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Summary of the risk management plan (RMP) for Translarna (ataluren)

This is a summary of the risk management plan (RMP) for Translarna, which details the measures to be taken in order to ensure that Translarna 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 Translarna, which can be found on Translarna's EPAR page.

Overview of disease epidemiology

Translarna (ataluren) is a medicine used to treat patients aged 5 years and older with Duchenne muscular dystrophy (DMD) who are able to walk. DMD is a rare genetic disease that gradually causes weakness and loss of muscle function. It mainly affects boys and occurs in 1 in 3,500 male births. The disease is caused by defects ('mutations') in the gene for dystrophin, a protein that helps to protect muscles from injury as muscles contract and relax. Translarna is for use in the group of Duchenne patients whose disease is caused by a defect in the dystrophin gene called 'nonsense mutation'. Approximately 13% of boys with DMD have this specific genetic defect.

Summary of treatment benefits

Translarna has been studied in one main study involving 174 patients, aged 5 to 20 years. In the study, patients were randomly assigned to receive either placebo (a dummy treatment), ataluren at a low dose of 40 mg/kg daily or ataluren at a high dose of 80 mg/kg daily. The main measure of effectiveness was the change in the distance the patient could walk in six minutes after 48 weeks of treatment.

Although an initial analysis of the results of all the data from the study did not show a significant difference in the distances patients in the Translarna and placebo groups could walk, further analyses indicated that patients receiving the 40 mg/kg daily dose experienced a slower decline in walking ability than patients receiving placebo. There was no difference between the 80 mg/kg daily dose and placebo in the distance patients could walk in 6 minute following 48 weeks of treatment.

Other measures of muscle function (climbing stairs, descending stairs, and walking/running 10 meters) suggested an improvement in the group receiving Translarna at 40 mg/kg daily compared with placebo.

The safety data from this study showed that Translarna was well tolerated at both doses.

Unknowns relating to treatment benefits

Nearly all patients included in the main and supporting studies with Translarna were white Caucasians. There is no evidence to suggest that results would be any different in non-white patients.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Potentiation of aminoglycoside renal (kidney) toxicity	Since ataluren may increase the toxic effect of aminoglycoside on the kidneys, patients' risk of kidney injury is further increased if they receive ataluren while receiving aminoglycoside antibiotics.	Patients who receive aminoglycoside antibiotics (such as gentamicin, tobramycin, or streptomycin) into a vein should not take ataluren during the time they are receiving the antibiotics.
Changes in lipid (fat) profile	Patients who take ataluren may experience increases in their cholesterol and/or triglyceride (types of fat) blood levels.	Patients should have annual blood tests to determine if there is an increase in their cholesterol and/or triglycerides. If that is the case, appropriate measures (for example, modifying diet or taking a lipid-lowering medicine) should be taken to minimise or stop the increase.

Important potential risks

Risk	What is known
Hypertension (high blood pressure) with concomitant use of systemic corticosteroids	Patients who take ataluren together with certain medicines called corticosteroids may be at risk of having high blood pressure.
Renal (kidney) toxicity	Patients who take ataluren may be at risk of kidney toxicity, as reflected by increases in blood parameters that measure kidney function.
Hepatic (liver) toxicity	Patients who take ataluren may be at risk of liver toxicity, as reflected by increases in blood parameters that measure liver function.
Hibernoma	Some rats given ataluren at high doses developed hibernomas, which is a benign tumour of the brown fat tissue.
Cancer	Some rats given ataluren at high doses developed tumours of the urinary bladder.

Missing information

Risk	What is known
Effect of co-administration of ataluren with nephrotoxic medicines (medicines that are toxic to the kidneys) other than aminoglycosides	Patients who receive aminoglycoside antibiotics into a vein while taking ataluren are at increased risk of injury to their kidneys. It is not known if the same risk occurs when taking ataluren together with other medicines known to cause kidney injury.
Use in patients with moderate	No studies have been conducted with ataluren in patients with liver

Risk	What is known
to severe hepatic (liver) impairment	problems.
Use in patients with moderate to severe renal (kidney) impairment	No studies have been conducted with ataluren in patients with kidney problems.
Use in children younger than 5 years	Ataluren has not been studied in DMD patients younger than 5 years, so the safety and effectiveness of ataluren in these patients is not known.
Use in patients whose ethnic origin is other than Caucasian	There is very limited information on the use of ataluren in patients who are not Caucasian.
Extended long-term safety	There is information on the safety of ataluren given continuously for 1 year, and given not continuously for several years, but there is a minimal amount of information on the safety of ataluren given continuously for more than 2 years.
Off-label use of ataluren in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene	Ataluren has not been tested in DMD patients who do not have a nonsense mutation in the dystrophin gene, but it is not expected to have any benefit for these patients.
Changes in the effects, including side effects, of certain other medicines that are broken down by an enzyme called UGT1A9 when taken together with ataluren	Based on laboratory studies, ataluren may affect plasma levels of certain other medicines that are metabolised by an enzyme called UGT1A9, such as the anaesthetic propofol, which is commonly used in children. Propofol is usually used for a limited time (hours), so co-administration can be avoided by temporarily interrupting ataluren treatment. Other medicines of this type are not commonly used in children (such as mycophenolate mofetil, which is used for prevention of organ transplant rejection).
Changes in the effects of ataluren, including side effects, when it is taken with certain medicines that increase the amounts or activity of an enzyme called UGT1A9	Based on laboratory studies, medicines known as inducers of UGT1A9 may affect ataluren blood levels. One medicine of this type which is commonly used in children for sleep-inducing or prevention of seizures is called phenobarbital. Other medicines of this type are not commonly used in children (such as rifampicin, which is used for treatment of tuberculosis).
Changes in the effects of ataluren, including side effects, when it is taken with certain medicines that reduce the amounts or activity of a drug transporter called BCRP	Based on laboratory studies, medicines known as inhibitors of BCRP may affect ataluren plasma levels. Many medicines of this type are not commonly used in children, and include ciclosporin (used for prevention of organ transplant rejection), eltrombopag (used for the treatment of thrombocytopenia due to chronic immune [idiopathic] thrombocytopenic purpura), and gefitinib (used for the treatment of specific types of non-small cell lung cancer).
Changes in the effects, including side effects, of certain other medicines when	Based on laboratory studies, ataluren may affect blood levels of certain other medicines that are transported into cells by proteins called organic anion transporter 1 (OAT1), organic anion transporter

Risk	What is known
ataluren is taken with them because their absorption and distribution are mediated by transporters called OAT1, OAT3, and/or OATP1B3	3 (OAT3), or organic anion transporting polypeptide 1B3 (OATP1B3). Some of these medicines are commonly used in children, and include oseltamivir (for prevention of influenza), aciclovir (for treatment of chickenpox [varicella]), and ciprofloxacin (for treatment of infections); however, the usual treatment durations are relatively short (days to weeks) so co-administration can be avoided by temporarily interrupting ataluren treatment. Other medicines of these types may be used long term in DMD patients, and include agents for the treatment or prevention of congestive heart failure (such as captopril, furosemide, bumetanide, valsartan) or for lipid lowering (such as pravastatin, rosuvastatin, atorvastatin, pitavastatin). However, many other medicines of these types are not commonly used in children, and include agents for the treatment of chronic hepatitis B and/or HIV (such as adefovir, lamivudine, tenofovir, zalcitabine, zidovudine), or other illnesses more commonly seen in older adults, including methotrexate (for rheumatoid arthritis, psoriasis), famotidine (for the treatment of active duodenal ulcer, gastroesophageal reflux disease), benzylpenicillin (for severe infections), sitagliptin (for type 2 diabetes), and telmisartan and olmesartan (for essential hypertension in adults).

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 Translarna can be found on Translarna'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
Post-approval registry [Working title: "Long-Term Observational Study of Ataluren	To obtain information on the safety and effectiveness of ataluren in	Changes in lipid profile Hypertension with concomitant use of corticosteroids	Planned	4Q 2015 (1-year interim) 4Q 2016 (2-year interim)

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Safety and Effectiveness in Usual Care"]	patients who have not to date participated in clinical trials with ataluren.	Kidney toxicity Liver toxicity Effect of co-administration of ataluren with nephrotoxic medicines other than aminoglycosides given into a vein Use in patients with moderate to severe liver impairment Use in patients with moderate to severe kidney impairment Potential use in children from 6 months to 5 years Use in patients whose ethnic origin is other than Caucasian Extended long-term safety Off-label use in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene Effect of co-administration of ataluren with certain medicines not yet evaluated in formal drug-drug interaction studies		4Q 2017 (3-year interim) 4Q 2018 (4-year interim) 4Q 2019 (5-year interim) 4Q 2020 (6-year interim) 4Q 2021 (7-year interim) 4Q 2022 (final)
7-day tolerability and pharmacokinetic study in neonatal dogs	To support planned future clinical studies in children	Use in children from 6 months to 5 years	Planned	December 2014
1-month juvenile dose range-finding toxicology and toxicokinetic study planned in neonatal dogs (age correlating with dosing in newborn paediatric patients to 2 years of age), Study 2 of	To support planned future clinical studies in children	Use in children from 6 months to 5 years	Planned	December 2014

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
EMA/PDCO/476743/2012 PDCO document.				
3-month juvenile toxicology and toxicokinetic study planned in neonatal dogs (age correlating with dosing in newborn paediatric patients to 2 years of age), Study 3 of EMA/PDCO/476743/2012 PDCO document	To support planned future clinical studies in children	Use in children from 6 months to 5 years	Planned	December 2014
β3 adrenergic binding assay with ataluren and the M4 metabolite, if such a study is technically feasible	Further investigation of ataluren's potential effect in the development of hibernomas	Development of hibernomas	Planned	December 2014
Plan to investigate further post-authorisation the potential effects of ataluren and metabolite M4 in brown adipose tissue of rats	Further investigation of ataluren's potential effect in the development of hibernomas	Development of hibernomas	Planned	4Q 2015
Open-label safety and PK study in children age 6 months to 5 years, Study 6 of EMA/PDCO/476743/2012 PDCO document	To evaluate the safety and blood levels of ataluren in children	Potential use in children from 6 months to 5 years	Planned	December 2016
Safety and PK study in patients with moderate to severe hepatic impairment	To provide guidance for ataluren dosing in patients with moderate to severe liver impairment	Use in patients with moderate to severe liver impairment	Planned	3Q 2017
Safety and PK study in patients with moderate to severe renal impairment	To provide guidance for ataluren dosing in patients with moderate to severe kidney impairment	Use in patients with moderate to severe kidney impairment	Planned	4Q 2017

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Safety and PK study of co-administration of ataluren and a sensitive probe inducer of UGT1A9	To provide guidance for dosing ataluren with the specific concomitant medication	Effect of co-administration of ataluren with certain medicines not yet evaluated in formal drug-drug interaction studies	Planned	2Q 2015
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of UGT1A9	To provide guidance for dosing ataluren with the specific concomitant medication	Effect of co-administration of ataluren with certain medicines not yet evaluated in formal drug-drug interaction studies	Planned	4Q 2015
Safety and PK study of co-administration of ataluren and a sensitive probe inhibitor of the transporter breast cancer resistant protein (BCRP)	To provide guidance for dosing ataluren with the specific concomitant medication	Effect of co-administration of ataluren with certain medicines not yet evaluated in formal drug-drug interaction studies	Planned	2Q 2016
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of organic anion transporter 1 (OAT1)	To provide guidance for dosing ataluren with the specific concomitant medication	Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned	4Q 2016
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of organic anion transporter 3 (OAT3)	To provide guidance for dosing ataluren with the specific concomitant medication	Effect of co-administration of ataluren with certain medicines not yet evaluated in formal drug-drug interaction studies	Planned	2Q 2017
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of organic anion transporting polypeptide 1B3 (OATP1B3)	To provide guidance for dosing ataluren with the specific concomitant medication	Effect of co-administration of ataluren with certain medicines not yet evaluated in formal drug-drug interaction studies	Planned	2Q 2018

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
PTC124-GD-020-DMD – Phase 3	Primary objective: Determine the ability of ataluren to slow disease progression as assessed by 6MWD (6 minute walking distance) in patients with nonsense mutation DMD. Secondary endpoints are to evaluate changes in muscle function through assessment of timed function tests: time to run/walk 10 meters, time to ascend 4 stairs and time to descend 4 stairs; North Star Ambulatory Assessment; QOL instrument (PODCI); and patient or parent/caregiver survey of activities of daily living.	Confirmatory study	Started	Final report 4Q 2015

Studies which are a condition of the marketing authorisation

The phase 3 study PTC124-GD-020-DMD is a condition of the marketing authorisation for Translarna.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 07-2014.