PRODUCT MONOGRAPH

Pr PROCHYMAL®

(remestemcel-L)
Adult Human Mesenchymal Stem Cells (hMSCs)

Cell suspension for intravenous infusion,
100 x 10^6 hMSCs per 15 mL, 2.5 x 10^6 hMSCs per mL after reconstitution

PROCHYMAL is indicated in the management of acute Graft versus Host Disease (aGvHD) in pediatric patients. Acute GvHD should be refractory to treatment with systemic corticosteroid therapy and/or other immunosuppressive agents. Prochymal may be used for Grades C and D of the disease in any organ. Prochymal may also be used in the management of Grade B aGvHD involving any visceral organ, including the GI tract and the liver, but excluding skin.

Prochymal has been granted marketing authorisation with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorisation.

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Date of Revision:
March 6, 2014

Submission Control No. : 172934

Date of Approval:

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This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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[Pr]PROCHYMAL®

(remestemcel-L)

PART I: HEALTH PROFESSIONAL INFORMATION

PROCHYMAL is indicated in the management of acute Graft versus Host Disease (aGvHD) in pediatric patients. Acute GvHD should be refractory to treatment with systemic corticosteroid therapy and/or other immunosuppressive agents. Prochymal may be used for Grades C and D of the disease in any organ. Prochymal may also be used in the management of Grade B aGvHD involving any visceral organ, including the GI tract and the liver, but excluding skin.

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SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Liquid containing 100 x 10^6 hMSCs per 15 mL. The diluted product contains 2.5 x 10^6 hMSCs per mL.	Dimethyl sulphoxide (DMSO) Human serum albumin (HSA) *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

PROCHYMAL (remestemcel-L, human mesenchymal stem cells [hMSCs] for intravenous infusion) is a liquid cell suspension of ex-vivo cultured adult human mesenchymal stem cells intended for intravenous infusion. The mesenchymal stem cells are derived from the bone marrow of unrelated and human leukocyte antigen (HLA)–unmatched healthy adult donors. Patient-specific blood type or HLA matching is not required for the administration of hMSCs due to the product's low immunogenic profile.

The hMSCs are undifferentiated stem cells of mesodermal origin. They are primary cells that have not been genetically manipulated or immortalized during the manufacturing process. The

hMSCs are manufactured under aseptic conditions in a process that involves isolation and culture expansion.

PROCHYMAL is provided as a frozen cell suspension in a cryogenic bag. The cells should be thawed and diluted prior to intravenous administration.

INDICATIONS AND CLINICAL USE

NOC/c

PROCHYMAL is indicated for in the management of acute Graft versus Host Disease (aGvHD) in pediatric patients. Acute GvHD should be refractory to treatment with systemic corticosteroid therapy and/or other immunosuppressive agents. Prochymal may be used for Grades C and D of the disease in any organ. Prochymal may also be used in the management of Grade B aGvHD involving any visceral organ, including the GI tract and the liver, but excluding skin.

Approval with conditions is based on clinical study of severe refractory aGvHD patients that demonstrated a clinically significant Overall Response of their aGvHD 28 days following start of PROCHYMAL.

PROCHYMAL should be administered under the supervision of a qualified health professional experienced in the management of aGvHD.

Once reconstituted, PROCHYMAL is a clear to opalescent, pale yellow liquid with no visible particulates in solution. Parenteral drug product should be inspected visually for particulate matter prior to administration. Reconstituted PROCHYMAL with visible particulate matter should be discarded.

CONTRAINDICATIONS

NOC/c

Since PROCHYMAL is indicated for use in refractory aGvHD, a life-threatening condition, there is no absolute contraindication to its use.

WARNINGS AND PRECAUTIONS

NOC/c

Extreme caution should be exercised when administering PROCHYMAL to patients who have a known or suspected hypersensitivity to any ingredient in the formulation of PROCHYMAL or component of the container. Caution should be used when administering PROCHYMAL to patients with a known sensitivity to porcine (pig) or bovine (cow) products, as trace amounts of these components may remain in the final product.

The long term effects of PROCHYMAL in growing children are unknown.

Respiratory/Infusional Toxicity

Dose limiting toxicity, as determined from animal studies, is due to the accumulation of MSCs in the microvasculature of the lungs leading to breathing difficulty and pulmonary collapse. Dose-limiting toxicity has not been determined clinically.

Prochymal should be administered intravenously at a controlled rate and under the supervision of a qualified health professional who is experienced in the management of acute GvHD.

It is recommended that oxygen saturation (SaO_2/SAT) is monitored by pulse oximetry during infusion of the product. If there are signs of adverse reaction, discontinue the infusion.

Ectopic tissue formation

Human MSCs have the potential to differentiate into several tissues of mesenchymal origin such as bone, fat, and cartilage under appropriate conditions. The cells maintain an undifferentiated phenotype during culture expansion.

Ectopic tissue formation was evaluated in preclinical toxicology studies and clinical studies. No cases of ectopic tissue formation were observed due to product administration. For more information, see the Genotoxicity, Carcinogenicity, Tumorigenicity and Ectopic Tissue Formation section under Toxicology in PART II: SCIENTIFIC INFORMATION.

It is recommended that patients have an imaging study (Computed tomography or CT scan) within the three months prior to starting PROCHYMAL. The imaging study should be repeated if there is a suspected case of ectopic tissue formation that has been deemed by a physician as possibly related to the use of PROCHYMAL.

Hypersensitivity

Caution should be used when administering PROCHYMAL to patients with a known sensitivity to porcine or bovine products, because these components are used in the manufacturing process and trace amounts may remain in the final product. In patients with known or suspected hypersensitivity to PROCHYMAL, the intended benefit of treatment should be carefully weighed against the potential risks.

Infectious Complications

Patients undergoing treatment for aGvHD are typically severely immunocompromised. Treatment with Prochymal may lead to further immunosupression. Therefore, the potential exists for an increased risk of infectious complications. Careful patient monitoring and appropriate anti-infective prophylaxis are recommended.

Transmission of infectious agents

Use of PROCHYMAL carries a potential risk of transmission of adventitious or infectious agents. Standard and advanced measures are in place to counteract this risk, however, as with any blood or marrow derived product, the possibility of transmitting infectious agents cannot be completely excluded. Specific measures to reduce this potential risk are outlined below:

- Strict adherence to the National Standards of Canada CAN/CSA-Z900.1, " *Cells, Tissues and Organs for Transplantation and Assisted Reproduction: General Requirements*", and the National Standards of Canada CAN/CSA-Z900.2.5, *"Lymphohematopoietic Cells for Transplantation"* and the FDA Donor Suitability Guidance.

- Rigorous donor screening including physical exam and medical/social history questionnaire.
- Donor testing for infectious diseases including HIV-1 and 2, hepatitis B and hepatitis C viruses, HTLV, Syphilis, West Nile Virus, CMV and EBV. These tests are repeated again during manufacturing, and then also testing for HHV-6A, HHV-6B, HHV-8, Parvovirus B-19 and HPV is performed using DNA and RNA PCR techniques.
- Use of reagents in manufacture that are sterile and have undergone viral inactivation where appropriate. Bovine serum used in the manufacturing process is carefully sourced from TSE-free countries to minimize the risk of TSE infectivity.
- Testing of the final product, including standard tests such as sterility, endotoxin and mycoplasma testing, as well as advanced tests such as in vitro and in vivo adventitious viral contaminant tests and thin section electron microscopy. All of the testing must be negative before the product can be released for use.

The risk of viral disease transmission from use of PROCHYMAL is estimated to be lower than that of blood products commonly in use (e.g. packed red blood cells and platelets).

Special Populations

Pregnant Women:

There has been no experience with pregnant women receiving infusions of PROCHYMAL. The use of PROCHYMAL in pregnant women is not recommended. The use of PROCHYMAL in pregnant women is not recommended.

Lactating Women:

There has been no experience with breast-fed infants from lactating women receiving infusions of PROCHYMAL. The use of PROCHYMAL in lactating women is not recommended.

Renal and hepatic dysfunction

Patients with aGvHD have a complicated medical history and are suffering from many confounding medical conditions. PROCHYMAL has been extensively studied in patients with liver dysfunction (Liver aGvHD). Patients with significant renal dysfunction have been excluded from the clinical trials, therefore guidance on treating these patients cannot be provided.

Solid Tumors and Active Relapse

While not common, patients can receive hematopoietic cell transplantation for treatment of a solid tumor. Patients who have undergone hematopoietic cell transplantation for solid tumor have been excluded from PROCHYMAL clinical trials. Also, patients in active relapse of their underlying disease (the reason for their hematopoietic cell transplant, i.e. acute myeloid leukemia) have not been studied.

ADVERSE REACTIONS

NOC/c

Adverse Drug Reaction Overview

High adverse events rates are common in the management of aGvHD and include serious and life-threatening infections, hypertension, hyperglycemia, neutropenia, pyrexia, abdominal pain, edema, depression, hypotension, back pain, cough, dyspnea, rigors, hypocalcemia, myalgia,

thrombocytopenia, headache, renal impairment, arthralgia, and gastrointestinal haemorrhage.[1]

The most common adverse events observed for PROCHYMAL in clinical trials of pediatric aGvHD were infections, gastrointestinal disorders, and respiratory, thoracic and mediastinal disorders.

Adverse event rates for infections and infestations were slightly elevated in patients receiving Prochymal versus placebo in Study 280, indicating a possible increased risk of infection. Given that infection is a common and expected event following hematopoietic cell transplantation and steroid and other immunosuppressant agent treatment for aGVHD, it is difficult to attribute cause in such a heavily confounded population. The adverse event profile from the administration of PROCHYMAL was not significantly different from placebo treated patients nor out of the scope of what is typically seen in this patient population.

Clinical Trial Adverse Drug Reactions

The focus of this section is on the safety of PROCHYMAL in pediatric patients observed in the following studies:

- Protocol 280, a completed, randomized, placebo-controlled phase 3 clinical trial of the efficacy and safety of PROCHYMAL in the treatment of International Bone Marrow Transplant Registry (IBMTR) Grade B-D, steroid-refractory aGvHD that failed to respond to steroid treatment (28 pediatric patients with 14 in the PROCHYMAL group and 14 in the placebo group)

- Protocol 275, an ongoing treatment protocol in which the safety and treatment outcomes of pediatric patients (2 months to 17 years of age) receiving PROCHYMAL for the treatment of refractory, Grade B-D aGvHD were assessed (75 pediatric patients)

- Twelve, single-patient, emergency-use treatment protocols (hereafter referred to as the single-pt, EM-use protocols) in which pediatric patients 0-17 years of age received PROCHYMAL for the treatment of refractory Glucksberg Grade III or IV or IBMTR Grade B-D aGvHD

Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice. Adverse drug reaction information from the clinical trials is useful for identifying drug-related adverse events and for approximating rates and should not be compared to the rates in the clinical trials of another drug.

Because of the high number of adverse events normally experienced by aGvHD patients and because large clinical studies are not feasible in this population, it is difficult to determine the causality of adverse events that occur at low rates.[1]

While serious adverse events (SAEs) were collected in all clinical trials, general treatment-emergent adverse events (TEAEs) were only collected for the placebo controlled trial, Protocol 280. Due to the small number of patients for whom TEAE and SAE data are available, the

TEAEs and SAEs from all three studies have been listed in Table 1 providing a comprehensive view of adverse events across studies (irrespective of causality).

Table 1: Treatment-Emergent Adverse Events and Serious Adverse Events Occurring in >1 Patient in the PROCHYMAL Treatment Group in Protocol 280 and Serious Adverse Events Occurring in >1 PROCHYMAL-Treated Patient Across Studies (Protocol 280, Protocol 275 and the Single-patient Emergency-use Protocols)

Event (MedDRA System Organ Class, Preferred Term)	AEs Protocol 280		SAEs Protocol 280		SAEs Protocol 275	SAEs Single-pt, EM-use Protocols
	Treatment Group		Treatment Group			
	Prochymal N=14	Placebo N=13	Prochymal N=14	Placebo N=13	Prochymal N=75	Prochymal N=12
Infections and infestations	**11 (78.6%)**	**9 (69.2%)**	**8 (57.1%)**	**6 (46.2%)**	**22 (29.3%)**	**9 (75.0%)**
Adenovirus infection	1 (7.1%)	3 (23.1%)	1 (7.1%)	1 (7.7%)	1 (1.3%)	0
Aspergillosis	1 (7.1%)	0	0	0	2 (2.7%)	0
Bacteraemia	2 (14.3%)	0	1 (7.1%)	0	0	1 (8.3%)
BK virus infection	2 (14.3%)	1 (7.7%)	0	0	0	0
Central line infection	1 (7.1%)	2 (15.4%)	1 (7.1%)	1 (7.7%)	1 (1.3%)	0
Cytomegalovirus infection	4 (28.6%)	1 (7.7%)	1 (7.1%)	0	0	0
Enterococcal infection	0	0	0	0	2 (2.7%)	0
Epstein-Barr virus infection	1 (7.1%)	1 (7.7%)	0	0	0	2 (16.7%)
Fungal infection	0	0	0	0	1 (1.3%)	1 (8.3%)
Fusarium infection	0	0	0	0	0	2 (16.7%)
Klebsiella bacteraemia	1 (1.7%)	0	1 (1.7%)	0	1 (1.3%)	0
Mucormycosis	0	0	0	0	2 (2.7%)	0
Parainfluenzae virus infection	1 (7.1%)	1 (7.7%)	1 (7.1%)	0	1 (1.3%)	0
Pneumonia	2 (14.3%)	0	1 (7.1%)	0	1 (1.3%)	0
Sepsis	0	1 (7.7%)	0	1 (7.7%)	2 (2.7%)	3 (25.0%)
Septic shock	0	0	0	0	2 (2.7%)	0
Staphylococcal bacteraemia	2 (14.3%)	1 (7.7%)	1 (7.1%)	1 (7.7%)	2 (2.7%)	0
Gastrointestinal disorders	**9 (64.3%)**	**6 (46.2%)**	**5 (35.7%)**	**2 (15.4%)**	**8 (10.7%)**	**0**
Gastrointestinal haemorrhage	1 (7.1%)	3 (23.1%)	1 (7.1%)	1 (7.7%)	2 (2.7%)	0
Upper gastrointestinal haemorrhage	2 (14.3%)	0	1 (7.1%)	0	0	0
Vomiting	1 (7.1%)	1 (7.7%)	0	0	2 (2.7%)	0
Respiratory, thoracic and mediastinal disorders	**7 (50.0%)**	**7 (53.8%)**	**5 (35.7%)**	**4 (30.8%)**	**13 (17.3%)**	**6 (50.0%)**
Acute respiratory distress syndrome	1 (7.1%)	0	1 (7.1%)	0	1 (1.3%)	0
Cough	2 (14.3%)	0	0	0	0	0
Respiratory distress	2 (14.3%)	1 (7.7%)	2 (14.3%)	1 (7.7%)	2 (2.7%)	2 (16.7%)
Respiratory failure	2 (14.3%)	2 (15.4%)	2 (14.3%)	2 (15.4%)	7 (9.3%)	3 (25.0%)
Skin and subcutaneous tissue disorders	**5 (35.7%)**	**2 (15.4%)**	**0**	**0**	**0**	**0**
Keratosis pilaris	2 (14.3%)	0	0	0	0	0
Vascular disorders	**4 (28.6%)**	**4 (30.8%)**	**0**	**1 (7.7%)**	**4 (5.3%)**	**0**

Event (MedDRA System Organ Class, Preferred Term)	AEs Protocol 280		SAEs Protocol 280		SAEs Protocol 275	SAEs Single-pt, EM-use Protocols
	Treatment Group		Treatment Group			
	Prochymal N=14	Placebo N=13	Prochymal N=14	Placebo N=13	Prochymal N=75	Prochymal N=12
Hypertension	4 (28.6%)	1 (7.7%)	0	0	3 (4.0%)	0
Metabolism and nutrition disorders	**4 (28.6%)**	**3 (23.1%)**	**3 (21.4%)**	**0**	**1 (1.3%)**	**1 (8.3%)**
Dehydration	2 (14.3%)	0	2 (14.3%)	0	0	0
Hyperglycaemia	2 (14.3%)	1 (7.7%)	0	0	0	0
Hyperkalaemia	2 (14.3%)	0	0	0	0	0
Endocrine disorders	**3 (21.4%)**	**1 (7.7%)**	**0**	**0**	**0**	**0**
Adrenal insufficiency	3 (21.4%)	1 (7.7%)	0	0	0	0
Immune system disorders	**3 (21.4%)**	**4 (30.8%)**	**2 (14.3%)**	**3 (23.1%)**	**5 (6.7%)**	**2 (16.7%)**
Acute graft versus host disease in intestine	0	0	0	0	2 (2.7%)	0
Graft versus host disease	3 (21.4%)	2 (15.4%)	2 (14.3%)	2 (15.4%)	3 (4.0%)	1 (8.3%)
Nervous system disorders	**3 (21.4%)**	**5 (38.5%)**	**2 (14.3%)**	**1 (7.7%)**	**3 (4.0%)**	**4 (33.3%)**
Convulsion	1 (7.1%)	1 (7.7%)	1 (7.1%)	0	1 (1.3%)	2 (16.7%)
Encephalopathy	1 (7.1%)	0	1 (7.1%)	0	1 (1.3%)	0
Haemorrhage intracranial	1 (7.1%)	0	1 (7.1%)	0	1 (1.3%)	0
Reversible posterior leukoencephalopathy syndrome	1 (7.1%)	0	0	0	1 (1.3%)	1 (8.3%)
Renal and urinary disorders	**3 (21.4%)**	**1 (7.7%)**	**1 (7.1%)**	**0**	**4 (5.3%)**	**0**
Renal failure	2 (14.3%)	1 (7.7%)	1 (7.1%)	0	2 (2.7%)	0
Cardiac Disorders	**2 (14.3%)**	**2 (15.4%)**	**0**	**0**	**4 (5.3%)**	**1 (8.3%)**
Pericardial effusion	1 (7.1%)	1 (7.7%)	0	0	2 (2.7%)	0
General disorders and administration site conditions	**2 (14.3%)**	**3 (23.1%)**	**1 (7.1%)**	**3 (23.1%)**	**8 (10.7%)**	**3 (25.0%)**
Multi-organ failure	0	0	0	0	6 (8.0%)	1 (8.3%)
Pyrexia	2 (14.3%)	1 (7.7%)	1 (7.1%)	1 (7.7%)	0	1 (8.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (7.1%)**	**0**	**0**	**0**	**2 (2.7%)**	**2 (16.7%)**
Lymphoproliferative disorder	0	0	0	0	0	2 (16.7%)

Adverse events

In Protocol 280, in subjects receiving PROCHYMAL, TEAEs most commonly occurred in the *infections, gastrointestinal disorders*, and *respiratory, thoracic and mediastinal disorders* system organ classes (irrespective of causality).

Serious Adverse Events

Across studies and treatment groups, SAEs occurred most frequently in the *infections and infestations* and *respiratory, thoracic and mediastinal disorders* system organ classes (irrespective of causality).

DRUG INTERACTIONS

Overview

No specific drug interaction studies have been conducted with PROCHYMAL. PROCHYMAL has been administered along with steroids and immunosuppressive drugs in clinical trials to treat refractory aGvHD. No clinically relevant drug interactions have been reported.

Human MSCs are naturally occurring cells in the human body and should not interfere with the absorption, distribution, metabolism, or excretion of another drug.

The effects of PROCHYMAL on the ability to drive or operate machinery have not been established to date.

The effects of lifestyle choices such as smoking and alcohol consumption on PROCHYMAL have not been established.

Drug-Drug Interactions

Interactions with other drugs have not been established. A wide range of medications have been administered concomitantly with PROCHYMAL in clinical studies in aGvHD and no clinically relevant drug interactions have been observed.

Drug-Food Interactions

There have not been any reports of food interactions with PROCHYMAL. Since Prochymal is administered intravenously, interaction with food or drink is not expected. MSCs are naturally occurring cells in the body and would not be expected to have any interactions with food.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established. There have been no indications in preclinical or clinical testing that PROCHYMAL has a direct effect on laboratory tests.

DOSAGE AND ADMINISTRATION

NOC/c

Recommended Dose and Dosage Adjustment

Pre-treatment

To reduce the potential for infusion reaction, it is recommended that patients receive premedication with hydrocortisone and diphenhydramine. Premedication should occur 30-60 minutes prior to administration of PROCHYMAL.

Initial Treatment

Dosing of PROCHYMAL is based on body weight. The recommended dose of PROCHYMAL is 2×10^6 hMSC/kg (actual body weight) administered intravenously at a controlled rate of 4-6 mL/minute by infusion pump for patients weighing 35 kg and over.

For patients under 35 kg in weight, PROCHYMAL should be infused over the course of 60 minutes.

Patients should be treated with PROCHYMAL twice per week for 4 consecutive weeks. Infusions should be administered at least 3 days apart.

A therapy assessment should be performed after the fourth week of treatment as described below to determine whether continued treatment is warranted.

Method of calculating dose

Cell Dose = Patient body weight (kg) × (2×10^6 hMSC/kg)

There are 100×10^6 hMSCs in each frozen product bag.

Detailed instructions for PROCHYMAL preparation and administration can be found under Administration in this section on DOSAGE AND ADMINISTRATION.

Continued Treatment

A therapy assessment should be performed after initial treatment is completed to determine whether continued treatment is warranted. Continued treatment can be initiated if the patient has achieved a response to treatment without safety issues. The recommended continued treatment dosing of PROCHYMAL is 2×10^6 hMSC/kg administered once a week for 4 weeks.

GvHD Recurrence after Treatment

Patients who have a recurrence of aGvHD (Grades B-D) after the 8 week treatment regimen can be treated with another PROCHYMAL cycle starting with the *Initial Treatment* dosing schedule.

Administration

PROCHYMAL should be administered under the supervision of a qualified health professional who is experienced in the management of aGvHD.

PROCHYMAL infusion should be discontinued at the discretion of the treating physician for any evidence of an acute infusion reaction including shortness of breath, difficulty breathing, hypoxia or other signs of acute respiratory distress.

PROCHYMAL is provided with a drug preparation kit that contains the items required to reconstitute the drug as described below. Detailed instructions are provided in the Drug Preparation Manual for PROCHYMAL.

Reconstitute one cryogenic cell storage bag (15mL) of PROCHYMAL for each 50 kg of patient weight or increment thereof. After removal from the cassette, place the PROCHYMAL bag into

a resealable plastic bag. Immerse the sealed bag into a waterbath (37ºC) and gently rock the bag to mix the suspension for 3-5 minutes to thaw. Do not squeeze or break the frozen PROCHYMAL during the thawing process. Aseptically add 25mL of Plasma-Lyte A® or equivalent diluent to an infusion bag and drain the contents of the PROCHYMAL bag into the infusion bag to mix. Reconstituted, PROCHYMAL contains approximately 100 x 10^6 hMSCs/40 mL or 2.5 x 10^6 hMSCs/mL. Adjust to the appropriate dose by discarding the unneeded volume of PROCHYMAL in the infusion bag.

Once reconstituted, PROCHYMAL should be kept at room temperature and infused within 5 hours from thawing of the product.

STORAGE AND STABILITY

Store at ≤ -135°C in the vapor phase of a liquid nitrogen freezer.

The reconstituted product can be kept at room temperature and should be used within 5 hours from thaw.

SPECIAL HANDLING INSTRUCTIONS

PROCHYMAL is packaged in a cryogenic cell storage bag and shipped and stored at ultra-low temperatures (≤ -135°C).

For shipment, the bag of cells is encased in a protective aluminum cassette and shipped in a cryoshipper that maintains an ultra low freezing temperature of ≤ -135°C (Figure 1). Cryoprotective gloves are required to handle product at this temperature. PROCHYMAL can be transferred to a liquid nitrogen freezer on-site for longer-term storage. Ensure that PROCHYMAL is properly stored in the vapor phase and not submersed in liquid nitrogen.

Figure 1: Cryoshipper and PROCHYMAL bag in protective aluminum cassette

DOSAGE FORMS, COMPOSITION AND PACKAGING

PROCHYMAL should be dosed according to the instructions found under "DOSAGE AND ADMINISTRATION". The instructions provide a schedule for dosing during the first 4-8 weeks of treatment as well as guidance regarding recurrence of aGvHD.

PROCHYMAL is a 15 mL formulation containing approximately $100x10^6$ viable hMSCs in Plasma-Lyte A® containing 5% human serum albumin (HSA) and 10% dimethyl sulfoxide (DMSO). The active agent in PROCHYMAL is ex-vivo cultured adult human mesenchymal stem cells (hMSCs). The HSA, DMSO and Plasma-Lyte A® are excipients required to maintain stable, viable cells through the freezing and thawing process. Plasma-Lyte A®, pH= 7.4, is an electrolyte solution with physiologic osmolality and pH.

PROCHYMAL is packaged frozen in a 50 mL cryogenic freezing container that is a non-pyrogenic (≤ 0.5 EU/mL per USP), gamma sterilized (25 – 40 kGy), ethylene vinyl acetate (EVA) freezing container with integrally attached tubing set, port seals and label pocket.

OVERDOSAGE

Overdose has not been reported and the maximum tolerated dose of PROCHYMAL has not been established in humans. Doses up to 10×10^6 hMSC/kg have been administered to patients in clinical trials without dose limiting toxicity. In animal studies, dose limiting toxicity was due to respiratory distress attributed the accumulation of cells in the microvasculature.

The chance of clinically significant overdose is minimal given that the product is packed for single-patient use, requires cold-chain storage in liquid nitrogen, and cannot be self-administered. In case of overdose it is recommended that the patient be monitored closely for symptoms of adverse effects. Care should be supportive and focused on treatment of the patient's symptoms.

ACTION AND CLINICAL PHARMACOLOGY

NOC/c

Mechanism of Action

PROCHYMAL's activity against aGvHD, a T-cell mediated disease, is due to the immunomodulatory properties of hMSCs. PROCHYMAL counteracts inflammatory processes by downregulating the production of the pro-inflammatory cytokines, tumor necrosis factor-alpha (TNF-α) and interferon-gamma. When cell-surface receptors on hMSCs are bound by TNF-α, the cells produce prostaglandin-E2 (PGE_2), which blocks T-cell release of TNF-α. T-cell proliferation is thereby downregulated. T-cell expression of interleukin-2 (IL-2) expression is also decreased. Reduction of pro-inflammatory cytokines limits tissue damage, and PROCHYMAL has been shown to secrete growth factors that are known to promote tissue repair.

Pharmacodynamics

In vitro and *in vivo* preclinical data indicate that PROCHYMAL has the potential to treat an inflammatory, immune-mediated disease such as aGvHD due to its cellular properties of inhibition of immune and inflammatory responses at target sites, protection of inflamed tissue from collateral damage, and facilitation of damaged tissue repair.

Pharmacokinetics

Preclinical studies using radiolabeling, genetic analysis through FISH, DNA analysis, MRI, and

fluorescent labeling, have been performed to determine the distribution profile of PROCHYMAL. The studies demonstrated that hMSCs clear from the blood within hours of administration. MSCs infused into the venous system experience a significant pulmonary first-pass effect, initially distributing to the lungs within minutes of infusion. This is the result of the physical size of the cells passing through the pulmonary capillary bed, which is the first capillary system the cells encounter. At 24 hours post infusion, a majority of the cells are found in the lungs with lesser amounts in the liver, kidneys, and spleen. At 48 hours, cells are detected at similar levels in the lungs and liver.

PART II: SCIENTIFIC INFORMATION

PROCHYMAL is indicated in the management of acute Graft versus Host Disease (aGvHD) in pediatric patients. Acute GvHD should be refractory to treatment with systemic corticosteroid therapy and/or other immunosuppressive agents. Prochymal may be used for Grades C and D of the disease in any organ. Prochymal may also be used in the management of Grade B aGvHD involving any visceral organ, including the GI tract and the liver, but excluding skin.

Prochymal has been granted marketing authorisation with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorisation.

PHARMACEUTICAL INFORMATION

Drug Substance

Brand Name: PROCHYMAL®

Proper Name (USAN): remestemcel-L

Common Name: *ex-vivo* cultured adult human mesenchymal stem cells.

Physicochemical properties: According to the International Society for Cellular Therapy position paper, "Minimal Criteria for Defining Multipotent Mesenchymal Stromal Cells." *The International Society for Cellular Therapy Position Statement* [2], the following criteria are characteristic of human mesenchymal stem cells:

1) adherence to plastic;
2) specific antigen (Ag) expression;
3) multipotent differentiation potential;
4) lack of expression of MHC Class II molecules (baseline state).

The positive expression of markers CD166 and CD105 for the hMSC phenotype is used to confirm identity. The negative marker CD45 is not expressed by hMSCs but is expressed by hematopoietic stem cells. This marker is important due to its identification of potential contaminant of the hMSC population. The $CD45^-/CD166^+/CD105^+$ phenotype of hMSCs, detected by flow cytometry, correlates with multipotent differentiation potential.[3]

The key characteristics that are used to define hMSCs are as follows:

Table 2: hMSC Key Characteristics

• Macroscopic Appearance	Opaque, off-white to pale amber in color absent from cell clumps and particulate matter and intact package integrity.
• Identity (Cell Surface Markers)	
Positive Marker	CD105 (Endoglin), CD166 (Activated Leukocyte Adhesion Molecule)
Negative Marker	CD45 (Leukocyte common antigen)
• Potency	
TNF RI Expression	Min: ≥108 pg/mL
Inhibition of IL-2Rα Expression	≥ 30% inhibition of IL-2Rα expression

Product Characteristics

PROCHYMAL is a formulation of ex-vivo cultured adult human mesenchymal stem cells intended for intravenous infusion. The cells are packaged, frozen and available for immediate use. Typing is not required between donor and recipient. The product is thawed, diluted and transferred to an infusion bag immediately prior to intravenous administration.

CLINICAL TRIALS

NOC/c

Acute GvHD

Acute GvHD is a severe, life-threatening disease caused by patient exposure to allogeneic lymphocytes following hematopoietic stem cell transplantation (HSCT). There are no approved therapies for aGvHD. Standard of care is corticosteroids as a first line agent in the treatment of aGvHD. Patients with the most severe forms of refractory aGvHD that do not respond to steroid therapy have expected one-year survival rates of only 5% to 30%. [4-8] Acute GvHD is the largest component of transplant related mortality.[9]

Standardized grading systems have been developed to classify aGvHD by severity and are generally predictive of outcome. This is accomplished in a two step process – first by staging each organ system, then by integrating the individual organ stages to arrive at an overall aGvHD grade. Acute GvHD organ staging is based on degree of severity of the affected organs, with involvement of each organ receiving a score of 0-4 (no involvement to severe) (Table 3). These individual organ scores are then integrated using the Center for International Blood and Marrow Transplant Research (CIBMTR) grading system for aGvHD. This system classifies patients with aGvHD with a severity grade ranging from A – D, with grade A being mild and grades C and D being severe (Table 4).

Table 3: Organ Severity Score Criteria for Pediatric Patients

Organ	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin	No rash	Rash on <25% BSA	Rash ≥25% to ≤50% BSA	Rash >50% generalized erythroderma	Bullae and desquamation
Gastrointestinal Tract	Diarrhea <280 mL/m^2 per day or <500 mL/day	Diarrhea 280-555 mL/m^2 per day or 501-1000 mL/day	Diarrhea 556-883 mL/m^2 per day or 1001-1500 mL/day	Diarrhea >883 mL/m^2 per day or >1500mL/day	Excessive diarrhoea with severe abdominal pain; with or without ileus; or stool with frank blood or melena.
Liver	Bilirubin <2 mg/dL (< 34 µM)	Bilirubin 2.1-3.0 mg/dL (34-50 µM)	Bilirubin 3.1-6.0 mg/dL (51-102 µM)	Bilirubin 6.1-15 mg/dL (103-255 µM)	Bilirubin >15 mg/dL (> 255 µM)

BSA = body surface area.

Table 4: CIBMTR Severity Index for Acute GvHD Grading

Organ	Grade A	Grade B	Grade C	Grade D
Skin	1	2	3	4
GI Tract	0	1-2	3	4
Upper GI Tract	0	1	-	-
Liver	0	1-2	3	4

CIBMTR=Center for International Bone Marrow Transplant Registry, GI=gastrointestinal, GvHD=graft versus host disease

Study Design

Data from two clinical studies provide evidence of PROCHYMAL's efficacy in pediatric patients for the treatment of refractory aGvHD (Table 5).

Table 5: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
275	Single arm treatment protocol in patients with steroid-refractory aGvHD	2.0 x 10^6 hMSC/kg, given IV, 8-12 infusions ≥72 hours apart	75 (all pediatric)	8.6 years (0.2-17.5)	M and F
280	Phase 3, double blind, placebo-controlled in patients with steroid-refractory aGvHD	2.0 x 10^6 hMSC/kg, given IV, 8-12 infusions ≥72 hours apart	28 pediatric: (14 PROCHYMAL + 14 Placebo)	PROCHYMAL = 6.5 years (1.3-14.8); Placebo = 9.3 years (0.4-17.6)	M and F

Study 275

Protocol 275 was a single-arm, multi-center study of pediatric patients with Grades B-D acute GvHD secondary to allogeneic HSCT or donor lymphocyte infusion (DLI) who failed to respond to steroid treatment and other therapies. Failure to respond to steroid treatment was defined as

Grades B-D acute GvHD that was not improving after at least 3 days of systemic steroid therapy (≥1 mg/kg/day methylprednisolone or equivalent).

PROCHYMAL was administered twice weekly over a four week period, for a total of eight infusions. PROCHYMAL was administered at a dose of 2 x 10^6 hMSC/kg per infusion. Continued therapy, consisting of one infusion per week for 4 weeks was administered if warranted.

Patients were evaluated for efficacy and safety until death, withdrawal, or for 100 days post first infusion (Day 0), whichever occurred first. Additionally, survival status was captured through 180 days post onset of GvHD to facilitate comparison with historical controls. The severity of acute GvHD was assessed using International Bone Marrow Transplant Registry (IBMTR) Grading. Acute GvHD assessments of the skin, liver, and gut were performed at Program Entry, Day 28, and Day 100/End-of-treatment. Response to treatment of aGvHD was assessed by the proportion of patients achieving Overall Response (CR + PR) at Day 28 and Day 100. Response at Day 28 has been shown to correlate with improved survival.[10]

Since Protocol 275 was a single arm study, a historical control was used to assess if there was an effect of treatment on overall survival. This benchmark was generated from the Center for International Blood and Marrow Transplant Research (CIBMTR) database, which allowed for presentation of survival post onset of aGvHD for pediatric patients.

Study 280

Protocol 280 was a double blind, placebo-controlled trial testing PROCHYMAL in patients with steroid-refractory aGvHD containing a subpopulation of twenty-eight (28) pediatric patients (14 PROCHYMAL and 14 placebo). Patients with Grades B-D aGvHD who had failed to respond to steroid treatment and secondary to allogeneic hematopoietic stem cell transplant (HSCT) or donor leukocyte infusion (DLI) were enrolled and evaluated for efficacy and safety until death, withdrawal, or 180 days post first infusion, whichever occurred first. Patients were randomized to PROCHYMAL plus standard of care or placebo plus standard of care.

Study Demographics

Baseline disease characteristics across studies are presented in Table 6. In terms of baseline disease characteristics, the reasons for HSCT were varied and included both haematological malignancies and genetic disease. Most patients in each of the studies received a transplant source from an unrelated donor. The majority of patients in Protocol 280 received their transplant source from cord blood. A substantial percentage (37%) of patients in Protocol 275 had cord blood as the transplant source.

There were two main differences in patient characteristics between the studies – severity of disease and treatment refractory status. As expected for refractory aGvHD patients, most patients in each of the studies were assessed with severe aGvHD (Grade C/D) at study baseline. However, the patient population in Protocol 275 had more severe aGvHD than the patients in Protocol 280. Additionally, most patients (60%) in Protocol 275 were refractory to three agents including steroids. In contrast, patients in Protocol 280 were randomized immediately after failing steroids only.

Table 6: Baseline Disease Characteristics of Pediatric Patients in Efficacy Studies of PROCHYMAL

Characteristic	Protocol 280		Protocol 275 N=75
	PROCHYMAL N=14	Placebo N=14	
Underlying Malignancy or Leukemic Disease			
Acute Lymphoblastic Leukemia (ALL)	5 (35.7%)	3 (21.4%)	18 (24.0%)
Acute Myeloid Leukemia-Primary (AML)	1 (7.1%)	1 (7.1%)	16 (21.3%)
Chronic Myeloid Leukemia (CML)	1 (7.1%)	0	1 (1.3%)
Myelodysplastic Syndrome (MDS)	0	3 (21.4%)	7 (9.3%)
Non-Hodgkin's Lymphoma	0	1 (7.1%)	1 (1.3%)
Genetic Disease	4 (28.6%)	6 (42.9%)	16 (21.3%)
Other	3 (21.4%)	0	16 (21.3%)
Type of Transplant			
Bone Marrow	4 (28.6%)	5 (35.7%)	25 (33.3%)
Peripheral Blood Hematopoietic Stem Cells	0	1 (7.1%)	16 (21.3%)
Cord Blood	10 (71.4%)	8 (57.1%)	28 (37.3%)
Donor Lymphocyte Infusion	0	0	5 (6.7%)
Missing	0	0	1 (1.3%)
Donor type			
Related	1 (7.1%)	3 (21.4%)	11 (14.7%)
Unrelated	13 (92.9%)	11 (78.6%)	64 (85.3%)
Grade of aGvHD at Baseline			
IBMTR			
Grade B	3 (21.4%)	3 (21.4%)	9 (12.0%)
Grade C	8 (57.1%)	8 (57.1%)	21 (28.0%)
Grade D	3 (21.4%)	3 (21.4%)	45 (60.0%)

Results

Response to treatment

The primary efficacy endpoint for the pivotal study, Protocol 275, was defined as overall response (OR) at Day 28 following the first infusion of PROCHYMAL. This OR analysis was also applied to the pediatric subpopulation of Protocol 280. The response definitions listed in Table 7 were used in both studies.

Table 7: Response Criteria

Abbreviation	Definition
CR	Complete Response: resolution of aGvHD in all involved organs
PR	Partial Response: organ improvement of at least one stage without worsening of any other organ
OR	Overall Response: CR + PR
Responder	Subjects achieving an OR
Non-Responder	Subjects not achieving OR

Response rates are presented in Table 8. Response to treatment at Day 28 with PROCHYMAL was similar in the two studies, with 61-64% of previously refractory patients experiencing an OR. The placebo arm from Protocol 280 had an OR rate of 36%. By Day 100 response rates increased to 77% in 275 and 71% and 50% for the PROCHYMAL and placebo arms of 280 respectively.

Table 8: Overall Response in Pediatric Patients in Efficacy Studies of PROCHYMAL

	Protocol 275 (All Grades)	**Protocol 280 (All Grades)**	
	(N=75)	PROCHYMAL (N=14)	Placebo (N=14)
Response[1] at Day 28	61%	64%	36%
Response[1] by Day 100	77%	86%	57%

[1]Overall Response as defined in Table 7

Survival Analysis

Protocol 275

For Protocol 275, survival through Day 100, as a function of Day 28 response was evaluated to determine the clinical value of the Day 28 OR endpoint. In Protocol 275, patients achieving an OR at Day 28 had a 78% probability of surviving through Day 100, whereas patients who did not achieve an OR at Day 28 had only a 31% probability of survival. This difference was significant ($p<0.001$) and validates the clinical utility of Day 28 response as an endpoint.

Historical Benchmark

For Protocol 275, survival was analyzed by comparing the treatment population to an historical control set provided by the CIBMTR (Table 9). While certain limitations of the analysis exist, the data provides a useful benchmark for comparison. This analysis showed a statistically significant benefit for Prochymal in overall survival at 180 days post onset of aGvHD over the CIBMTR population ($p=0.028$), which was most pronounced in patients with severe aGvHD (Grade C/D). For Grade D patients, the confidence intervals on survival did not overlap.

Table 9: Survival Probability through 180 Days Post Onset of Acute GvHD for Prochymal Patients in Protocol 275 and a CIBMTR Dataset

	Maximum Grade B or II		**Maximum Grade C or III**		**Maximum Grade D or IV**	
	Prochymal N=4	**CIMBTR N=199**	**Prochymal N=19**	**CIMBTR N=308**	**Prochymal N=51**	**CIMBTR N=327**
Probability of survival at 180 days post onset	75%	71%	68%	69%	51%	31%
95% CI	33, 100	64, 77	48, 89	64, 74	37, 65	26, 36
P-value						0.028

CIBMTR= Center for International Blood and Marrow Transplant Research.

Protocol 280

Table 10 presents the survival status of patients in Protocol 280 at Days 100 and 180 following the first infusion of study treatment (Prochymal or placebo) by aGvHD Grade at baseline. A greater percentage of patients receiving Prochymal (11 patients, 78.6%) compared to placebo (7 patients, 50.0%) survived at 100 days after the first infusion. Patients with either (Grade B) or severe (C/D) aGvHD at baseline for the study appeared to have a greater survival at 100 days when treated with Prochymal.

Table 10: Survival at Days 100 and 180 after First Infusion – Protocol 280, ITT Population

	Stratum				All aGvHD Grades		
	aGvHD Grade B		aGvHD Grade C/D				
	Prochymal (N=3)	Placebo (N=3)	Prochymal (N=11)	Placebo (N=11)	Prochymal (N=14)	Placebo (N=14)	
At Day 100							
Survived >100 days	3 (100%)	1 (33.3%)	8 (72.7%)	6 (54.5%)	11 (78.6%)	7 (50.0%)	p=0.13
Survived ≤100 days[1]	0	2 (66.7%)	3 (27.3%)	5 (45.5%)	3 (21.4%)	7 (50.0%)	
Confirmed deaths	0	2 (66.7%)	3 (27.3%)	3 (27.3%)	3 (21.4%)	5 (35.7%)	
Unknown	0	0	0	2 (18.2%)	0	2 (14.3%)	
At Day 180							
Survived >100 days	2 (66.7%)	1 (33.3%)	7 (63.6%)	6 (54.5%)	9 (64.3%)	7 (50.0%)	p=0.46
Survived ≤100 days[1]	1 (33.3%)	2 (66.7%)	4 (36.4%)	5 (45.5%)	5 (35.7%)	7 (50.0%)	
Confirmed deaths	1 (33.3%)	2 (66.7%)	4 (36.4%)	3 (27.3%)	5 (35.7%)	5 (35.7%)	
Unknown	0	0	0	2 (18.2%)	0	2 (14.3%)	

[1] Patient considered dead if survival status at Day 100 or 180 was unknown.
p-value is from the Cochran-Mantel-Haenszel test stratified by aGvHD grade at study entry.
aGvHD=acute graft versus host disease, ITT=intention-to-treat.

Effect of Continuing Therapy

In Study 275, the additional benefit of continued therapy beyond the initial regimen of 8 biweekly infusions was assessed. Physicians elected to continue therapy in 40 patients. Twenty-three (58%) of the patients receiving continuing therapy experienced an additional response to continued therapy. Of the 23 responders, two patients were complete responders at Day 28 who maintained their response through Day 100. The other 21 patients showed additional improvement in their GvHD beyond their Day 28 assessment, 16 of whom achieved a complete response.

DETAILED PHARMACOLOGY

Animal Studies

Pharmacodynamic Summary

In Vitro Pharmacodynamic Studies

The immunomodulatory effects of MSCs have been demonstrated in vitro. MSCs extensively suppress the proliferative activity of allogeneic T lymphocytes stimulated with alloantigen, mitogen, or anti-CD3 or anti-CD28 antibodies in vitro, likely through secreted factors (including PGE_2 and IDO) in a dose-dependent and genetically unrestricted manner. [11-15]

MSCs provide tissue protection and tissue repair effects, through reduction of pro-inflammatory cytokines and secretion of factors including KGF (also known as FGF-7), and VEGF.[16, 17]

In Vivo Pharmacodynamics

MSCs have shown the ability to modulate T cells by prolonging the survival of an allogeneic skin graft in a baboon model of skin graft rejection. [12]

MSCs have been shown to stimulate the growth of new blood vessels, a process crucial to tissue repair, in a mouse model of ischemia, through secretion of factors such as VEGF. [18]

MSCs have been shown to promote regeneration of tissue in the gut as indicated by repair of irradiation-damaged small intestinal mucosa in mice.[19]

Safety Pharmacology

A pulmonary safety pharmacology study in rats at doses up to $25x10^6$ cells/kg demonstrated that all pulmonary function parameters remained within normal values.

A cardiac safety pharmacology study in swine at doses up to 10×10^6 cells/kg showed IV infusion of porcine MSCs did not cause electrocardiogram disturbances, changes in hemoglobin saturation, heart rate, or respiration rate. There was no acute infusional toxicity and no other toxicities observed at 6 and 24 weeks after infusion.

Pharmacokinetic Summary

PROCHYMAL is administered intravenously.

Several in vivo biodistribution studies have been conducted in healthy animals (nude mice 20, rats[21], and sheep [22] and irradiation models (dogs [23], baboons [24, 25] and macaques[26]) to demonstrate the biodistribution of MSCs after IV administration. MSCs distribute to the lungs within minutes of infusion. [20, 21] At 24 hours post infusion, a majority of the cells are found in the lungs with lesser amounts in the liver, kidneys, and spleen. [20] At 48 hours, cells are detected at similar levels in the lungs and liver. [21]

Following total body irradiation in dogs [23] , baboons [24, 25] , and macaques[26], MSCs will preferentially distribute to sites of inflammation and tissue damage such as the bone marrow, GI tract, and skin, the organs that have sustained the most tissue damage.

The metabolism and excretion of cellular components (nucleic acids, amino acids, lipids, etc) in the normal course of cell turnover in the body is well understood. It is expected that the infused cells will be metabolized the same way; therefore these studies were not conducted. No effects on kidney functionality were observed based on urinalysis data in animal studies.

Human MSCs are naturally occurring cells in the human body and should not interfere with the pharmacokinetics of another drug.

Human Studies

Pharmacodynamic Summary

Currently there are no techniques available to measure the pharmacodynamic effects of hMSCs in patients with aGvHD. Currently, the effects of MSCs are measured through clinical outcomes (see Clinical Trials section under PHARMACEUTICAL INFORMATION). For more information regarding pharmacodynamics, see *In Vivo Pharmacodymamics* under Animal Studies in this DETAILED PHARMACOLOGY section.

Pharmacokinetic Summary

Pharmacokinetic studies for PROCHYMAL are limited to tissue distribution studies as explained in the Pharmacokinetic Summary under Animal Studies in this DETAILED PHARMACOLOGY section. Currently there are no techniques available to measure the distribution of hMSCs in patients with aGvHD.

TOXICOLOGY

Animal Studies

In vivo animal studies have been conducted to evaluate the safety of PROCHYMAL following administration to mice, rats, dogs, and baboons. Additional safety data were obtained in safety pharmacology studies in rats and swine (see Pharmacodynamic Summary section under DETAILED PHARMACOLOGY).

Single-Dose Toxicology

In a single-dose toxicology study in rats, the no-observed adverse effect level (NOAEL) following IV administration was $40x10^6$ MSC/kg and the maximum tolerated dose (MTD) was $65x10^6$ MSCs/kg.

Repeated-Dose Toxicology

In a repeat-dose toxicology study in rats, the no-observed adverse effect level (NOAEL) following IV administration was a cumulative dose of $80x10^6$ MSC/kg when dosing twice per week. There were no effects on host immune cell quantities or host immune system functionality, and no biologically significant alloantibody formation was found. A 6-month immunotoxicology study in normal, healthy baboons supports these findings.

Genotoxicity, Carcinogenicity, Tumorigenicity and Ectopic Tissue Formation

Standard genotoxicity and 2-year carcinogenicity studies were not conducted as they were not relevant for a cell therapy. Ectopic tissue formation was evaluated in preclinical toxicology studies and clinical studies. A standard 6-week tumorigenicity study in nude mice was performed. There was no evidence of tumor formation attributed to hMSCs. In addition, there has been no evidence of tumor or ectopic tissue formation in long-term dosing studies (up to 12 months) in canine, swine, and baboon models. No cases of ectopic tissue formation were observed due to product administration in clinical studies.

Reproductive and Developmental Toxicity

Animal reproduction and developmental toxicology studies were not conducted as they were not relevant for the aGvHD patient population.

Table 11: Summary of Animal Safety Studies

STUDY TYPE DONOR / RECIPIENT ("N")	STUDY DESIGN / ROUTE / DOSE / RATE / TARGET	OUTCOMES
Single-Dose Toxicity		
Pilot single-dose study (GLP) ACI rat/Fischer 344 rat (Total N=120)	Dosing: single dose, IV infusion (5 mL/kg, 30 seconds) Doses: 3×10^6-37.5×10^6 MSC/kg Sacrifice: 1 week post-injection	Mortality at doses of 15×10^6 MSC/kg and higher. Adverse signs at 8×10^6 MSC/kg. NOAEL of 3×10^6 MSC/kg; however, MSC test article was determined to have low viability (not representative of clinical drug product).
Biodistribution Study with toxicity endpoints ACI rat/Fischer 244 rat (Total N=24)	Dosing: single dose, IV infusion (4 mL/kg, 21-25 seconds) Dose: 10×10^6 MSC/kg (Iridium-labeled cells) Sacrifice: 1, 24, or 240 hours after dosing	No toxicities attributed to dosing of MSCs, no changes in organ weights. Adverse signs were transient and attributed to toxic effects of the iridium label attached to the cells.
Pivotal single-dose study (GLP) ACI rat / Fischer 344 rat (Total N=80)	Dosing: single dose, IV infusion (5 mL/kg, 0.8 mL/minute) Doses (Main study): 0 (vehicle), 10×10^6, 40×10^6, or 65×10^6 cells/kg (the dose of 75×10^6 MSC/kg was tested in the pilot phase of the study) Sacrifice: 1 and 2 weeks post-injection	No mortalities due to MSC injections. Adverse signs of red discharge, red urine, at highest dose, but no other toxicities at other doses. NOEL at 40.0×10^6 MSC/kg. MTD at 65.0×10^6 MSC/kg
Irradiation-Engraftment study with tissue distribution and toxicity endpoints Autologous / Beagle dog (Total N=12)	Dosing: single dose, IV infusion (50mL/15 min) Doses: up to 15×10^6 MSCs/kg (retrovirus-tagged cells) Sacrifice: 96-99 days after dosing	No acute infusional toxicities and no apparent toxicities were observed. The highest dose tested was safely administered. Evidence of transgene in bone marrow at day 98.
Irradiation-Engraftment study with toxicity endpoints Autologous / Beagle dog (Total N=15)	Dosing: single dose, IV infusion (3.33-2.5 mL/min) Doses: 0, 2×10^6, or 20.0×10^6 MSCs/kg Sacrifice: day 57 or day 86	No acute infusional toxicities. Normal hematopoietic recovery and bone marrow cellularity. No ectopic tissue formation.

STUDY TYPE DONOR / RECIPIENT ("N")	STUDY DESIGN / ROUTE / DOSE / RATE / TARGET	OUTCOMES
Repeat-Dose Toxicity		
Pilot repeat-dose study ACI rat/ Fischer rat (Total N=22)	Dosing: 5 doses (every 3-4 days over 2 weeks), IV infusion (5 mL/kg, 2 minutes) Doses: 0.0 (vehicle), 10×10^6, 20×10^6, or 50×10^6 MSCs/kg Sacrifice: 2 weeks post infusion	Mortality at highest dose (50×10^6 MSCs/kg) shortly after dosing. MTD: 20×10^6 MSCs/kg (cumulative dose of 100×10^6 rMSCs/kg after 5 infusions)
Pivotal repeat-dose study (GLP) with immunotoxicology endpoints ACI rat / Fischer rat (320)	Dosing: 8.5 weeks (13 doses, twice per week for 4 ½ weeks and then once per week for 4 weeks), IV infusion via tail vein (5 mL/kg, 2 minutes) Doses: 0, $2x10^6$, $10x10^6$, or $20x10^6$ MSCs/kg Sacrifice: 1 month after 1st dose (*i.e.*, after 9th dose) or 3 months after 1st dose	No adverse signs or mortalities up to cumulative dose of $80x10^6$; all mortalities were in rapid-dose phase of study (2 doses/week). In remaining animals, MSCs well tolerated at all dose levels. No significant test article related effects identified. No significant effects on host immune cell quantities or host immune system functionality. No biologically significant levels of alloantibodies detected.
Repeat-dose study (GLP) with immunologic testing Baboon / MHC Mis-matched baboon (Total N=9)	Dosing: 2 doses; Day 1 – IV infusion; Day 43 – IM injection Doses: 0.0 or 5×10^6 MSCs/kg (same doses on each dosing day) Sacrifice: 6 months	No mortalities and no evidence of acute toxicity or immunotoxicities. Transient development of allo-antibodies. No evidence that MSCs primed recipient T-cells to donor alloantigens on MLR. No ectopic tissue formation.
Carcinogenicity Studies		
Tumorigenicity study Human / Athymic nude mice (Total N=108)	Dosing: SC injection (0.1 mL) into left inguinal fold at left flank Doses: 0 (vehicle) or 1×10^6 MSCs/animal Sacrifice: day 42	No tumors or other lesions attributable to MSC injections.

Abbreviations: GLP, good laboratory practice; IV, intravenous; MSCs, mesenchymal stem cells; MTD, maximum tolerated dose; N, number; NOAEL, No-Observed-Adverse-Effect Level; NOEL, No-Observed-Effect Level; SC, subcutaneous

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PART III: CONSUMER INFORMATION

PROCHYMAL is indicated in the management of acute Graft versus Host Disease (aGvHD) in pediatric patients. Acute GvHD should be refractory to treatment with systemic corticosteroid therapy and/or other immunosuppressive agents. Prochymal may be used for Grades C and D of the disease in any organ. Prochymal may also be used in the management of Grade B aGvHD involving any visceral organ, including the GI tract and the liver, but excluding skin.

Prochymal has been granted marketing authorisation with conditions, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorisation.

What is a Notice of Compliance with Conditions (NOC/c)?
An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

PROCHYMAL®
adult human mesenchymal stem cells (hMSCs)

This leaflet is Part III of a three-part "Product Monograph" published when PROCHYMAL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PROCHYMAL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

PROCHYMAL is a formulation of adult human mesenchymal stem cells (hMSCs) that have been isolated and expanded in number from donated bone marrow. Human MSCs are a distinct population of cells within bone marrow that help control immunological reactions, protect tissue, promote tissue regeneration, and prevent scarring. These cells can be used without matching to the recipient through blood typing or human leukocyte antigen (HLA) typing.

What the medication is used for:
PROCHYMAL is indicated in the management of acute Graft versus Host Disease (aGvHD) in pediatric patients. Acute GvHD should be refractory to treatment with systemic corticosteroid therapy and/or other immunosuppressive agents. Prochymal may be used for Grades C and D of the disease in any organ. Prochymal may also be used in the management of Grade B aGvHD involving any visceral organ, including the GI tract and the liver, but excluding skin.

What it does:
PROCHYMAL is used to control immunological reactions, protect tissue from further destruction, and allow damaged tissue to heal.

Acute GvHD is a disease where the immune cells from the hematopoietic stem cell (HSC) transplant that you received are attacking your body's organs because they recognize your body's organs as foreign.

PROCHYMAL contains a large number of hMSCs which should provide you with enough MSCs to reduce the extensive immune reaction caused by aGvHD. The cells should also help protect your healthy tissue from further destruction and allow for healing.

When it should not be used:
Caution should be used when administering PROCHYMAL to patients with a known sensitivity to porcine (pig) or bovine (cow) products because these components may be present in trace amounts. In patients with known or suspected hypersensitivity to PROCHYMAL, the intended benefit of treatment should be carefully weighed against the potential risks.

What the medicinal ingredient is:
Ex-vivo cultured adult human mesenchymal stem cells (hMSCs)

What the important nonmedicinal ingredients are:
Dimethyl sulfoxide (DMSO), human serum albumin (HSA), and Plasmalyte A®.
For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
PROCHYMAL is a solution for intravenous infusion.

It is supplied as a frozen liquid suspension of human mesenchymal stem cells. There are 100 million hMSCs in each bag of PROCHYMAL. The dose of cells that is delivered to a patient is based on the patient's weight. The frozen cells are thawed, diluted, and transferred to an infusion bag for intravenous administration.

WARNINGS AND PRECAUTIONS

The long term effects of PROCHYMAL in growing children are unknown.

BEFORE you use PROCHYMAL talk to your doctor if:

- you are allergic to bovine (cow) or porcine (pig) products.

INTERACTIONS WITH THIS MEDICATION

Drug interactions between PROCHYMAL and other drugs have not been tested. There are currently no known drug interactions with PROCHYMAL.

PROPER USE OF THIS MEDICATION

Usual dose:
PROCHYMAL should only be administered under the supervision of a health care professional. The dose of PROCHYMAL that is recommended is 2 million cells per kg of body weight.

It is recommended that PROCHYMAL be infused at a rate of 4-6 mL per minute.

PROCHYMAL should be delivered 2 times per week and at least 3 days apart for the first 4 weeks. Then PROCHYMAL should be administered 1 time per week for the following 4 weeks if indicated.

If a recurrence of aGvHD occurs outside the treatment window, the treatment cycle for PROCHYMAL should be repeated.

Overdose:
Overdose has not been reported and the maximum tolerated dose of PROCHYMAL has not been established in humans. If an overdose does occur, then the patient should be monitored and treated for symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

PROCHYMAL should only be administered under the supervision of a health care professional.

It is recommended that oxygen saturation (SaO_2/SAT) is monitored by pulse oximetry during infusion of the product. Your infusion will be stopped if needed.

Undesirable effects, such as allergic reactions or difficulty breathing should be communicated immediately to your caregiver.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

PROCHYMAL should be handled by a health care professional and must be stored at ≤ -135°C in an ultra low temperature freezer. Cryoprotective gloves should be worn when handling PROCHYMAL at extremely cold temperatures. When PROCHYMAL arrives in a cryoshipper, it can be transferred to a liquid nitrogen freezer for longer term storage if needed. The stem cells will die if storage instructions are not carefully followed.

MORE INFORMATION

A copy of this document plus the full product monograph, prepared for health professionals, can be attained by contacting the sponsor, Mesoblast International Sàrl, at 1-212-880-2060.

This leaflet was prepared by Mesoblast International Sàrl

Last revised: March 6, 2014