PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Trecondyv®

treosulfan for injection

Lyophilized powder, 1 g / vial and 5 g / vial, intravenous infusion

Antineoplastic agents, alkylating agents

Medexus Inc.
35 Nixon Road, Unit 1
Bolton, Ontario
L7E 1K1

Date of Initial Approval:

June 25, 2021

Submission Control No: 244137

RECENT MAJOR LABEL CHANGES

None.

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Trecondyv® (treosulfan) is indicated in combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT)

- in adult patients with AML or MDS at increased risk for standard conditioning therapies,
- in pediatric patients older than 1 year old with AML or MDS

Administration of treosulfan should be supervised by a physician experienced in conditioning treatment followed by alloHSCT.

Limitations of Use
Trecondyv® is not indicated for patients undergoing allo HSCT for Fanconi anemia and other DNA breakage repair disorders.

1.1 Pediatrics

Pediatrics (> 1 year to 18 years): The use of Trecondyv® has not been fully investigated in the pediatric population.

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use of Trecondyv® in the geriatric population is not associated with significant differences in safety or effectiveness.

No dose adjustment is necessary in any subset of the elderly population.

2 CONTRAINDICATIONS

Treosulfan is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

- Active non-controlled infectious disease
- Severe concomitant cardiac, lung, liver, and renal impairment
- Fanconi anemia and other DNA breakage repair disorders
- Pregnancy
- Administration of live vaccine

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions:

- **Myelosuppression**
- **Causes severe and prolonged myelosuppression.**
- **Hematopoietic stem cell transplantation is required to prevent potentially fatal complications of the prolonged myelosuppression**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Administration of Trecondyv® should be supervised by a physician experienced in conditioning treatment followed by alloHSCT.

4.2 Recommended Dose and Dosage Adjustment

Trecondyv® is given in combination with fludarabine.

The recommended dose and schedule of administration is:

- Treosulfan 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -4, -3, -2) before stem cell infusion (day 0). The total treosulfan dose is 30 g/m²;
- Fludarabine 30 mg/m² BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (day -6, -5, -4, -3, -2) before stem cell infusion (day 0). The total fludarabine dose is 150 mg/m²;
- Treosulfan should be administered before fludarabine on days -4, -3, -2 (FT_{10} regimen).

Health Canada has not authorized the use of Trecondyv® in children less than 1 year of age.

No dose adjustment is necessary for mild or moderate liver or renal impairment, but treosulfan is contraindicated in patients with severe impairment (see section **CONTRAINDICATION**).

4.3 Administration

Trecondyv® is for intravenous use as a two-hour infusion. Intravenous administration should be performed using a safe technique to avoid extravasation.

When handling treosulfan, inhalation, skin contact or contact with mucous membranes should be avoided. Pregnant personnel should be excluded from handling cytotoxics.

Consider providing prophylactic anti-emetic therapy during Trecondyv® treatment.

4.4 Reconstitution

Dissolve Trecondyv® with 0.45% or 0.9% Sodium Chloride Injection or 5% Glucose Injection or Water for Injection.

Trecondyv® is dissolved in its original glass container by shaking with solvent. Reconstituted

solutions of Trecondyv® may be combined into a larger glass vial, EVA bag or PE bag.

In case solubility issues are observed when shaking, prolonged standing time or slight warming of the reconstituted solution (hand warm) are useful to improve solubility.

Table 1 - Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Vial Capacity	Nominal Concentration per mL
1 g	20 mL	38 mL	50 mg/mL
5 g	100 mL	119 mL	50 mg/mL

The reconstituted solution of Trecondyv® is stable for 3 days if stored at 15°C to 30°C. Do not store under refrigeration (2°C - 8°C) as this might result in the formation of precipitate. Do not use if the solution contains a precipitate [see STORAGE, STABILITY AND DISPOSAL(11)]

In the absence of compatibility studies, treosulfan must not be mixed with other medicinal products.

4.5 Missed Dose

A missed dose would increase the risk for a primary graft failure.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

There is no known antidote to Trecondyv® other than hematopoietic stem cell transplantation. In the absence of hematopoietic stem cell transplantation, the recommended dose for Trecondyv® would constitute an overdose of treosulfan.

The principal toxic effect of treosulfan is profound myeloablation and pancytopenia. In addition, acidosis, skin toxicity, nausea, vomiting and gastritis may occur. The hematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Lyophilized powder 1 g or 5 g per vial	None

Trecondyv® is supplied as a sterile, white crystalline, lyophilized powder in single use glass vials containing 1 g or 5 g treosulfan.

Trecondyv® 1 g lyophilized powder
Colourless type I glass vial, with rubber stopper and aluminium cap containing 1 g of treosulfan.

Trecondyv® 5 g lyophilized powder
Colourless type I glass vial, with rubber stopper and aluminium cap containing 5 g of treosulfan.

Trecondyv® is available in cartons of 1 or 5 vials each.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information [Section 3].

The following warnings pertain to different physiologic effects of Trecondyv® in the setting of allo HSCT.

General
Treosulfan is considered an irritant. Intravenous application should be performed using a safe technique. If extravasation is suspected, general safety measures should be implemented. No specific measure has been proven to be recommendable.

During a phase 3 clinical trial (MC-FludT.14/L Trial II) treatment emergent adverse events (TEAEs) were reported by 92.6% of patients in the treosulfan treatment group. TEAEs were most commonly reported in the SOCs “Gastrointestinal disorders”, “General disorders and administration site conditions”, and “Musculoskeletal and connective tissue disorders” (TEAEs reported by 68.1%, 56.3%, and 37.8% of patients, respectively).

TEAEs of at least CTCAE Grade III were reported by 54.8% of patients in the treosulfan treatment group. Severe Adverse Events (SAEs) were reported by 8.5% of patients in the treosulfan treatment group.

Carcinogenesis and Mutagenesis
Secondary malignancies are well-established complications in long-term survivors after alloHSCT.

The possible risk of a second malignancy should be explained to the patient. On the basis of human data, treosulfan has been classified by the International Agency for Research on Cancer (IARC) as a human carcinogen Group 1.

Cardiovascular
Patients with severe cardiac impairment diagnosed by ECG and left ventricular ejection fraction (LVEF) < 40% or with severe pulmonary impairment were excluded from the pivotal clinical study and therefore the safety and efficacy of TRECONDYV in these patients have not been established.

During the clinical program of treosulfan cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia) and cardiac failure occurred in 18.1% and 1.0% of the adult patients treated with treosulfan-based conditioning regimen, respectively. The treatment emergent serious cardiac adverse events - left ventricular systolic dysfunction, myocardial infarction, paroxysmal atrial tachycardia and right ventricular dysfunction - were reported in the treosulfan treatment group

during a phase 3 clinical trial (MC-FludT.14/L Trial II), although none was considered related to treosulfan.

No thorough clinical QT/QTc study was performed to rule out the effect of TRECONDYV on in vivo QT prolongation. In vitro studies on electrophysiological activity of treosulfan on key cardiac ion channels and tests of proarrhythmic potential in human induced pluripotent stem cell (iPS) derived cardiomyocytes, using a microelectrode array (MEA) assay, did not reveal dose-limiting functional or structural changes.

Driving and Operating Machinery
Treosulfan has moderate influence on the ability to drive and use machines. It is likely that certain adverse reactions of treosulfan like nausea, vomiting or dizziness could affect these functions.

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Gastrointestinal
Oral mucositis (including high-grade severity) is a very common undesirable effect of treosulfan-based conditioning followed by alloHSCT (8). Use of mucositis prophylaxis (e.g. topical antimicrobials, barrier protectants, ice and adequate oral hygiene) is recommended.

Graft vs Host Diseases

Graft vs. Host Disease (GvHD) is commonly observed in patients treated with an allogeneic HSCT. Respective results obtained with 10 g/m²/d x 3 regimen are shown in the following table.

Table 3: Summary of Graft vs Host Disease observed in an active-controlled trial (MC-FludT.14/L Trial II)

Parameter	Treosulfan	Busulfan	P value
Number of patients	268	283	
Acute GvHD, all Grades; % (95% CI)	52.8 (46.8, 58.8)	57.2 (51.5, 63.0)	0.2038
Acute GvHD, Grades III/IV; % (95% CI)	6.4 (3.4, 9.3)	8.1 (4.9, 11.3)	0.4267
Chronic GvHD[a]; % (95% CI)	61.7 (55.1, 68.3)	60.3 (53.8, 66.7)	0.9964
Extensive chronic GvHD; % (95% CI)	19.8 (14.5, 25.1)	28.6 (22.5, 34.7)	0.0750

Hepatic
Transaminases, bilirubin, gamma-glutamyl transferase and alkaline phosphatase are commonly increased in patients treated with treosulfan-based conditioning.

Hematologic
Profound myelosuppression with pancytopenia is the desired therapeutic effect of treosulfan-based conditioning treatment, occurring in all patients. It is therefore recommended to monitor blood cell counts frequently until recovery of the hematopoietic system. During phases of severe neutropenia (median duration of neutropenic period is 14-17.5 days in adults and 21-24 days in pediatric patients as observed in study MC-FludT.17/M) the risk of infection is increased.

Prophylactic or empiric anti-infective treatment (bacterial, viral, fungal) should therefore be

considered. Growth factors (G-CSF, GM-CSF), platelet and/or red blood cell support should be given as indicated.

Monitoring and Laboratory Tests (see also section 8.4)
Patients receiving TRECONDYV should be monitored daily with a complete blood count, including differential count and quantitative platelet count, until engraftment has been demonstrated.

To detect hepatotoxicity, serum transaminases, alkaline phosphatase, and bilirubin should be evaluated daily through transplant day 28.

Cardiac function should be monitored regularly in patients receiving TRECONDYV.

Neurologic
During the clinical program of treosulfan, headache and dizziness occurred in 24.5% and 9.0% of the adult patients treated with treosulfan-based conditioning regimen, respectively. The treatment emergent serious neurologic adverse events - intracranial hemorrhage and syncope - were reported in the treosulfan treatment group during a phase 3 clinical trial (MC-FludT.14/L Trial II). In only one patient, who experienced encephalitis infection and intracranial hemorrhage as a complication of sepsis, the event was considered related to treosulfan.

Respiratory
During the clinical program of treosulfan epistaxis and dyspnea occurred in 10.3% and 8.6% of the adult patients treated with treosulfan-based conditioning regimen, respectively. The treatment emergent serious respiratory adverse events – respiratory failure, bronchopulmonary hemorrhage and lung infection - were reported in the treosulfan treatment group during a phase 3 clinical trial (MC-FludT.14/L Trial II). Only lung infection was considered related to treosulfan. There was a significant association between age and respiratory toxicity in pediatric patients treated with treosulfan-based conditioning.

Sexual Health
Reproduction
Both sexually active men and women of childbearing potential have to use effective contraception during and up to 6 months after treatment.

Function
Ovarian suppression and amenorrhea with menopausal symptoms commonly occur in pre-menopausal patients.

Fertility
Treosulfan can impair fertility. Therefore, men treated with treosulfan are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with treosulfan.

Skin
An increase of skin disorders (e.g. rash, dermatitis) was observed when patients received sodium bicarbonate-containing hydration in the course of treosulfan infusion because this might accelerate the pH-dependent formation of alkylating epoxides [see Mechanism of Action (10.1)]. On the days of chemotherapy, skin cream should be omitted.
Dermatitis diaper may occur in small children because of excretion of treosulfan in the urine.

Therefore, diapers should be changed frequently during the 6–8 hours after each infusion of treosulfan.

7.1 Special Populations

7.1.1 Pregnant Women

There is no experience from the use of treosulfan in pregnant women. Treosulfan is contraindicated during pregnancy [see CONTRAINDICATIONS (2)].

7.1.2 Breast-feeding

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

Breast-feeding should be discontinued during treatment with treosulfan.

7.1.3 Pediatrics

Pediatrics (> 1 year to 18 years): The use of Trecondyv® has not been fully investigated in the pediatric population.

7.1.4 Geriatrics

Eighty-one (13.2%) of the 613 adult patients treated within the clinical trial program for Trecondyv® were above the age of 65 years.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Profound myelosuppression/pancytopenia is the desired therapeutic effect of conditioning therapy and occurs in all patients. Blood cell counts usually recover after HSCT.

The most common (> 10%) adverse reactions observed in 5 clinical studies in 613 adults with treosulfan-based conditioning followed by alloHSCT include gastrointestinal disorders (nausea 38.5%, stomatitis 36.4%, vomiting 22.5%, diarrhea 15.2%), increases of bilirubin 17.9%, fatigue 14.8%, infections 12.9%, and febrile neutropenia 10.9%.

The most common (> 10%) adverse reactions observed in two clinical studies in 115 pediatric patients with treosulfan-based conditioning followed by alloHSCT include gastrointestinal disorders (stomatitis 67.0%, vomiting 41.7%, diarrhea 34.8%, nausea 27.8%, abdominal pain 17.4%), hepatotoxicity 26.1%, pyrexia 13.0%, infections 12.2%, increased alanine aminotransferase 11.3%, alopecia 10.4%, and pruritus 10.4%.

8.2 Clinical Trial Adverse Reactions (Adults)

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

The frequencies of adverse reactions reported in the table below are derived from a large active-controlled phase III clinical trial (MC-FludT.14/L Trial II) in a total of 551 adult patients where a conditioning regimen of treosulfan plus fludarabine was compared to a reduced intensity conditioning regimen consisting of busulfan plus fludarabine (NCT00822393). Median age of patients in the whole group was 60 years (range 31-70); 61% of patients were male; the underlying diseases were acute myeloid leukemia (64%) and myelodysplastic syndromes (36%).

Treosulfan was administered at a dose of 10 g/m² BSA on 3 consecutive days; Busulfan was administered at a dose of 3.2 mg/kg on 2 consecutive days. Fludarabine was added in both groups at a dose of 30 mg/m² on 5 consecutive days.

Table 3: Summary of the Incidence (occurring in ≥ 5% of Treated Patients) of Non-Hematologic Treatment Emergent Adverse Events by System Organ Class and Preferred Term (MedDRA 20.0) in an active-controlled trial (MC-FludT.14/L Trial II)

Nonhematological Treatment Emergent Adverse Events (TEAEs)	Percent Incidence			
	TEAEs all grades		TEAEs grade III/IV	
Treatment group	**Treosulfan n = 270**	**Busulfan n = 283**	**Treosulfan n = 270**	**Busulfan n = 283**
Infections and infestations				
Infections	27.0	23.7	15.2	9.2
Immune system disorders				
Allergic reaction	5.6	7.8	0.4	0.4
Metabolism and nutrition disorders				
Anorexia	8.9	9.2	1.9	1.4
Hypomagnesemia	5.2	2.8	0	0
Nervous system disorders				
Headache	16.3	18.4	1.1	0.7
Dizziness	6.3	4.9	0	0.4
Ear and labyrinth disorders				
Vertigo	4.4	8.5	0	0.7
Vascular disorders				
Hypertension	14.1	21.2	7.8	9.5
Hypotension	7.0	4.2	1.9	1.8
Respiratory, thoracic and mediastinal disorders				
Epistaxis	6.7	7.8	0	0.7
Dyspnea	5.2	7.8	0.7	1.4
Gastrointestinal disorders				
Mucositis oral (stomatitis)	37.8	47.7	5.9	7.4
Nausea	33.0	41.0	3.0	6.0

Nonhematological Treatment Emergent Adverse Events (TEAEs)	Percent Incidence			
	TEAEs all grades		TEAEs grade III/IV	
Treatment group	**Treosulfan n = 270**	**Busulfan n = 283**	**Treosulfan n = 270**	**Busulfan n = 283**
Vomiting	21.9	19.4	0.7	1.4
Diarrhea	15.9	18.4	1.5	1.4
Constipation	12.2	11.7	0.4	0
Abdominal pain	10.7	9.9	1.5	0.7
Skin and subcutaneous tissue disorders				
Rash maculo-papular	11.9	8.8	1.1	1.4
Pruritus	5.9	4.2	0.4	0
Purpura	5.2	3.5	0	0
Musculoskeletal and connective tissue disorders				
Back pain	14.8	13.1	2.6	0.4
Bone pain	13.7	9.9	0.7	0.7
Arthralgia	10.0	3.5	0.7	0.4
Pain in extremity	8.5	3.9	0.7	1.1
General disorders and administration site conditions				
Fatigue	12.2	12.4	1.1	0
Fever	34.4	35.7	0.7	3.2
Edema limbs	22.6	13.4	0.4	1.4
Chills	7.4	5.7	0.4	0
Localized edema	5.9	4.9	0.4	0
Pain	5.9	2.8	0.4	0
Investigations				
Alanine transaminase (ALT) increased	8.5	6.4	5.2	3.2
Aspartate transaminase (AST) increased	8.5	4.9	4.4	2.5
Bilirubin increased	9.3	6.4	3.3	2.8
Gamma-glutamyltransferase (γGT) increased	7.4	12.0	4.4	8.8
Weight gain	7.0	6.4	0	0

8.3 Less Common Clinical Trial Adverse Reactions (Adults)

Additional Adverse Reactions observed with treosulfan-based conditioning followed by

alloHSCT in 5 clinical trials in adult patients by System Organ Class and Preferred Term.

Blood and lymphatic system disorders: Febrile neutropenia
Cardiac disorders: Cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia), cardiac arrest, cardiac failure, myocardial infarction, pericardial effusion
Eye disorders: Dry eye
Gastrointestinal disorders: Oral pain, gastritis, dyspepsia, dysphagia, gastrointestinal hemorrhage, mouth hemorrhage, abdominal distension, esophageal or gastrointestinal pain, dry mouth, neutropenic colitis, esophagitis, anal inflammation, mouth ulceration
General disorders and administration site conditions: Edema, non-cardiac chest pain, injection site reaction, feeling cold
Hepatobiliary disorders: Veno-occlusive liver disease, hepatotoxicity, hepatic failure, hepatomegaly, hepatic pain
Immune system disorders: Hypersensitivity
Infections and infestations: Sepsis, septic shock
Investigations: Alkaline phosphatase increased, C reactive protein increased, weight decreased, blood creatinine increased, blood lactate dehydrogenase increased
Metabolism and nutrition disorders: Hyperglycemia, acidosis, impaired glucose tolerance, electrolyte imbalance
Musculoskeletal and connective tissue disorders: Myalgia, muscular weakness
Neoplasms benign, malignant and unspecified (including cysts and polyps): Treatment related second malignancy
Nervous system disorders: Peripheral sensory neuropathy, intracranial hemorrhage, encephalopathy, extrapyramidal disorder, syncope, paresthesia
Psychiatric disorders: Insomnia, confusional state, agitation
Renal and urinary disorders: Acute kidney injury, hematuria, urinary tract pain, renal failure, hemorrhagic cystitis, dysuria
Respiratory, thoracic and mediastinal disorders: Pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, cough, laryngeal or oropharyngeal pain, hiccups, hypoxia, dysphonia
Skin and subcutaneous tissue disorders: Erythema, palmar plantar erythrodysesthesia syndrome, alopecia, erythema multiforme, dermatitis acneiform, rash, hyperhidrosis, dry skin, generalized erythema, dermatitis, skin necrosis or ulcer, skin hyperpigmentation
Vascular disorders: Flushing, hematoma, embolism, hemorrhage

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data (Adults)

Hematologic
Significant suppression of the patient's blood cell counts is a typical epiphenomenon of alloHSCT which occurs in all patients. To reduce the occurrence of cytopenia-caused side effects (anemia: fatigue etc., leukopenia: infections; thrombocytopenia: bleeding), patients usually receive blood transfusions during the critical aplastic phase between HSCT and the next 4 weeks.

Table 4: Duration of cytopenias in adult patients treated with the FT_{10} regimen

Duration (days)	Neutropenia	Leukocytopenia	Thrombocytopenia	
	$< 0.5 \times 10^9$/L	$< 1 \times 10^9$/L	$< 20 \times 10^9$/L	$< 50 \times 10^9$/L
Median	14	14	13	15
25%/75% percentiles	12 / 21	11 / 18	0 / 38	10 / 84

Clinical chemistry
A significant proportion of patients had already laboratory liver parameters above the upper limit

of normal (ULN) at baseline.

Table 5: Percent of 613 adult patients with laboratory values above ULN; n (% of patients)

Time point	Laboratory parameter				
	AST	ALT	γGT	AP	Bilirubin
Baseline	95 (15.6%)	165 (27.0%)	202 (33.4%)	73 (12.2%)	38 (6.2%)
Day -3	141 (24.9%)	189 (32.4%)	276 (48.3%)	57 (10.2%)	144 (24.6%)
Day -1	86 (14.8%)	183 (30.9%)	284 (49.0%)	42 (7.4%)	188 (31.6%)
Day +6	168 (28.4%)	336 (56.2%)	357 (61.0%)	56 (9.8%)	243 (40.5%)
Day +14	34 (5.8%)	125 (20.9%)	346 (59.2%)	122 (21.4%)	173 (29.0%)
Day +28	96 (16.7%)	157 (26.7%)	307 (54.1%)	116 (20.5%)	108 (18.5%)
AST = aspartate transaminase; ALT = alanine transaminase; γGT = gamma-glutamyltransferase; AP = alkaline phosphatase					

Mean creatinine values were in normal range and did not much change during treatment with treosulfan-based conditioning.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Safety of treosulfan (10-14 g/m² on 3 consecutive days) combined with fludarabine (and mostly with thiotepa) was evaluated in two clinical trials in pediatric patients that included 70 patients with malignant diseases (AML, MDS, acute lymphoblastic leukemia [ALL], juvenile myelomonocytic leukemia [JMML]) and 45 patients with various non-malignant diseases.

Compared to adult patients, the following differences were observed. Gastrointestinal disorders (75.7% vs. 62.5%) and hepatobiliary disorders (27.8% vs. 1.8%) were more frequently observed in pediatric patients. The median (25%/75% percentiles) duration of neutropenia was 22 (17 / 26) days in pediatric patients with malignant diseases and 20 (16 / 26) days in patients with non-malignant disorders and therefore significantly longer than in adult patients (14 [12 / 21] days). However, the overall incidence of infections in 115 pediatric patients was 12.2% and thus comparable to that seen in adults.

8.6 Less Common Clinical Trial Adverse Reactions (Pediatrics)

Additional Adverse Reactions observed with treosulfan-based conditioning followed by alloHSCT in 2 clinical trials in pediatric patients by System Organ Class and Preferred Term.

Blood and lymphatic system disorders: Febrile neutropenia
Eye disorders: Conjunctival hemorrhage, dry eye
Gastrointestinal disorders: Dysphagia, oral pain, neutropenic colitis, anal inflammation, dyspepsia, proctitis, gastrointestinal pain, constipation
General disorders and administration site conditions: Chills, fatigue, pain
Hepatobiliary disorders: Veno-occlusive liver disease, hepatomegaly
Investigations: Aspartate aminotransferase increased, bilirubin increased, gamma-glutamyltransferase increased
Metabolism and nutrition disorders: Alkalosis, electrolyte imbalance, hypomagnesemia
Musculoskeletal and connective tissue disorders: Pain in extremities
Neoplasms benign, malignant and unspecified (including cysts and polyps): Treatment related second malignancy
Nervous system disorders: Headache, paresthesia, seizure
Psychiatric disorders: Insomnia, confusional state, agitation
Renal and urinary disorders: Acute kidney injury, renal failure, noninfective cystitis

Reproductive system and breast disorders: Scrotal erythema
Respiratory, thoracic and mediastinal disorders: Oropharyngeal pain, epistaxis, hypoxia
Skin and subcutaneous tissue disorders: Dermatitis exfoliative, maculopapular rash, rash, erythema, pain of skin, skin hyperpigmentation, skin ulcer, erythema multiforme, urticaria, dermatitis bullous, dermatitis acneiform, palmar plantar erythrodysesthesia syndrome, dermatitis diaper
Vascular disorders: Capillary leak syndrome, hypertension, hypotension

8.7 Post-Market Adverse Reactions

A report from an investigator-initiated trial performed in children with primary immunodeficiencies listed four cases of seizures occurring after a conditioning regimen with treosulfan.

9 DRUG INTERACTIONS

9.1 Overview

Drug interactions with treosulfan were not studied *in vivo*. Detailed *in vitro* studies did not completely exclude potential interactions between high plasma concentrations of treosulfan and CYP3A4, CYP2C19, or P-gp substrates.

Physiologically-based pharmacokinetic (PBPK) modeling with the sensitive index substrates midazolam, omeprazole, and digoxin for CYP3A4, CYP2C19, and P-gp predicted a weak interaction ($AUC_{ratio} \geq 1.25$ and < 2) for CYP3A4, and CYP2C19, and a negligible ($AUC_{ratio} < 1.25$) interaction for P-gp. Therefore, medicinal products with a narrow therapeutic index that are substrates for CYP3A4 or CYP2C19 should not be given during treatment with treosulfan.

9.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Treosulfan is a prodrug of a bifunctional alkylating agent with cytotoxic activity to hematopoietic stem cells. The activity of treosulfan is due to the spontaneous, pH-dependent conversion into a mono-epoxide intermediate and di-epoxybutan.

These epoxides alkylate and cross-link nucleophilic centers of deoxyribonucleic acid (DNA) and other biological molecules involved in various physiological functions and are considered responsible for the stem cell depleting, immune-suppressive and antineoplastic effects.

10.2 Pharmacodynamics

Treosulfan has a broad antineoplastic and antileukemic activity. This was demonstrated against transplanted mouse and rat lymphomas/leukemias, sarcomas and hepatomas, human tumor xenografts, human tumor biopsies and cell lines.

The immunosuppressive effects of treosulfan are attributed to its toxicity against primitive and committed hematopoietic progenitor cells, T and NK cells, reduction of cellularity of primary and secondary lymphatic organs and a preclusive effect on the 'cytokine storm' that precedes the

development of Graft-versus-Host-Disease (GvHD) and is involved in the pathogenesis of hepatic sinusoidal-obstruction syndrome (HSOS). Due to the high engraftment rates after administration of the recommended Trecondyv® doses no clear dose-response relationship with regard to engraftment or time to engraftment after alloHSCT was described.

10.3 Pharmacokinetics

The pharmacokinetics of Trecondyv® was studied in 24 adult patients participating in a prospective trial of a treosulfan-fludarabine conditioning regimen prior to alloHSCT. Patients received 14 g/m²/day treosulfan intravenously for 3 consecutive days.

With a terminal half-life close to 2 hours and no quantifiable pre-dose concentrations on the second and third day of treatment, there was no evidence of Trecondyv® accumulation in plasma after multiple dosing. Median values of all pharmacokinetic parameters were quite comparable for the first and third administration. Further pharmacokinetic parameters are available from the literature for dose levels ranging from 8 to 14 g/m² treosulfan infused over 2 hours.

Table 6: Summary of Treosulfan's Pharmacokinetic Parameters in Adult Patients (Arithmetic means ± standard deviation)

TREO dose g/m²	n	C_{max} mcg/mL	$AUC_{0-\infty}$ mcg/mL × h	Half-life h	CL_{tot} mL/min	V_{ss} L	Reference
8	4	181 ± 36	541 ± 107	1.75 ± 0.06	255 ± 59	30 ± 8	Hilger et al.
10	3	306 ± 94	940 ± 293	1.99 ± 0.61	190 ± 63	26 ± 12	
12	8	260 ± 35	898 ± 104	2.1 ± 0.5	225 ± 23	34 ± 5	Beelen et al.
14	10	322 ± 47	1104 ± 173	2.0 ± 0.6	216 ± 32	31 ± 7	
12	4	461 ± 102	1365 ± 293	1.73 ± 0.10	154 ± 35	16.9 ± 4.3	Nemecek et al.
14	12	409 ± 84	1309 ± 262	1.83 ± 0.30	185 ± 37	22.1 ± 3.8	
14	24	471 ± 87	1462 ± 261	1.84 ± 0.30	298 ± 63	46.9 ±9.0	MC-FludT.14/L Trial I

C_{max} = maximum plasma concentration; $AUC_{0-\infty}$ = Area under the concentration versus time curve from time point zero up to infinity; CL_{tot} = total clearance; V_{ss} = volume of distribution at steady state

References:

Hilger RA et al. Clinical pharmacokinetics of intravenous treosulfan in patients with advanced solid tumors. Cancer Chemother Pharmacol. 1998; 42: 99-104

Beelen DW et al. Dose-escalated treosulphan in combination with cyclophosphamide as a new preparative regimen for allogeneic haematopoietic stem cell transplantation in patients with an increased risk for regimen-related complications. Bone Marrow Transplant. 2005; 35(3):233-41

Nemecek ER et al. Conditioning with treosulfan and fludarabine followed by allogeneic hematopoietic cell transplantation for high-risk hematologic malignancies. Biol Blood Marrow Transplant. 2011 Mar; 17(3):341-50

Absorption: After intravenous administration, peak plasma levels are reached at the end of the infusion time. Maximum plasma levels (mean ± SD) in adult patients after a 2-hour intravenous infusion are provided in Table 6.

Distribution: Treosulfan is rapidly distributed in the body; however, its penetration through the blood-brain-barrier is quite limited [see Nonclinical Toxicology (16)]. The volume of distribution in adult patients is about 20–47 liters. No dose accumulation with the recommended daily treatment on three consecutive days was observed.
A microscale thermophoresis method demonstrated that treosulfan does not bind to human serum albumin.

Metabolism: Under physiological conditions (pH 7.4, temperature 37 °C), the pharmacologically inactive treosulfan is converted spontaneously (non-enzymatically) into the active monoepoxide intermediate (2S,3S)-1,2-epoxybutane-3,4-diol-4-methanesulfonate) and finally to L-diepoxibutane (2S,3S)-1,2:3,4-diepoxybutane).

Elimination: Plasma concentrations of treosulfan decline exponentially and are best described by a first order elimination process fitted by a two-compartment model.
The terminal half-life ($T_{1/2ß}$) of intravenously administered treosulfan is approximately 2 hours. Approximately14–40% of the treosulfan dose is excreted unchanged with the urine within 24 hours.

Special Populations and Conditions

Pediatrics (> 1 year to 18 years)*:* The use of Trecondyv® has not been fully investigated in the pediatric population.

Geriatrics: Between patients < 50 years and ≥ 50 years of age, only small differences in the pharmacokinetic parameters were observed.

Sex: Median values of C_{max}, AUC, half-life, total clearance and volume of distribution were quite comparable in male and female patients.

Hepatic Insufficiency: No pharmacokinetic studies with treosulfan were conducted in patients with severe hepatic impairment, because such patients are generally excluded from alloHSCT.

Renal Insufficiency: No pharmacokinetic studies with treosulfan were conducted in patients with severe renal impairment, because such patients are generally excluded from alloHSCT. About14–40% of treosulfan is excreted in urine; however, an influence of renal function on overall clearance of treosulfan was not observed.

11 STORAGE, STABILITY AND DISPOSAL

Unopened vials of Trecondyv® should be stored at room temperature 15°C to 30°C.

Trecondyv® dissolved in 0.45% or 0.9% Sodium Chloride Injection or 5% Glucose Injection or Water for Injection is stable for 3 days if stored at 15°C to 30°C.

Do not store under refrigeration (2°C -8°C) as this might result in the formation of precipitate. Do not use if the solution contains a precipitate.

12 SPECIAL HANDLING INSTRUCTIONS

Trecondyv® is a cytotoxic drug. Follow applicable special handling and disposal procedures.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

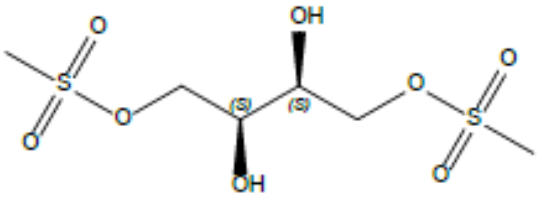
Drug Substance

Common name: treosulfan

Chemical name: (2S,3S)-2,3-dihydroxy-4-(methanesulfonyloxy)butyl methanesulfonate

Molecular formula and molecular mass: $C_6H_{14}O_8S_2$; 278.3 g/mol

Structural formula:



Physicochemical properties:

Physical description: White crystalline powder

pKa: 12.84

Solubility (25 °C): 13 % (m/v) in acetone; 7 % (m/v) in water; 1 % (m/v) in ethanol 96%; 0.05 % (m/v) in chloroform

Solubility of Treosulfan in water at pH 1 to pH 8 at 37°C is from 150 to 200 mg/mL.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 7 - Summary of patient demographics for clinical trials in alloHSCT

Study	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (male/female)
MC-FludT.14/L Trial I	Randomized, active controlled, parallel-group, open label, group-sequential phase III trial in adult patients with AML or MDS	Treosulfan arm: 14 g/m²/d IV infusion (2 hours) Day –6 to –4 before HSCT (day 0)	168	57.3 (21-70) years	76 / 92
		Control arm FB 3.2 mg/kg/d IV infusion (2 hours) Day –4 to –3 before HSCT (day 0)	152	57.8 (24-70) years	85 / 67
MC-FludT.14/L Trial II	Randomized, active controlled, parallel-group, open label, group-sequential phase III trial in adult patients with AML or MDS	Treosulfan arm: 10 g/m²/d IV infusion (2 hours) Day –4 to –2 before HSCT (day 0)	270	59.3 (37-70) years	163 / 107
		Control arm FB 3.2 mg/kg/d IV infusion (2 hours) Day –4 to –3 before HSCT (day 0)	283	59.9 (31-70) years	173 / 110
FB = Fludarabine plus busulfan					

MC-FludT.14/L consists of two separate active-controlled trials which differ in the treosulfan regimens used. Both trials compared treosulfan/ fludarabine with a reduced intensity conditioning (RIC) regimen of busulfan/fludarabine (FB2) in elderly and/or comorbid patients with AML or MDS who are not eligible for a standard MAC regimen. In the first trial, a treosulfan dose of 14 g/m²/d × 3 (FT_{14} regimen) was used. An interim analysis after inclusion of 330 patients showed a slightly higher incidence of transplant-related mortality (TRM) in the experimental arm, mainly due to an increased rate of infections because of a significantly prolonged duration of neutropenia compared to the RIC regimen FB2. To reduce the duration of neutropenia, the dose of treosulfan was reduced from 14 to 10 g/m²/d × 3 and the timing of treosulfan administration shifted from days -6/-5/-4 to -4/-3/-2 in the subsequent Trial II (FT_{10} regimen). Trial II is considered as the pivotal study because the dose regimen used is the final dose regimen that is proposed for adult patients with malignant diseases (see 4.2). The final study report of this trial is based on 570 patients.

Study Results
Event-free survival (EFS) at 2 years was the primary endpoint of the pivotal study 14/L Trial II. Superiority of the treosulfan regimen versus busulfan could be demonstrated. Analyses of EFS at 2 years for various pre-defined subgroups (donor type, risk group, disease, age group, HCT-CI score, remission status at study entry, and various combinations of these parameters) were always in favor of the treosulfan regimen (hazard ratio [HR] of FT_{10} *vs.* FB2 < 1), with only one exception (risk group II of MRD patients; HR 1.18 [95% CI 0.61, 2.26]).

Results of the primary and further secondary endpoints are summarized in Table 8.

Table 8 - Results of study 14/L Trial II in patients with AML or MDS at 2 years (Full analysis set)

Parameter	Treosulfan group % (95% CI)	Busulfan group % (95% CI)	Hazard ratio (95% CI)	P value
Number of patients	268	283		
Event-free survival[a]	65.7 (59.5, 71.2)	51.2 (45.0, 57.0)	0.64 (0.49, 0.84)[b]	0.00058[b,d]
Overall survival[a]	72.7 (66.8, 77.8)	60.2 (54.0, 65.8)	0.64 (0.48, 0.87)[b]	0.0037[b]
Cumulative incidence of non-relapse mortality	12.0 (8.0, 15.9)	20.4 (15.5, 25.2)	0.63 (0.41, 0.97)[c]	0.0343[c]
Cumulative incidence of relapse/progression	22.0 (16.9, 27.1)	25.2 (20.0, 30.3)	0.82 (0.59, 1.16)[c]	0.2631[c]

[a] Based on Kaplan-Meier estimates; [b] adjusted for donor type, risk group and center using Cox regression model; [c] adjusted for donor type as factor and risk group as stratum using Fine and Gray model; [d] P value for testing superiority

Pediatric studies

In pediatric patients, a conditioning regimen consisting of 10, 12 or 14 g/m²/d × 3 treosulfan (Day -6/-5/-4) plus fludarabine (30 mg/m²/d, Day -7 to -3) has been conducted. Safety and efficacy based on this study could not be established.

15 NON-CLINICAL TOXICOLOGY

Four week subchronic, intravenous treatment of rats with 10, 50 or 150 mg treosulfan/kg b.w./day (human equivalent dose [HED]: 1.6, 8.1, or 24.3 mg/kg b.w./day) resulted in hematologic changes, decreased relative spleen and thymus weights in the context of a lymphoid atrophy and bone marrow depression. Lymphohistiocytic infiltration in the skeletal musculature and signs of hematuria, preferentially in male animals, were observed. The no-observed-effect-level (NOEL) was below 10 mg /kg b.w./day. A linear dose-related systemic exposure of the animals to treosulfan and treosulfan monoepoxide was evident, without accumulation or sex-specific differences. Single intravenous administrations of 500 mg/kg b.w. treosulfan (HED: 81 mg/kg b.w.) to juvenile (PND 10) and young adult (PND 34 – 35) rats revealed a very low penetration of blood brain barrier by treosulfan. The treosulfan concentrations in brain tissue were 95% – 98% lower than in plasma. However, an approximately 3 fold higher exposure was found in the brain tissue of juvenile rats in comparison to young adults.

Subchronic treatment of juvenile rats from postnatal day 10 to 35 with daily doses of 10, 50 or 100 mg/kg b.w. treosulfan (human equivalent dose (HED): 1.6, 8.1, 16.2 mg/kg b.w.) resulted in completely reversible hematological changes in all dose groups. A slightly delayed physical development indicated by decreased body weight, reduced relative organs weights, and a slightly delayed time point of vaginal opening were noted in the high-dosed rats.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrTrecondyv®

treosulfan for injection, lyophilized powder

Read this carefully before you start taking **Trecondyv** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Trecondyv**.

Serious Warnings and Precautions:

Bone Marrow Suppression: The intended effect of Trecondyv is to suppress the bone marrow. This is to prepare you for a blood stem cell transplant from a donor. This is a very serious and potentially fatal condition. The only way to recover from this severe bone marrow suppression is with a blood stem cell transplant. Your healthcare professional will closely monitor the health of your blood cells while you are taking Trecondyv and after your transplant. Low blood cell levels will last longer in children and adolescents than in adults. If you experience any of the following symptoms tell your healthcare professional immediately:

- symptoms of infections including; fever, chills, sore throat, mouth sores
- weakness, fatigue
- easy bruising, bleeding of the nose, gums or mouth, tiny red spots on the skin
- rash
- shortness of breath
- pale skin, lips and nail beds

What is Trecondyv used for?
Trecondyv is used together with fludarabine to prepare patients for a blood stem cell transplant from a donor:

- in adults with the blood cancers Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) who are not able to tolerate the standard preparation therapies,
- in children and adolescent older than one year of age with AML or MDS.

How does Trecondyv work?
Trecondyv contains the medicinal ingredient treosulfan, which belongs to a group of medicines called alkylating agents. Trecondyv is used to prepare patients for blood stem cell transplant. Trecondyv destroys your bone marrow cells. This allows for the transplant of new blood stem cells from a donor which leads to the production of healthy blood cells.

What are the ingredients in Trecondyv?
Medicinal ingredients: treosulfan
Non-medicinal ingredients: None

Trecondyv comes in the following dosage forms:
lyophilized powder 1 g / vial or 5 g / vial.

Do not use Trecondyv if you:

- are allergic (hypersensitive) to treosulfan
- have an untreated infection
- have severe heart, lung, liver or kidney problems
- were born with a DNA breakage repair disorder, a condition that reduces the ability to repair DNA (which carries your genetic information), such as Fanconi anemia
- are pregnant, or think you may be pregnant
- have recently had, or are going to have, a live vaccine, such as the MMR (measles, mumps, rubella) or chickenpox vaccines

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Trecondyv. Talk about any health conditions or problems you may have, including if you:

- have heart or lung problems
- are breastfeeding. You must not breastfeed while you are taking Trecondyv

Other warnings you should know about:

- **Cancer Risk:** Trecondyv may increase the risk of having another cancer in the future.

- **Driving and Using Machines:** Trecondyv can cause nausea, vomiting and dizziness which may affect your ability to drive or use machines. Wait to see how you respond to Trecondyv before you drive or use machines.

- **Mouth Sores:** Inflammation of the tissues in the mouth and mouth sores are common side effects of Trecondyv. The following can help reduce inflammation and sores in the mouth:
    - Practicing good oral hygiene (keeping your mouth and teeth clean).
    - Using mouthwashes that kill bacteria (antimicrobial) or form a barrier of protection on the tissue.
    - Applying ice to the tissues in the mouth. This will reduce the blood flow and also the amount of Trecondyv that reaches these tissues.

- **Blood Tests**: Trecondyv is a cell-killing medicine that is used to decrease the number of blood cells. At the recommended dose, this is the desired effect. You will have regular blood tests during treatment to check that your blood cell counts do not fall too low. Your healthcare professional will also do blood tests to monitor the health of your liver and heart and to check for other side effects. Your healthcare professional will decide when to perform blood tests and interpret the results.

- **Serious Heart and Lung Side Effects:** Trecondyv can cause serious heart and lung side effects. You will be monitored for signs of these side effects. See the **Serious Side Effects and What To Do About Them** table below, for more information.

- **Birth Control for Men and Women:** Men and women must use effective birth control while taking Trecondyv and for 6 months after their last dose. You must not get pregnant or father a child while taking Trecondyv or for 6 months after. This is because Trecondyv may harm your/your female partner's unborn baby. Talk to your healthcare professional about the birth control options that are right for you.

- **Fertility in Men and Women**: Trecondyv may make you infertile. This means you might not be able to get pregnant or father a child after taking Trecondyv. In women Trecondyv may

cause you to stop ovulating and may also stop your period which may cause symptoms of menopause even if you are pre-menopausal. You should discuss ways to preserve your fertility with your healthcare professional before you start taking Trecondyv. Male patients should consider sperm preservation before they start taking Trecondyv.

- **Diaper rash**: Diaper rash with skin ulceration of the area around the anus may occur in children wearing diapers. This is because Trecondyv passes out in the urine and can damage the skin. Diapers should be changed frequently during the 6–8 hours after each dose of Trecondyv.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Trecondyv:
Trecondyv will be given to you by a healthcare professional experienced in preparing patients for a blood stem cell transplant. It is given by drip (infusion) into a vein before the blood stem cell transplant.

Usual dose:
Trecondyv is used together with fludarabine. Your healthcare professional will decide on your dose based on your height and weight. You will receive Trecondyv as a 2 hour infusion once a day for 3 days before the blood stem cell transplant. You will also receive fludarabine as a 30 minute infusion once a day for 5 days before the blood stem cell transplant. The schedule will look like this:
Day -6: fludarabine
Day -5: fludarabine
Day -4: Trecondyv followed by fludarabine
Day -3: Trecondyv followed by fludarabine
Day -2: Trecondyv followed by fludarabine
Day -1: no medicine
Day 0: blood stem cell transplant

Overdose:

If you think you have been given too much Trecondyv, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
You will be given Trecondyv in the hospital under supervision of your healthcare professional however, if you think you have missed a dose of Trecondyv, tell your healthcare professional as soon as possible.

What are possible side effects from using Trecondyv?

These are not all the possible side effects you may feel when taking Trecondyv. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- decreased appetite, indigestion
- constipation

- weight gain
- tiredness
- trouble sleeping (insomnia)
- headache
- dizziness
- flushing
- pain in the arms and legs, back pain
- muscle pain
- dry eyes

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
VERY COMMON **Bone marrow suppression:** infections (fever, chills, sore throat, mouth ulcers), weakness, fatigue, easy bruising, bleeding of the nose, gums or mouth, tiny red spots on the skin, rash, shortness of breath, pale skin, lips and nail beds		✓	
Stomatitis: inflammation of the tissues in the mouth, mouth pain, mouth sores and/or ulcers, bleeding in the mouth		✓	
Gastrointestinal problems: diarrhea, nausea, vomiting, stomach pain	✓		
Alopecia: hair loss		✓	
COMMON **Sepsis (infection of the blood):** fever, chills, very low body temperature, urinating less often, fast heartbeat, nausea, vomiting, diarrhea, fatigue, blotchy or discoloured skin, can lead to shock and death			✓
Heart rhythm problems: heartbeat is irregular, too fast or too slow		✓	
High blood pressure: headache, shortness of breath	✓		
Low blood pressure: lightheadedness, dizziness and fainting, especially when you go from lying or sitting to standing	✓		
Difficulty swallowing	✓		
Skin problems: rash with flat or	✓		

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
raised red bumps, redness, itching, dry skin, skin ulcers, blisters, changes in skin colour			
Bone pain	✓		
Kidney problems: decreased urination, blood in the urine, nausea, vomiting, swelling of the arms or legs, fatigue		✓	
Edema: swelling of the hands or feet	✓		
UNCOMMON **High blood sugar:** frequent urination, thirst, hunger	✓		
Nervous system problems (such as bleeding in the brain or brain damage): weakness or paralysis of arms, legs or face, difficulty speaking, severe headache, seeing, feeling or hearing things that are not there, loss of consciousness, confusion, disorientation, trembling, seizures, muscle twitching			✓
Confusion	✓		
Peripheral neuropathy (problems in the nerves of the arms or legs): numbness, reduced or increased sensitivity, tingling, burning pain	✓		
Vertigo: feeling of spinning or whirling	✓		
Lung problems (inflammation of the lung, fluid around the lung): shortness of breath, dry cough, fatigue, feeling of heaviness or tightness in the chest, chest pain		✓	
Liver problems (including liver failure): yellowing of the whites of the eyes or skin, itchiness, dark urine, pale stool, weight gain, abdominal swelling and pain, loss of appetite, shortness of breath, disorientation or confusion (more common in children and		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
adolescents)			
Chest pain	✓		
UNKNOWN FREQUENCY **Allergic reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Gastrointestinal bleeding: blood in the stool, vomiting blood			✓
Injection site reaction: pain, redness or swelling at the injection site	✓		
Heart failure: shortness of breath on exertion or when lying down, fatigue, weakness, swelling in your legs, ankles and feet, fast or irregular heartbeat, cough or wheezing with blood-tinged phlegm		✓	
Heart attack: chest pain, shortness of breath, weakness, lightheadedness, pain or discomfort in the jaw, neck, back, shoulder or arm			✓
Pulmonary embolism (blood clot in the lung): shortness of breath, sudden chest pain especially when breathing in, coughing up blood			✓
Thrombosis (blood clot): swelling, pain, redness and warmth in an arm or leg		✓	
Fainting		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Trecondyv will be stored by your healthcare professional.

If you want more information about Trecondyv:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.medexus.com, or by calling 1-877-633-3987.

This leaflet was prepared by Medexus Inc.

Last Revised: June 25, 2021