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Summary of the risk management plan (RMP) for Unituxin (dinutuximab)

This is a summary of the risk management plan (RMP) for Unituxin, which details the measures to be taken in order to ensure that Unituxin is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Unituxin, which can be found on Unituxin's EPAR page.

Overview of disease epidemiology

Unituxin is used to treat children with high-risk neuroblastoma, a rare cancer of nerve cells. Around 1,500 children are diagnosed with the condition each year in Europe with most aged below 2 years at the time of diagnosis. Neuroblastoma occurs in roughly the same number of boys as girls and is no more common in one race or ethnic group than in others.

Around 50% of patients have advanced disease at diagnosis and are considered to have high-risk neuroblastoma, a form of the cancer that has a high chance of returning after treatment. These patients require aggressive treatment, including chemotherapy, radiotherapy and stem-cell transplantation.

Summary of treatment benefits

A main study conducted in 230 patients with high-risk neuroblastoma showed that Unituxin (given with isotretinoin, granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-2) was more effective than isotretinoin alone at keeping patients alive and preventing the re-emergence of their cancer. After around 3 years, 80% of patients receiving Unituxin were alive compared with 67% of patients receiving isotretinoin alone.

Unknowns relating to treatment benefits

All of the patients in the main study with Unituxin had high-risk neuroblastoma. The effects of Unituxin in non-high-risk neuroblastoma are not known.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Infections	Infections were commonly reported with Unituxin (in up to 1 in 10 patients).	Infections can be prevented or treated with antibiotics, and careful monitoring can allow early detection of potential infections.

Risk	What is known	Preventability
		Treatment with Unituxin should not be started in patients who already have symptoms of an infection.
Haematological toxicities – decreased number of blood cells	In studies, subjects treated with Unituxin had lower than normal levels of platelets, white blood cells or red blood cells. Low levels of blood cells occurred very commonly (affecting more than 1 in 10 patients). This can mean that patients are more likely to bleed, to get an infection, or to be tired and irritable.	Blood cell levels can be monitored and the dose of Unituxin reduced if levels fall too low. A transfusion can also be given. Treatment with Unituxin should not be started in patients who have platelet or white blood cell levels that are too low.
Allergic reactions	Approximately half of the patients treated with Unituxin may have an allergic reaction. Signs of an allergic reaction may include skin rash, swelling, fever, feeling sick, aches and pains in joints, dizziness, a rapid heartbeat or palpitations, shortness of breath and difficulty breathing. Approximately one fifth of people treated with Unituxin have a severe reaction that requires urgent treatment.	Medication (e.g. an anti-histamine) is to be given before administering Unituxin in order to reduce the risk of allergic reactions. Careful monitoring for early signs of an allergic reaction is required. Treatment with Unituxin is to be given in a hospital setting so that urgent medical care is readily available.
Problems with the nerves in arms and legs (peripheral neuropathy)	Up to 1 in 10 patients treated with Unituxin may experience problems with their nerves, which can cause severe pain or altered sensation (sensory neuropathy) or cause weakness with movement (motor neuropathy).	If a severe neuropathy develops, treatment with Unituxin should be discontinued.
Effects on vision (blurred vision, sensitivity to light or dilated pupils)	Up to 1 in 10 patients treated with Unituxin may experience effects on their vision, which can limit daily activities and may cause visual impairment.	If a severe effect on eye sight is noted, further treatment with Unituxin may not be possible.
Low blood pressure	Patients treated with Unituxin may have low blood pressure that can make them feel dizzy or faint. This can be severe and require urgent treatment. Low blood pressure may affect more than 1 in 10 patients.	Careful monitoring can detect a reduction in blood pressure early, before it becomes severe. Treatment with Unituxin is always given in a hospital setting so that urgent medical care is readily available.

Risk	What is known	Preventability
Capillary leak syndrome - generalized body swelling, muscle aches, light-headedness, fatigue, shortness of breath and decreased urination	Approximately half of the patients treated with Unituxin may experience capillary leak syndrome. This condition can range from mild to serious and can include body swelling and breathing difficulties which require urgent medical care.	Careful monitoring can allow capillary leak syndrome to be identified early so that treatment can be given to prevent worsening of the condition. Treatment with Unituxin is always given in a hospital setting so that urgent medical care is readily available.
Vomiting and diarrhoea	Vomiting and diarrhoea are very common side effects and may affect more than 1 in 10 patients treated with Unituxin. These events may be severe and require medical care.	Medication can be given to prevent and/or treat vomiting and diarrhoea.
Pain	Approximately 7 in 10 patients treated with Unituxin experience pain due to the way that the medicine works. This pain is frequently severe and can interfere with daily activities.	Pain medication is always given before starting treatment with Unituxin. The dose and rate at which Unituxin is given can also be reduced to help manage symptoms of pain.
Cytokine release syndrome – an infusion reaction that may cause chills, headache and fast heartbeat	Up to 1 in 10 patients treated with Unituxin experience cytokine release syndrome due to the way that Unituxin works. This can be severe but does resolve after treatment.	The patient should be carefully monitored during and immediately after the infusion so symptoms can be treated. Treatment with Unituxin is always given in a hospital setting so that medical care is readily available.
High blood pressure	Patients treated with Unituxin may have high blood pressure that may have no symptoms or result in a headache. High blood pressure may more than 1 in 10 people.	Patients with known high blood pressure can receive treatment prior to and during the infusion to ensure that blood pressure remains under control. In addition, patients without a history of high blood pressure are monitored during the infusion.

Important potential risks

Risk	What is known
Hepatic (liver) dysfunction	More than 1 in 10 patients treated with Unituxin may experience increases in blood levels of their liver enzymes. These increases can be mild or severe.
Medication errors	So far, no errors have been reported in the way that Unituxin is given. However, there is always the possibility that Unituxin or one of the other medicines given with it may be administered at the wrong dose or in the

Risk	What is known
	wrong way. There is limited information on how likely errors are or what the risks might be if they were to happen.
Use in children aged 0–11 months	There is no relevant use of Unituxin in children aged 0–11 months in the indication of high-risk neuroblastoma following myeloablative therapy and stem-cell transplantation.
Irregular heart beat (arrhythmia)	More than 1 in 10 patients treated with Unituxin may experience a heartbeat that is too fast. Up to 1 in 10 patients treated with Unituxin may experience high blood pressure and up to 1 in 100 patients may experience an abnormal heart rhythm that is rapid and irregular.
Immunogenicity (risk of antibody production)	As with all therapeutic proteins, there is potential for immunogenicity. Data from 543 subjects participating in studies showed that dinutuximab triggers an immune response in less than 14% of subjects with high-risk neuroblastoma with less than 5% of those subjects developing what is known as a positive neutralising antibody response. However, the clinical significance of this response is unknown.
Atypical haemolytic uraemic syndrome	This uncommon adverse reaction may occur in up to 1 in 100 people. This is 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.

Missing information

Risk	What is known
Limited information on the long-term effects of treatment early in childhood	Unituxin is given to children and adolescents who have an advanced form of cancer and have already undergone a lot of treatment, including chemotherapy, radiotherapy and stem-cell transplantation. Unituxin is known to increase periods with no symptoms and survival in these children and there is information available on the short-term safety of Unituxin in these children. However, there is limited information on the longer-term effects of Unituxin on physical, mental and sexual development.
Overdose	There is always the possibility of a higher than recommended dose being used either deliberately or accidentally. What side effects might result from a higher dose is not known.
Taking other medicines with Unituxin (drug interactions)	Unituxin is given with a combination of other products: GM-CSF, IL-2 and isotretinoin. Some of those products are not authorised for use in children in the EU. During clinical trials, no interactions between the medicines were seen; however, as specific tests have not been completed, drug interactions cannot be excluded.
Effects in patients with liver problems (hepatic impairment), kidney problems	In clinical studies, patients with liver, kidney and heart disease were not studied in large enough numbers. There is information for doctors on changing the doses for patients with liver and kidney disease but not for heart disease. The doctor is to use their clinical judgement for patients with heart disease.

Risk	What is known
(renal impairment) and heart and blood vessel problems (cardiovascular impairment)	

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Unituxin can be found on Unituxin's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Long-term non-interventional prospective observational registry in patients who received Unituxin for the treatment of high-risk neuroblastoma	To evaluate long-term safety outcomes associated with the central and peripheral nervous system and the prevalence of organ dysfunction including the long-term effects on growth and endocrine development, hearing loss and cardiac toxicity in patients who received Unituxin for high-risk neuroblastoma and have survived > 5 years without relapse. To evaluate event-free survival (EFS) and overall survival (OS)	Long-term effects Central and peripheral nervous system Growth and endocrine development Hearing loss Cardiac toxicity	Planned	Protocol submission: Q4 2015 First patient enrolled: Q4 2016 Enrolment complete: Q4 2028 Yearly interim results date: Beginning 1 year after 1st patient enrolled (Q4 2017). First survival data expected 5 years post-study start

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	in all patients enrolled for up to five years. To compare the late effect safety outcomes of patients treated with Unituxin and cytokines versus patients not exposed using historical control data (e.g. literature).			(~Q4 2021) Study completion: Q4 2029
Post-authorisation safety study	To assess the incident rate of human-anti-chimeric antibody (HACA). To determine the incidence of neutralizing antibody in HACA positive samples. To assess the safety and tolerability of Unituxin combination in high-risk neuroblastoma patients.	Immunogenicity	Planned	First patient enrolled: Q1 2016 Study completion date: Q4 2018
Non-clinical toxicology study	Measure chronic toxicity on the central and peripheral nervous system	Central and peripheral nervous system toxicity	Planned	Final report submission: May 2018
Safety and tolerability	Assess risk of serious infusion reaction and neuropathy an the overall safety and tolerability of Unituxin Assess variations in antibody dependent cell-mediated toxicity on safety and tolerability lots.	Infusion reaction Neuropathy Overall safety and tolerability	Planned	Final report submission: December 2017
Analysis of laboratory data for	Analyse laboratory data including serum	Grade 4 Allergic reactions	Planned	Final report submission:

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
allergic conditions	complement, IgE, tryptase, histamine, and human anti-chimeric antibody levels obtained in patients with documented Grade 4 allergic reactions to allow for improved characterization of these adverse reactions and to determine if the clinical presentation and laboratory data obtained were consistent with an allergic reaction or infusion reaction			March 2017
Assay development	Develop and validate an assay for the detection of neutralising antibodies in the presence of dinutuximab levels	N/A	Planned	Final report submission: October 2015
Neutralizing antibody study	Assess the neutralizing anti-body response to dinutuximab with a validated assay.	Clinical impact of neutralizing antibody	Planned	Interim report: September 2016 Final report submission: June 2019
Non-human glycans study	Collect data on antibodies against non-human glycans from the ANBL0032 study and their impact on safety and efficacy	Clinical impact of antibodies against non-human glycans	Planned	2016

Studies which are a condition of the marketing authorisation

Following studies are conditions of the marketing authorisation:

- Long-term non-interventional prospective observational registry in patients who received Unituxin for the treatment of high-risk neuroblastoma
- Post-authorisation safety study (immunogenicity)

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 06-2015.