ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Unituxin 3.5 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of concentrate contains 3.5 mg of dinutuximab.

Each vial contains 17.5 mg of dinutuximab in 5 mL.

Dinutuximab is a chimeric human/mouse monoclonal antibody produced in a murine myeloma cell line (Sp2/0) by recombinant DNA technology.

Excipient with known effect:

Each 5 mL vial contains 17.2 mg sodium. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unituxin is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months to 17 years, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation (ASCT). It is administered in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and isotretinoin.

4.2 Posology and method of administration

Unituxin is restricted to hospital-use only and must be administered under the supervision of a physician experienced in the use of oncological therapies. It must be administered by a healthcare professional prepared to manage severe allergic reactions including anaphylaxis in an environment where full resuscitation services are immediately available.

Posology

Unituxin is to be administered by intravenous infusion over five courses at a daily dose of 17.5 mg/m^2. It is administered on Days 4–7 during Courses 1, 3, and 5 (each course lasting approximately 24 days) and on Days 8–11 during Courses 2 and 4 (each course lasting approximately 28 days).

The treatment regimen consists of dinutuximab, GM-CSF, IL-2, and isotretinoin, administered over six consecutive courses. The complete dosing regimen is outlined in Table 1 and Table 2.

Table 1: Courses 1, 3, and 5 dosing schedule for Unituxin, GM-CSF and isotretinoin

Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15-24**
GM-CSF[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dinutuximab[2]				X	X	X	X								
Isotretinoin[3]											X	X	X	X	X

[1.] Granulocyte macrophage colony-stimulating factor (GM-CSF): 250 μg/m^2/day, administered by either subcutaneous injection (strongly recommended) or intravenous infusion over 2 hours.
[2.] Dinutuximab: 17.5 mg/m^2/day, administered by intravenous infusion over 10–20 hours.
[3.] Isotretinoin: for body weight greater than 12 kg: 80 mg/m^2 administered orally twice daily for a total dose of 160 mg/m^2/day; for body weight up to 12 kg: 2.67 mg/kg administered orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

Table 2: Courses 2 and 4 dosing schedule for Unituxin and IL-2; Courses 2, 4, and 6 dosing schedule for isotretinoin

Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12-14**	**15-28**
IL-2[1]	X	X	X	X				X	X	X	X		
Dinutuximab[2]								X	X	X	X		
Isotretinoin[3]													X

[1.] Interleukin-2 (IL-2): 3 MIU/m^2/day administered by continuous intravenous infusion over 96 hours on Days 1-4 and4.5 MIU/m^2/day on Days 8-11.
[2.] Dinutuximab: 17.5 mg/m^2/day, administered by intravenous infusion over 10-20 hours.
[3.] Isotretinoin: for body weight greater than 12 kg: 80 mg/m^2 administered orally twice daily for a total dose of 160 mg/m^2/day; for body weight up to 12 kg: 2.67 mg/kg administered orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

Prior to starting each treatment course, refer to Table 3 for a list of criteria that must be evaluated.

Table 3: Clinical criteria that must be evaluated prior to the start of each treatment course of Unituxin

Central nervous system (CNS) toxicity
• Delay course initiation until CNS toxicity is Grade 1 or resolved and/or seizure disorder is well controlled
Hepatic dysfunction
• Delay initiation of first course until alanine aminotransferase (ALT) is less than 5 times upper limit of normal (ULN). Delay initiation of courses 2-6 until ALT is less than 10 times ULN.
Thrombocytopenia
• Delay course initiation until platelet count is at least 20,000/μL. • If patient has CNS metastases, delay course initiation and give platelet transfusion to maintain platelet count at least 50,000/μL.
Respiratory dysfunction
• Delay course initiation until dyspnoea at rest has been resolved and/or peripheral oxygen saturation is at least 94 % on room air.
Renal dysfunction
• Delay course initiation until creatinine clearance or glomerular filtration rate (GFR) is at least 70 mL/min/1.73 m^2
Systemic infection or sepsis
• Delay course initiation until systemic infection or sepsis has resolved.
Leukopaenia
• Delay initiation of first course until absolute phagocyte count (APC) is at least 1,000/μL.

In addition to the above criteria, clinician judgement must be exercised in the evaluation of the patient's cardiovascular functions.

Dose modification

Table 4 provides dose modification guidance for dinutuximab, GM-CSF and IL-2. If patients meet criteria for discontinuation of these medications, treatment may continue with isotretinoin as clinically indicated.

Table 4: Dose modification guidance for the management of treatment-emergent adverse reactions during administration of dinutuximab in combination with GM-CSF, IL-2 and isotretinoin.

Allergic reactions	
Grade 1 or 2	
Onset of symptoms	• Reduce rate of infusion to 0.875 mg/m^2/h. • Administer supportive measures (see section 4.4).
After resolution	• Resume infusion at the original rate. If not tolerated, reduce rate to 0.875 mg/m^2/h.
Grade 3 or 4	
Onset of symptoms	• Immediately discontinue dinutuximab and intravenous GM-CSF or IL-2. • Administer supportive measures (see section 4.4).
After resolution	• If signs and symptoms resolve rapidly with the above measures, dinutuximab infusion may be resumed at a rate of 0.875 mg/m^2/h. • Do not resume GM-CSF or IL-2 until the following day. • For GM-CSF courses, administer GM-CSF at 50 % of the dose starting the next day, and if tolerated, GM-CSF may be given at full dose after completing dinutuximab dosing for that course. • For IL-2 courses, administer IL-2 at 50 % of the dose starting the next day and continue for the remainder of the course. • If symptoms recur with the addition of GM-CSF or IL-2 discontinue GM-CSF or IL-2 and dinutuximab. • If symptoms resolve the following day, resume dinutuximab at tolerated rate without GM-CSF or IL-2.
Recurrence	• Discontinue dinutuximab and GM-CSF or IL-2 for that day. • If symptoms resolve that day, resume the next day with premedication in the intensive care setting (see section 4.4).
Subsequent courses	• Maintain tolerated dinutuximab infusion rate for all subsequent courses with GM-CSF or IL-2.
Anaphylaxis	
Grade 3 or 4	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.
Capillary leak syndrome	
Grade 3 (severe)	
Onset of symptoms	• Discontinue dinutuximab and intravenous GM-CSF or IL-2. • Administer supportive measures (see section 4.4).
After resolution	• Resume dinutuximab infusion at 0.875 mg/m^2/h. • Resume GM-CSF or IL-2 the following day at 50 % of the dose until the last dose of dinutuximab for that course.
Subsequent courses	• If patient tolerated 50 % dose of GM-CSF or IL-2, start at this dose and dinutuximab rate of 0.875 mg/m^2/h. If tolerated, increase GM-CSF or IL-2 to full dose the next day. • If GM-CSF is not tolerated at 50 % of the dose, administer dinutuximab alone for the remainder of the GM-CSF courses. • If IL-2 is not tolerated at 50 % of the dose, substitute with GM-CSF for the remainder of the IL-2 courses.
Grade 4(life-threatening)	
Onset of symptoms	• Discontinue dinutuximab and GM-CSF or IL-2 for that course. • Administer supportive measures (see section 4.4).
Subsequent courses	• If capillary leak syndrome occurred during IL-2 course, substitute

	GM-CSF for remainder of IL-2 courses. • If capillary leak syndrome occurred during GM-CSF course, administer dinutuximab alone for subsequent GM-CSF courses.
Hyponatraemia	
Grade 4(life-threatening) - < 120 mmol/L despite appropriate fluid management	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.
Hypotension	
Symptomatic and/or systolic BP less than 70 mmHg or a decrease that is more than 15% below baseline	
Onset of symptoms	• Discontinue dinutuximab and intravenous GM-CSF or IL-2. • Administer supportive measures (see section 4.4).
After resolution	• Resume dinutuximab infusion at 0.875 mg/m^2/h. • If blood pressure (BP) remains stable for at least 2 hours, resume GM-CSF or IL-2. • If BP remains stable for at least 2 hours after resuming GM-CSF or IL-2, increase the dinutuximab infusion to 1.75 mg/m^2/h.
Recurrence	• Discontinue dinutuximab and GM-CSF or IL-2. • Resume dinutuximab at 0.875 mg/m^2/h once BP is stable.
After resolution	• Resume GM-CSF or IL-2 the following day at 50 % of the dose if BP remains stable. • Start GM-CSF or IL-2 at 50 % of the dose when administered with dinutuximab. Then increase to full dose if tolerated for the remainder of the course. • If GM-CSF is not tolerated at 50 % of the dose, administer dinutuximab alone for the remainder of the course. • If IL-2 is not tolerated at 50 % of the dose, administer dinutuximab alone for the remainder of the course.
Subsequent courses	• Start GM-CSF or IL-2 at 50 % of the dose, increase to full dose if tolerated the next day. • If GM-CSF is not tolerated at 50 % of the dose, administer dinutuximab alone for the remainder of the GM-CSF courses. • If IL-2 is not tolerated at 50 % of the dose, substitute with GM-CSF for remainder of the IL-2 courses.
Neurological disorders of the eye	
Dilated pupil with sluggish light reflex	
Onset of symptoms	• Discontinue dinutuximab and GM-CSF or IL-2.
After resolution	• Administer dinutuximab at 0.875 mg/m^2/h and resume GM-CSF or IL-2.
Recurrence	• Discontinue dinutuximab, GM-CSF, and IL-2 for remaining courses.
Subsequent courses	• If abnormalities remain stable or improve before the next course administer dinutuximab at 0.875 mg/m^2/h and full dose GM-CSF or IL-2. • If tolerated without worsening symptoms, administer dinutuximab at 1.75 mg/m^2/h for subsequent courses. • If symptoms recur, discontinue dinutuximab, GM-CSF, and IL-2 for remaining courses.
Serum sickness	
Grade 4 (life-threatening)	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.
Systemic infection or sepsis	
Grade 3 or 4	
Onset of symptoms	• Discontinue dinutuximab and GM-CSF or IL-2 for remainder of course.
After resolution	• Proceed with subsequent planned dinutuximab and GM-CSF or IL-2 courses.
Pain	
Grade 4	
	• Discontinue dinutuximab and GM-CSF or IL-2.

Peripheral neuropathy	
Grade 2 peripheral motor neuropathy	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.
Grade 3 (sensory changes for more than 2 weeks, objective motor weakness) or Grade 4	
	• Discontinue dinutuximab and GM-CSF or IL-2.
Atypical Haemolytic Uraemic Syndrome	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.

Paediatric population

The safety and efficacy of Unituxin in children aged less than 12 months have not yet been established.

Method of administration

Unituxin should not be administered as an intravenous push or bolus. It should be administered by intravenous infusion over 10 hours. The infusion is started at a dose rate of 0.875 mg/m^2/h and continued at this rate for 30 minutes; the rate is then increased to 1.75 mg/m^2/h and continued at this rate for the remainder of the infusion, if tolerated. The infusion duration may be extended up to 20 hours to help minimise reactions during infusion (see sections 4.4 and 4.8) that do not respond adequately to other supportive measures. The infusion must be terminated after 20 hours, even if the full dose cannot be delivered within this timeframe.

Pre-medication should always be considered before starting each infusion (see section 4.4).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity (Grade 4) to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Allergic reactions
Antihistamine premedication (e.g. hydroxyzine or diphenhydramine) should be administered by intravenous injection approximately 20 minutes before starting each dinutuximab infusion. It is recommended that antihistamine medicinal product be repeated every 4–6 hours as required during infusion of Unituxin. Patients should be monitored for signs and symptoms of infusion reactions for 4 hours after the completion of the Unituxin infusion.

Epinephrine (adrenaline) and hydrocortisone for intravenous administration should be immediately available at the bedside during administration of dinutuximab to manage life-threatening allergic reactions. It is recommended that treatment for such reactions include hydrocortisone administered by intravenous bolus, and epinephrine administered by intravenous bolus once every 3–5 minutes as necessary according to clinical response.

Depending on the severity of the allergic reaction, the rate of infusion should be reduced or treatment discontinued (see sections 4.2 and 4.8).

Capillary leak syndrome
Capillary leak syndrome is more likely when dinutuximab is co-administered with IL-2. It is recommended to administer oral metolazone or intravenous furosemide every 6–12 hours as required. Supplemental oxygen, respiratory support, and albumin replacement therapy should be used as necessary according to clinical response.

Characteristic symptoms and signs include hypotension, generalized oedema, ascites, dyspnoea, pulmonary oedema and acute renal failure associated with hypoalbuminaemia and haemoconcentration.

Pain
Severe pain (Grade 3 or 4) occurs most frequently during the first 4-day course of dinutuximab, often subsiding over time with subsequent courses.

For severe pain, the Unituxin infusion rate should be decreased to 0.875 mg/m^2/hour. Unituxin should be discontinued if pain is not adequately controlled despite infusion rate reduction and institution of maximum supportive measures (see sections 4.2 and 4.8).

Paracetamol should be administered orally 20 minutes prior to starting each dinutuximab infusion, and repeated every 4-6 hours as needed. Regular dosing every 4–6 hours is recommended when IL-2 is coadministered. If required for persistent pain, ibuprofen should be administered orally every 6 hours between doses of paracetamol. Ibuprofen should not be administered if there is evidence of thrombocytopenia, bleeding, or renal dysfunction.

An opioid, such as morphine sulphate, is recommended to be administered by intravenous infusion prior to each dinutuximab infusion and continued as an intravenous infusion during and until 2 hours after completion of the treatment. It is recommended that additional intravenous bolus doses of an opioid are administered as needed for treatment of pain up to once every 2 hours during the dinutuximab infusion. If morphine is not tolerated, then fentanyl or hydromorphone may be utilised.

Lidocaine may be administered as an intravenous infusion (2 mg/kg in 50 mL of 0.9 % sodium chloride) over 30 minutes prior to the start of each dinutuximab infusion and continued via intravenous infusion at 1 mg/kg/h up to 2 hours after completion of the treatment. Lidocaine infusion should be discontinued if the patient develops dizziness, perioral numbness, or tinnitus.

Gabapentin may be administered at the time of starting morphine premedication, at an oral dose of 10 mg/kg/day. The dose may be subsequently increased (up to a maximum of 60 mg/kg/day or 3600 mg/day) as needed for pain management.

Hypotension
Intravenous sodium chloride 9 mg/mL (0.9%) solution for injection (10 mL/kg) should be administered over one hour just prior to the dinutuximab infusion. If hypotension occurs, this can be repeated, or intravenous albumin or packed red blood cells can be administered as clinically indicated. It is recommended that vasopressor therapy is also administered if necessary to restore an adequate perfusion pressure.

Neurological disorders of the eye
Eye disorders may occur, especially with repeated courses (see section 4.8). These changes usually resolve over time. Patients should have an ophthalmic examination before initiating therapy and be monitored for visual changes.

Hepatic dysfunction
Regular monitoring of liver function is recommended during dinutuximab immunotherapy.

Systemic infections
Patients typically have a central venous catheter in situ and as a consequence of prior ASCT are likely to be immunocompromised during therapy, and therefore, at risk of developing systemic infection. Patients should have no evidence of systemic infection and any identified infection should be under control before beginning therapy.

Laboratory test abnormalities
Electrolyte abnormalities have been reported in patients who received Unituxin (see section 4.8). Electrolytes should be monitored daily during therapy with Unituxin.

Atypical Haemolytic Uraemic Syndrome
Haemolytic uraemic syndrome in the absence of documented infection and resulting in renal insufficiency, electrolyte abnormalities, anaemia, and hypertension has been reported. Supportive measures should be instituted including control of hydration status, electrolyte abnormalities, hypertension, and anaemia.

Sodium intake
This medicine contains less than 1 mmol sodium (23 mg) per dose. This means it is essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. A risk for interactions with concomitantly used medicinal products cannot be excluded.

Corticosteroids
It is not recommended to use systemic corticosteroid medicinal products due to possible interference with immune activation which is necessary for the therapeutic action of dinutuximab.

Intravenous immunoglobulin
It is not recommended to use intravenous immunoglobulin after ASCT. If necessary, its use must be limited to the first 100 days after ASCT, as immunoglobulin may interfere with dinutuximab-dependent cellular cytotoxicity. Immunoglobulin must not be given within two weeks before and one week after completing each course of Unituxin.

Pharmacokinetic interactions
No interaction studies have been performed.

Pharmacodynamic interactions
Severe allergic reactions are more likely when dinutuximab is co-administered with IL-2. Therefore caution should be taken when both medicinal products are combined (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of dinutuximab in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Hence, this medicinal product is not recommended during pregnancy and in women of childbearing potential not using contraception. It is recommended that women of childbearing potential use contraception for 6 months after discontinuation of treatment with Unituxin.

Breast-feeding
Human IgG is known to be secreted in human milk. There is insufficient information on the excretion of dinutuximab in human milk. Breast-feeding should be discontinued during treatment with Unituxin. The recommended interval time between treatment discontinuation and breastfeeding is 6 months.

Fertility
The effects of dinutuximab on fertility in humans are unknown. In animals, fertility studies have not been conducted; however in male and female rats, no adverse effects on reproductive organs were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Unituxin has major influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions reported in four clinical studies (ANBL0032, ANBL0931, CCG-0935A, and DIV-NB-201) of dinutuximab in patients (N=984) with high-risk neuroblastoma are summarized in Table 5. Adverse reactions are defined as those adverse events that occurred at a higher frequency in the dinutuximab, GM-CSF, IL-2 and isotretinoin-treated group compared with the isotretinoin-treated control group during the ANBL0032 randomised, controlled, pivotal study, and that have a plausible mechanistic relationship to treatment with dinutuximab. Originally reported terms have been coded to preferred terms (using the Medical Dictionary for Regulatory Activities [MedDRA]).

Table 5 summarizes adverse drug reactions reported when dinutuximab was administered in combination with GM-CSF, IL-2, and isotretinoin. As this medicinal product is used in combination with GM-CSF, IL-2, and isotretinoin, it is difficult to ascertain the causal relationship of each adverse reaction to a particular medicinal product.

The most frequently occurring (more than 30% of patients) adverse reactions reported during the neuroblastoma studies were hypotension (67 %), pain (66 %), hypersensitivity (56 %), pyrexia (53 %), urticaria (49 %), capillary leak syndrome (45 %), anaemia (45 %), hypokalaemia (41 %), platelet count decreased (40 %), hyponatraemia (37 %), alanine aminotransferase increased (35 %), decreased lymphocyte count (34%) and decreased neutrophil count (31%). Additional adverse reactions characteristic of an allergic response were also reported – including anaphylactic reaction (18 %) and bronchospasm (4 %).

Tabulated list of adverse reactions

Adverse reactions reported for subjects receiving dinutuximab in combination with GM-CSF, IL-2, and isotretinoin are summarised in Table 5. These adverse reactions are presented by MedDRA system organ class and frequency. Frequency categories are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions that have occurred during studies in high risk neuroblastoma patients receiving dinutuximab in combination with GM-CSF, IL-2, and isotretinoin.

System Organ Class	Very Common	Common	Uncommon
Infections and infestations		Device-related infection, infection susceptibility increased, bacteraemia, enterocolitis	
Blood and lymphatic system disorders	Anaemia	Febrile neutropenia	Atypical haemolytic uraemic syndrome
Immune system disorders	Anaphylactic reaction, hypersensitivity	Cytokine release syndrome	Serum sickness
Endocrine disorders			Hyperthyroidism
Metabolism and nutrition disorders	Hypokalaemia, hyponatraemia, hypocalcaemia, hypophosphataemia, hypoalbuminaemia, hyperglycaemia, decreased appetite	Hypomagnesaemia, acidosis, hypoglycaemia,	
Nervous system disorders		Neuralgia, peripheral neuropathy, headache	Posterior reversible encephalopathy syndrome
Eye disorders		Vision blurred,	Unequal pupils

System Organ Class	Very Common	Common	Uncommon
		photophobia, mydriasis	
Cardiac disorders	Tachycardia (sinusal, atrial, ventricular)		Atrial fibrillation, ventricular arrhythmia
Vascular disorders	Capillary leak syndrome, hypotension, hypertension		
Respiratory, thoracic and mediastinal disorders	Hypoxia, cough, dyspnoea	Bronchospasm, pulmonary oedema	Stridor, laryngeal oedema
Gastrointestinal disorders	Diarrhoea, vomiting, nausea	Constipation, lower gastrointestinal haemorrhage	
Skin and subcutaneous tissue disorders	Urticaria, pruritus	Maculo-papular rash	
Renal and urinary disorders		Urinary retention, proteinuria, haematuria	Renal failure
General disorders and administration site conditions	Pyrexia, pain[1], face oedema	Peripheral oedema, chills, fatigue, irritability Injection site reaction	
Investigations	Decreased platelet count, decreased lymphocyte count, decreased white blood cell count, decreased neutrophil count, increased aspartate aminotransferase, increased alanine aminotransferase	Increased gamma-glutamyltransferase, increased blood creatinine, increased weight	Blood culture positive

[1] Includes preferred terms abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia.

Description of selected adverse reactions

Refer to section 4.2 for advice on tapering off or discontinuation of this medicinal product. Refer to section 4.4 for actions to be taken for specific adverse reactions.

Allergic reactions
Serious infusion reactions requiring urgent intervention including blood pressure support, bronchodilator therapy, corticosteroids, infusion rate reduction, infusion interruption, or permanent discontinuation of Unituxin included facial and upper airway oedema, dyspnoea, bronchospasm, stridor, urticaria, and hypotension. Infusion reactions generally occurred during or within 24 hours of completing the Unituxin infusion. Serious anaphylactic/allergic reactions were reported in 14% of patients. Due to overlapping signs and symptoms, it was not possible to distinguish between infusion reactions and hypersensitivity/allergic reactions in some cases.

Capillary leak syndrome
Capillary leak syndrome was a very common adverse reaction (45 % of patients) that occurred more frequently when Unituxin was co-administered with IL-2; it was severe (≥ Grade 3) in 14% of patients.

Pain
Pain typically occurred during the Unituxin infusion and was most commonly reported as abdominal pain, generalized pain, extremity pain, back pain, neuralgia, musculoskeletal chest pain, and arthralgia; 41% of patients suffered severe pain. Analgesics including intravenous opioids should be administered prior to each dose of Unituxin and continued until two hours following completion of Unituxin infusion.

Peripheral sensory neuropathy was reported in 3% of patients and peripheral motor neuropathy in 2% of patients; less than 1% of patients experienced serious peripheral neuropathy.

Laboratory test abnormalities
Electrolyte abnormalities occurring in at least 25 % of patients who received Unituxin included hyponatraemia and hypokalaemia.

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

4.9 Overdose

No cases of dinutuximab overdose have been reported. In clinical trials, scheduled dinutuximab doses of up to 120 mg/m^2 (60 mg/m^2/day) have been administered with an adverse reaction profile similar to that described in section 4.8. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01XC16

Mechanism of action

Dinutuximab is a monoclonal chimeric antibody composed of murine variable heavy and light chain regions and the human constant region for the heavy chain IgG1 and light chain kappa. Dinutuximab reacts specifically with the ganglioside GD2, which is highly expressed on the surface of neuroblastoma cells and minimally expressed on the surface of normal human neurons, peripheral pain fibres, and skin melanocytes.

Pharmacodynamic effects

Dinutuximab has been shown to bind to neuroblastoma cell lines known to express GD2 in vitro. In addition, it has been shown to induce both antibody dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity in vitro. Specifically, in the presence of human effector cells including peripheral blood mononuclear cells (PBMC) and granulocytes from normal human donors, dinutuximab was found to mediate the lysis of several neuroblastoma cell lines in a dose-dependent manner. Granulocytes were found to be more effective than PBMCs in mediating dinutuximab dependent cytotoxicity of neuroblastoma cells, with enhanced cell lysis observed with the addition of GM-CSF. Additionally, in vivo studies demonstrate that dinutuximab either alone or in combination with IL-2 can partially inhibit tumour growth in mice. Augmentation of ADCC in the presence of GM-CSF and IL-2 provided the rationale for combining these cytokines with dinutuximab in clinical studies.

Non-clinical studies demonstrate that dinutuximab-induced neurotoxicity is likely due to the induction of mechanical allodynia that may be mediated by reactivity of dinutuximab with GD2 antigen located on the surface of peripheral nerve fibres and/or myelin.

Clinical efficacy and safety

ANBL0032 was a randomised, controlled study that evaluated the effects of dinutuximab administered in combination with GM-CSF, IL-2, and isotretinoin compared with isotretinoin alone in high-risk neuroblastoma subjects. High-risk neuroblastoma was based on the patient age (greater than 12 months) and tumour stage at diagnosis and / or the presence of biological risk factors, such as MYCN amplification.

Patients were aged 11 months to 15 years and had previously achieved at least a partial response to induction chemotherapy, followed by ASCT and radiotherapy. Following ASCT, 226 subjects were randomly assigned 1:1 to either a standard therapy arm (six courses of isotretinoin) or a dinutuximab immunotherapy arm (five courses of dinutuximab in combination with alternating GM-CSF and IL-2; combined with isotretinoin concurrently for six courses). Dinutuximab was administered at a dose equivalent to 17.5 mg/m^2/day on four consecutive days (Days 4–7) of Courses 1–5. GM-CSF was administered at a dose of 250 µg/m^2/day during Courses 1, 3, and 5 and dosed daily for 14 days. IL-2 was administered concurrently with dinutuximab as a continuous intravenous infusion for four days during Week 1 of Courses 2 and 4 at a dose of 3.0 MIU/m^2/day, and during Week 2 of Courses 2 and 4 at a dose of 4.5 MIU/m^2/day. During the last two weeks in each of the six courses, subjects in both the control and the dinutuximab immunotherapy arms were also given oral isotretinoin at a dose of 160 mg/m^2/day (given as 80 mg/m^2 twice daily).

The primary efficacy outcome measure was investigator-assessed event-free survival (EFS) defined as time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy, or death. The primary intent-to-treat (ITT) analysis found an improvement in EFS associated with dinutuximab immunotherapy plus isotretinoin, as compared to isotretinoin alone. The 2-year estimates of EFS were 66 % among subjects receiving dinutuximab immunotherapy plus isotretinoin as compared with 48 % in subjects receiving isotretinoin alone (log-rank test p = 0.033) although this difference did not reach formal statistical significance according to the pre-specified plan for interim analyses. In addition, overall survival (OS) was evaluated with 3 years of follow-up after the EFS analysis as a secondary endpoint with a significant improvement observed among ITT subjects randomly allocated to receive dinutuximab immunotherapy plus isotretinoin as compared with isotretinoin alone. The 3-year estimates of OS were 80 % compared with 67 % among subjects receiving dinutuximab immunotherapy plus isotretinoin and isotretinoin alone, respectively (log-rank test p = 0.0165). Long-term overall survival was evaluated with 5 years of follow up after the EFS analysis and continued to demonstrate a survival advantage for patients who received dinutuximab immunotherapy compared to those who received isotretinoin alone. The 5 year estimates of OS were 74 % for dinutuximab immunotherapy compared to 57 % for isotretinoin alone (log-rank test p = 0.030).

Subgroup analyses of EFS and OS response indicated that patients with minimal residual disease, DNA hyperploidy, and those having received a purged bone marrow may not have benefited from dinutuximab immunotherapy.

Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. Data from 409 subjects participating in several neuroblastoma studies and having samples available for the determination of human anti-chimeric antibodies (HACA) demonstrated that 71 (17%) developed binding antibodies and 15 (4%) developed a neutralising antibody response. Plasma concentrations of dinutuximab, especially trough levels, tended to be lower in patients with HACA. There was no apparent correlation between the development of these antibodies and allergic reactions.

The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay and for these reasons, comparison of the incidence of antibodies to dinutuximab with the incidence of antibodies to other products may be misleading.

Paediatric population

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

5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of dinutuximab were evaluated in a clinical study of Unituxin in combination with GM-CSF, IL-2, and isotretinoin. In this study, 27 children with high-risk neuroblastoma (age: 3.9 ± 1.9 years) received up to 5 cycles of Unituxin at 17.5 mg/m^2/day as an intravenous infusion over 10 to 20 hours for 4 consecutive days every 28 days. The mean (± standard deviation) maximum plasma concentration observed after the 4th infusion was 11.5 (± 2.3) mcg/mL. In a population pharmacokinetic analysis, the geometric mean volume of distribution at steady state was estimated at 5.2 L.

Biotransformation

Dinutuximab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed.

Elimination

The geometric mean clearance was estimated at 0.025 L/hr and increased with body size. The terminal half-life was estimated at 10 (+ 6) days.

A population pharmacokinetic analysis conducted on all clinical data available suggests that the disposition of dinutuximab is not altered by age, race, gender, concomitant medications (IL-2, GM-CSF) and the presence of capillary leak syndrome, renal or hepatic impairment. However, the presence of HACA appears to increase the clearance of dinutuximab by approximately 60%.

5.3 Preclinical safety data

General toxicology

Dinutuximab (or the murine monoclonal antibody 14.18) has been administered to mice, rabbits, rats, and dogs in single- or repeat-dose regimens that exceed the dose that is used clinically. Findings of note included treatment related adverse reactions of the liver in rats (characterized by centrilobular congestion, abnormal cell division, hepatocellular necrosis and pericentral vein/interlobular fibrosis) which may be related to circulatory disturbances and changes indicative of increased haematopoiesis (high reticulocyte ratio and/or platelet count, increased cellularity of the haematopoietic cells in the femoral and sternal bone marrow, and/or extramedullary haematopoiesis in the liver and spleen). These changes were noted to be very slight to slight in severity and recovered or tended to recover following the cessation of dosing. No clinical signs of CNS toxicity were observed.

Safety pharmacology

Dinutuximab was administered to cynomolgous monkeys resulting in effects on the cardiovascular system, which consisted of moderate increases in blood pressure (one of three animals) and heart rate (two of three animals). No direct effects on electrocardiogram parameters or on the respiratory system were observed.

Other

No non-clinical studies to evaluate the potential of dinutuximab to cause carcinogenicity, genotoxicity, or developmental and reproductive toxicity have been conducted. In male and female rats, administration of dinutuximab resulted in no adverse effects on reproductive organs at exposures that were at least 60-fold higher than those observed clinically.

Non-clinical data reveal no special hazard for humans based on conventional studies conducted to date. These studies support the current dinutuximab dosing regimen of 17.5 mg/m^2/day administered for four consecutive days during five monthly courses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Polysorbate 20 (E 432)
Sodium chloride
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

18 months

Diluted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at ambient conditions (less than 25°C).

From a microbiological point of view, unless the method of opening/reconstituting/dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store and transport refrigerated (2°C – 8°C).

Do not freeze.

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

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear Type I glass vial with a bromobutyl rubber stopper and aluminium flip-off seal containing 5 mL of concentrate for solution for infusion.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

The exact volume of Unituxin concentrate for solution for infusion required for the patient dose (see section 4.2) must be injected into a 100 mL bag of sodium chloride 9 mg/mL (0.9 %) solution for injection.

The required volume of dinutuximab should be withdrawn and injected into a 100 mL bag of sodium chloride 9 mg/mL (0.9 %) solution for injection. The solution should be mixed by gentle inversion.

Dilution must be carried out under aseptic conditions. From a microbiological point of view, the product should be used immediately. For shelf life after dilution, see section 6.3. The diluted solution for infusion must be used within 24 hours of preparation.

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

7. MARKETING AUTHORISATION HOLDER

United Therapeutics Europe, Ltd.
Unither House
Curfew Bell Road
Chertsey
Surrey
KT16 9FG
United Kingdom
Tel: +44 (0)1932 664884
Fax: +44 (0)1932 573800
E-mail: druginfo@unither.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1022/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

United Therapeutics Corporation
1040 Spring Street
Silver Spring, Maryland 20910
USA

Name and address of the manufacturer responsible for batch release

Penn Pharmaceutical Services Limited
23-24 Tafarbaubach Industrial Estate, Tredegar, Gwent
NP22 3AA
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

Description	**Due date**
Non-interventional post authorisation safety study (PASS): In order to evaluate the long-term safety outcomes of dinutuximab in high-risk neuroblastoma patients (including central and peripheral nervous system, prevalence of organ dysfunction, long-term effects on growth and endocrine development, hearing loss, cardiac toxicity and survival data) the applicant should conduct and submit the results of a safety registry. The study protocol should be submitted within 3 months of the EC decision. The clinical study report should be submitted by	06/2029
PASS: In order to better characterise the safety and immunogenicity of Unituxin and its impact on drug exposure, the applicant should conduct and submit the results of a safety study. The clinical study report should be submitted by	12/2018

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Unituxin 3.5 mg/mL concentrate for solution for infusion
dinutuximab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL of concentrate contains 3.5 mg of dinutuximab.
Each 5 mL vial contains 17.5 mg of dinutuximab.

3. LIST OF EXCIPIENTS

Histidine
Polysorbate 20
Sodium chloride
Water for injections

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial
17.5 mg/5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

United Therapeutics Europe, Ltd.
Unither House
Curfew Bell Road
Chertsey, Surrey KT16 9FG
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1022/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

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

Unituxin 3.5 mg/mL sterile concentrate
dinutuximab
Intravenous use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

17.5 mg/5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Unituxin 3.5 mg/mL concentrate for solution for infusion
dinutuximab

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

Occasionally a young person who is taking this medicne may be reading the package leaflet, but usually it will be a parent/carer. Nevertheless the leaflet will refer to 'you' throughout.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Unituxin is and what it is used for

What Unituxin is

Unituxin is a cancer medicine that contains the active substance dinutuximab. It belongs to a group of medicines called 'monoclonal antibodies'. These work like the antibodies produced naturally by the body. They help the immune system to target certain cells, such as cancer cells, by 'sticking' to them.

What Unituxin is used for

Unituxin is used to treat 'high-risk neuroblastoma' in babies, children and adolescents aged 12 months to 17 years old.

Neuroblastoma is a type of cancer that grows from abnormal nerve cells in the body. Some neuroblastomas are classed as 'high risk' if the cancer has spread to various parts of the body and contains certain types of cells. High-risk neuroblastomas are more likely to come back again after treatment.

To reduce the risk of the cancer coming back, Unituxin is given at the last stage of the treatment to eliminate small amounts of disease which may still be present after the cancer has responded to chemotherapy, surgery, and an autologous (self-donating) blood cell transplant.

How Unituxin works

Unituxin recognises and attaches to a cell surface target called 'GD2'. GD2 is found on the surface of neuroblastoma cells. When Unituxin attaches to the GD2 on the cancer cells, the patient's immune system starts to attack these cells and kill them.

Unituxin has been shown to delay the progression or relapse of the disease and to increase survival.

2. What you need to know before you are given Unituxin

Do not take Unituxin if
- you are allergic to dinutuximab or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor or nurse before you are given dinutuximab.

Warnings and precautions
Talk to your doctor or nurse before you are given Unituxin if:
- you have ever had fits (convulsions)
- you have liver problems
- you have a low number of white blood cells or platelets in your blood – shown in tests
- you have breathing problems such as shortness of breath when resting
- you have kidney problems
- you have any infections.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before being given Unituxin.

You might notice the following when you first receive Unituxin and during the course of treatment:

- **Allergic reactions, which may be severe (anaphylactic reactions), or other reactions to the infusion** – Tell your doctor or nurse straight away if you have any kind of reaction during or after the infusion. These are very common (affecting more than 1 in 10 people). Signs of an allergic reaction may include skin rash, hives, swelling in the face or throat, dizziness, a rapid heart beat or palpitations, being short of breath and difficulty breathing, fever, feeling sick, aches and pains in your joints. You will be closely monitored for these signs while being given the medicine. You will be given an anti-histamine medicine which helps to prevent allergic reactions.

- **Capillary Leak Syndrome** due to leakage of blood components through small blood vessel walls - this may cause rapid swelling to arms, legs and other parts of your body, rapid drop in blood pressure, lightheadedness and breathing difficulties

- **Pain** – tell your doctor or nurse if you get any pain. This is very common during treatment (affecting more than 1 in 10 people). You will be given pain relieving medicines (such as paracetamol, ibuprofen and morphine) to help prevent and reduce the pain. See section 4 for more information about pain side effects.

- **Low blood pressure** – this may make you feel dizzy or faint.

- **Problems with your eyes** – tell your doctor or nurse if you notice any problems with your eyes or changes to your vision.

- **Infections of the blood** – tell your doctor if you notice fever, shaking chills, or feel faint or dizzy.

- **Problems with your nerves** – you may notice numbness, tingling or burning in your hands, feet, legs or arms, reduced sensation or weakness with movement (peripheral neuropathy).

See section 4 for a full list of known side effects.

Tests and checks

Your doctor will do blood tests and may do eye tests while you are taking this medicine.

Other medicines and Unituxin

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.
In particular, tell your doctor or nurse if you have recently received:
- medicines called 'corticosteroids' – these can affect the activity of your immune system which is important for Unituxin to work.
- 'intravenous immunoglobulin' – you should not have this type of medicine in the two weeks before Unituxin treatment and for at least one week after treatment has finished.

If any of the above apply to you (or you are not sure), tell your doctor or nurse before you are given Unituxin.

Pregnancy

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before being given this medicine.
- If it is possible for you to become pregnant and you are not using contraception, talk to your doctor before being given this medicine.
- It is recommended to use contraception for 6 months after discontinuation of this medicine.

Breast-feeding

- If you are breastfeeding, talk to your doctor or nurse before being given this medicine.
- You should not breastfeed during treatment with this medicine. This is because it is not known if the medicine can pass into breast-milk. The recommended interval time between treatment discontinuation and breastfeeding is 6 months.

Driving and using machines

Unituxin has many side effects, and this will affect your ability to drive and use machines

Unituxin contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose. This means it is essentially 'sodiumfree'.

3. How Unituxin will be given

Unituxin will be given to you by a doctor or nurse while you are in hospital. It is given as a drip into one of your veins (intravenous infusion).
Unituxin is used with three other medicines:
- Isotretinoin
- GM-CSF
- IL-2

These medicines will be given to you over six courses. Each course lasts one month. You will not be given all of the medicines in every course.

How much is given

Unituxin will be given to you in five of the six courses. The recommended dose is 17.5 mg/m^2. Your doctor will work out your dose based on your body surface area.

During courses (months) 1, 3 and 5

- Unituxin is given as a drip into one of your veins – for about 10 hours each day for four days.
- GM-CSF is given as either an injection under the skin or as a drip into one of your veins each day for 14 days.
- You will be given isotretinoin to take by mouth for the last 14 days of each course.

During courses (months) 2 and 4

- Unituxin is given as a drip into one of your veins – for about 10 hours each day for four days.
- IL-2 is given as a drip into one of your veins for four days in a row (continuous infustion) – for the first four days of the first week and the first four days of the second week of each course.
- You will be given isotretinoin to take by mouth for the last 14 days of each course.

During course (month) 6

- You will only be given isotretinoin to take by mouth.

Your doctor or nurse will check you during and after the infusion. To reduce the risk of side effects, your doctor may increase the time allowed for the Unituxin infusion up to 20 hours. If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine, which is given with GM-CSF, IL-2 and isotretinoin can cause side effects, although not everybody gets them.

Tell your doctor or nurse straight away if you notice the following:

- Any kind of allergic reaction or other reaction at the injection site – symptoms may include a skin rash, hives, swelling in the face or throat, dizziness, a rapid heart beat or palpitations, being short of breath and difficulty breathing, fever, feeling sick, aches and pains in your joints .

- Rapid swelling of the arms, legs and other parts of your body, rapid drop in blood pressure, lightheadedness and breathing difficulties (Capillary Leak Syndrome).

- Any kind of pain: in the stomach, throat, chest, face, hands, feet, legs or arms (such as numbness, tingling or burning) back, neck, joint, bone, muscle, mouth, eye, genitals.

These are very common (may affect more than 1 in 10 people).
If you notice any of these effects, tell your doctor or nurse straight away.

Other side effects that you may experience with this medicine include:

Very common side effects (may affect more than 1 in 10 people):
- cough
- itching
- loss of appetite
- diarrhoea, being sick
- low blood pressure that may make you feel dizzy or faint or high blood pressure
- abnormal blood tests such as low platelets, low red or white blood cells, low level of albumin (this can cause swelling and make you feel weak and tired), abnormal liver function, low level of potassium, sodium, calcium, phosphates, or high level of glucose.

Common side effects (may affect up to 1 in 10 people):
- weight loss, weight gain
- chills
- headache
- feeling tired, irritable
- constipation, blood in stools
- damage to the nerves around the body which may affect movement
- blurred vision, being sensitive to light, the pupils of your eyes staying large (‘dilated’)
- not being able to urinate, blood or protein in your urine

- higher risk of getting infections especially from the devices used to give you the medicine, blood or gut infections
- skin problems where the injection was given, a red rash with small bumps
- abnormal blood tests such as low levels of magnesium, glucose, high level of acids or creatinine.

Uncommon side effects (may affect up to 1 in 100 people):
- unequal pupils
- fluid in or around the lungs
- kidney failure
- over-active thyroid
- serum sickness – an illness similar to an allergy
- abnormal heart rhythm
- swelling in the back part of the brain (Posterior Reversible Encephalopathy Syndrome) – symptoms may include high blood pressure, headache, fits, change in vision or behaviour, feeling drowsy or tired.
- atypical haemolytic uraemic syndrome (aHUS) – an illness that affects the blood system and kidney – symptoms may include flu-like symptoms that do not go away, confusion, lethargy, loss of appetite, or dark coloured urine.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Unituxin

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

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

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

Chemical and physical in-use stability has been demonstrated at ambient conditions (less than 25 °C). From a microbiological point of view, the diluted solution should be used immediately.

Do not use this medicine if you notice any particulate matter or discolouration prior to administration.

Do not throw away any medicines via wastewater or household waste. The doctor or nurse will throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Unituxin contains
- The active substance is dinutuximab. Each vial contains 17.5 mg of dinutuximab in 5 mL. Each mL of concentrate contains 3.5 mg of dinutuximab.
- The other ingredients are histidine, polysorbate 20 (E 432), sodium chloride and water for injection. See section 2 for further information about sodium.

What Unituxin looks like and contents of the pack

Unituxin is a clear, colourless solution for infusion, provided in a clear glass vial. One carton contains one vial.

Marketing Authorisation Holder and Manufacturer

United Therapeutics Europe, Ltd.
Unither House
Curfew Bell Road
Chertsey
Surrey
KT16 9FG
United Kingdom
Tel: +44 (0)1932 664884
Fax: +44 (0)1932 573800
E-mail: druginfo@unither.com

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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Posology and method of administration

Unituxin is restricted to hospital-use only and must be administered under the supervision of a physician experienced in the use of oncological therapies. It must be administered by a healthcare professional prepared to manage severe allergic reactions including anaphylaxis in an environment where full resuscitation services are immediately available.

Posology

Unituxin is to be administered by intravenous infusion over five courses at a daily dose of 17.5 mg/m^2. It is administered on Days 4–7 during Courses 1, 3, and 5 (each course lasting approximately 24 days) and on Days 8–11 during Courses 2 and 4 (each course lasting approximately 28 days).

The treatment regimen consists of dinutuximab, GM-CSF, IL-2, and isotretinoin, administered over six consecutive courses. The complete dosing regimen is outlined in Table 1 and Table 2.

Table 6: Courses 1, 3, and 5 dosing schedule for Unituxin, GM-CSF and isotretinoin

Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15-24**
GM-CSF[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dinutuximab[2]				X	X	X	X								
Isotretinoin[3]											X	X	X	X	X

[1.] Granulocyte macrophage colony-stimulating factor (GM-CSF): 250 µg/m^2/day, administered by either subcutaneous injection (strongly recommended) or intravenous infusion over 2 hours.
[2.] Dinutuximab: 17.5 mg/m^2/day, administered by intravenous infusion over 10–20 hours.
[3.] Isotretinoin: for body weight greater than 12 kg: 80 mg/m^2 administered orally twice daily for a total dose of 160 mg/m^2/day; for body weight up to 12 kg: 2.67 mg/kg administered orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

Table 7: Courses 2 and 4 dosing schedule for Unituxin and IL-2; Courses 2, 4, and 6 dosing schedule for isotretinoin

Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12-14**	**15-28**
IL-2[1]	X	X	X	X				X	X	X	X		
Dinutuximab[2]								X	X	X	X		
Isotretinoin[3]													X

[1.] Interleukin-2 (IL-2): 3 MIU/m^2/day administered by continuous intravenous infusion over 96 hours on Days 1-4 and4.5 MIU/m^2/day on Days 8-11.
[2.] Dinutuximab: 17.5 mg/m^2/day, administered by intravenous infusion over 10-20 hours.
[3.] Isotretinoin: for body weight greater than 12 kg: 80 mg/m^2 administered orally twice daily for a total dose of 160 mg/m^2/day; for body weight up to 12 kg: 2.67 mg/kg administered orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

Prior to starting each treatment course, refer to Table 3 for a list of criteria that must be evaluated.

Table 8: Clinical criteria that must be evaluated prior to the start of each treatment course of Unituxin

Central nervous system (CNS) toxicity
• Delay course initiation until CNS toxicity is Grade 1 or resolved and/or seizure disorder is well controlled
Hepatic dysfunction
• Delay initiation of first course until alanine aminotransferase (ALT) is less than 5 times upper limit of normal (ULN). Delay initiation of courses 2-6 until ALT is less than 10 times ULN.
Thrombocytopenia
• Delay course initiation until platelet count is at least 20,000/μL. • If patient has CNS metastases, delay course initiation and give platelet transfusion to maintain platelet count at least 50,000/μL.
Respiratory dysfunction
• Delay course initiation until dyspnoea at rest has been resolved and/or peripheral oxygen saturation is at least 94 % on room air.
Renal dysfunction
• Delay course initiation until creatinine clearance or glomerular filtration rate (GFR) is at least 70 mL/min/1.73 m^2
Systemic infection or sepsis
• Delay course initiation until systemic infection or sepsis has resolved.
Leukopaenia
• Delay initiation of first course until absolute phagocyte count (APC) is at least 1,000/μL.

In addition to the above criteria, clinician judgement must be exercised in the evaluation of the patient's cardiovascular functions.

Dose modification

Table 4 provides dose modification guidance for dinutuximab, GM-CSF and IL-2. If patients meet criteria for discontinuation of these medications, treatment may continue with isotretinoin as clinically indicated.

Table 9: Dose modification guidance for the management of treatment-emergent adverse reactions during administration of dinutuximab in combination with GM-CSF, IL-2 and isotretinoin.

Allergic reactions	
Grade 1 or 2	
Onset of symptoms	• Reduce rate of infusion to 0.875 mg/m^2/h. • Administer supportive measures.
After resolution	• Resume infusion at the original rate. If not tolerated, reduce rate to 0.875 mg/m^2/h.

Grade 3 or 4	
Onset of symptoms	• Immediately discontinue dinutuximab and intravenous GM-CSF or IL-2. • Administer supportive measures.
After resolution	• If signs and symptoms resolve rapidly with the above measures, dinutuximab infusion may be resumed at a rate of 0.875 mg/m^2/h. • Do not resume GM-CSF or IL-2 until the following day. • For GM-CSF courses, administer GM-CSF at 50 % of the dose starting the next day, and if tolerated, GM-CSF may be given at full dose after completing dinutuximab dosing for that course. • For IL-2 courses, administer IL-2 at 50 % of the dose starting the next day and continue for the remainder of the course. • If symptoms recur with the addition of GM-CSF or IL-2 discontinue GM-CSF or IL-2 and dinutuximab. • If symptoms resolve the following day, resume dinutuximab at tolerated rate without GM-CSF or IL-2.
Recurrence	• Discontinue dinutuximab and GM-CSF or IL-2 for that day. • If symptoms resolve that day, resume the next day with premedication in the intensive care setting.
Subsequent courses	• Maintain tolerated dinutuximab infusion rate for all subsequent courses with GM-CSF or IL-2.
Anaphylaxis	
Grade 3 or 4	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.
Capillary leak syndrome	
Grade 3 (severe)	
Onset of symptoms	• Discontinue dinutuximab and intravenous GM-CSF or IL-2. • Administer supportive measures.
After resolution	• Resume dinutuximab infusion at 0.875 mg/m^2/h. • Resume GM-CSF or IL-2 the following day at 50 % of the dose until the last dose of dinutuximab for that course.
Subsequent courses	• If patient tolerated 50 % dose of GM-CSF or IL-2, start at this dose and dinutuximab rate of 0.875 mg/m^2/h. If tolerated, increase GM-CSF or IL-2 to full dose the next day. • If GM-CSF is not tolerated at 50 % of the dose, administer dinutuximab alone for the remainder of the GM-CSF courses. • If IL-2 is not tolerated at 50 % of the dose, substitute with GM-CSF for the remainder of the IL-2 courses.
Grade 4(life-threatening)	
Onset of symptoms	• Discontinue dinutuximab and GM-CSF or IL-2 for that course. • Administer supportive measures.
Subsequent courses	• If capillary leak syndrome occurred during IL-2 course, substitute GM-CSF for remainder of IL-2 courses. • If capillary leak syndrome occurred during GM-CSF course, administer dinutuximab alone for subsequent GM-CSF courses.
Hyponatraemia	
Grade 4(life-threatening) - < 120 mmol/L despite appropriate fluid management	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.
Hypotension	
Symptomatic and/or systolic BP less than 70 mmHg or a decrease that is more than 15% below baseline	
Onset of symptoms	• Discontinue dinutuximab and intravenous GM-CSF or IL-2. • Administer supportive measures.
After resolution	• Resume dinutuximab infusion at 0.875 mg/m^2/h. • If blood pressure (BP) remains stable for at least 2 hours, resume GM-CSF or IL-2. • If BP remains stable for at least 2 hours after resuming GM-CSF or IL-2,

	increase the dinutuximab infusion to 1.75 mg/m^2/h.
Recurrence	• Discontinue dinutuximab and GM-CSF or IL-2. • Resume dinutuximab at 0.875 mg/m^2/h once BP is stable.
After resolution	• Resume GM-CSF or IL-2 the following day at 50 % of the dose if BP remains stable. • Start GM-CSF or IL-2 at 50 % of the dose when administered with dinutuximab. Then increase to full dose if tolerated for the remainder of the course. • If GM-CSF is not tolerated at 50 % of the dose, administer dinutuximab alone for the remainder of the course. • If IL-2 is not tolerated at 50 % of the dose, administer dinutuximab alone for the remainder of the course.
Subsequent courses	• Start GM-CSF or IL-2 at 50 % of the dose, increase to full dose if tolerated the next day. • If GM-CSF is not tolerated at 50 % of the dose, administer dinutuximab alone for the remainder of the GM-CSF courses. • If IL-2 is not tolerated at 50 % of the dose, substitute with GM-CSF for remainder of the IL-2 courses.
Neurological disorders of the eye	
Dilated pupil with sluggish light reflex	
Onset of symptoms	• Discontinue dinutuximab and GM-CSF or IL-2.
After resolution	• Administer dinutuximab at 0.875 mg/m^2/h and resume GM-CSF or IL-2.
Recurrence	• Discontinue dinutuximab, GM-CSF, and IL-2 for remaining courses.
Subsequent courses	• If abnormalities remain stable or improve before the next course administer dinutuximab at 0.875 mg/m^2/h and full dose GM-CSF or IL-2. • If tolerated without worsening symptoms, administer dinutuximab at 1.75 mg/m^2/h for subsequent courses. • If symptoms recur, discontinue dinutuximab, GM-CSF, and IL-2 for remaining courses.
Serum sickness	
Grade 4 (life-threatening)	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.
Systemic infection or sepsis	
Grade 3 or 4	
Onset of symptoms	• Discontinue dinutuximab and GM-CSF or IL-2 for remainder of course.
After resolution	• Proceed with subsequent planned dinutuximab and GM-CSF or IL-2 courses.
Pain	
Grade 4	
	• Discontinue dinutuximab and GM-CSF or IL-2.
Peripheral neuropathy	
Grade 2 peripheral motor neuropathy	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.
Grade 3 (sensory changes for more than 2 weeks, objective motor weakness) or Grade 4	
	• Discontinue dinutuximab and GM-CSF or IL-2.
Atypical Haemolytic Uraemic Syndrome	
	• Permanently discontinue dinutuximab and GM-CSF or IL-2.

Paediatric population

The safety and efficacy of Unituxin in children aged less than 12 months have not yet been established.

Method of administration

Unituxin should not be administered as an intravenous push or bolus. It should be administered by intravenous infusion over 10 hours. The infusion is started at a dose rate of 0.875 mg/m^2/h and continued at this rate for 30 minutes; the rate is then increased to 1.75 mg/m^2/h and continued at this rate for the remainder of the infusion, if tolerated. The infusion duration may be extended up to 20 hours to help minimise reactions during infusion that do not respond adequately to other supportive measures. The infusion must be terminated after 20 hours, even if the full dose cannot be delivered within this timeframe.

Pre-medication should always be considered before starting each infusion.

For instructions on dilution of the medicinal product before administration see section 6.6 of the SmPC.

Contraindications

Hypersensitivity (Grade 4) to the active substance or to any of the excipients listed in section 6.1 of the SmPC.

Special warnings and precautions for use

Allergic reactions
Antihistamine premedication (e.g. hydroxyzine or diphenhydramine) should be administered by intravenous injection approximately 20 minutes before starting each dinutuximab infusion. It is recommended that antihistamine medicinal product be repeated every 4–6 hours as required during infusion of Unituxin. Patients should be monitored for signs and symptoms of infusion reactions for 4 hours after the completion of the Unituxin infusion.

Epinephrine (adrenaline) and hydrocortisone for intravenous administration should be immediately available at the bedside during administration of dinutuximab to manage life-threatening allergic reactions. It is recommended that treatment for such reactions include hydrocortisone administered by intravenous bolus, and epinephrine administered by intravenous bolus once every 3–5 minutes as necessary according to clinical response.

Depending on the severity of the allergic reaction, the rate of infusion should be reduced or treatment discontinued.

Capillary leak syndrome
Capillary leak syndrome is more likely when dinutuximab is co-administered with IL-2. It is recommended to administer oral metolazone or intravenous furosemide every 6–12 hours as required. Supplemental oxygen, respiratory support, and albumin replacement therapy should be used as necessary according to clinical response.

Characteristic symptoms and signs include hypotension, generalized oedema, ascites, dyspnoea, pulmonary oedema and acute renal failure associated with hypoalbuminaemia and haemoconcentration.

Pain
Severe pain (Grade 3 or 4) occurs most frequently during the first 4-day course of dinutuximab, often subsiding over time with subsequent courses.

For severe pain, the Unituxin infusion rate should be decreased to 0.875 mg/m^2/hour. Unituxin should be discontinued if pain is not adequately controlled despite infusion rate reduction and institution of maximum supportive measures.

Paracetamol should be administered orally 20 minutes prior to starting each dinutuximab infusion, and repeated every 4-6 hours as needed. Regular dosing every 4–6 hours is recommended when IL-2 is coadministered. If required for persistent pain, ibuprofen should be administered orally every 6 hours between doses of paracetamol. Ibuprofen should not be administered if there is evidence of thrombocytopenia, bleeding, or renal dysfunction.

An opioid, such as morphine sulphate, is recommended to be administered by intravenous infusion prior to each dinutuximab infusion and continued as an intravenous infusion during and until 2 hours after completion of the treatment. It is recommended that additional intravenous bolus doses of an opioid are administered as needed for treatment of pain up to once every 2 hours during the dinutuximab infusion. If morphine is not tolerated, then fentanyl or hydromorphone may be utilised.

Lidocaine may be administered as an intravenous infusion (2 mg/kg in 50 mL of 0.9 % sodium chloride) over 30 minutes prior to the start of each dinutuximab infusion and continued via intravenous infusion at 1 mg/kg/h up to 2 hours after completion of the treatment. Lidocaine infusion should be discontinued if the patient develops dizziness, perioral numbness, or tinnitus.

Gabapentin may be administered at the time of starting morphine premedication, at an oral dose of 10 mg/kg/day. The dose may be subsequently increased (up to a maximum of 60 mg/kg/day or 3600 mg/day) as needed for pain management.

Hypotension

Intravenous sodium chloride 9 mg/mL (0.9%) solution for injection (10 mL/kg) should be administered over one hour just prior to the dinutuximab infusion. If hypotension occurs, this can be repeated, or intravenous albumin or packed red blood cells can be administered as clinically indicated. It is recommended that vasopressor therapy is also administered if necessary to restore an adequate perfusion pressure.

Neurological disorders of the eye

Eye disorders may occur, especially with repeated courses. These changes usually resolve over time. Patients should have an ophthalmic examination before initiating therapy and be monitored for visual changes.

Hepatic dysfunction

Regular monitoring of liver function is recommended during dinutuximab immunotherapy.

Systemic infections

Patients typically have a central venous catheter in situ and as a consequence of prior ASCT are likely to be immunocompromised during therapy, and therefore, at risk of developing systemic infection. Patients should have no evidence of systemic infection and any identified infection should be under control before beginning therapy.

Laboratory test abnormalities

Electrolyte abnormalities have been reported in patients who received Unituxin. Electrolytes should be monitored daily during therapy with Unituxin.

Atypical Haemolytic Uraemic Syndrome

Haemolytic uraemic syndrome in the absence of documented infection and resulting in renal insufficiency, electrolyte abnormalities, anaemia, and hypertension has been reported. Supportive measures should be instituted including control of hydration status, electrolyte abnormalities, hypertension, and anaemia.

Sodium intake

This medicine contains less than 1 mmol sodium (23 mg) per dose. This means it is essentially ‘sodium free’.