHPs survived 17 of 35 (49%) (p=0.11, log-rank test) 21 of 35 (60%) (p=0.03, log-rank test)
60-day survival Control	Number of control NHPs survived 10 of 34 (29%)
Mean duration of exposure to Imreplys	18 days or until ANC increased above 1 000 cells/µL

Abbreviations: ANC: absolute neutrophil count; LD: lethal dose: NHP: non-human primate; TBI: total body irradiation

The adequate and well-controlled (AWC) efficacy and confirmatory AWC efficacy non-human primate (NHP) studies are summarised in Table 5.

Table 5: Randomised, placebo-controlled efficacy study in the Rhesus monkey model of TBI-induced H-ARS (Study 3)

Design	Randomised, placebo-controlled efficacy study in the NHP model of TBI-induced H-ARS
Number of animals	308 NHPs (154 male: 154 female)
Treatment	Daily starting 48-, 72-, 96-, or 120-hours post-irradiation until ANC returned to ≥ 1 000/µL for 3 consecutive days. Treatment was stopped if the ANC was ≥ 10 000/µL
Radiation dose	7.13 Gy TBI
Primary objective	Evaluate the efficacy of sargramostim (7 mcg/kg/day) versus placebo when initiated at 48, 72, 96, or 120 hours post-TBI in NHPs exposed to 7.13 Gy TBI
Primary endpoint	60-day survival
Secondary objectives	Assess efficacy on haematology parameters and incidence of infection
Results	
60-day survival 48-hours 72-hours 96-hours 120-hours	Number of sargramostim-treated NHPs survived 30 of 44 (68%) 33 of 44 (75%) 30 of 44 (68%) 37 of 44 (84%)
60-day survival Control	Number of control NHPs survived 38 of 44 (86%)
Mean duration of exposure to Imreplys	Approximately 16 days until ANC ≥ 1 000 cells/µL for 3 consecutive days or ANC ≥ 10 000 cells/µL

* The 60-day survival results have not been statistically controlled for multiplicity. As a result, the strength of the evidence is limited, and findings should be interpreted with caution.
Abbreviations: ANC: absolute neutrophil count; NHP: non-human primate; TBI: total body irradiation

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with sargramostim. In Rhesus monkeys exposed to radiation lower than 2 Gy and treated with 7 mcg/kg/day of sargramostim via subcutaneous injection for 14-days, no anti-drug antibodies were observed. It is expected that the effect of radiation impairs the ability of human body developing anti-drug antibodies.

No clinical safety signals have been associated with anti-drug or neutralising anti-drug antibodies in non-myelosuppressed patients, to date.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Imreplys in one or more subsets of the paediatric population in treatment of acute radiation syndrome (see section 4.2 for information on paediatric use).

Exceptional circumstances

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease and for scientific and ethical reasons it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of sargramostim are not available in patients acutely exposed to myelosuppressive doses of radiation.

Modelling and simulation of the healthy human adult pharmacokinetic data indicate that sargramostim C_{max} and area under the curve (AUC) exposures at dose of 7 mcg/kg in healthy adults are expected to exceed sargramostim C_{max} (97.6% of patients) and AUC (100% of patients) exposures at the same dose of 7 mcg/kg in Rhesus monkeys.

The pharmacokinetics of sargramostim in healthy paediatric patients were estimated by scaling the adult population pharmacokinetic model to the paediatric population. The model-predicted mean AUC_{0-24} values at 7, 10, and 12 mcg/kg doses of sargramostim in paediatric patients weighing greater than 40 kg (~adolescents), 15 to 40 kg (~young children), and 0 to less than 15 kg (~newborns to toddlers), respectively, were similar to AUC values in adults after a 7 mcg/kg dose.

Based on a population pharmacokinetics analysis of lyophilised sargramostim data, the mean C_{max} after a 7 mcg/kg subcutaneous dose (equivalent to a 250 mcg/m^2 dose in a 70 kg human with a body surface area of 1.96 m^2) was 3.03 ng/mL and mean AUC_{024} was 21.3 ng•h/mL. There is no accumulation of sargramostim after repeated subcutaneous dosing and steady state conditions are met after a single subcutaneous dose.

Absorption

After subcutaneous administration, sargramostim was detected in the serum early (15 min) and reached maximum serum concentrations between 2.5 and 4 h.

A more than dose proportional increase in AUC was observed following a single subcutaneous administration of sargramostim across the 2 to 8 mcg/kg dose range in healthy male subjects.

Distribution

In a study, healthy subjects were administered 250 mcg sargramostim by intravenous infusion over 2 hours. The observed volume of distribution (V_z) after intravenous administration was 14 L.

Biotransformation

Specific metabolism studies were not conducted, because sargramostim is a protein and is expected to degrade to small peptides and individual amino acids.

Elimination

When sargramostim was administered subcutaneously to healthy adult volunteers, it had a terminal elimination half-life of 1.4 h. The observed total body clearance/subcutaneous bioavailability (CL/F) was 23.9 l/h.

5.3 Preclinical safety data

Toxicology

In a repeated-dose toxicity study, sargramostim was administered subcutaneously daily to cynomolgus monkeys at doses of 20 and 200 mcg/kg/day for 30 days. The lympho-haematopoietic system was identified as the primary target of toxicity: an increase in white blood cells and platelets as well as splenic inflammatory and lymphoid cell infiltration were observed at ≥ 20 mcg/kg/day.

Moderate to moderately severe bone marrow myeloid hyperplasia and mononuclear cell infiltrates in the heart and other organs were observed at 200 mcg/kg/day at terminal sacrifice, and moderate to moderately severe thymic atrophy was observed at 200 mcg/kg/day in both terminal and recovery animals. All findings were considered related to the pharmacology of sargramostim and therefore are potentially clinically relevant; however, the majority of the findings were observed at a dose that is approximately 17 to 29-fold greater than clinical exposure at the recommended human doses (7 to 12 mcg/kg/day) based on body weight scaling.

A similar pattern of toxicity but at a lower dose (20 mcg/kg/day) was observed in a 42-day repeated-dose toxicity study in which cynomolgus monkeys were subcutaneously administered 20, 63 and 200 mcg/kg/day with a sargramostim formulation containing ethylenediaminetetraacetic acid (EDTA), different from Imreplys. In this study, the systemic exposure (AUC) at 20 mcg/kg/day was approximately 2-fold greater than the clinical exposure at the recommended human doses (7 to 12 mcg/kg/day).

Reproductive and developmental toxicity

All reprotoxicity studies were carried out with a sargramostim formulation containing EDTA, different from Imreplys.

In the fertility and early embryonic development study, sargramostim was administered subcutaneously to rabbits at doses of 25, 70 and 200 mcg/kg/day from 6 days prior to artificial insemination and continuing through gestation day (GD) 7. Maternal toxicity was evident at ≥ 70 mcg/kg/day. A decrease in implantation sites and an increase in preimplantation loss and reduction in viable embryos was observed at 200 mcg/kg/day. The AUC at the no-observed-adverse-effect-level (NOAEL) for female reproductive and early embryonic developmental toxicity of 70 mcg/kg/day was initially (at the start of the dosing period) approximately 7.2-fold the clinical exposure at the recommended adult clinical dose (7 mcg/kg/day).

In the embryo-foetal developmental study, pregnant rabbits were administered subcutaneously doses of sargramostim during the period GD 6 to GD19 or GD19 to GD28 at 25, 70, and 200 mcg/kg/day.

Maternal toxicity was evident at ≥ 25 mcg/kg/day. An increase in late resorptions and reduced foetal weights were observed at ≥ 70 mcg/kg/day. An increase in spontaneous abortions and post-implantation loss, a reduction in viable foetuses and a reduced gravid uterine and placental weight were evident at 200 mcg/kg/day. The AUC at the NOAEL for embryo-foetal toxicity of 25 mcg/kg/day was initially (at the start of the dosing period) approximately 2.9-fold the clinical exposure at the recommended adult clinical dose (7 mcg/kg/day).

In the pre- and postnatal development study, rabbits were administered SC doses of sargramostim during GD6 to GD19, GD19 to parturition, or lactation day (LD)1 to LD14 at 25, 70, and 200 mcg/kg/day. Maternal toxicity was observed at ≥ 25 mcg/kg/day. At doses ≥ 25 mcg/kg/day, a reduction in postnatal offspring survival was observed when rabbits were dosed during lactation. The high-dose of 200 mcg/kg caused a decreased pup body weight when rabbits were dosed during lactation and from GD19 to parturition. Treatment from GD6-GD19 and GD19-parturition at 200 mcg/kg/day resulted in abortions, while after GD6-GD19 treatment with 200 mcg/kg/day total litter loss, early resorptions, reduced number of kits born and reduced live litter size on Post Natal Day 0 were also observed. There is no NOAEL for neonatal toxicity. The AUC of 25 mcg/kg/day dose was initially (at the start of the dosing period) approximately 2.6-fold the clinical exposure at the recommended adult clinical dose (7 mcg/kg/day).

By the end of the dosing periods, the systemic exposures decreased due to the production of anti-sargramostim antibodies reaching 1-fold, 0.2-fold and 0.2-fold the clinical exposure in the fertility and early embryonic development, embryo-foetal developmental and pre- and postnatal development studies, respectively.

Genotoxicity and carcinogenicity

Studies to evaluate the mutagenic and carcinogenic potential of sargramostim have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sucrose
Trometamol
Hydrochloric Acid (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened vial
4 years

Additional information:

- If unopened vials reach temperatures up to 25 °C, they are stable up to 1 year when protected from light.
- If unopened vials reach temperatures up to 40 °C, they are stable up to 1 month when protected from light.

- Do not expose to more than 1 Gy of ionising radiation. If unopened vials are exposed to up to 1 Gy of ionising radiation, they are stable up to 2 weeks at temperatures up to 40 °C when protected from light.

After reconstitution
After reconstitution with water for injections (not co-packaged with Imreplys), chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C – 8 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C – 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vials in the outer carton in order to protect from light.

6.5 Nature and contents of container

Pack size of five 8 mL (Type I clear glass) vials.

6.6 Special precautions for disposal and other handling

Do not shake.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Partner Therapeutics Ltd.,
28 - 32 Pembroke Street Upper,
Dublin 2, Ireland.
D02NT28
Tel: +353.1264.1754
e-mail: info@partnertx.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1924/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Partner Therapeutics, Inc.
2625 162nd St SW
Lynnwood, WA 98087
USA

Name and address of the manufacturer responsible for batch release

Paesel + Lorei GmbH & Co KG
Nordring 11
D-47495 Rheinberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The MAH shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to further characterise the efficacy and safety of sargramostim in the treatment of acute exposure to myelosuppressive doses of radiation with Haematopoietic Syndrome of Acute Radiation Syndrome (H-ARS), the MAH shall conduct and submit the results of study PTX-01-001, a retrospective observational study to evaluate the efficacy and safety of sargramostim in individuals exposed to myelosuppressive doses of radiation following an ionising radiation event, according to an agreed protocol.	Protocol submission: 30 June 2025 Due date: final study results within 6 months after the use of the product in an incident.
In order to ensure adequate monitoring of safety and efficacy of sargramostim in the treatment of acute exposure to myelosuppressive doses of radiation with Haematopoietic Syndrome of Acute Radiation Syndrome (H-ARS), the MAH shall provide yearly updates on any new information concerning the safety and efficacy of sargramostim.	Protocol submission: NA Due date: to be submitted as part of the annual re-assessment

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Imreplys 250 microgram powder for solution for injection
sargramostim

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains sargramostim 250 mcg
After reconstitution each mL contains 250 mcg sargramostim.

3. LIST OF EXCIPIENTS

Contains mannitol (E421), sucrose, trometamol, and hydrochloric acid. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
5 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
For single-use only.
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Partner Therapeutics Ltd.,
28 - 32 Pembroke Street Upper,
Dublin 2, Ireland.
D02NT28

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1924/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imreplys 250 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Imreplys 250 microgram powder for injection
sargramostim
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Imreplys 250 microgram powder for solution for injection
sargramostim

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask a doctor, pharmacist, nurse or healthcare provider.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to a doctor, pharmacist or nurse or healthcare provider. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Imreplys is and what it is used for

Imreplys contains the active substance sargramostim which is similar to a natural protein in the body called granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF helps the bone marrow produce white and platelet blood cells, which are crucial for fighting infections and healing injuries. This medicine is used to treat adults and children from birth suddenly exposed to high amounts of radiation. This condition is called: Haematopoietic Sub-syndrome of Acute Radiation Syndrome (H-ARS). Radiation can severely lower white blood cell counts (increasing infection risk), platelet counts (leading to bleeding), and red blood cells, causing anaemia and potential organ damage.

Sargramostim has also been shown to improve blood cell counts in patients with certain blood cancers undergoing chemotherapy or after bone marrow transplant. Like cancer patients, people who have been exposed to radiation and develop H-ARS will have weakened immune systems and reduced blood cell counts.

2. What you need to know before you use Imreplys

Do not use Imreplys
- if you are allergic to sargramostim or any of the other ingredients of this medicine (listed in section 6).
- if you have had a serious allergic reaction, including anaphylaxis, to human GM-CSF (sargramostim) or other products that are made from yeast.

Warnings and precautions

Talk to your doctor, pharmacist, nurse or healthcare provider before using Imreplys.

A generalised allergy is an uncommon, but serious reaction to Imreplys. This may include a rash over your entire body, hives, trouble breathing, a fast pulse, sweating, and feeling faint. In severe cases, a generalised allergy may be life-threatening. If you think you are having a generalised allergy to Imreplys, stop taking Imreplys and contact a doctor, pharmacist, nurse or healthcare provider immediately.

Exposure to acute or sudden high-dose radiation can be a life-threatening condition. The possible benefit of Imreplys in reducing the threat to life from exposure to high-dose radiation should be considered in comparison to possible risks of taking the medicine.

Some side effects of Imreplys can also be symptoms of radiation exposure, or of other treatments you have received. Contact a doctor, pharmacist, nurse or healthcare provider immediately if after taking Imreplys:

- You develop a fever over 38 °C
- You notice any signs of infection including chills, sore throat, or congestion (such as a stuffy nose)
- You have trouble breathing, or you develop wheezing, fainting, extensive skin rash, hives, or you feel you are having an allergic reaction
- You experience sudden weight gain or other signs of fluid build-up, such as swollen legs or feet
- You develop chest pain, chest discomfort, or a rapid or irregular pulse

If you are concerned about any other side effects or symptoms you may be having, contact a doctor, pharmacist, nurse or healthcare provider.

During sargramostim treatment, where possible, a doctor, pharmacist, nurse or healthcare provider should monitor your blood cell counts. As a result of testing, your Imreplys dose may be adjusted, or your Imreplys treatment may be stopped.

If you have cancer, and in particular if you currently are being treated for cancer, contact your cancer doctor as soon as practical after radiation exposure, whether or not you have started Imreplys.

Other medicines and Imreplys
Tell your doctor, or pharmacist, nurse or healthcare provider if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor, or pharmacist or nurse for advice before taking this medicine.
Your doctor will consider the benefit and risk of using Imreplys for you and your baby.
It is not known if sargramostim will harm your unborn baby.

Driving and using machines
No effects on the ability to drive or use machines while taking Imreplys have been reported.

3. How to use Imreplys

Always use this medicine exactly as your doctor, pharmacist, nurse or other healthcare provider has told you. Check with them your if you are not sure.

Administration of Imreplys should occur ***as soon as possible*** after exposure to acute high doses of radiation.

The recommended dose of Imreplys to be injected under the skin (subcutaneous injection) is shown below.

- 7 micrograms/kg in children and adolescents weighing greater than 40 kg, and in adults
- 10 micrograms/kg in children and adolescents weighing 15 kg to 40 kg
- 12 micrograms/kg in newborns, infants or children weighing less than 15 kg

Your doctor, pharmacist, nurse or healthcare provider will tell you the right volume to be injected to you or to your child.

Your doctor, pharmacist, nurse or healthcare provider will tell you how long you or your child need to be treated with Imreplys until blood cell counts have sufficiently improved, as determined by blood tests. If it is not possible to do blood tests to determine blood cell counts, Imreplys may be stopped after 23 consecutive days of dosing.

Individual patient dose (mcg)	**Individual patient dose (mcg) = weight (kg) × dose in mcg/kg** • Actual body weight at initiation of treatment should always be used when calculating initial dose. • Divide total mcg by 250 mcg/mL to determine the number of mL needed.
Adult, or child or adolescent > 40 kg example (80 kg body weight)	Individual patient dose (mcg) = 80 kg × 7 mcg/kg = 560 mcg 560 mcg of Imreplys will be needed, i.e., 2 full vials of Imreplys and a partial third vial (the remaining drug in the third vial should be discarded). 560 mcg ÷ 250 mcg/mL = 2.2 mL. Hence a 3 mL syringe may be needed.
Child or adolescent 15 – 40 kg example (20 kg body weight)	Individual patient dose (mcg) = 20 kg × 10 mcg/kg = 200 mcg 200 mcg of Imreplys will be needed, i.e., 1 partial vial of Imreplys (the remaining drug in the vial should be discarded). 200 mcg ÷ 250 mcg/mL = 0.80 mL. Hence a 1 mL syringe may be needed.
Newborn, infant or child < 15 kg example (5 kg body weight)	Individual patient dose (mcg) = 5 kg × 12 mcg/kg = 60 mcg 60 mcg of Imreplys will be needed, i.e., 1 partial vial of Imreplys (the remaining drug in the vial should be discarded). 60 mcg ÷ 250 mcg/mL = 0.24 mL. Hence a 1 mL syringe may be needed.
Your dose	Individual patient dose (mcg) = ___kg × ___mcg/kg = ___mcg ___ mcg of Imreplys will be needed (___full vials, and [**1** or **no**] partial vial [discard any remaining drug if a partial vial is required]). ___ mcg ÷ 250 mcg/mL = ___ mL. Hence a ___ mL syringe may be needed.

If you inject more Imreplys than you should
Contact a doctor, pharmacist, nurse or healthcare provider as soon as practical. A healthcare provider may want to monitor you.
If you forget a dose of Imreplys

Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some patients taking sargramostim may experience unwanted side effects, most of which are mild to moderate and not serious.

The most serious side effect is a serious allergic reaction (including anaphylaxis); if this happens to you, stop taking Imreplys and contact a doctor, pharmacist, nurse or healthcare provider immediately.

Other important side effects are high fever (over 38 °C), signs of an infection (such as chills, sore throat, congestion, runny nose), having trouble breathing or wheezing, feeling faint, developing extensive skin rash or hives or other signs of an allergic reaction, having sudden weight gain, swollen legs or feet, or other signs of fluid build-up, chest pain, chest discomfort or rapid or irregular pulse. If you experience any of these side effects, contact a doctor, pharmacist, nurse or healthcare provider immediately.

Very common side effects (may affect more than 1 in 10 people):
Diarrhoea, vomiting, feeling like you have the flu, feeling tired or weak, muscle aches, abnormal blood test results, headache, back pain, weight loss, stomach pain, gastrointestinal bleeding, bone pain, stomach upset, vomiting blood, joint pain, general body pain, throat pain, feeling tense or worried, and bleeding in the eye.

You may also get a mild fever (less than 38 °C) about one to 4 hours after an injection, or you may have swelling, redness, and/or discomfort where Imreplys is injected. The skin may become red, painful, or swollen. This may be suggestive of a reaction at the site of injection. This usually will not require you to stop taking sargramostim. If a reaction at the site of the injection occurs, contact a doctor, pharmacist, nurse or other healthcare provider. The following steps may be taken to prevent further reactions at the site of the injection:

- At least 30 minutes before you plan to inject, remove Imreplys and water for injections vials from the refrigerator and allow them to come to room temperature before injecting
- Use a different injection site each time you inject
- Avoid rubbing the skin before or after injecting

Common side effects (may affect up to 1 in 10 people):
Dilatation of blood vessels.

If you are concerned about these or any other side effects, contact a doctor, pharmacist, nurse or other healthcare provider.

Reporting of side effects
If you get any side effects, including those that are not listed in this leaflet, talk to your doctor, pharmacist, nurse or other healthcare provider. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Imreplys

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vials in the original outer carton in order to protect from light.

Special precautions:

- If unopened vials reach temperatures up to 25 °C, they are stable up to 1 year when protected from light.

- If unopened vials reach temperatures up to 40 °C, they are stable up to 1 month when protected from light.
- Do not expose to more than 1 Gy of ionising radiation. If unopened vials are exposed to up to 1 Gy of ionising radiation, they are stable up to 2 weeks at temperatures up to 40 °C when protected from light.

If you do not have refrigeration, you may store the sealed product at room temperature (15 °C – 25 °C) for up to one year. Sealed vials of Imreplys that have been exposed to temperatures greater than 25 °C and not more than 40 °C may be kept for one month.

After dilution with water for injections, Imreplys solution can be stored in the refrigerator (2 °C – 8 °C) for up to 24 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Imreplys contains

- The active substance is sargramostim. Each glass vial contains 250 mcg sargramostim. After reconstitution, each 1 mL contains 250 mcg sargramostim.
- The other excipients are mannitol (E421), sucrose, trometamol, and hydrochloric acid.

What Imreplys looks like and contents of the pack

Imreplys powder for solution for injection (powder for injection) is a white lyophilised powder supplied in a carton containing five 250 mcg single-dose glass vials.

Marketing Authorisation Holder
Partner Therapeutics Ltd.,
28 - 32 Pembroke Street Upper,
Dublin 2, Ireland.
D02NT28
Ireland
+353.1264.1754
info@partnertx.com

Manufacturer
Paesel + Lorei GmbH & Co KG
Nordring 11
D-47495 Rheinberg
Germany

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

How to prepare and inject Imreplys

Imreplys will be injected under your skin (subcutaneous injection). Your doctor, pharmacist, nurse, or other health care provider will tell you the volume (mL) to be injected.

Follow all instructions provided by your doctor, pharmacist, nurse or other health care provider. Do not change your dose or stop Imreplys unless a doctor, pharmacist, nurse or other health care provider tells you to.

Imreplys vials are for single-use only.

More than one vial of Imreplys may be needed for each dose depending on the patient's weight. As an example, if an adult patient's weight is 80 kg, three vials of Imreplys will be needed and each vial will need water for injections to dissolve the drug.

Below is a list of items to use that are **not included** within the Imreplys package, but are essential for proper administration:

- Water for injections in a vial or ampoule (this is a special type of water which is manufactured specifically for use to prepare medicines for injections).
- Disposable, metered syringe and needle to *add* water for injections to dissolve Imreplys in the vial. A filter needle should be used if a glass ampoule of water for injection is used.
- Disposable syringe and needle to *inject* the Imreplys solution dose after it has been dissolved with the water for injections. Please note that when choosing the right syringe, it is important to ensure that the syringe's size is adequate to inject the required volume of the drug. Typical syringe sizes (total volume) are 2 mL, 3 mL, and 5 mL.
- Alcohol pads to clean your skin at the site of injection and to clean the tops of the vial(s) and/or ampoule(s)
- Cotton ball or gauze pad
- Adhesive bandage strip
- Needle and syringe disposal container

Caregiver/self-administration

Imreplys may be self-administered or administered by a caregiver.

Comprehensive instructions for the preparation and administration of the reconstituted Imreplys vial are given in the package leaflet, section 3, "How to use Imreplys".

Imreplys vial(s) and the items for proper administration should be kept out of the reach of children.

Step 1: Prepare

Wash your hands thoroughly with soap and water. Dry them with a clean towel.

Please look at the date of expiry on the Imreplys vial and other supplies to ensure that the product(s) have not expired.

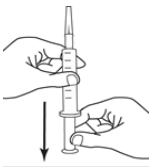
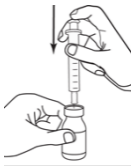
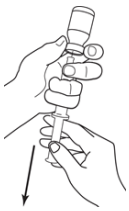
For each dose, place needed Imreplys and water for injections on a clean, well-lit surface, and allow them to reach room temperature before preparing an injection.

- **Do not** try to warm products by using a heat source such as hot water or microwave.
- **Do not** leave Imreplys vial(s) in direct light. Keep vial(s) in the box until time of use.
- **Do not** shake Imreplys.

Remove the dark blue plastic cap(s) from the Imreplys vial and the cap(s)/tops from the water for injections vial(s). Do not remove the vial stoppers. Do not remove the silver-coloured metal ring around the top(s) of the vial(s). *Figure demonstrates step for a Imreplys vial.*	

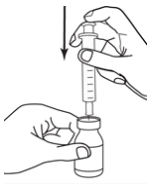
If using ampoule(s) of water for injections, clean with an alcohol pad prior to opening. To open a glass ampoule, it should be held in an upright position. Check all fluid is removed from neck of ampoule. If not, gently flick the top of the ampoule until the fluid runs back down into it. If there is a dot on the ampoule, ensure the dot is facing away from you. Use a gauze pad or paper towel to hold the top of the ampoule, protecting your fingers. Hold the ampoule in one hand, using the other hand to snap the neck of the ampoule away from you. If using a plastic ampoule, twist the top of the ampoule until it is removed.	
Clean each vial stopper with a new alcohol pad for each vial. Let vial air dry by themselves (do not blow on them).	

Step 2. Withdraw the water for injections into a syringe

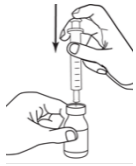
Repeat Steps 2 and 3 for each Imreplys vial needed for your dose as prescribed by your doctor, pharmacist, nurse, or other healthcare provider. Locate the needle and syringe to withdraw the water for injections. A filter needle should be used if a glass ampoule is used. If the needle is not attached to the syringe, attach it onto the syringe with the needle cap still on. If a water for injections vial is used: Pull the needle cap off straight and away from your body. Do not allow the needle to touch anything. Pull back on the plunger of the syringe to add 1 mL of air to the syringe.	
Insert the needle straight down in the centre of the rubber stopper on the water for injections vial. Push the syringe plunger down to push all air from the syringe into the vial. Keep your finger on the plunger so the air does not come back into the syringe. Keep the needle in the vial and turn the vial upside down. Make sure the liquid is covering the needle tip.	
Keep the vial upside down and slowly pull back on the syringe plunger until 1 mL of water for injections is in the syringe barrel before removing syringe and needle from the vial. If there are air bubbles in the syringe, gently tap the syringe barrel with your finger until the air bubbles rise to the needle end of the syringe. Gently push the plunger up to push the air bubbles out of the syringe. Repeat these steps as needed until you have 1 mL of water for injections in the syringe with no air bubbles. Remove syringe with attached needle from vial, discard vial, and go to Step 3. If a water for injections ampoule is used: Pull the filter needle cap off straight and away from your body. Do not allow the needle to touch anything.	

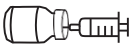
Insert the filter needle straight down in the water for injections ampoule. Make sure the liquid is covering the filter needle tip. Slowly pull back on the syringe plunger until 1 mL of water for injections is in the syringe barrel. If there are air bubbles in the syringe, remove syringe with filter needle attached from ampoule and point upward. Gently tap the syringe barrel with your finger until the air bubbles rise to the needle end of the syringe. Gently push the plunger up to push the air bubbles out of the syringe. Repeat these steps as needed until you have 1 mL of water for injections in the syringe with no air bubbles. Remove filter needle from syringe. Attach new needle (filter not needed) for next step. Discard ampoule and go to Step 3.	 

Step 3. Dissolve the Imreplys powder with the water for injections you withdrew in Step 2.

Insert the needle on the syringe containing water for injections through the centre of the rubber stopper on the Imreplys vial stopper. Slowly push the syringe plunger down until all water for injections from the syringe is in the Imreplys vial. Pull the syringe and needle completely out of the vial of Imreplys and discard into the needle and syringe disposal container.	
Keeping the Imreplys vial upright on a flat surface, gently turn the Imreplys vial in a circular pattern until the powder is completely dissolved and the solution is clear and colourless. Do not shake the vial. Once reconstituted, it must be stored in a refrigerator at 2 to 8°C, and used within 24 hours. Do not store above 8°C. Do not freeze. **Repeat Steps 2 and 3 for each Imreplys vial needed for your dose as prescribed by your doctor, pharmacist, nurse, or other health care provider.**	

Step 4. Withdraw the Imreplys solution into a syringe

Review your prescription to confirm what volume (mL) of Imreplys solution you should inject under the skin.	
Place the vial(s) of Imreplys solution on a flat surface. If the vial(s) is cold, allow it to warm to room temperature for at least 30 minutes. Clean the Imreplys vial stopper(s) with a new alcohol pad. Let it air dry.	
Locate the needle and syringe to withdraw Imreplys solution. If the needle is not attached to the syringe, attach it onto the syringe with the needle cap still on. Pull the needle cap off straight and away from your body pointing up. Do not allow the needle to touch anything.	
Keep the Imreplys solution vial(s) upright on a flat surface and insert the needle straight down through the centre of the stopper.	

Keep the needle in the vial and turn the vial upside down (if needed). Make sure the Imreplys solution is covering the needle tip. Slowly pull back on the syringe plunger to fill the syringe barrel to the correct amount (mL) that matches the dose listed on your prescription. Multiple vials of Imreplys solution may be needed.	
Keep the needle in the vial and check for air bubbles in the syringe. If there are air bubbles in the syringe, gently tap the syringe barrel with your finger until the air bubbles rise to the top of the syringe. Gently push the plunger to push the air bubbles out of the syringe. Keep the needle tip in the liquid and pull the plunger back to the number on the syringe barrel that matches your dose (mL). Repeat these steps as needed.	
Check again to make sure you have the correct dose in the syringe. It is important that you use the exact dose prescribed by a doctor, pharmacist, nurse, or other healthcare provider. DO NOT remove the needle from the vial. Lie the vial down on its side with needle still in the vial.	

Step 5: Select and prepare an injection site

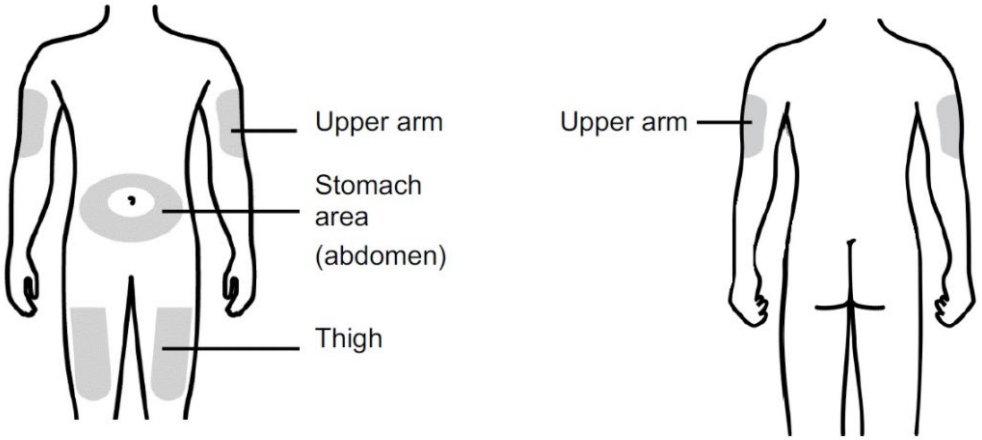
Clean the area immediately around the injection site you plan to use with an alcohol pad. Let your skin dry. **Do not** touch this area again before injecting.

Do not use the same injection site area you used for the previous injection. **Avoid** injecting into areas where the skin is burnt or broken (ulcerated), painful, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

You may use any of the following sites for an injection:

- Thigh
- Stomach area except for a 5 cm area right around your navel or belly button
- Outer area of upper arm (only if someone else is giving you the injection)

The preferred administration site for infants and paediatric patients is the thigh.



Step 6: Inject Imreplys solution under the skin (subcutaneously)

Remove the syringe and needle that contains your prescribed Imreplys dose from the vial. Pinch your injection site between your thumb and first finger. Be careful not to touch the injection site itself. Keep skin pinched while injecting. Hold the syringe with your other hand. Insert the needle into the skin quickly at a 45-to-90-degree angle. There will be less discomfort or pain the more quickly you insert the needle into the pinched skin. Using slow and constant pressure, push the syringe plunger until all of the Imreplys solution is injected. When done, gently pull the needle out of your skin. Cover the site with cotton ball or gauze if there is blood. Apply an adhesive bandage strip over the cotton ball or gauze, if needed. Do not rub the injection site.	

Step 7: Proper disposal

Do the following: Appropriately discard all supplies as described below. After one use • Immediately discard syringe with needle into a needle and syringe disposal container. • Immediately discard used Imreplys vial into an appropriate waste container. • Make sure all other materials are discarded into proper containers. The syringe, needle, Imreplys vial, and water for injections must NEVER be reused. If you do not have a needle or syringe disposal container, you may use a household container that is a puncture-resistant, leak-proof container. **Important:** Always keep the needle and syringe disposal container out of the reach of children.	

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.