24.0 APPENDICES

Appendix A: Pharmacist Lead CTCAE Grading PED-Pro CTCAE Grading

Dry mouth

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Dry mouth
Definition	A disorder characterized by reduced salivary flow in the oral cavity.
Grade 1	Symptomatic (i.e., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min
Grade 2	Moderate symptoms: oral intake alterations (i.e., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min
Grade 3	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1mL/min
Grade 4	-
Grade 5	-

Difficulty swallowing

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Dysphagia
Definition	A disorder characterized by difficulty in swallowing.
Grade 1	Symptomatic, able to eat regular diet
Grade 2	Symptomatic and altered eating/swallowing
Grade 3	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death

Mouth/throat pain

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Oral pain
Definition	A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL

Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Voice quality changes

CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Voice alteration
Definition	A disorder characterized by a change in the sound and/or speed of the voice.
Grade 1	Mild or intermittent change from normal voice
Grade 2	Moderate or persistent change from normal voice; still understandable
Grade 3	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology
Grade 4	-
Grade 5	-

Hoarseness

CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Hoarseness
Definition	A disorder characterized by harsh and raspy voice arising from or spreading to the larynx.
Grade 1	Mild or intermittent voice change; fully understandable; self-resolves
Grade 2	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated
Grade 3	Severe voice changes including predominantly whispered speech
Grade 4	-
Grade 5	-

Sore throat

CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Sore throat
Definition	A disorder characterized by marked discomfort in the throat.

Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL; limiting ability to swallow
Grade 4	-
Grade 5	-

Taste changes

CTCAE - SOC	Nervous system disorders
CTCAE Term	Dysgeusia
Definition	A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.
Grade 1	Altered taste but no change in diet
Grade 2	Altered taste with change in diet (i.e., oral supplements); noxious or unpleasant taste; loss of taste
Grade 3	-
Grade 4	-
Grade 5	-

Decreased appetite

CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Anorexia
Definition	A disorder characterized by a loss of appetite.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated
Grade 3	Associated with significant weight loss or malnutrition (i.e., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death

Nausea

CTCAE - SOC	Gastrointestinal disorders

CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Heartburn

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Gastroesophageal reflux disease
Definition	A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.
Grade 1	Mild symptoms: intervention not indicated
Grade 2	Moderate symptoms: medical intervention indicated
Grade 3	Severe symptoms: operative intervention indicated
Grade 4	-

Grade 5	-

Gas

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Flatulence
Definition	A disorder characterized by a discharge of excessive gas from the lower GI tract.
Grade 1	Mild symptoms: intervention not indicated
Grade 2	Moderate; persistent; psychosocial sequelae
Grade 3	-
Grade 4	-
Grade 5	-

Bloating

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Bloating
Definition	A disorder characterized by subject-reported feeling of uncomfortable fullness of the abdomen.
Grade 1	No change in bowel function or oral intake
Grade 2	Symptomatic, decreased oral intake; change in bowel function
Grade 3	-
Grade 4	-
Grade 5	-

Hiccups

CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Hiccups
Definition	A disorder characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.
Grade 1	Mild symptoms; intervention not indicated

Grade 2	Moderate symptoms: medical intervention indicated; limiting instrumental ADL
Grade 3	Severe symptoms; interfering with sleep; limiting self-care ADL
Grade 4	-
Grade 5	-

Constipation

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Constipation
Definition	A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.
Grade 1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema
Grade 2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	Obstipation with manual evacuation indicated, limiting self-care ADL
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death

Diarrhea

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movements.
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death

Abdominal pain

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Abdominal pain

Definition	A disorder characterized by a sensation of marked discomfort in the abdominal region.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Fecal incontinence

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Faecal incontinence
Definition	A disorder characterized by inability to control the escape of stool from the rectum.
Grade 1	Occasional use of pads required
Grade 2	Daily use of pads required
Grade 3	Severe symptoms: elective operative intervention indicated
Grade 4	-
Grade 5	-

Shortness of breath

CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Dyspnea
Definition	A disorder characterized by an uncomfortable sensation of difficulty breathing.
Grade 1	Shortness of breath with moderate exertion
Grade 2	Shortness of breath with minimal exertion; limiting instrumental ADL
Grade 3	Shortness of breath at rest; limiting self-care ADL
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death

Cough

CTCAE - SOC	Respiratory, thoracic, and mediastinal disorders
CTCAE Term	Cough
Definition	A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.
Grade 1	Mild symptoms: non-prescription intervention indicated
Grade 2	Moderate symptoms, medical intervention indicated, limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

Wheezing

CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Wheezing
Definition	A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways.
Grade 1	Detectable airway noise with minimal symptoms
Grade 2	Moderate symptoms: medical intervention indicated; limiting instrumental ADL
Grade 3	Severe respiratory symptoms limiting self-care ADL; oxygen therapy or hospitalization indicated
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death

Sneezing

CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Sneezing
Definition	A disorder characterized by the involuntary expulsion of air from the nose.
Grade 1	Mild symptoms: intervention not indicated
Grade 2	Moderate symptoms: medical intervention indicated
Grade 3	-
Grade 4	-

Grade 5	-

Swelling

CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Generalized edema
Definition	A disorder characterized by fluid accumulation in the tissues of the body including the skin.
Grade 1	Noted on exam; 1+ pitting edema
Grade 2	Interfering with instrumental ADLs; oral therapy initiated
Grade 3	Interferes with self-care ADL; intravenous therapy indicated; skin breakdown
Grade 4	Life-threatening consequences
Grade 5	-

Heart palpitations

CTCAE - SOC	Cardiac disorders
CTCAE Term	Palpitations
Definition	A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart.
Grade 1	Mild symptoms: intervention not indicated
Grade 2	Intervention indicated
Grade 3	-
Grade 4	-
Grade 5	-

Skin Dryness

CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Dry skin
Definition	A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture.
Grade 1	Covering <10% BSA and no associated erythema or pruritus
Grade 2	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL

Grade 3	Covering >30% BSA and associated with pruritus; limiting self-care ADL
Grade 4	-
Grade 5	-

Acne

CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Rash acneiform
Definition	A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.
Grade 1	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness.
Grade 2	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms
Grade 3	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated
Grade 4	Life-threatening consequences: papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated
Grade 5	Death

Hair loss

CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Alopecia
Definition	A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location.
Grade 1	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss, but it does not require a wig or hair piece to camouflage
Grade 2	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact
Grade 3	-
Grade 4	-
Grade 5	-

Itching

CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Pruritus
Definition	A disorder characterized by an intense itching sensation.
Grade 1	Mild or localized; topical intervention indicated
Grade 2	Widespread and intermittent; skin changes from scratching (i.e., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL
Grade 3	Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated
Grade 4	-
Grade 5	-

Hives

CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Urticaria
Definition	A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.
Grade 1	Urticarial lesions covering <10% BSA; topical intervention indicated
Grade 2	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated
Grade 3	Urticarial lesions covering >30% BSA; IV intervention indicated
Grade 4	-
Grade 5	-

Sensitivity to sunlight

CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Photosensitivity
Definition	A disorder characterized by an increase in sensitivity of the skin to light.
Grade 1	Painless erythema and erythema covering <10% BSA
Grade 2	Tender erythema covering 10 - 30% BSA
Grade 3	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (i.e., narcotics or NSAIDs)
Grade 4	Life-threatening consequences: urgent intervention indicated

Grade 5	Death

Skin ulceration

CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Skin ulceration
Definition	A disorder characterized by a circumscribed, erosive lesion on the skin.
Grade 1	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema
Grade 2	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat
Grade 3	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia
Grade 4	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss
Grade 5	Death

Numbness and tingling

CTCAE - SOC	Nervous system disorders
CTCAE Term	Paresthesia
Definition	A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and/or warmth.
Grade 1	Mild symptoms
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

Dizziness

CTCAE - SOC	Nervous system disorders
CTCAE Term	Dizziness
Definition	A disorder characterized by a disturbing sensation of light-headedness, unsteadiness, giddiness, spinning or rocking.
Grade 1	Mild unsteadiness or sensation of movement
Grade 2	Moderate unsteadiness or sensation of movement; limiting instrumental ADL

Grade 3	Severe unsteadiness or sensation of movement; limiting self-care ADL
Grade 4	-
Grade 5	-

Blurred vision

CTCAE - SOC	Eye disorders
CTCAE Term	Blurred vision
Definition	A disorder characterized by visual perception of unclear or fuzzy images.
Grade 1	Intervention not indicated
Grade 2	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL
Grade 3	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL
Grade 4	Best corrected visual acuity of 20/200 or worse in the affected eye
Grade 5	-

Flashing lights

CTCAE - SOC	Eye disorders
CTCAE Term	Flashing lights
Definition	A disorder characterized by a sudden or brief burst of light.
Grade 1	Symptomatic but not limiting ADL
Grade 2	Limiting instrumental ADL
Grade 3	Limiting self-care ADL
Grade 4	-
Grade 5	-

Watery eyes

CTCAE - SOC	Eye disorders
CTCAE Term	Watering eyes
Definition	A disorder characterized by excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct.

Grade 1	Intervention not indicated
Grade 2	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)
Grade 3	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)
Grade 4	Best corrected visual acuity of 20/200 or worse in the affected eye
Grade 5	-

Ringing in ears

CTCAE - SOC	Ear and labyrinth disorders
CTCAE Term	Tinnitus
Definition	A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.
Grade 1	Mild symptoms: intervention not indicated
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

Dry eyes

CTCAE - SOC	Eye disorders
CTCAE Term	Dry eye
Definition	A disorder characterized by dryness of the cornea and conjunctiva.
Grade 1	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants
Grade 2	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)
Grade 3	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL
Grade 4	-
Grade 5	-

Concentration

CTCAE - SOC	Nervous system disorders

CTCAE Term	Concentration impairment
Definition	A disorder characterized by a deterioration in the ability to concentrate.
Grade 1	Mild inattention or decreased level of concentration
Grade 2	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL
Grade 3	Severe impairment in attention or decreased level of concentration; limiting self-care ADL
Grade 4	-
Grade 5	-

Memory

CTCAE - SOC	Nervous system disorders
CTCAE Term	Memory impairment
Definition	A disorder characterized by a deterioration in memory function.
Grade 1	Memory impairment
Grade 2	Mild memory impairment
Grade 3	Moderate memory impairment; limiting instrumental ADL
Grade 4	Severe memory impairment; limiting self-care ADL
Grade 5	-

General pain

CTCAE - SOC	
CTCAE Term	Pain
Definition	A disorder characterized by the sensation of marked discomfort, distress or agony.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Headache

CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Muscle pain

CTCAE - SOC	Musculoskeletal and connective tissue disorders
CTCAE Term	Myalgia
Definition	A disorder characterized by marked discomfort sensation originating from a muscle or group of muscles.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Joint pain

CTCAE - SOC	Musculoskeletal and connective tissue disorders
CTCAE Term	Arthralgia
Definition	A disorder characterized by a sensation of marked discomfort in a joint.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-

Grade 5	-

Insomnia

CTCAE - SOC	Psychiatric disorders
CTCAE Term	Insomnia
Definition	A disorder characterized by difficulty in falling asleep and/or remaining asleep.
Grade 1	Mild difficulty falling asleep, staying asleep or waking up early
Grade 2	Moderate difficulty falling asleep, staying asleep or waking up early
Grade 3	Severe difficulty in falling asleep, staying asleep or waking up early
Grade 4	-
Grade 5	-

Fatigue

CTCAE - CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Fatigue
Definition	A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.
Grade 1	Fatigue relieved by rest
Grade 2	Fatigue not relieved by rest, limiting instrumental ADL
Grade 3	Fatigue not relieved by rest, limiting self-care ADL
Grade 4	-
Grade 5	-

Anxious

CTCAE - SOC	Psychiatric disorders
CTCAE Term	Anxiety
Definition	A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.
Grade 1	Mild symptoms: intervention not indicated

Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL; hospitalization indicated
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	-

Sad

CTCAE - SOC	Psychiatric disorders
CTCAE Term	Depression
Definition	A disorder characterized by melancholic feelings of grief or unhappiness.
Grade 1	Mild depressive symptoms
Grade 2	Moderate depressive symptoms; limiting instrumental ADL
Grade 3	Severe depressive symptoms; limiting self-care ADL; hospitalization not indicated
Grade 4	Life-threatening consequences, threats of harm to self or others; hospitalization indicated
Grade 5	Death

Suicidal ideation

CTCAE - SOC	Psychiatric disorders
CTCAE Term	Suicidal ideation
Definition	A disorder characterized by thoughts of taking one's own life.
Grade 1	Increased thoughts of death but no wish to kill oneself
Grade 2	Suicidal ideation with no specific plan or intent
Grade 3	Specific plan to commit suicide without serious intent to die which may not require hospitalization
Grade 4	Specific plan to commit suicide with serious intent to die which requires hospitalization
Grade 5	-

Painful urination

CTCAE - SOC	Renal and urinary disorders
CTCAE Term	Dysuria
Definition	A disorder characterized by painful urination.

Grade 1	Present
Grade 2	-
Grade 3	-
Grade 4	-
Grade 5	-

Urinary urgency

CTCAE - SOC	Renal and urinary disorders
CTCAE Term	Urinary urgency
Definition	A disorder characterized by a sudden compelling urge to urinate.
Grade 1	Present
Grade 2	Limiting instrumental ADL; medical management indicated
Grade 3	-
Grade 4	-
Grade 5	-

Urinary frequency

CTCAE - SOC	Renal and urinary disorders
CTCAE Term	Urinary frequency
Definition	A disorder characterized by urination at short intervals.
Grade 1	Present
Grade 2	Limiting instrumental ADL; medical management indicated
Grade 3	-
Grade 4	-
Grade 5	-

Change in usual urine colour

CTCAE - SOC	Renal and urinary disorders
CTCAE Term	Urine discoloration

Definition	A disorder characterized by a change in the colour of the urine.
Grade 1	Present
Grade 2	-
Grade 3	-
Grade 4	-
Grade 5	-

Urinary incontinence

CTCAE - SOC	Renal and urinary disorders
CTCAE Term	Urinary incontinence
Definition	A disorder characterized by inability to control the flow of urine from the bladder.
Grade 1	Occasional (i.e., with coughing, sneezing, etc.), pads not indicated
Grade 2	Spontaneous; pads indicated; limiting instrumental ADL
Grade 3	Intervention indicated (i.e., clamp, collagen injections); operative intervention indicated; limiting self-care ADL
Grade 4	-
Grade 5	-

Bruising

CTCAE - SOC	Injury, poisoning and procedural complications
CTCAE Term	Bruising
Definition	A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.
Grade 1	Localized or in a dependent area
Grade 2	Generalized
Grade 3	-
Grade 4	-
Grade 5	-

Chills

CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Chills
Definition	A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.
Grade 1	Mild sensation of cold; shivering; chattering of teeth
Grade 2	Moderate tremor of the entire body; narcotics indicated
Grade 3	Severe or prolonged, not responsive to narcotics
Grade 4	-
Grade 5	-

Increased sweating

CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Hyperhidrosis
Definition	A disorder characterized by excessive sweating.
Grade 1	Limited to one site (palms, soles, or axillae); self-care interventions
Grade 2	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact
Grade 3	Associated with electrolyte/hemodynamic imbalance Associated with electrolyte/hemodynamic imbalance
Grade 4	-
Grade 5	-

Hot flashes

CTCAE - SOC	Vascular disorders
CTCAE Term	Hot flashes
Definition	A disorder characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied by sweating upon cooling.
Grade 1	Mild symptoms: intervention not indicated
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-

Grade 5	-

Nosebleed

CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Epistaxis
Definition	A disorder characterized by bleeding from the nose.
Grade 1	Mild symptoms: intervention not indicated
Grade 2	Moderate symptoms: medical intervention indicated (i.e., nasal packing, cauterization; topical vasoconstrictors)
Grade 3	Transfusion: invasive intervention indicated (i.e., hemostasis of bleeding site)
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death

Falls

CTCAE - SOC	Injury, poisoning and procedural complications
CTCAE Term	Fall
Definition	A finding of sudden movement downward, usually resulting in injury.
Grade 1	Minor with no resultant injuries; intervention not indicated
Grade 2	Symptomatic; non-invasive intervention indicated
Grade 3	Hospitalization indicated; invasive intervention indicated
Grade 4	-
Grade 5	-

Muscle weakness

CTCAE - SOC	Musculoskeletal and connective tissue disorders
CTCAE Term	Generalized muscle weakness
Definition	A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites.
Grade 1	Symptomatic; perceived by patient but not evident on physical exam
Grade 2	Symptomatic; evident on physical exam; limiting instrumental ADL
Grade 3	Limiting self-care ADL

Grade 4	-
Grade 5	-

Restlessness

CTCAE - SOC	Psychiatric disorders
CTCAE Term	Restlessness
Definition	A disorder characterized by an inability to rest, relax or be still.
Grade 1	Mild symptoms: intervention not indicated
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care AD
Grade 4	-
Grade 5	-

Appendix B: Pharmacist Lead CTCAE grading of any symptoms attributable to prescribed PGx actionable drugs.

Omeprazole

White blood cell decreased

Drug	Omeprazole
CTCAE - SOC	Investigations
CTCAE Term	White blood cell decreased
Definition	A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.
Grade 1	<LLN -3000/mm3;<LLN – 3.0 x 10e9/L
Grade 2	<3000-2000/mm3; <3.0 -2.0 x10e9/L
Grade 3	<2000-1000/mm3;<2.0 -1.0 x10e9/L
Grade 4	<1000/mm3; <1.0 x10e9/L
Grade 5	-

Define	White blood cell count

Platelet count decreased

Drug	Omeprazole
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased
Definition	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Grade 1	<LLN -75,000/mm3;<LLN – 75.0 x10e9/L
Grade 2	<75,000-50,000/mm3;<75.0-50.0 x10e9/L
Grade 3	<50,000-25,000/mm3;<50.0 – 25.0 x10e9/L
Grade 4	<25,000/mm3; <25/0 x10e9/L
Grade 5	-
Define	Platelet count

Hyponatremia

Drug	Omeprazole
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hyponatremia
Definition	A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.
Grade 1	<LLN -130mmol/L
Grade 2	125-129 mmol/L and asymptomatic
Grade 3	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Grade 4	<120 mmol/L; life-threatening consequences

Grade 5	Death
Define	Sodium concentration

Insomnia

Drug	Omeprazole
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Insomnia
Definition	A disorder characterized by difficulty in falling asleep and/or remaining asleep.
Grade 1	Mild difficulty falling asleep, staying asleep or waking up early
Grade 2	Moderate difficulty falling asleep, staying asleep or waking up early
Grade 3	Severe difficulty in falling asleep, staying asleep or waking up early
Grade 4	-
Grade 5	-

Hallucinations

Drug	Omeprazole
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Hallucinations
Definition	A disorder characterized by a false sensory perception in the absence of an external stimulus.
Grade 1	Mild hallucinations (i.e., perceptual distortions)
Grade 2	Moderate hallucinations
Grade 3	Severe hallucinations: hospitalization not indicated
Grade 4	Life-threatening consequences, threats of harm to self or others; hospitalization indicated

Grade 5	Death

Confusion

Drug	Omeprazole
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Confusion
Definition	A disorder characterized by a lack of clear and orderly thought and behaviour.
Grade 1	Mild disorientation
Grade 2	Moderate disorientation; limiting instrumental ADL
Grade 3	Severe disorientation; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	-

Headache

Drug	Omeprazole
CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Bronchospasm

Drug	Omeprazole
CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Bronchospasm
Definition	A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL
Grade 3	Limiting self-care ADL; supplemental oxygen indicated
Grade 4	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Grade 5	Death

Abdominal pain

Drug	Omeprazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Abdominal pain
Definition	A disorder characterized by a sensation of marked discomfort in the abdominal region.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Constipation

Drug	Omeprazole

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Constipation
Definition	A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.
Grade 1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema
Grade 2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	Obstipation with manual evacuation indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Diarrhea

Drug	Omeprazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movements.
Grade 1	Increase of <4 stools per day over baseline, mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Nausea

Drug	Omeprazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

Drug	Omeprazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Dry mouth

Drug	Omeprazole

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Dry mouth
Definition	A disorder characterized by reduced salivary flow in the oral cavity.
Grade 1	Symptomatic (i.e., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min
Grade 2	Moderate symptoms; oral intake alterations (i.e., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min
Grade 3	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1mL/min
Grade 4	-
Grade 5	-

Blood bilirubin increased

Drug	Omeprazole
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased
Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-

Define	Bilirubin level

Aspartate aminotransferase increased

Drug	Omeprazole
CTCAE - SOC	Investigations
CTCAE Term	Aspartate aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	AST or SGOT level

GGT increased

Drug	Omeprazole
CTCAE - SOC	Investigations
CTCAE Term	GGT increased
Definition	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gammaglutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal

Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	GGT level

Alanine aminotransferase increased

Drug	Omeprazole
CTCAE - SOC	Investigations
CTCAE Term	Alanine aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	ALT or SGPT level

Rash

Drug	Omeprazole
Contents	Skin and subcutaneous tissue disorders
CTCAE Term	Rash (Skin and subcutaneous tissue disorders - Other, specify)

Definition	Skin and subcutaneous tissue disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Photosensitivity

Drug	Omeprazole
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Photosensitivity
Definition	A disorder characterized by fear and avoidance of light.
Grade 1	Painless erythema and erythema covering <10% BSA
Grade 2	Tender erythema covering 10 - 30% BSA
Grade 3	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (i.e., narcotics or NSAIDs)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Erythema multiforme

Drug	Omeprazole
CTCAE - SOC	Skin and subcutaneous tissue disorders

CTCAE Term	Erythema multiforme
Definition	A disorder characterized by target lesions (a pink-red ring around a pale center).
Grade 1	Target lesions covering <10% BSA and not associated with skin tenderness
Grade 2	Target lesions covering 10 - 30% BSA and associated with skin tenderness
Grade 3	Target lesions covering >30% BSA and associated with oral or genital erosions
Grade 4	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated
Grade 5	Death

Stevens-Johnson syndrome

Drug	Omeprazole
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Stevens-Johnson syndrome
Definition	A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.
Grade 1	-
Grade 2	-
Grade 3	Skin sloughing covering <10% BSA with associated signs (i.e., erythema, purpura, epidermal detachment, and mucous membrane detachment)
Grade 4	Skin sloughing covering 10 - 30% BSA with associated signs (i.e., erythema, purpura, epidermal detachment and mucous membrane detachment)
Grade 5	Death

Muscle weakness

Drug	Omeprazole
CTCAE - SOC	Musculoskeletal and connective tissue disorders

CTCAE Term	Generalized muscle weakness
Definition	A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites.
Grade 1	Symptomatic; perceived by patient but not evident on physical exam
Grade 2	Symptomatic; evident on physical exam; limiting instrumental ADL
Grade 3	Limiting self-care ADL
Grade 4	-
Grade 5	-
Define	Limb/area (if acute)

Pantoprazole

Hypertension

Drug	Pantoprazole
CTCAE - SOC	Vascular disorders
CTCAE Term	Hypertension
Definition	Hypertension
Grade 1	Pediatric: Systolic/diastolic BP >90th percentile but< 95th percentile; Adolescent: BP ≥120/80 even if < 95th percentile
Grade 2	Pediatric and adolescent: Recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated; systolic and /or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile; Adolescent: Systolic between 130-139 or diastolic between 80-89 even if < 95th percentile
Grade 3	Pediatric and adolescent: Systolic and/or diastolic > 5 mmHg above the 99th percentile
Grade 4	Adult and Pediatric: Life threatening consequences (i.e., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
Grade 5	Death

Define	Blood pressure (BP)

Headache

Drug	Pantoprazole
CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Dysgeusia

Drug	Pantoprazole
CTCAE - SOC	Nervous system disorders
CTCAE Term	Dysgeusia
Definition	A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.
Grade 1	Altered taste but no change in diet
Grade 2	Altered taste with change in diet (i.e., oral supplements); noxious or unpleasant taste; loss of taste
Grade 3	-
Grade 4	-
Grade 5	-

Constipation

Drug	Pantoprazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Constipation
Definition	A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.
Grade 1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema
Grade 2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	Obstipation with manual evacuation indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Diarrhea

Drug	Pantoprazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movement
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated

Grade 5	Death

Nausea

Drug	Pantoprazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

Drug	Pantoprazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Dry mouth

Drug	Pantoprazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Dry mouth
Definition	A disorder characterized by reduced salivary flow in the oral cavity.
Grade 1	Symptomatic (i.e., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min
Grade 2	Moderate symptoms; oral intake alterations (i.e., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min
Grade 3	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1mL/min
Grade 4	-
Grade 5	-

Tinnitus

Drug	Pantoprazole
CTCAE - SOC	Ear and labyrinth disorders
CTCAE Term	Tinnitus
Definition	A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

Blood bilirubin increased

Drug	Pantoprazole
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased
Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Aspartate aminotransferase increased

Drug	Pantoprazole
CTCAE - SOC	Investigations
CTCAE Term	Aspartate aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal

Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	AST or SGOT level

GGT increased

Drug	Pantoprazole
CTCAE - SOC	Investigations
CTCAE Term	GGT increased
Definition	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gammaglutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	GGT level

Alanine aminotransferase increased

Drug	Pantoprazole

CTCAE - SOC	Investigations
CTCAE Term	Alanine aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	ALT or SGPT level

Hyperlidemia

Drug	Pantoprazole
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hyperlipidemia
Definition	A disorder characterized by laboratory test results that indicate an elevation in the concentration of lipids in blood.
Grade 1	Requiring diet changes
Grade 2	Requiring pharmaceutical intervention
Grade 3	Hospitalization; pancreatitis
Grade 4	Life-threatening consequences
Grade 5	-

Define	Triglyceride, cholesterol level

Hyponatremia

Drug	Pantoprazole
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hyponatremia
Definition	A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.
Grade 1	<LLN -130mmol/L
Grade 2	125-129 mmol/L and asymptomatic
Grade 3	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Grade 4	<120 mmol/L; life-threatening consequences
Grade 5	Death
Define	Sodium concentration

Hypomagnesemia

Drug	Pantoprazole
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hypomagnesemia
Definition	A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood.
Grade 1	<LLN -1.2 mg/dL; <LLN -0.5 mmol/L
Grade 2	<1.2 -0.9 mg/dL; <0.5-0.4 mmol/L
Grade 3	<0.9 -0.7 mg/dL; <0.4 -0.3 mmol/L
Grade 4	<0.7 mg/dL; <0.3 mmol; life- threatening consequences

Grade 5	Death
Define	Magnesium concentration

Anemia

Drug	Pantoprazole
CTCAE - SOC	Blood and lymphatic system disorders
CTCAE Term	Anemia
Definition	A disorder characterized by a reduction in the amount of hemoglobin in 100 mL of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.
Grade 1	Hemoglobin (Hgb) <LLN – 10.0 g/dL; <LLN -6.2mmol/L; <LLN – 100g/L
Grade 2	Hgb <10.0 -8.0 g/dL; <6.2 – 4.9 mmol/L <100 -80g/L
Grade 3	Hgb <8.0 g/dL; <4.9 mmol/L <80 g/L; transfusion indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death
Define	Hemoglobin (Hgb)

White blood cell decreased

Drug	Pantoprazole
CTCAE - SOC	Investigations
CTCAE Term	White blood cell decreased
Definition	A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.
Grade 1	<LLN -3000/mm3;<LLN – 3.0 x 10e9/L
Grade 2	<3000-2000/mm3; <3.0 -2.0 x10e9/L

Grade 3	<2000-1000/mm3;<2.0 -1.0 x10e9/L
Grade 4	<1000/mm3; <1.0 x10e9/L
Grade 5	-
Define	White blood cell count

Platelet count decreased

Drug	Pantoprazole
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased
Definition	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Grade 1	<LLN -75,000/mm3;<LLN – 75.0 x10e9/L
Grade 2	<75,000-50,000/mm3;<75.0-50.0 x10e9/L
Grade 3	<50,000-25,000/mm3;<50.0 – 25.0 x10e9/L
Grade 4	<25,000/mm3; <25/0 x10e9/L
Grade 5	-
Define	Platelet count

Rash

Drug	Pantoprazole
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Rash (Skin and subcutaneous tissue disorders - Other, specify)
Definition	Skin and subcutaneous tissue disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Blurred vision

Drug	Pantoprazole
CTCAE - SOC	Eye disorders
CTCAE Term	Blurred vision
Definition	A disorder characterized by visual perception of unclear or fuzzy images.
Grade 1	Intervention not indicated
Grade 2	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL
Grade 3	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL
Grade 4	Best corrected visual acuity of 20/200 or worse in the affected eye
Grade 5	-

Voriconazole

White blood cell decreased

Drug	Voriconazole
CTCAE - SOC	Investigations

CTCAE Term	White blood cell decreased
Definition	A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.
Grade 1	<LLN -3000/mm3;<LLN – 3.0 x 10e9/L
Grade 2	<3000-2000/mm3; <3.0 -2.0 x10e9/L
Grade 3	<2000-1000/mm3;<2.0 -1.0 x10e9/L
Grade 4	<1000/mm3; <1.0 x10e9/L
Grade 5	-
Define	White blood cell count

Platelet count decreased

Drug	Voriconazole
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased
Definition	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Grade 1	<LLN -75,000/mm3;<LLN – 75.0 x10e9/L
Grade 2	<75,000-50,000/mm3;<75.0-50.0 x10e9/L
Grade 3	<50,000-25,000/mm3;<50.0 – 25.0 x10e9/L
Grade 4	<25,000/mm3; <25/0 x10e9/L
Grade 5	-
Define	Platelet count

Anemia

Drug	Voriconazole

CTCAE - SOC	Blood and lymphatic system disorders
CTCAE Term	Anemia
Definition	A disorder characterized by a reduction in the amount of hemoglobin in 100 mL of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.
Grade 1	Hemoglobin (Hgb) <LLN – 10.0 g/dL; <LLN -6.2mmol/L; <LLN – 100g/L
Grade 2	Hgb <10.0 -8.0 g/dL; <6.2 – 4.9 mmol/L <100 -80g/L
Grade 3	Hgb <8.0 g/dL; <4.9 mmol/L <80 g/L; transfusion indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death
Define	Hemoglobin (Hgb)

Eosinophilia

Drug	Voriconazole
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased
Definition	A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood.
Grade 1	>ULN and >Baseline
Grade 2	-
Grade 3	Steroids initiated
Grade 4	-
Grade 5	-
Define	Eosinophil count

Hypothyroidism

Drug	Voriconazole
CTCAE - SOC	Endocrine disorders
CTCAE Term	Hypothyroidism
Definition	A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Symptomatic; thyroid replacement indicated; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL; hospitalization indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Hyperthyroidism

Drug	Voriconazole
CTCAE - SOC	Endocrine disorders
CTCAE Term	Hyperthyroidism
Definition	A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL; hospitalization indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Hypoglycaemia

Drug	Voriconazole
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hypoglycemia
Definition	A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.
Grade 1	<LLN -55 mg/dL; <LLN -3.0 mmol/L
Grade 2	<55-40 mg/dL; <3.0 -2.2 mmol/L
Grade 3	<40-30 mg/dL; <2.2-1.7 mmol/L
Grade 4	<30 mg/dL; <1.7mmol/L; life-threatening consequences; seizures
Grade 5	Death

Define	Glucose concentration

Hyponatremia

Drug	Omeprazole
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hyponatremia
Definition	A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.
Grade 1	<LLN -130mmol/L
Grade 2	125-129 mmol/L and asymptomatic
Grade 3	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Grade 4	<120 mmol/L; life-threatening consequences
Grade 5	Death
Define	Sodium concentration

Hypokalemia

Drug	Voriconazole
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hypokalemia
Definition	A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.
Grade 1	<LLN – 3.0 mmol/L
Grade 2	Symptomatic with <LLN -3.0 mmol/L; intervention indicated
Grade 3	<3.0 -2.5 mmol/L; hospitalization indicated
Grade 4	<2.5 mmol/L; life-threatening consequences

Grade 5	Death
Define	Potassium concentration

Insomnia

Drug	Voriconazole
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Insomnia
Definition	A disorder characterized by difficulty in falling asleep and/or remaining asleep.
Grade 1	Mild difficulty falling asleep, staying asleep or waking up early
Grade 2	Moderate difficulty falling asleep, staying asleep or waking up early
Grade 3	Severe difficulty in falling asleep, staying asleep or waking up early
Grade 4	-
Grade 5	-

Confusion

Drug	Voriconazole
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Confusion
Definition	A disorder characterized by a lack of clear and orderly thought and behavior.
Grade 1	Mild disorientation
Grade 2	Moderate disorientation; limiting instrumental ADL
Grade 3	Severe disorientation; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	-

Headache

Drug	Voriconazole
CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Tremor

Drug	Voriconazole
CTCAE - SOC	Nervous system disorders
CTCAE Term	Tremor
Definition	A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.
Grade 1	Mild symptoms
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

Dizziness

Drug	Voriconazole
CTCAE - SOC	Nervous system disorders
CTCAE Term	Dizziness
Definition	A disorder characterized by a disturbing sensation of light-headedness, unsteadiness, giddiness, spinning or rocking.
Grade 1	Mild unsteadiness or sensation of movement
Grade 2	Moderate unsteadiness or sensation of movement; limiting instrumental ADL
Grade 3	Severe unsteadiness or sensation of movement; limiting self-care ADL
Grade 4	-
Grade 5	-

Seizure

Drug	Voriconazole
CTCAE - SOC	Nervous system disorders
CTCAE Term	Seizure
Definition	A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.
Grade 1	Brief partial seizure and no loss of consciousness
Grade 2	Brief generalized seizure
Grade 3	New onset seizures (partial or generalized); multiple seizures despite medical intervention
Grade 4	Life-threatening consequences; prolonged repetitive seizures
Grade 5	Death

Peripheral neuropathy

Drug	Voriconazole
CTCAE - SOC	Nervous system disorders
CTCAE Term	Peripheral sensory neuropathy
Definition	A disorder characterized by damage or dysfunction of the peripheral sensory nerves.
Grade 1	Asymptomatic
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	-
Define	Sensory or Motor?

Blurred vision

Drug	Voriconazole
CTCAE - SOC	Eye disorders
CTCAE Term	Blurred vision
Definition	A disorder characterized by visual perception of unclear or fuzzy images.
Grade 1	Intervention not indicated
Grade 2	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL
Grade 3	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL
Grade 4	Best corrected visual acuity of 20/200 or worse in the affected eye
Grade 5	-

Eye Pain

Drug	Voriconazole
CTCAE - SOC	Eye disorders
CTCAE Term	Eye pain
Definition	A disorder characterized by a sensation of marked discomfort in the eye.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Vertigo

Drug	Voriconazole
CTCAE - SOC	Ear and labyrinth disorders
CTCAE Term	Vertigo
Definition	A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).
Grade 1	Mild symptoms
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

Tinnitus

Drug	Voriconazole

CTCAE - SOC	Ear and labyrinth disorders
CTCAE Term	Tinnitus
Definition	A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

Tachycardia

Drug	Voriconazole
CTCAE - SOC	Cardiac disorders
CTCAE Term	Sinus or supraventricular tachycardia
Definition	A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Non-urgent medical intervention indicated
Grade 3	Symptomatic, urgent intervention indicated
Grade 4	Life-threatening consequences
Grade 5	Death
Define	Supraventricular?

Bradycardia

Drug	Voriconazole

CTCAE - SOC	Cardiac disorders
CTCAE Term	Sinus bradycardia
Definition	A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Symptomatic, intervention not indicated; change in medication initiated
Grade 3	Symptomatic, intervention indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Palpitations

Drug	Voriconazole
CTCAE - SOC	Cardiac disorders
CTCAE Term	Palpitations
Definition	A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Intervention indicated
Grade 3	-
Grade 4	-
Grade 5	-

Electrocardiogram QT corrected interval prolonged

Drug	Voriconazole
CTCAE - SOC	Investigations

CTCAE Term	Electrocardiogram QT corrected interval prolonged
Definition	A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.
Grade 1	Average QTc 450 - 480 ms
Grade 2	Average QTc 481 - 500 ms
Grade 3	Average QTc >= 501 ms; >60 ms change from baseline
Grade 4	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia
Grade 5	-
Define	Average QTc

Acute respiratory distress syndrome

Drug	Voriconazole
CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Acute respiratory distress syndrome
Definition	A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.
Grade 1	-
Grade 2	-
Grade 3	Present with radiologic findings; intubation not indicated
Grade 4	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Grade 5	Death

Diarrhea

Drug	Voriconazole

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movement
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Vomiting

Drug	Voriconazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Abdominal pain

Drug	Voriconazole

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Abdominal pain
Definition	A disorder characterized by a sensation of marked discomfort in the abdominal region.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Nausea

Drug	Voriconazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Constipation

Drug	Voriconazole

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Constipation
Definition	A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.
Grade 1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema
Grade 2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	Obstipation with manual evacuation indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Pancreatitis

Drug	Voriconazole
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Pancreatitis
Definition	A disorder characterized by inflammation of the pancreas with no documented pancreas infection.
Grade 1	-
Grade 2	Enzyme elevation; radiologic findings only
Grade 3	Severe pain; vomiting; medical intervention indicated (i.e., analgesia, nutritional support)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Oral pain

Drug	Voriconazole

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Oral pain
Definition	A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Blood bilirubin increased

Drug	Voriconazole
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased
Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Aspartate aminotransferase increased

Drug	Voriconazole
CTCAE - SOC	Investigations
CTCAE Term	Aspartate aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	AST or SGOT level

GGT increased

Drug	Voriconazole
CTCAE - SOC	Investigations
CTCAE Term	GGT increased
Definition	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gammaglutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal

Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	GGT level

Alanine aminotransferase increased

Drug	Voriconazole
CTCAE - SOC	Investigations
CTCAE Term	Alanine aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	ALT or SGPT level

Rash

Drug	Voriconazole
CTCAE - SOC	Skin and subcutaneous tissue disorders

CTCAE Term	Rash (Skin and subcutaneous tissue disorders - Other, specify)
Definition	Skin and subcutaneous tissue disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Stevens-Johnson syndrome

Drug	Voriconazole
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Stevens-Johnson syndrome
Definition	A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.
Grade 1	Target lesions covering <10% BSA and not associated with skin tenderness
Grade 2	Target lesions covering 10 - 30% BSA and associated with skin tenderness
Grade 3	Skin sloughing covering <10% BSA with associated signs (i.e., erythema, purpura, epidermal detachment, and mucous membrane detachment)
Grade 4	Skin sloughing covering 10 - 30% BSA with associated signs (i.e., erythema, purpura, epidermal detachment and mucous membrane detachment)
Grade 5	Death

Photosensitivity

Drug	Voriconazole
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Photosensitivity
Definition	A disorder characterized by an increase in sensitivity of the skin to light.
Grade 1	Painless erythema and erythema covering <10% BSA
Grade 2	Tender erythema covering 10 - 30% BSA
Grade 3	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (i.e., narcotics or NSAIDs)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Back pain

Drug	Voriconazole
CTCAE - SOC	Musculoskeletal and connective tissue disorders
CTCAE Term	Back pain
Definition	A disorder characterized by a sensation of marked discomfort in the back region.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Chronic kidney disease

Drug	Voriconazole

CTCAE - SOC	Renal and urinary disorders
CTCAE Term	Chronic kidney disease
Definition	A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.
Grade 1	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN -60 mL/min/1.73 m2 or proteinuria 2+ present: urine protein/creatinine >0.5
Grade 2	eGFR or CrCl 59 - 30 mL/min/1.73 m2
Grade 3	eGFR or CrCl 29 - 15 mL/min/1.73 m2
Grade 4	eGFR or CrCl < 15 mL/min/1.73 m2; dialysis or renal transplant indicated
Grade 5	Death
Define	Creatinine, GFR, Urea level

Chest pain

Drug	Vorinconazole
CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Non-cardiac chest pain
Definition	A disorder characterized by a sensation of marked discomfort in the chest unrelated to a heart disorder.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-
Define	Related to cardiac event? Y/N and define

Chills

Drug	Vorinconazole
CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Chills
Definition	A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.
Grade 1	Mild sensation of cold; shivering; chattering of teeth
Grade 2	Moderate tremor of the entire body; narcotics indicated
Grade 3	Severe or prolonged, not responsive to narcotics
Grade 4	-
Grade 5	-

Tramadol

Anaphylaxis

Drug	Tramadol
CTCAE - SOC	Immune system disorders
CTCAE Term	Anaphylaxis
Definition	A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.
Grade 1	-
Grade 2	-
Grade 3	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension

Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Blood antidiuretic hormone abnormal

Drug	Tramadol
CTCAE - SOC	Investigations
CTCAE Term	Blood antidiuretic hormone abnormal
Definition	A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Symptomatic; medical intervention indicated
Grade 3	Hospitalization indicated
Grade 4	
Grade 5	
Define	Antidiuretic hormone (ADH) level

Hyponatremia

Drug	Tramadol
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hyponatremia
Definition	A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.
Grade 1	<LLN -130mmol/L
Grade 2	125-129 mmol/L and asymptomatic

Grade 3	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Grade 4	<120 mmol/L; life-threatening consequences
Grade 5	Death
Define	Sodium concentration

Hallucinations

Drug	Tramadol
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Hallucinations
Definition	A disorder characterized by a false sensory perception in the absence of an external stimulus.
Grade 1	Mild hallucinations (i.e., perceptual distortions)
Grade 2	Moderate hallucinations
Grade 3	Severe hallucinations; hospitalization not indicated
Grade 4	Life-threatening consequences, threats of harm to self or others; hospitalization indicated
Grade 5	Death

Confusion

Drug	Tramadol
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Confusion
Definition	A disorder characterized by a lack of clear and orderly thought and behaviour.
Grade 1	Mild disorientation
Grade 2	Moderate disorientation; limiting instrumental ADL

Grade 3	Severe disorientation; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	-

Insomnia

Drug	Tramadol
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Insomnia
Definition	A disorder characterized by difficulty in falling asleep and/or remaining asleep.
Grade 1	Mild difficulty falling asleep, staying asleep or waking up early
Grade 2	Moderate difficulty falling asleep, staying asleep or waking up early
Grade 3	Severe difficulty in falling asleep, staying asleep or waking up early
Grade 4	-
Grade 5	-

Dizziness

Drug	Tramadol
CTCAE - SOC	Nervous system disorders
CTCAE Term	Dizziness
Definition	A disorder characterized by a disturbing sensation of light-headedness, unsteadiness, giddiness, spinning or rocking.
Grade 1	Mild unsteadiness or sensation of movement
Grade 2	Moderate unsteadiness or sensation of movement; limiting instrumental ADL
Grade 3	Severe unsteadiness or sensation of movement; limiting self-care ADL

Grade 4	-
Grade 5	-

Headache

Drug	Tramadol
CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Seizure

Drug	Tramadol
CTCAE - SOC	Nervous system disorders
CTCAE Term	Seizure
Definition	A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.
Grade 1	Brief partial seizure and no loss of consciousness
Grade 2	Brief generalized seizure
Grade 3	New onset seizures (partial or generalized); multiple seizures despite medical intervention

Grade 4	Life-threatening consequences; prolonged repetitive seizures
Grade 5	Death

Blurred vision

Drug	Tramadol
CTCAE - SOC	Eye disorders
CTCAE Term	Blurred vision
Definition	A disorder characterized by visual perception of unclear or fuzzy images.
Grade 1	Intervention not indicated
Grade 2	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL
Grade 3	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL
Grade 4	Best corrected visual acuity of 20/200 or worse in the affected eye
Grade 5	-

Sinus Tachycardia

Drug	Tramadol
CTCAE - SOC	Cardiac disorders
CTCAE Term	Sinus or supraventricular tachycardia
Definition	A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Non-urgent medical intervention indicated

Grade 3	Symptomatic, urgent intervention indicated
Grade 4	Life-threatening consequences
Grade 5	Death
Define	Supraventricular?

Sinus Bradycardia

Drug	Tramadol
CTCAE - SOC	Cardiac disorders
CTCAE Term	Sinus bradycardia
Definition	A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Symptomatic, intervention not indicated; change in medication initiated
Grade 3	Symptomatic, intervention indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Dyspnea

Drug	Tramadol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Dyspnea
Definition	A disorder characterized by an uncomfortable sensation of difficulty breathing.
Grade 1	Shortness of breath with moderate exertion
Grade 2	Shortness of breath with minimal exertion; limiting instrumental ADL
Grade 3	Shortness of breath at rest; limiting self-care ADL

Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Nausea

Drug	Tramadol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

Drug	Tramadol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences

Grade 5	Death

Constipation

Drug	Tramadol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Constipation
Definition	A disorder characterized by irregular and infrequent or difficult evacuation of the bowels
Grade 1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema
Grade 2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	Obstipation with manual evacuation indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Dry mouth

Drug	Tramadol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Dry mouth
Definition	A disorder characterized by reduced salivary flow in the oral cavity.
Grade 1	Symptomatic (i.e., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow > 0.2 mL/min
Grade 2	Moderate symptoms; oral intake alterations (i.e., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min
Grade 3	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1mL/min

Grade 4	-
Grade 5	-

Diarrhea

Drug	Tramadol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movement
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Flatulence

Drug	Tramadol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Flatulence
Definition	A disorder characterized by a discharge of excessive gas from the lower GI tract.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Moderate; persistent; psychosocial sequelae
Grade 3	-

Grade 4	-
Grade 5	-

Blood bilirubin increased

Drug	Tramadol
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased
Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Aspartate aminotransferase increased

Drug	Tramadol
CTCAE - SOC	Investigations
CTCAE Term	Aspartate aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal

Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	AST or SGOT level

GGT increased

Drug	Tramadol
CTCAE - SOC	Investigations
CTCAE Term	GGT increased
Definition	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gammaglutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	GGT level

Alanine aminotransferase increased

Drug	Tramadol
CTCAE - SOC	Investigations
CTCAE Term	Alanine aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	ALT or SGPT level

Dysuria

Drug	Tramadol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Dysuria
Definition	A disorder characterized by painful urination
Grade 1	Present
Grade 2	-
Grade 3	-
Grade 4	-
Grade 5	-

Define	Infection present?

Ondansetron

Anaphylaxis

Drug	Ondansetron
CTCAE - SOC	Immune system disorders
CTCAE Term	Anaphylaxis
Definition	A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.
Grade 1	-
Grade 2	-
Grade 3	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Headache

Drug	Ondansetron
CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain

Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Blurred vision

Drug	Ondansetron
CTCAE - SOC	Eye disorders
CTCAE Term	Blurred vision
Definition	A disorder characterized by visual perception of unclear or fuzzy images.
Grade 1	Intervention not indicated
Grade 2	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL
Grade 3	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL
Grade 4	Best corrected visual acuity of 20/200 or worse in the affected eye
Grade 5	-

Chest pain

Drug	Ondansetron
CTCAE - SOC	Cardiac disorders
CTCAE Term	Chest pain - cardiac

Definition	A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation i.e., angina pectoris.
Grade 1	Mild pain
Grade 2	Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable
Grade 3	Pain at rest; limiting self-care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina
Grade 4	-
Grade 5	-

Ventricular arrythmia

Drug	Ondansetron
CTCAE - SOC	Cardiac disorders
CTCAE Term	Ventricular arrhythmia
Definition	A disorder characterized by a dysrhythmia that originates in the ventricles.
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Non-urgent medical intervention indicated
Grade 3	Urgent intervention indicated
Grade 4	Life-threatening consequences; hemodynamic compromise
Grade 5	Death

Sinus Bradycardia

Drug	Ondansetron
CTCAE - SOC	Cardiac disorders
CTCAE Term	Sinus bradycardia

Definition	A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Symptomatic, intervention not indicated; change in medication initiated
Grade 3	Symptomatic, intervention indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Electrocardiogram QT corrected interval prolonged

Drug	Ondansetron
CTCAE - SOC	Investigations
CTCAE Term	Electrocardiogram QT corrected interval prolonged
Definition	A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.
Grade 1	Average QTc 450 - 480 ms
Grade 2	Average QTc 481 - 500 ms
Grade 3	Average QTc >= 501 ms; >60 ms change from baseline
Grade 4	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia
Grade 5	-
Define	Average QTc

Hypotension

Drug	Ondansetron
CTCAE - SOC	Vascular disorders
CTCAE Term	Hypotension

Definition	A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment.
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Non-urgent medical intervention indicated
Grade 3	Medical intervention indicated; hospitalization indicated
Grade 4	Life-threatening consequences and urgent intervention indicated
Grade 5	Death

Hiccups

Drug	Ondansetron
CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Hiccups
Definition	A disorder characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Moderate symptoms; medical intervention indicated; limiting instrumental ADL
Grade 3	Severe symptoms; interfering with sleep; limiting self-care ADL
Grade 4	-
Grade 5	-

Constipation

Drug	Ondansetron
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Constipation

Definition	A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.
Grade 1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema
Grade 2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	Obstipation with manual evacuation indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Blood bilirubin increased

Drug	Ondansetron
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased
Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Aspartate aminotransferase increased

Drug	Ondansetron

CTCAE - SOC	Investigations
CTCAE Term	Aspartate aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	AST or SGOT level

GGT increased

Drug	Ondansetron
CTCAE - SOC	Investigations
CTCAE Term	GGT increased
Definition	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gammaglutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal

Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	GGT level

Alanine aminotransferase increased

Drug	Ondansetron
CTCAE - SOC	Investigations
CTCAE Term	Alanine aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	ALT or SGPT level

Rash

Drug	Ondansetron
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Rash (Skin and subcutaneous tissue disorders - Other, specify)

Definition	Skin and subcutaneous tissue disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Oxycodone

Nausea

Drug	Oxycodone
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

Drug	Oxycodone

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Constipation

Drug	Oxycodone
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Constipation
Definition	Constipation: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels
Grade 1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema
Grade 2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	Obstipation with manual evacuation indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Abdominal pain

Drug	Oxycodone

CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Abdominal pain
Definition	A disorder characterized by a sensation of marked discomfort in the abdominal region.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Diarrhea

Drug	Oxycodone
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movement
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Bronchospasm

Drug	Oxycodone

CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Bronchospasm
Definition	A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL
Grade 3	Limiting self-care ADL; supplemental oxygen indicated
Grade 4	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Grade 5	Death

Respiratory depression

Drug	Oxycodone
CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Respiratory depression (Respiratory, thoracic and mediastinal disorders - Other, specify)
Definition	Respiratory, thoracic and mediastinal disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Somnolence

Drug	Oxycodone
CTCAE - SOC	Nervous system disorders
CTCAE Term	Drowsiness
Definition	A disorder characterized by characterized by excessive sleepiness and drowsiness.
Grade 1	Mild but more than usual drowsiness or sleepiness
Grade 2	Moderate sedation; limiting instrumental ADL
Grade 3	Obtundation or stupor
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Dizziness

Drug	Oxycodone
CTCAE - SOC	Nervous system disorders
CTCAE Term	Dizziness
Definition	A disorder characterized by a disturbing sensation of light-headedness, unsteadiness, giddiness, spinning or rocking.
Grade 1	Mild unsteadiness or sensation of movement
Grade 2	Moderate unsteadiness or sensation of movement; limiting instrumental ADL
Grade 3	Severe unsteadiness or sensation of movement; limiting self-care ADL
Grade 4	-
Grade 5	-

Headache

Drug	Oxycodone

CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Confusion

Drug	Oxycodone
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Confusion
Definition	A disorder characterized by a lack of clear and orderly thought and behavior.
Grade 1	Mild disorientation
Grade 2	Moderate disorientation; limiting instrumental ADL
Grade 3	Severe disorientation; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	-

Hallucinations

Drug	Oxycodone
CTCAE - SOC	Psychiatric disorders

CTCAE Term	Hallucinations
Definition	A disorder characterized by a false sensory perception in the absence of an external stimulus.
Grade 1	Mild hallucinations (i.e., perceptual distortions)
Grade 2	Moderate hallucinations
Grade 3	Severe hallucinations; hospitalization not indicated
Grade 4	Life-threatening consequences, threats of harm to self or others; hospitalization indicated
Grade 5	Death

Anxiety

Drug	Oxycodone
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Anxiety
Definition	A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL; hospitalization indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	-

Sinus Bradycardia

Drug	Oxycodone
CTCAE - SOC	Cardiac disorders

CTCAE Term	Sinus bradycardia
Definition	A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Symptomatic, intervention not indicated; change in medication initiated
Grade 3	Symptomatic, intervention indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Chest pain

Drug	Oxycodone
CTCAE - SOC	Cardiac disorders
CTCAE Term	Chest pain - cardiac
Definition	A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation i.e., angina pectoris.
Grade 1	Mild pain
Grade 2	Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable
Grade 3	Pain at rest; limiting self-care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina
Grade 4	-
Grade 5	-

Palpitations

Drug	Oxycodone
CTCAE - SOC	Cardiac disorders

CTCAE Term	Palpitations
Definition	A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Intervention indicated
Grade 3	-
Grade 4	-
Grade 5	-

Tacrolimus

Anemia

Drug	Tacrolimus
CTCAE - SOC	Blood and lymphatic system disorders
CTCAE Term	Anemia
Definition	A disorder characterized by a reduction in the amount of hemoglobin in 100 mL of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.
Grade 1	Hemoglobin (Hgb) <LLN – 10.0 g/dL; <LLN -6.2mmol/L; <LLN – 100g/L
Grade 2	Hgb <10.0 -8.0 g/dL; <6.2 – 4.9 mmol/L <100 -80g/L
Grade 3	Hgb <8.0 g/dL; <4.9 mmol/L <80 g/L; transfusion indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death
Define	Hemoglobin (Hgb)

White blood cell decreased

Drug	Tacrolimus
CTCAE - SOC	Investigations
CTCAE Term	White blood cell decreased
Definition	A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.
Grade 1	<LLN -3000/mm3;<LLN – 3.0 x 10e9/L
Grade 2	<3000-2000/mm3; <3.0 -2.0 x10e9/L
Grade 3	<2000-1000/mm3;<2.0 -1.0 x10e9/L
Grade 4	<1000/mm3; <1.0 x10e9/L
Grade 5	-
Define	White blood cell count

Platelet count decreased

Drug	Tacrolimus
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased
Definition	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Grade 1	<LLN -75,000/mm3;<LLN – 75.0 x10e9/L
Grade 2	<75,000-50,000/mm3;<75.0-50.0 x10e9/L
Grade 3	<50,000-25,000/mm3;<50.0 – 25.0 x10e9/L
Grade 4	<25,000/mm3; <25/0 x10e9/L
Grade 5	-
Define	Platelet count

Neutrophil count decreased

Drug	Tacrolimus
CTCAE - SOC	Investigations
CTCAE Term	Neutrophil count decreased
Definition	A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.
Grade 1	<LLN - 1500/mm3;<LLN – 1.5 x10e9/L
Grade 2	<1500-1000/mm3;<1.5-1.0 x10e9/L
Grade 3	<1000-500/mm3; <1.0 -0.5 x 10e9/L
Grade 4	<500/mm3; <0.5 x10e9/L
Grade 5	-
Define	Neutrophil count

Anaphylaxis

Drug	Tacrolimus
CTCAE - SOC	Immune system disorders
CTCAE Term	Anaphylaxis
Definition	A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.
Grade 1	-
Grade 2	-
Grade 3	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension

Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Hirsutism

Drug	Tacrolimus
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Hirsutism
Definition	A disorder characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen).
Grade 1	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair
Grade 2	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact
Grade 3	-
Grade 4	-
Grade 5	-

Hyperglycemia

Drug	Tacrolimus
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hyperglycemia
Definition	A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.

Grade 1	Abnormal glucose above baseline with no medical intervention
Grade 2	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes
Grade 3	Insulin therapy initiated; hospitalization indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death
Define	Glucose concentration

Hyperkalemia

Drug	Tacrolimus
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hyperkalemia
Definition	A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.
Grade 1	>ULN - 5.5 mmol/L
Grade 2	>5.5 - 6.0 mmol/L; intervention initiated
Grade 3	>6.0 - 7.0 mmol/L; hospitalization indicated
Grade 4	>7.0 mmol/L; life-threatening consequences
Grade 5	Death
Define	Potassium concentration

Hypermagnesemia

Drug	Tacrolimus
CTCAE - SOC	Metabolism and nutrition disorders

CTCAE Term	Hypermagnesemia
Definition	A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.
Grade 1	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L
Grade 2	-
Grade 3	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L
Grade 4	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
Grade 5	Death
Define	Magnesium concentration

Hypophosphatemia

Drug	Tacrolimus
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hypophosphatemia
Definition	A disorder characterized by laboratory test results that indicate an elevation in the concentration of phosphate in a blood
Grade 1	Laboratory finding only and intervention not indicated
Grade 2	Oral replacement therapy indicated
Grade 3	Severe or medically significant but not immediately lifethreatening; hospitalization or prolongation of existing hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death
Define	Phosphate concentration

Hypocalcaemia

Drug	Tacrolimus

CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hypocalcaemia
Definition	A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood
Grade 1	Corrected serum calcium of <LLN – 8.0 mg/dL; LLN – 2.0 mmol/L; Ionized calcium <LLN – 1.0 mmol/L
Grade 2	Corrected serum calcium of <8.0 -7.0 mg/dL; <2.0 -1.75 mmol/L; Ionized calcium <1.0 -0.9 mmol/L; symptomatic
Grade 3	Corrected serum calcium of <7.0 6.0 mg/dL; <1.75 -1.5 mmol/L; Ionized calcium <0.9 -0.8 mmol/L; hospitalisation indicated
Grade 4	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences
Grade 5	Death
Define	Calcium concentration

Hypertriglyceridemia

Drug	Tacrolimus
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hypertriglyceridemia
Definition	A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.
Grade 1	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L
Grade 2	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L
Grade 3	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L
Grade 4	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences
Grade 5	Death

Define	Triglyceride concentration

Insomnia

Drug	Tacrolimus
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Insomnia
Definition	A disorder characterized by difficulty in falling asleep and/or remaining asleep.
Grade 1	Mild difficulty falling asleep, staying asleep or waking up early
Grade 2	Moderate difficulty falling asleep, staying asleep or waking up early
Grade 3	Severe difficulty in falling asleep, staying asleep or waking up early
Grade 4	-
Grade 5	-

Tremor

Drug	Tacrolimus
Contents	Nervous system disorders
CTCAE Term	Tremor
Definition	A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.
Grade 1	Mild symptoms
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

Headache

Drug	Tacrolimus
CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Peripheral neuropathy

Drug	Tacrolimus
CTCAE - SOC	Nervous system disorders
CTCAE Term	Peripheral sensory neuropathy
Definition	A disorder characterized by damage or dysfunction of the peripheral sensory nerves.
Grade 1	Asymptomatic
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	-
Define	Sensory or Motor?

Intercranial haemorrhage

Drug	Tacrolimus
CTCAE - SOC	Nervous system disorders
CTCAE Term	Intracranial hemorrhage
Definition	A disorder characterized by damage or dysfunction of the peripheral sensory nerves.
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate symptoms; intervention indicated
Grade 3	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or invasive intervention indicated; hospitalization
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Encephalopathy

Drug	Tacrolimus
CTCAE - SOC	Nervous system disorders
CTCAE Term	Encephalopathy
Definition	A disorder characterized by a pathologic process involving the brain.
Grade 1	Mild symptoms
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Hypertonia

Drug	Tacrolimus
CTCAE - SOC	Nervous system disorders
CTCAE Term	Hypertonia (Musculoskeletal and connective tissue disorder - Other, specify)
Definition	Musculoskeletal and connective tissue disorder - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Myasthenia

Drug	Tacrolimus
CTCAE - SOC	Nervous system disorders
CTCAE Term	Myasthenia gravis
Definition	A disorder characterized by weakness and rapid fatigue of any of the skeletal muscles.
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated

Grade 5	Death

Blurred vision

Drug	Tacrolimus
CTCAE - SOC	Eye disorders
CTCAE Term	Blurred vision
Definition	A disorder characterized by visual perception of unclear or fuzzy images.
Grade 1	Intervention not indicated
Grade 2	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL
Grade 3	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL
Grade 4	Best corrected visual acuity of 20/200 or worse in the affected eye
Grade 5	-

Tachycardia

Drug	Tacrolimus
CTCAE - SOC	Cardiac disorders
CTCAE Term	Sinus tachycardia
Definition	A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.
Grade 1	Asymptomatic, intervention not indicated
Grade 2	Symptomatic; non-urgent medical intervention indicated
Grade 3	Urgent medical intervention indicated

Grade 4	-
Grade 5	-

Heart failure

Drug	Tacrolimus
CTCAE - SOC	Cardiac disorders
CTCAE Term	Heart failure
Definition	A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure. Navigational Note: If left sided use Cardiac disorders: Left ventricular systolic dysfunction; also consider Cardiac disorders: Restrictive cardiomyopathy, Investigations: Ejection fraction decreased.
Grade 1	Asymptomatic with laboratory (i.e., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities
Grade 2	Symptoms with moderate activity or exertion
Grade 3	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms
Grade 4	Life-threatening consequences; urgent intervention indicated (i.e., continuous IV therapy or mechanical hemodynamic support)
Grade 5	Death

Restrictive cardiomyopathy

Drug	Tacrolimus
CTCAE - SOC	Cardiac disorders
CTCAE Term	Restrictive cardiomyopathy
Definition	A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility.

Grade 1	Imaging findings only
Grade 2	Symptomatic without signs of heart failure
Grade 3	Symptomatic heart failure or other cardiac symptoms, responsive to intervention; new onset of symptoms
Grade 4	Refractory heart failure or other poorly controlled cardiac symptoms
Grade 5	Death

Palpitations

Drug	Tacrolimus
CTCAE - SOC	Cardiac disorders
CTCAE Term	Palpitations
Definition	A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Intervention indicated
Grade 3	-
Grade 4	-
Grade 5	-

Electrocardiogram QT corrected interval prolonged

Drug	Tacrolimus
CTCAE - SOC	Investigations
CTCAE Term	Electrocardiogram QT corrected interval prolonged
Definition	A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.
Grade 1	Average QTc 450 - 480 ms

Grade 2	Average QTc 481 - 500 ms
Grade 3	Average QTc >= 501 ms; >60 ms change from baseline
Grade 4	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia
Grade 5	-

Dyspnea

Drug	Tacrolimus
CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Dyspnea
Definition	A disorder characterized by an uncomfortable sensation of difficulty breathing.
Grade 1	Shortness of breath with moderate exertion
Grade 2	Shortness of breath with minimal exertion; limiting instrumental ADL
Grade 3	Shortness of breath at rest; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Cough

Drug	Tacrolimus
CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Cough
Definition	A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.
Grade 1	Mild symptoms; non-prescription intervention indicated

Grade 2	Moderate symptoms, medical intervention indicated; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	-
Grade 5	-

Diarrhea

Drug	Tacrolimus
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movement
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Nausea

Drug	Tacrolimus
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits

Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

Drug	Tacrolimus
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Constipation

Drug	Tacrolimus
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Constipation
Definition	A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.
Grade 1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema

Grade 2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	Obstipation with manual evacuation indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Flatulence

Drug	Tacrolimus
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Flatulence
Definition	A disorder characterized by a discharge of excessive gas from the lower GI tract.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Moderate; persistent; psychosocial sequelae
Grade 3	-
Grade 4	-
Grade 5	-

Pancreatitis

Drug	Tacrolimus
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Pancreatitis
Definition	A disorder characterized by inflammation of the pancreas with no documented pancreas infection.
Grade 1	-
Grade 2	Enzyme elevation; radiologic findings only

Grade 3	Severe pain; vomiting; medical intervention indicated (i.e., analgesia, nutritional support)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Blood bilirubin increased

Drug	Tacrolimus
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased
Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Aspartate aminotransferase increased

Drug	Tacrolimus
CTCAE - SOC	Investigations
CTCAE Term	Aspartate aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.

Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	AST or SGOT level

GGT increased

Drug	Tacrolimus
CTCAE - SOC	Investigations
CTCAE Term	GGT increased
Definition	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gammaglutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	GGT level

Alanine aminotransferase increased

Drug	Tacrolimus
CTCAE - SOC	Investigations
CTCAE Term	Alanine aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	ALT or SGPT level

Rash

Drug	Tacrolimus
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Rash (Skin and subcutaneous tissue disorders - Other, specify)
Definition	Skin and subcutaneous tissue disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL

Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Chronic kidney disease

Drug	Tacrolimus
CTCAE - SOC	Renal and urinary disorders
CTCAE Term	Chronic kidney disease
Definition	A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.
Grade 1	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN -60 mL/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5
Grade 2	eGFR or CrCl 59 - 30 mL/min/1.73 m2
Grade 3	eGFR or CrCl 29 - 15 mL/min/1.73 m2
Grade 4	eGFR or CrCl < 15 mL/min/1.73 m2; dialysis or renal transplant indicated
Grade 5	Death
Define	Creatinine, GFR, Urea

Fever

Drug	Tacrolimus
CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Fever
Definition	A disorder characterized by elevation of the body's temperature above the upper limit of normal.

Grade 1	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)
Grade 2	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)
Grade 3	>40.0 degrees C (>104.0 degrees F) for <=24 hrs
Grade 4	>40.0 degrees C (>104.0 degrees F) for >24 hrs
Grade 5	Death

Febrile neutropenia

Drug	Tacrolimus
CTCAE - SOC	Blood and lymphatic system disorders
CTCAE Term	Febrile neutropenia
Definition	A disorder characterized by an ANC 38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour
Grade 1	-
Grade 2	-
Grade 3	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Generalised edema

Drug	Tacrolimus
CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Generalised edema

Definition	A disorder characterized by fluid accumulation in the tissues of the body including the skin
Grade 1	Noted on exam; 1+ pitting edema
Grade 2	Interfering with instrumental ADLs; oral therapy initiated
Grade 3	Interferes with self-care ADL; intravenous therapy indicated; skin breakdown
Grade 4	Life-threatening consequences
Grade 5	-
Define	Limb (if acute)

Rasburicase

Fever

Drug	Rasburicase
CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Fever
Definition	A disorder characterized by elevation of the body's temperature above the upper limit of normal.
Grade 1	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)
Grade 2	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)
Grade 3	>40.0 degrees C (>104.0 degrees F) for <=24 hrs
Grade 4	>40.0 degrees C (>104.0 degrees F) for >24 hrs
Grade 5	Death

Vomiting

Drug	Rasburicase
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Nausea

Drug	Rasburicase
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Diarrhea

Drug	Rasburicase
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movement
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Headache

Drug	Rasburicase
CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Seizure

Drug	Rasburicase
CTCAE - SOC	Nervous system disorders
CTCAE Term	Seizure
Definition	A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin
Grade 1	Brief partial seizure and no loss of consciousness
Grade 2	Brief generalized seizure
Grade 3	New onset seizures (partial or generalized); multiple seizures despite medical intervention
Grade 4	Life-threatening consequences; prolonged repetitive seizures
Grade 5	Death

Hemolysis

Drug	Rasburicase
CTCAE - SOC	Blood and lymphatic system disorders
CTCAE Term	Hemolysis
Definition	A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.
Grade 1	Laboratory evidence of hemolysis only (i.e., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin
Grade 2	Evidence of hemolysis and >=2 g decrease in hemoglobin
Grade 3	Transfusion or medical intervention indicated (i.e., steroids)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Rash

Drug	Rasburicase
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Rash (Skin and subcutaneous tissue disorders - Other, specify)
Definition	Skin and subcutaneous tissue disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Bronchospasm

Drug	Rasburicase
CTCAE - SOC	Respiratory, thoracic and mediastinal disorders
CTCAE Term	Bronchospasm
Definition	A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.
Grade 1	Mild symptoms; intervention not indicated
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL
Grade 3	Limiting self-care ADL; supplemental oxygen indicated
Grade 4	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Grade 5	Death

Allopurinol

Rash

Drug	Allopurinol
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Rash (Skin and subcutaneous tissue disorders - Other, specify)
Definition	Skin and subcutaneous tissue disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL

Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Photosensitivity

Drug	Allopurinol
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Photosensitivity
Definition	A disorder characterized by an increase in sensitivity of the skin to light.
Grade 1	Painless erythema and erythema covering <10% BSA
Grade 2	Tender erythema covering 10 - 30% BSA
Grade 3	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (i.e., narcotics or NSAIDs)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Anaphylaxis

Drug	Allopurinol
CTCAE - SOC	Immune system disorders
CTCAE Term	Anaphylaxis
Definition	A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.
Grade 1	-

Grade 2	-
Grade 3	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Blood bilirubin increased

Drug	Allopurinol
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased
Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Aspartate aminotransferase increased

Drug	Allopurinol
CTCAE - SOC	Investigations
CTCAE Term	Aspartate aminotransferase increased

Definition	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	AST or SGOT level

GGT increased

Drug	Allopurinol
CTCAE - SOC	Investigations
CTCAE Term	GGT increased
Definition	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gammaglutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

Grade 5	-
Define	GGT level

Alanine aminotransferase increased

Drug	Allopurinol
CTCAE - SOC	Investigations
CTCAE Term	Alanine aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	ALT or SGPT level

Nausea

Drug	Allopurinol
Contents	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits

Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

Drug	Allopurinol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Oral pain

Drug	Allopurinol
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Oral pain
Definition	A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.
Grade 1	Mild pain

Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

White blood cell decreased

Drug	Allopurinol
CTCAE - SOC	Investigations
CTCAE Term	White blood cell decreased
Definition	A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.
Grade 1	<LLN -3000/mm3;<LLN – 3.0 x 10e9/L
Grade 2	<3000-2000/mm3; <3.0 -2.0 x10e9/L
Grade 3	<2000-1000/mm3;<2.0 -1.0 x10e9/L
Grade 4	<1000/mm3; <1.0 x10e9/L
Grade 5	-
Define	White blood cell count

Platelet count decreased

Drug	Allopurinol
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased
Definition	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Grade 1	<LLN -75,000/mm3;<LLN – 75.0 x10e9/L

Grade 2	<75,000-50,000/mm3;<75.0-50.0 x10e9/L
Grade 3	<50,000-25,000/mm3;<50.0 – 25.0 x10e9/L
Grade 4	<25,000/mm3; <25/0 x10e9/L
Grade 5	-
Define	Platelet count

Anemia

Drug	Allopurinol
CTCAE - SOC	Blood and lymphatic system disorders
CTCAE Term	Anemia
Definition	A disorder characterized by a reduction in the amount of hemoglobin in 100 mL of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.
Grade 1	Hemoglobin (Hgb) <LLN – 10.0 g/dL; <LLN -6.2mmol/L; <LLN – 100g/L
Grade 2	Hgb <10.0 -8.0 g/dL; <6.2 – 4.9 mmol/L <100 -80g/L
Grade 3	Hgb <8.0 g/dL; <4.9 mmol/L <80 g/L; transfusion indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death
Define	Hemoglobin (Hgb)

Eosinophilia

Drug	Allopurinol
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased

Definition	A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood.
Grade 1	>ULN and >Baseline
Grade 2	-
Grade 3	Steroids initiated
Grade 4	-
Grade 5	-
Define	Eosinophil count

Headache

Drug	Allopurinol
CTCAE - SOC	Nervous system disorders
CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Peripheral neuropathy

Drug	Allopurinol
CTCAE - SOC	Nervous system disorders
CTCAE Term	Peripheral sensory neuropathy

Definition	A disorder characterized by damage or dysfunction of the peripheral sensory nerves.
Grade 1	Asymptomatic
Grade 2	Moderate symptoms; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	-
Define	Sensory or Motor?

Blurred vision

Drug	Allopurinol
CTCAE - SOC	Eye disorders
CTCAE Term	Blurred vision
Definition	A disorder characterized by visual perception of unclear or fuzzy images.
Grade 1	Intervention not indicated
Grade 2	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL
Grade 3	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL
Grade 4	Best corrected visual acuity of 20/200 or worse in the affected eye
Grade 5	-

Hypertension

Drug	Allopurinol
Contents	Vascular disorders

CTCAE Term	Hypertension
Definition	A disorder characterized by a pathological increase in blood pressure.
Grade 1	Pediatric: Systolic/diastolic BP >90th percentile but< 95th percentile; Adolescent: BP ≥120/80 even if < 95th percentile
Grade 2	Pediatric and adolescent: Recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated; systolic and /or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile; Adolescent: Systolic between 130-139 or diastolic between 80-89 even if < 95th percentile
Grade 3	Pediatric and adolescent: Systolic and/or diastolic > 5 mmHg above the 99th percentile
Grade 4	Adult and Pediatric: Life threatening consequences (i.e., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
Grade 5	Death
Define	BP

Mercaptopurine (6-MP)

Anemia

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Blood and lymphatic system disorders
CTCAE Term	Anemia
Definition	A disorder characterized by a reduction in the amount of hemoglobin in 100 mL of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.
Grade 1	Hemoglobin (Hgb) <LLN – 10.0 g/dL; <LLN -6.2mmol/L; <LLN – 100g/L
Grade 2	Hgb <10.0 -8.0 g/dL; <6.2 – 4.9 mmol/L <100 -80g/L

Grade 3	Hgb <8.0 g/dL; <4.9 mmol/L <80 g/L; transfusion indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death
Define	Hemoglobin (Hgb)

White blood cell decreased

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Investigations
CTCAE Term	White blood cell decreased
Definition	A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.
Grade 1	<LLN -3000/mm3;<LLN – 3.0 x 10e9/L
Grade 2	<3000-2000/mm3; <3.0 -2.0 x10e9/L
Grade 3	<2000-1000/mm3;<2.0 -1.0 x10e9/L
Grade 4	<1000/mm3; <1.0 x10e9/L
Grade 5	-
Define	White blood cell count

Platelet count decreased

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased
Definition	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Grade 1	<LLN -75,000/mm3;<LLN – 75.0 x10e9/L

Grade 2	<75,000-50,000/mm3;<75.0-50.0 x10e9/L
Grade 3	<50,000-25,000/mm3;<50.0 – 25.0 x10e9/L
Grade 4	<25,000/mm3; <25/0 x10e9/L
Grade 5	-
Define	Platelet count

Rash

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Rash (Skin and subcutaneous tissue disorders - Other, specify)
Definition	Skin and subcutaneous tissue disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Hypoglycaemia

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hypoglycemia
Definition	A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.

Grade 1	<LLN -55 mg/dL; <LLN -3.0 mmol/L
Grade 2	<55-40 mg/dL; <3.0 -2.2 mmol/L
Grade 3	<40-30 mg/dL; <2.2-1.7 mmol/L
Grade 4	<30 mg/dL; <1.7mmol/L; life-threatening consequences; seizures
Grade 5	Death
Define	Glucose concentration

Nausea

Drug	Mercaptopurine (6-MP)
Contents	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated

Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Diarrhea

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movement
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Oral pain

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Oral pain
Definition	A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.
Grade 1	Mild pain

Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Blood bilirubin increased

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased
Definition	Blood bilirubin increased; A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Aspartate aminotransferase increased

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Investigations
CTCAE Term	Aspartate aminotransferase increased

Definition	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	AST or SGOT level

GGT increased

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Investigations
CTCAE Term	GGT increased
Definition	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gammaglutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-

Define	GGT level

Alanine aminotransferase increased

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Investigations
CTCAE Term	Alanine aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	ALT or SGPT level

Photosensitivity

Drug	Mercaptopurine (6-MP)
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Photosensitivity
Definition	A disorder characterized by an increase in sensitivity of the skin to light.
Grade 1	Painless erythema and erythema covering <10% BSA
Grade 2	Tender erythema covering 10 - 30% BSA

Grade 3	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (i.e., narcotics or NSAIDs)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Thioguanine (6-TG)

White blood cell decreased

Drug	Thioguanine (6-TG)
CTCAE - SOC	Investigations
CTCAE Term	White blood cell decreased
Definition	A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.
Grade 1	<LLN -3000/mm3;<LLN – 3.0 x 10e9/L
Grade 2	<3000-2000/mm3; <3.0 -2.0 x10e9/L
Grade 3	<2000-1000/mm3;<2.0 -1.0 x10e9/L
Grade 4	<1000/mm3; <1.0 x10e9/L
Grade 5	-
Define	White blood cell count

Platelet count decreased

Drug	Thioguanine (6-TG)
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased

Definition	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Grade 1	<LLN -75,000/mm3;<LLN – 75.0 x10e9/L
Grade 2	<75,000-50,000/mm3;<75.0-50.0 x10e9/L
Grade 3	<50,000-25,000/mm3;<50.0 – 25.0 x10e9/L
Grade 4	<25,000/mm3; <25/0 x10e9/L
Grade 5	-
Define	Platelet count

Nausea

Drug	Thioguanine (6-TG)
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

Drug	Thioguanine (6-TG)
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting

Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Diarrhea

Drug	Thioguanine (6-TG)
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movement
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Blood bilirubin increased

Drug	Thioguanine (6-TG)
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased

Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Blood bilirubin increased

Drug	Thioguanine (6-TG)
CTCAE - SOC	Investigations
CTCAE Term	Blood bilirubin increased
Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Aspartate aminotransferase increased

Drug	Thioguanine (6-TG)
CTCAE - SOC	Investigations
CTCAE Term	Aspartate aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	AST or SGOT level

GGT increased

Drug	Thioguanine (6-TG)
CTCAE - SOC	Investigations
CTCAE Term	GGT increased
Definition	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gammaglutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal

Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	GGT level

Alanine aminotransferase increased

Drug	Thioguanine (6-TG)
CTCAE - SOC	Investigations
CTCAE Term	Alanine aminotransferase increased
Definition	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.
Grade 1	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
Grade 2	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	ALT or SGPT level

Veno-occlusive liver disease (VOD)

Drug	Thioguanine (6-TG)
CTCAE - SOC	Investigations

CTCAE Term	
Definition	Refractory platelets and one or more of: hepatomegaly, ascites, weight gain, hyper-bilirubinaemia
Define	Present? Y/N

Photosensitivity

Drug	Thioguanine (6-TG)
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Photosensitivity
Definition	A disorder characterized by an increase in sensitivity of the skin to light.
Grade 1	Painless erythema and erythema covering <10% BSA
Grade 2	Tender erythema covering 10 - 30% BSA
Grade 3	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (i.e., narcotics or NSAIDs)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Irinotecan

Nausea

Drug	Irinotecan
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Nausea
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.
Grade 1	Loss of appetite without alteration in eating habits

Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Grade 4	-
Grade 5	-

Vomiting

Drug	Irinotecan
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Vomiting
Definition	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grade 1	Intervention not indicated
Grade 2	Outpatient IV hydration; medical intervention indicated
Grade 3	Tube feeding, TPN, or hospitalization indicated
Grade 4	Life-threatening consequences
Grade 5	Death

Diarrhea

Drug	Irinotecan
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Diarrhea
Definition	A disorder characterized by an increase in frequency and/or loose or watery bowel movement
Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline

Grade 2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
Grade 3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Constipation

Drug	Irinotecan
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Constipation
Definition	A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.
Grade 1	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema
Grade 2	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	Obstipation with manual evacuation indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Flatulence

Drug	Irinotecan
CTCAE - SOC	Gastrointestinal disorders
CTCAE Term	Flatulence
Definition	A disorder characterized by a discharge of excessive gas from the lower GI tract.
Grade 1	Mild symptoms; intervention not indicated

Grade 2	Moderate; persistent; psychosocial sequelae
Grade 3	-
Grade 4	-
Grade 5	-

White blood cell decreased

Drug	Irinotecan
CTCAE - SOC	Investigations
CTCAE Term	White blood cell decreased
Definition	A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.
Grade 1	<LLN -3000/mm3;<LLN – 3.0 x 10e9/L
Grade 2	<3000-2000/mm3; <3.0 -2.0 x10e9/L
Grade 3	<2000-1000/mm3;<2.0 -1.0 x10e9/L
Grade 4	<1000/mm3; <1.0 x10e9/L
Grade 5	-
Define	White blood cell count

Platelet count decreased

Drug	Irinotecan
CTCAE - SOC	Investigations
CTCAE Term	Platelet count decreased
Definition	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.
Grade 1	<LLN -75,000/mm3;<LLN – 75.0 x10e9/L

Grade 2	<75,000-50,000/mm3;<75.0-50.0 x10e9/L
Grade 3	<50,000-25,000/mm3;<50.0 – 25.0 x10e9/L
Grade 4	<25,000/mm3; <25/0 x10e9/L
Grade 5	-
Define	Platelet count

Anemia

Drug	Irinotecan
CTCAE - SOC	Blood and lymphatic system disorders
CTCAE Term	Anemia
Definition	A disorder characterized by a reduction in the amount of hemoglobin in 100 mL of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.
Grade 1	Hemoglobin (Hgb) <LLN – 10.0 g/dL; <LLN -6.2mmol/L; <LLN – 100g/L
Grade 2	Hgb <10.0 -8.0 g/dL; <6.2 – 4.9 mmol/L <100 -80g/L
Grade 3	Hgb <8.0 g/dL; <4.9 mmol/L <80 g/L; transfusion indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death
Define	Hemoglobin (Hgb)

Neutrophil count decreased

Drug	Irinotecan
CTCAE - SOC	Investigations
CTCAE Term	Neutrophil count decreased

Definition	A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.
Grade 1	<LLN - 1500/mm3;<LLN – 1.5 x10e9/L
Grade 2	<1500-1000/mm3;<1.5-1.0 x10e9/L
Grade 3	<1000-500/mm3; <1.0 -0.5 x 10e9/L
Grade 4	<500/mm3; <0.5 x10e9/L
Grade 5	-
Define	Neutrophil count

Hyperkalemia

Drug	Irinotecan
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Hyperkalemia
Definition	A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.
Grade 1	>ULN - 5.5 mmol/L
Grade 2	>5.5 - 6.0 mmol/L; intervention initiated
Grade 3	>6.0 - 7.0 mmol/L; hospitalization indicated
Grade 4	>7.0 mmol/L; life-threatening consequences
Grade 5	Death
Define	Potassium concentration

Hypermagnesemia

Drug	Irinotecan
CTCAE - SOC	Metabolism and nutrition disorders

CTCAE Term	Hypermagnesemia
Definition	A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.
Grade 1	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L
Grade 2	-
Grade 3	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L
Grade 4	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
Grade 5	Death
Define	Magnesium concentration

Fever

Drug	Irinotecan
CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Fever
Definition	A disorder characterized by elevation of the body's temperature above the upper limit of normal.
Grade 1	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)
Grade 2	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)
Grade 3	>40.0 degrees C (>104.0 degrees F) for <=24 hrs
Grade 4	>40.0 degrees C (>104.0 degrees F) for >24 hrs
Grade 5	Death

Headache

Drug	Irinotecan
CTCAE - SOC	Nervous system disorders

CTCAE Term	Headache
Definition	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Grade 1	Mild pain
Grade 2	Moderate pain; limiting instrumental ADL
Grade 3	Severe pain; limiting self-care ADL
Grade 4	-
Grade 5	-

Chills

Drug	Irinotecan
CTCAE - SOC	General disorders and administration site conditions
CTCAE Term	Chills
Definition	A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.
Grade 1	Mild sensation of cold; shivering; chattering of teeth
Grade 2	Moderate tremor of the entire body; narcotics indicated
Grade 3	Severe or prolonged, not responsive to narcotics
Grade 4	-
Grade 5	-

Blood bilirubin increased

Drug	Irinotecan
CTCAE - SOC	Investigations

CTCAE Term	Blood bilirubin increased
Definition	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.
Grade 1	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Grade 2	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal
Grade 3	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
Grade 4	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Grade 5	-
Define	Bilirubin level

Dehydration

Drug	Irinotecan
CTCAE - SOC	Metabolism and nutrition disorders
CTCAE Term	Dehydration
Definition	A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.
Grade 1	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor
Grade 2	IV fluids indicated
Grade 3	Hospitalization indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Alkaline phosphatase increased

Drug	Irinotecan

CTCAE - SOC	Investigations
CTCAE Term	Alkaline phosphatase increased
Definition	A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.
Grade 1	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Grade 2	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal
Grade 3	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
Grade 4	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Grade 5	-
Define	Alkaline phosphatase level

Rash

Drug	Irinotecan
CTCAE - SOC	Skin and subcutaneous tissue disorders
CTCAE Term	Rash (Skin and subcutaneous tissue disorders - Other, specify)
Definition	Skin and subcutaneous tissue disorders - Other, specify
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated

Grade 5	Death

Insomnia

Drug	Irinotecan
CTCAE - SOC	Psychiatric disorders
CTCAE Term	Insomnia
Definition	A disorder characterized by difficulty in falling asleep and/or remaining asleep.
Grade 1	Mild difficulty falling asleep, staying asleep or waking up early
Grade 2	Moderate difficulty falling asleep, staying asleep or waking up early
Grade 3	Severe difficulty in falling asleep, staying asleep or waking up early
Grade 4	-
Grade 5	-

Dizziness

Drug	Irinotecan
CTCAE - SOC	Nervous system disorders
CTCAE Term	Dizziness
Definition	A disorder characterized by a disturbing sensation of light-headedness, unsteadiness, giddiness, spinning or rocking.
Grade 1	Mild unsteadiness or sensation of movement
Grade 2	Moderate unsteadiness or sensation of movement; limiting instrumental ADL
Grade 3	Severe unsteadiness or sensation of movement; limiting self-care ADL
Grade 4	-
Grade 5	-

Thromboembolic event

Drug	Irinotecan
CTCAE - SOC	Nervous system disorders
CTCAE Term	Thromboembolic event
Definition	A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.
Grade 1	Medical intervention not indicated (i.e., superficial thrombosis)
Grade 2	Medical intervention indicated
Grade 3	Urgent medical intervention indicated (i.e., pulmonary embolism or intracardiac thrombus)
Grade 4	Life-threatening consequences with hemodynamic or neurologic instability
Grade 5	Death
Define	Type of event

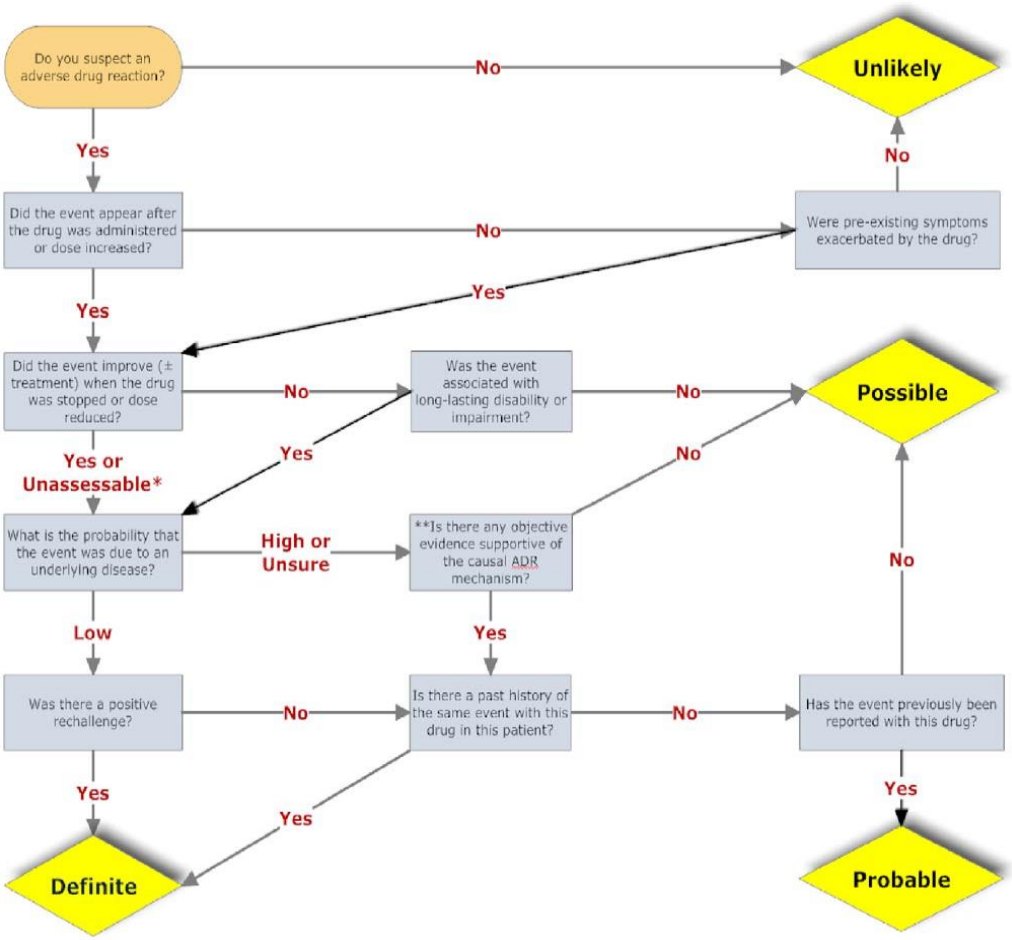
Stroke

Drug	Irinotecan
CTCAE - SOC	Nervous system disorders
CTCAE Term	Thromboembolic event
Definition	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage
Grade 1	Incidental radiographic findings only
Grade 2	Mild to moderate neurologic deficit; limiting instrumental ADL
Grade 3	Severe neurologic deficit; limiting self-care ADL; hospitalization
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Gait disturbance

Drug	Irinotecan
CTCAE - SOC	Nervous system disorders
CTCAE Term	Thromboembolic event
Definition	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage
Grade 1	Mild change in gait (i.e., wide-based, limping or hobbling)
Grade 2	Moderate change in gait (i.e., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL
Grade 3	Limiting self-care ADL
Grade 4	-
Grade 5	-

Appendix C: Liverpool ADR Causality Assessment of Reported ADRs



*Unassessable refers to situations where the medicine is administered on one occasion (e.g. Vaccine), the patient receives intermittent therapy (e.g. Chemotherapy), or is on medication which cannot be stopped (e.g. Immunosuppressants)

** Examples of objective evidence: positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient

Appendix D: Review of the participants electronic medical record and medication reconciliation (Trial endpoint data):

- Trial Number
- Date of birth
- Primary Disease
- Prescription drug(s) leading to eligibility to enrol
- Baseline dose of drug(s) leading to enrolment
- Randomisation Arms: Standard of Care versus Intervention Arm
- Actionable Variant identified

I. Yes/No
II. Actionable gene (drop down)
III. Diplotype (free text)
IV. Metaboliser state (drop down)

- Assessed during every Semi-Structured Interview
  I. Ped-PRO-CTCAE Survey
  II. CTCAE grading of Ped-PRO-CTCAE
  III. CTCAE grading of PGx actionable drugs
  IV. Liverpool ADR CAT (for all reported symptoms)
    - definite, probable, possible
  V. Medication list including dose, route, frequency
  VI. Number of changes made to actionable gene drug dosage since last review
    - Gene: Drug pair
    - Changes made (drop down: increased starting dose; decreased starting dose; increased dose, decreased dose, cessation of therapy, cessation of therapy and alternate agent)
  VII. Medication dose changes since last review
    - Attributable to ADR (yes, no)
    - Attributable to lack of efficacy (yes, no)
  VIII. Therapeutic drug monitoring since last review
    - Drug, date of TDM, drug level
  IX. Quality of Life Assessments (CHU9D)

Appendix E: MARVEL-PIC informed consent (Adolescent and Young Adult)

Thank you for taking the time to read this **Patient (Adolescent and Young Adult) Information and Consent Form**. We are inviting you to take part in a study where we are trying to better understand the frequency and severity of side-effects you may be experiencing during your treatment and whether knowing your genetic predisposition to drug reactions improves these side effects.

This form is 10 pages long. Please make sure you have all the pages.

What is an Information and Consent Form?

An Information and Consent Form tells you what is involved if you agree to participate in this study. It helps you decide whether or not you want to take part in the project. Please read it carefully.

Before you make a decision, you can ask us as many questions as you would like so that you are fully informed. You may also want to talk to your family, friends or other healthcare workers.

Taking part in the study is up to you

You get to choose whether or not you take part in the study. If you decide you do not want to take part, this is ok. It will not affect your relationship with staff at the Children's Cancer Centre at The Royal Children's Hospital or what treatment you will receive.

Signing the consent form

If you want to take part in this study, please sign the consent at the end of this document. By signing the consent form you are telling us that you:

- understand what you have read
- have had a chance to ask questions and received satisfactory answers
- consent to taking part in the study

We will give you a copy of this Information and Consent Form to keep.

1. What is the project about?

We are inviting you to take part in our study called MARVEL-PIC 'Minimising Adverse drug Reactions and Verifying Economic Legitamacy - Pharmacogenomic Implementation in Children.

Most diseases or illnesses require treatment with medication, which can either cure the disease or control the symptoms. Unfortunately, many medications used during treatment can have side effects. Some side effects are mild, some are more severe and can be serious. Every person has different side effects from medication.

Your genetics or genes (the basic building blocks of life) play an important role in how you respond to medication. Humans have around 20,000 genes which all have specific functions relating to different processes in the body. For example, some genes produce an enzyme or protein which breaks down medications. Variability in these genes may make some people break down a medication very quickly whereas others may break it down very slowly.

Currently, very few genetic tests are routinely used to help doctors prescribe your medication. Almost all patients receive a standard dose and choice of medication, regardless of how they break down or respond to the medication. Recent research advances mean we can now test a person's genes to better understand if a particular dose is likely to help them or result in side effects. This process is called personalised medicine.

As one example, a patient with acute lymphoblastic leukemia will have a pharmacogenomic test requested by their doctor to test for genetic variations in an enzyme called thiopurine methyltransferase (TPMT). About 10% of people have genetic variations in an enzyme called thiopurine methyltransferase (TPMT). Testing for TPMT helps doctors decide what dose is best suited to you and helps prevent serious side effects. Doctors can use protocols and guidelines that have already been studied and published to help them make these dosing decisions.

The purpose of this study is to find out if personalising medication based on genetic results lowers the chance of experiencing serious side effects. In this study we will look at personalising medication related to medications you receive to stop chemotherapy side effects i.e. supportive care (pain killers, anti-vomit medications), rather than cancer therapy. Therefore, there should be no changes to cancer treatment approach.

This study will use a randomisation approach where you will receive either

(a) standard of care (or current approach to treatment) **OR**

(b) extended pharmacogenomic testing (study arm)

If you are randomised to receive the study arm, additional genetic information about how your body handles medication will be provided to your treating team early in the study (within 4 weeks). For patients in the standard of care arm, it will be provided at week 13 of the study.

Information will be collected to find out if the new method improves medication side effects by symptom and quality of life surveys and short interviews.

If during participation of this study, we find you have a rare or severe side effect of therapy the researchers will endeavor to investigate your whole genome sequencing to better understand the cause of this. Genetic testing can raise important issues. If something is found in the genetic testing, you may need to tell your child about this in the future. For example, the test results may show that you have an increased risk of developing a particular condition. This increased risk does not mean that you will develop the condition. If we find that you have any genetic condition that you do not know about, we will contact your doctor and you to discuss the findings. We will also refer you to a genetic counsellor. They will help you free of charge.
The study randomisation is outlined in the below diagram:

2. Who is running the project?

This study is being run through the Children's Cancer Centre (CCC) at The Royal Children's Hospital Melbourne. It is funded through a Medical Research Future Fund as part of the Victorian Paediatric Cancer Consortium (VPCC) together with funding from the Kids Cancer Project (KCP). A/Prof Rachel Conyers is the principal investigator in this project. You might also hear them referred to as the 'PI'. As Principal Investigator, they are in charge of this research study and the study team. They have written the plan for this study – this plan is also called the protocol. As the Principal Investigator, they will be in charge of analysing the information that we find in this study, and in charge of telling people about our findings. The

team working with A/Prof Conyers and involved in the project include Ms Tayla Stenta, Mr Ben Felmingham (Academic Pharmacist) and Ms Claire Moore (Academic Pharmacist – PhD student).

3. Why are we asking you to take part?

We are asking you to take part in this research study because you are:

A patient of the Children's Cancer Centre and:

- are aged between 0 and 18 years old
- have a cancer diagnosis ***OR***
- are receiving a haematopoietic stem cell transplant

4. What do you need to do in this research study?

If you take part in this research study we will:

- Take a small sample of blood (2-3 teaspoons) to look at your genes (if randomised to the investigational arm)
- Ask you to complete online symptom and quality of life surveys and brief semi-structured interviews. These surveys and interviews will be repeated up to 3 times during the 12-month study period.
- Access your Services Australia claims information (Medicare Benefits Schedule (MBS)/Pharmaceutical Benefits Scheme (PBS)) data after 12 weeks, and at the completion of the study.

This section gives you more information about each of these:

Online symptom survey

We will ask you to complete an online symptom survey. The survey is called the Ped-PRO-CTCAE and was developed by international experts. The survey has 47 questions about different symptoms that you may experience as a result of your treatment.

An example of a question that may be asked is 'in the last week how bad were you feeling sick to your stomach (nausea)'. The survey will ask you to grade how bad your symptoms were in the previous week as:

- did not have any
- a little bad
- bad
- very bad

The online survey will take up to approximately 20 minutes to complete depending on the number of symptoms that you may need to report on.

If you consent to participate in the study, a member from the study team will ask you for an email address that the survey link can be delivered to at the timepoints outlined in the study. This will be at week 1, 6 and 12 of the study.

The emailed survey link will take you directly to a secure database (REDCap) where your results will be recorded.

If you need to take a break from answering the survey questions, you may do so and will be able to come back and complete the survey questions from where you left off, after a short break.

a. Brief semi-structured interviews

A member of the study team will conduct brief semi-structured interviews 1-4 days after you complete the online survey.

In this interview your current medication(s) will be recorded together with discussing the symptoms you reported in the survey. This will help us further understand the severity of your symptoms.

The study team member will also access some data from the electronic medical record (with your consent) that will include:

- Your date of birth
- Your blood test results
- Doctors notes relating to symptoms reported in online survey

We will combine the review of your medication, online survey and medical record results to give a formal grading to any side effects experienced.

You can have the interview conducted whichever way you choose. You can choose to have it:

- over the phone,
- via an appropriate telehealth platform (i.e., Zoom) ***OR***
- in person

The interviews may take up to 20 minutes to complete.

b. Blood test for pharmacogenetic testing (Study Arm)

A blood test will be performed at a time when you are having other blood taken as part of your care.

The researchers have identified genes that will be tested for as part of this study. The genes are those whose genetic changes are closely linked to medication side effects.

A study report will be generated to summarise your genes and how they may alter your medication side effects. The reports will be put in your electronic medical record and be available to the doctors, nurses and pharmacists involved in your care. If you are in the study

arm these will be provided within 4 weeks. For those in the standard of care arm, additional results will be provided at week 13 of the study. Routine gene tests done as standard of care will be provided earlier (i.e., within 4 weeks).

Once the results are returned to your doctor they may use this information to guide the dosing of the medication. This may include altering drug doses or using a different medication. **It will be up to the doctor looking after you to decide whether or not to make these changes, taking into account other factors that relate to your medical history.**

c. Quality of life Surveys

A quality-of-life survey (CHU9D) is being used in the study. The survey has 9 items. It should take 5 – 10 minutes to complete.

The survey will provide information on how you are going across domains of worry, sadness, pain, tiredness, annoyance, school, sleep, daily routines and activities. In general, patients and their parents have reported that this survey is quick and easy to do. The survey will be provided electronically at 3 different times in the study: as a baseline, at 12 weeks and at 12 months.

d. Services Australia (MBS/PBS) Data

Your MBS/PBS data will help us to understand the cost of providing genetic testing to patients, and any potential cost savings. To access this data, we require you to sign this Patient Information and Consent Form and a separate Services Australia Participant Information Document and Participant Consent Form.

If you choose to withdraw from this study, we require you to sign a Services Australia Withdrawal of Consent form which the Research Assistant will forward to Services Australia.

Services Australia is not involved in this research other than to provide the information that you have consented to the release of, should you decide to participate in this study. Services Australia has confirmed that this research and any associated documents have received approval from a Human Research Ethics Committee (HREC) that is registered with and operates within guidelines set out by the National Health and Medical Research Council (NHMRC).

Table 1: What you need to do as you participate in this study.

Part of study	In-person or electronic?	How long will it take?	What does it involve?	Is it mandatory or optional?
Ped-PRO-CTCAE Survey	Electronic	Up to 20 minutes	Answering a series of questions about symptoms you may have experienced in the previous 7	Mandatory

			days to completing the survey. This survey is repeated 3 times during the study at week 1, 6 and 12.	
Brief Semi-structured Interview	Electronic Phone In-person	Up to 20 minutes	Confirm which medications, you are taking. Confirming symptoms reported from online survey to grade the severity.	Mandatory
Access to Electronic Medical Record	Permission only	N/A	The study researchers will access the electronic medical records to review blood test results and progress not that may be relevant to the study.	Mandatory
Pharmacogenetic Testing	In-person	10 minutes	A small blood sample will be taken at a time that other bloods are being taken once enrolled on study.	Mandatory for all patients.
Quality of Life Survey (CHU9D)	Electronic	10 minutes	Answering a series of questions about your quality of life. This survey is repeated 3 times during the study period. Week 1,	Mandatory

			12 and at 12 months.	

5. Can you withdraw from the project?

You can stop taking part in the study at any time. You just need to tell a member of the study team (refer to page 9 for contact details) that you would no longer like to participate. You do not need to tell us the reason why. Once you leave the study, we will no longer use your information.

Additionally, if you consented to Services Australia providing us with your MBS/PBS data, the Research Assistant will provide you with a Withdrawal of Consent form to be signed. Once signed, your record will be flagged to ensure that no further information will be collected for the purpose of the study as outlined on the withdrawal of consent form.

6. What are the possible benefits to you and other people in the future?

We are doing this study for research purposes. Our aim is to improve our understanding of the side-effects associated with cancer treatment and supportive care and how providing genetic information can help reduce these.

Receiving a genetic test to guide your medication prescription may lower the chances of experiencing a side effect, but this is not certain. If whole genome sequencing is done by the research team due to you having more severe than usual adverse effects, a member of the study team will discuss this further with you at the time.

7. What are the possible risks, side effects, and inconveniences?

- Additional time will be required to complete the surveys and semi-structured interview with the research team.
- There are small risks with taking blood tests during cancer therapy mainly related to bleeding and infection at the site of finger prick. We will make sure that blood tests are done at a time when routine other bloods are taken. Additional time will be required to take this extra blood test.
- There is a small chance that you may become upset when you are taking part in this study, particularly as it involves commenting on the side-effects you are having with therapy.

If this happens, you can take a break from the survey or the interview. If you feel that you may benefit from free counselling or another suitable support, services will be made available through the Children's Cancer Centre. This will be provided by someone who is not part of the study team. You may also decide to withdraw from the project if this occurs.

8. What will happen to my blood sample?

Your blood sample will be sent to researchers on this project within Murdoch Children's Research Institute and Victorian Clinical Genetics Service (VCGS). A small amount of the

sample will be used to obtain your genetic results and the remaining sample will be stored within the Children's Cancer Centre Tissue Bank. The sample may be used to re-confirm your genetic result. The testing will report on the genes that are responsible for side effects of medications listed in this project.

It is unlikely that the sample will be of any commercial value to Murdoch Children's Research Institute or Victorian Clinical Genetics Service. However, it is possible that there may be some commercial value in the future, although it is important to note that any commercial value is likely to be due to findings in a group of patients, rather than from samples from a single patient.

You will not be paid for taking part in the study.

9. How will we keep your information confidential?

We will collect and use personal and health information about you for research purposes. In this study, we will store your electronic information securely on an internal server, the REDCap database, stored at the Murdoch Children's Research Institute. Your consent form will be scanned and stored as a PDF file on the REDCap database.

All genetic results that are generated as part of the 'study arm' or 'standard of care arm' will be stored within electronic servers through the Victorian Clinical Genetics Service (VCGS). These servers are encrypted to protect information securely. The clinical report generated as part of the study (for 'study arm' randomisation) will be provided within the electronic medical record which will be available to your doctor and health professional team.

When requesting data from Services Australia and the Department of Health Victorian Centre for Data Linkage (CVDL), the research team will provide your identifiable information. The data will be provided to Services Australia and CVDL in a password protected file. Services Australia and CVDL will store this information on an encrypted server to protect information securely. They will not provide this information to any additional third parties.

The following people may access your identifiable information as part of this study:

- Research members involved with this study (these staff are staff members of either The Royal Children's Hospital and Murdoch Children's Research Institute, or the Victorian Clinical Genetics Service).
- RCH Human Research Ethics Committee.

We will not share your identifiable information with anyone else except as required by law.

Sharing information

To advance science, medicine and public health, we may share your de-identified data with any current and future funders, research studies, biobanks, medical journals or data research repositories. Some of these organisations may be located overseas. **Any data that we send overseas is not protected by Australian laws and regulations.** By signing the consent form for this study, you are giving us permission to do this. Please note this will not include any

data obtained from Services Australia, this data is intended for this study and not for any future research.

If we share your data, we will remove identifying details such as your name, date of birth and address and give the data a special code number.

We will also put security measures in place to protect your data if and when we transfer it to other people. We will make sure any files are completely de-identified and transferred via an encrypted file with access via password only.

Despite our best efforts, there is a small chance that your data could be re-identified by someone outside of this research study. In the unlikely event that this happens, someone from the research team will contact you. If, at any point, you think that your data may have been re-identified, please let us know.

Storage of information

We are required to keep information collected as part of this project for at least fifteen (15) years following the last publication of the project. Following that time, all information that was collected will be securely destroyed.

10. How will you find out the project results?

You have the right to access and correct the information we collect and store about you. This is in line with relevant Australian and/or Victorian privacy and other relevant laws. Please contact us if you would like to access this information. At the end of the research project, we may present the results at conferences. We may also publish the results in medical journals. We will do this in a way that protects your privacy.

At the end of the project we will send you a final letter. This letter will explain what we found out in this project – in other words, our project results. The letter will not have any information specifically about you.

Appendix F: MARVEL-PIC informed consent (Parent/Guardian)

Thank you for taking the time to read this **Parent /Guardian Information and Consent Form**. We are inviting your child to take part in a study where we are trying to better understand the frequency and severity of side-effects your child may be experiencing during their treatment and whether knowing your child's genetic predisposition to drug reactions improves these side effects.

This form is 11 pages long. Please make sure you have all the pages.

What is an Information and Consent Form?

An Information and Consent Form tells you what is involved if you agree to participate in the study. It helps you decide whether or not you want your child to take part in the project. Please read it carefully.

Before you make a decision, you can ask us as many questions as you would like so that you are fully informed. You may also want to talk to your family, friends or other healthcare workers.

Taking part in the study is up to you

You get to choose whether or not your child takes part in the study. If you decide you do not want them to take part, this is ok. It will not affect your relationship with the Children's Cancer Centre at The Royal Children's Hospital or any treatment your child receives.

Signing the consent form

If you want your child to take part in this study, please sign the consent at the end of this document. By signing the consent form you are telling us that you:

- understand what you have read
- have had a chance to ask questions and received satisfactory answers
- consent to taking part in the study

We will give you a copy of this Information and Consent Form to keep.

11. What is the project about?

We are inviting your child to take part in our study called MARVEL-PIC 'Minimising Adverse drug Reactions and Verifying Economic Legitamacy - Pharmacogenomic Implementation in Children.

Most diseases or illnesses require treatment with medication, which can either cure the disease or control the symptoms. Unfortunately, many medications we use when treating cancer or having a bone marrow transplantation can have side effects, some of which can be serious. Every child will differ in how their body responds to medication, which can result in differences in how well it works.

Your genetics or genes (the basic building blocks of life) play an important role in a child's response to medication. Humans have around 20,000 genes which all have specific functions relating to different processes in the body. For example, some genes produce an enzyme or protein which breaks down medications. Variability in these genes may make some people break down a medication very quickly whereas others may break it down very slowly.

Currently, very few pharmacogenetic tests are taken into account when a doctor prescribes your child's medication. Almost all patients receive a standard dose and choice of medication, regardless of how they break down or respond to the medication. Recent advances in technology mean we can now test a person's variation in genes and use the information to work out if a medication or particular dose is likely to help them or result in side effects. This process is called personalised medicine.

As one example a patient with acute lymphoblastic leukemia will have a pharmacogenomic test requested by their doctor to test for genetic variations in an enzyme called thiopurine methyltransferase (TPMT). About 10% of people have genetic variations in an enzyme called

thiopurine methyltransferase (TPMT). Testing for TPMT helps doctors decide what dose is best suited to you and helps prevent serious side effects. Doctors can use protocols and guidelines that have already been studied and published to help them make these dosing decisions.

The purpose of this study is to find out if personalising medication lowers the chance of experiencing serious side effects. In this study we will look at personalising medication related to supportive care (pain killers, anti-vomit medications) rather than cancer therapy. Therefore, there should be no changes to cancer treatment approach.

This study will use a randomisation approach where your child will receive either

(a) standard of care (current practice) **OR**

(b) extended pharmacogenomic testing (investigational arm)

If your child is randomised to receive the study arm, additional genetic information about how your child's body handles medication will be provided to your treating team early in the study (within 4 weeks). For patients in the standard of care arm, it will be provided at week 13 of the study.

Information will be collected to find out if the new method improves medication side effects by symptom and quality-of-life surveys and short interviews.

If during participation of this study, we find your child has a rare or severe side effect of therapy the researchers will endeavour to investigate your child's whole genome sequencing to better understand the cause of this. Genetic testing can raise important issues. If something is found in the genetic testing, you may need to tell your child about this in the future. For example, the test results may show that your child has an increased risk of developing a particular condition. This increased risk does not mean that they will develop the condition. If we find that your child has any genetic condition that you do not know about, we will contact your doctor and you to discuss the findings. We will also refer you to a genetic counsellor. They will help you free of charge.

The study randomisation is outlined in the below diagram:

12. Who is running the project?

This study is being run through the Children's Cancer Centre (CCC) at The Royal Children's Hospital Melbourne. It is funded through a Medical Research Future Fund as part of the Victorian Paediatric Cancer Consortium (VPCC) together with funding from the Kids Cancer Project (KCP). A/Prof Rachel Conyers is the principal investigator in this project. You might also hear them referred to as the 'PI'. As Principal Investigator, they are in charge of this research study and the study team. They have written the plan for this study – this plan is also called the protocol. As the Principal Investigator, they will be in charge of analysing the information that we find in this study, and in charge of telling people about our findings. The team working with A/Prof Conyers and involved in the project include Ms Tayla Stenta, Mr Ben Felmingham (Academic Pharmacist) and Ms Claire Moore (Academic Pharmacist – PhD student).

13. Why are we asking your child to take part?

We are asking your child to take part in this research study because they are:

A patient of the Children's Cancer Centre and:

- are aged between 0 and 18 years old
- have a cancer diagnosis ***OR***
- are receiving Bone Marrow Transplant Therapy

14. What does your child need to do in this research study?

If your child takes part in this research study we will:

- Take a 5-12 mL sample of blood (2-3 teaspoons) to look at your child's genes
- Ask you (on your child's behalf) to complete online symptom and quality-of-life surveys and brief semi-structured interviews. These surveys and interviews will be repeated up to 3 times during the 12-month study period.
- Access your child's Services Australia claims information (Medicare Benefits Schedule (MBS)/Pharmaceutical Benefits Scheme (PBS)) data after 12 weeks, and at the completion of the study.

This section gives you more information about each of these requirements:

e. Online symptom survey

As your child's carer, we will ask you to complete an online symptom survey. The survey is called the Ped-PRO-CTCAE and was developed by international experts to assess side-effects experienced during cancer therapy. The Ped-PRO-CTCAE survey consists of 47 questions about different symptoms that your child may experience as a result of the medications your child is taking. An example of a question that may be asked is 'in the last week how bad was your child's feeling sick to their stomach (nausea)'. The survey will ask you to grade how bad your child's symptoms were in the previous week as:

- did not have any
- a little bad
- bad
- very bad

The online survey will take up to approximately 20 minutes to complete depending on the number of symptoms that you may need to report on. You will receive a link to the survey via email 3 times during the study at week 1, 6 and 12 of the study. You can start the survey anytime during the first month of your child's cancer therapy or bone marrow transplant.

If you consent for your child to participate in the study, a member from the study team will ask you for an email address that the survey link can be delivered to at the timepoints outlined in the study. This will be at week 1, 6 and 12 of the study. The emailed survey link will take you directly to the online survey and your answers to the questions will be stored within the secure REDCap database. If you need to take a break from answering the survey questions, you may do so and will be able to come back and complete the survey questions from where you left off, after a short break.

f. Brief semi-structured interviews

A member of the study team will conduct brief semi-structured interviews 1-4 days after you complete the online survey. The purpose of the brief interview is to clarify the medication(s) your child is currently receiving and to clarify (where necessary) 'how bad' the symptom(s) reported in the survey were. This will be for the purpose of grading these symptoms. This includes information such as your child's:

- date of birth
- blood test results
- progress notes relating to symptoms reported in online survey

We will combine the review of your child's medication, online survey and medical record results to give a formal grading to any side effects experienced. The semi-structed interviews will be conducted in one of 3 ways:

- over the phone,
- via an appropriate telehealth platform ***OR***
- in person

The interviews may take up to 20 minutes to complete depending on the number of symptoms that have been self-reported via the online survey.

g. Blood test for pharmacogenetic testing

A blood test will be performed at a time of other bloods being taken for routine clinical care. This blood test will be taken for all patients. The researchers have identified priority genes that will be tested for as part of this study. Priority genes are those whose genetic changes are closely linked to medication side effects. A report will be generated to summarise your child's metaboliser states for priority genes. Priority genes will be released in a clinical report to the Study arm (within 4 weeks) or the Standard of care arm (at week 13) of the study. The reports will be put in your child's electronic medical record. Once the gene results are in the medical record, they can be used by doctors, pharmacists, nurses and other clinicians to make decisions around drug therapy.

Once the results are returned to your doctor they may use this information to personalise the prescription of the drugs. This may include altering drug doses or using a different medication. **It will be up to the doctor looking after you to decide whether or not to make these changes, taking into account other factors that relate to your medical history.**

h. Quality of life Surveys

A quality-of-life survey (CHU9D) is being used in the study. The CHU9D was developed for children and research has demonstrated its use in assessing a child or young persons quality-of-life. It consists of 9 items each with 5 response categories (scored 1-5). It should take 5-10 minutes to complete.

The survey will provide information to the researchers on your child's functioning across domains of worry, sadness, pain, tiredness, annoyance, school, sleep, daily routines and activities. In general, patients and their parents have reported that the CHU9D is quick and easy to complete. The quality-of-life surveys will be provided electronically to you at 3 different times in the study: as a baseline, at 12 weeks and at 12 months.

i. Services Australia (MBS/PBS) Data

Your MBS/PBS data will help us to understand and compare the costs associated with the standard of care and the extended pharmacogenomic testing (Study arm). To access this data, we require you to sign this Patient Information and Consent Form and a separate Services Australia Patient Information Document and Child Consent Form. If your child is < 14 years old, the Services Australia consent must be signed by a parent/guardian. If your child is 14 years or older, your child will be required to sign the Services Australia consent form. In addition, there is the potential that your child may need to be reconsented if they turn 14 before the request is made to Services Australia.

If you choose to withdraw from this study, we require you to sign a Services Australia Withdrawal of Consent form which the Research Assistant will forward to Services Australia.

Services Australia is not involved in this research other than to provide the information that you have consented to the release of, should you decide to participate in this study. Services Australia has confirmed that this research and any associated documents have received approval from a Human Research Ethics Committee (HREC) that is registered with and operates within guidelines set out by the National Health and Medical Research Council (NHMRC).

The following table illustrates what you will need to do in this study:

Table 1: What you need to do as your child's carer in this study

Part of study	In-person or electronic?	How long will it take?	What does it involve?	Is it mandatory or optional?
Ped-PRO-CTCAE Survey	Electronic	Up to 20 minutes	Answering a series of questions about symptoms your child may have experienced in the previous 7 days to completing the survey. This survey is repeated 3 times during the study at week 1, 6 and 12.	Mandatory

Brief Semi-structured Interview	Electronic Phone In-person	Up to 20 minutes	Confirming which medications your child is currently taking. Confirming symptoms reported from online survey to grade the severity.	Mandatory
Access to Electronic Medical Record	Permission only	N/A	The study researchers will access the electronic medical records to review blood test results and progress not that may be relevant to the study.	Mandatory
Pharmacogenetic Testing	In-person	10 minutes	A small blood sample will be taken at a time that other bloods are being taken once enrolled on study.	Mandatory for all patients.
Quality-of-Life Survey (CHU9D)	Electronic	10 minutes	Answering a series of questions about your child's quality-of-life. This survey is repeated 3 times during the study period. Week 1, 12 and at 12 months	Mandatory

15. Can your child withdraw from the project?

Your child can stop taking part in the study at any time. You just need to tell a member of the study team (refer to page 9 for contact details) that your child would no longer like to

participate. You do not need to tell us the reason why. Once you leave the study, we will no longer use your information.

Additionally, if you or your child consented to Services Australia providing us with your MBS/PBS data, the Research Assistant will provide you with a Services Australia Parent/Guardian Withdrawal of Consent form to be signed. Once signed, your child's record will be flagged to ensure that no further information will be collected for the purpose of the study as outlined on the withdrawal of consent form.

16. What are the possible benefits for your child and other people in the future?

We are doing this study for research purposes. Our aim is to progress our understanding of the side-effects associated with cancer treatment and supportive care particularly the severity and frequency of side-effects during cancer therapy or bone marrow transplant therapy, and if providing pharmacogenetic genetic testing improves the frequency and severity of these side-effects.

Receiving a genetic test to guide your child's drug prescription may lower the chances of experiencing a side effect, but this is not certain. If whole genome sequencing is done by the research team due to your child having more severe than usual adverse effects, a member of the study team will discuss this further with you at the time.

17. What are the possible risks, side effects, and inconveniences?

- Additional time will be required to complete the surveys and semi-structured interview with the research team.

- There are small risks with taking blood tests during cancer therapy mainly related to bleeding and infection at the site of finger prick. We will make sure that blood tests are done at a time when routine other bloods are taken. Additional time will be required to take this extra blood test.

- There is a small chance that you may become upset when you are taking part in this study, particularly as it involves commenting on side-effects of your child's treatment. If this happens, you can take a break from the survey or the interview. If you feel that you may benefit from free counselling or another suitable support, services will be made available through the Children's Cancer Centre. This will be provided by someone who is not part of the study team. You may also decide to withdraw your child from the project if this occurs.

18. What will happen to my child's blood sample?

Your child's blood sample will be sent to researchers on this project within Murdoch Children's Research Institute and Victorian Clinical Genetics Service (VCGS). A small amount of the sample will be used to obtain your child's genetic results, the remaining sample will be stored within the Children's Cancer Centre Tissue Bank. The sample may be used to re-confirm your child's result. We will report testing restricted to investigating genes that are responsible for side effects of medications.

It is unlikely that the sample will be of any commercial value to Murdoch Children's Research Institute or Victorian Clinical Genetics Service. However, it is possible that there may be some commercial value in the future, although it is important to note that any commercial value is likely to be due to findings in a group of patients, rather than from samples from a single patient.

You and your child will not be paid for taking part in the study, nor will you or your child derive financial benefit from future discoveries.

19. How will we keep your child's information confidential?

We will collect and use personal and health information about your child for research purposes. In this study, we will store your child's electronic information securely on an internal server, the REDCap database, stored at the Murdoch Children's Research Institute. Your consent form will be scanned and stored as a PDF file on the REDCap database.

All genetic results that are generated as part of the 'study arm' will be stored within electronic servers through the Victorian Clinical Genetics Service (VCGS). These servers are encrypted to protect information securely. The clinical report generated as part of the study (for 'study arm' randomisation) will be provided within the electronic medical record which will be available to your doctor and health professional team.

When requesting data from Services Australia and the Department of Health Victorian Centre for Data Linkage (CVDL), the research team will provide your child's identifiable information. The data will be provided to Services Australia and CVDL in a password protected file. Services Australia and CVDL will store this information on an encrypted server to protect information securely. They will not provide this information to any additional third parties.

The following people may access your child's identifiable information as part of this study:

- Research members involved with this study (these staff are staff members of either The Royal Children's Hospital and Murdoch Children's Research Institute, or the Victorian Clinical Genetics Service).
- RCH Human Research Ethics Committee.

We will not share your child's identifiable information with anyone else except as required by law.

Sharing information

To advance science, medicine and public health, we may share your child's de-identified data with any current and future funders, research studies, biobanks, medical journals or data research repositories. Some of these organisations may be located overseas. **Any data that we send overseas is not protected by Australian laws and regulations.** By signing the consent form for this study, you are giving us permission to do this. Please note this will not include any data obtained from Services Australia, this data is intended for this study and not for any future research.

If we share your child's data, we will remove identifying details such as your child's name, date of birth and address and give the data a special code number.

We will also put security measures in place to protect your child's data if and when we transfer it to other people. We will make sure any files are completely de-identified and transferred via an encrypted file with access via password only.

Despite our best efforts, there is a small chance that your child could be re-identified by someone outside of this research study. In the unlikely event that this happens, someone from the research team will contact you. If, at any point, you think that your child may have been re-identified, please let us know.

Storage of information

We are required to keep information collected as part of this project for at least fifteen (15) years following the last publication of the project. Following that time, all information that was collected will be securely destroyed.

20. How will you find out the project results?

You have the right to access and correct the information we collect and store about your child. This is in line with relevant Australian and/or Victorian privacy and other relevant laws. Please contact us if you would like to access this information. At the end of the research project, we may present the results at conferences. We may also publish the results in medical journals. We will do this in a way that protects your child's privacy.

At the end of the project we will send you a final letter. This letter will explain what we found out in this project – in other words, our project results. The letter will not have any information specifically about your child.

24. 0 FIGURES

Figure 1: MARVEL-PIC Study Randomisation and Overview

Figure 2: MARVEL-PIC Trial Timeline

Figure 1: Schedule of assessments