Physician's Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Translarna 125 mg

Translarna 250 mg

Translarna 1000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Translarna 125 mg: each sachet contains 125 mg ataluren.

Translarna 250 mg: each sachet contains 250 mg ataluren.

Translarna 1000 mg: each sachet contains 1000 mg ataluren.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension.
White to off-white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older (see section 5.1). Efficacy has not been demonstrated in non-ambulatory patients.

The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing (see section 4.4).

4.2 Posology and method of administration

Treatment with Translarna should only be initiated by specialist physicians with experience in the management of Duchenne/Becker muscular dystrophy.

Posology
Ataluren should be administered orally every day in 3 doses.

The first dose should be taken in the morning, the second at midday, and the third in the evening. Recommended dosing intervals are 6 hours between morning and midday doses,

6 hours between midday and evening doses, and 12 hours between the evening dose and the first dose on the next day.

The recommended dose is 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight).

Translarna is available in sachets of 125 mg, 250 mg or 1000 mg. The table below provides information on which sachet strength(s) to use in the preparation of the recommended dose by body weight range.

Weight Range (kg)		**Number of sachets**								
		Morning			**Midday**			**Evening**		
		125 mg sachets	**250 mg sachets**	**1000 mg sachets**	**125 mg sachets**	**250 mg sachets**	**1000 mg sachets**	**125 mg sachets**	**250 mg sachets**	**1000 mg sachets**
12	14	1	0	0	1	0	0	0	1	0
15	16	1	0	0	1	0	0	1	1	0
17	20	0	1	0	0	1	0	0	1	0
21	23	0	1	0	0	1	0	1	1	0
24	26	0	1	0	0	1	0	0	2	0
27	31	0	1	0	0	1	0	1	2	0
32	35	1	1	0	1	1	0	1	2	0
36	39	1	1	0	1	1	0	0	3	0
40	44	1	1	0	1	1	0	1	3	0
45	46	0	2	0	0	2	0	1	3	0
47	55	0	2	0	0	2	0	0	0	1
56	62	0	2	0	0	2	0	0	1	1
63	69	0	3	0	0	3	0	0	1	1
70	78	0	3	0	0	3	0	0	2	1
79	86	0	3	0	0	3	0	0	3	1
87	93	0	0	1	0	0	1	0	3	1
94	105	0	0	1	0	0	1	0	0	2
106	111	0	0	1	0	0	1	0	1	2
112	118	0	1	1	0	1	1	0	1	2
119	125	0	1	1	0	1	1	0	2	2

Delayed or missed dose

If there is a delay in the administration of ataluren of less than 3 hours after the morning or midday doses or less than 6 hours after the evening dose, the dose should be taken with no changes to the subsequent dose schedules. If there is a delay of more than 3 hours after the morning or midday doses or more than 6 hours after the evening dose, the dose should not be taken, and patients should resume their usual dosing schedule. Patients should not take a double or extra dose if a dose is missed. It is important to administer the correct dose.

Increasing the dose above the recommended dose may be associated with reduced effectiveness.

Special populations

Elderly
The safety and efficacy of ataluren in patients aged 65 and older have not yet been established. (See Section 5.2)

Renal and hepatic impairment
Safety and efficacy of ataluren in patients with renal and hepatic impairment have not been established (see section 4.4).

Paediatric population
The safety and efficacy of Translarna in children aged 6 months to 5 years have not yet been established. No data are available.

Method of administration

Translarna should be administered orally after mixing it to a suspension in liquid or in semi-solid food. Sachets should only be opened at the time of dose preparation. The full contents of each sachet should be mixed with at least 30 ml of liquid (water, milk, fruit juice), or 3 tablespoons of semi-solid food (yogurt or applesauce). The prepared dose should be mixed well before administration. The amount of the liquid or semi-solid food can be increased based on patient preference. Patients should take the entire dose.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use of intravenous aminoglycosides (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Patients who do not have a nonsense mutation
Patients must have a nonsense mutation in the dystrophin gene as part of their underlying disease state, as determined by genetic testing. Patients who do not have a nonsense mutation should not receive ataluren.

Hepatic and renal impairment
Patients with renal and hepatic impairments should be closely monitored.

Changes in lipid profile
Because changes in lipid profile (increased triglycerides and cholesterol) were reported for some patients in clinical trials, it is recommended that total cholesterol, LDL, HDL, and triglycerides be monitored on an annual basis in nmDMD patients receiving ataluren, or more frequently as needed based on the patient's clinical status.

Hypertension with use of concomitant systemic corticosteroids

Because hypertension with use of concomitant systemic corticosteroids was reported for some patients in clinical trials, it is recommended that resting systolic and diastolic blood pressure be monitored every 6 months in nmDMD patients receiving ataluren concomitantly with corticosteriods, or more frequently as needed based on the patient's clinical status.

Renal function monitoring

Because small increases in mean serum creatinine, blood urea nitrogen (BUN), and cystatin C were observed in the controlled study of nmDMD, it is recommended that serum creatinine, BUN, and cystatin C be monitored every 6 to 12 months in nmDMD patients receiving ataluren, or more frequently as needed based on the patient's clinical status.

Potential interactions with other medicinal products

Caution should be exercised when ataluren is co-administered with medicinal products that are substrates or inducers of UGT1A9, inhibitors of BCRP, or substrates of OAT1, OAT3, or OATP1B3 (see section 4.5).

Aminoglycosides

Aminoglycosides have been shown to reduce the readthrough activity of ataluren *in vitro*. In addition, ataluren was found to increase nephrotoxicity of intravenous aminoglycosides. The co-administration of these medicinal products with ataluren should be avoided (see section 4.3). Since the mechanism by which ataluren increases nephrotoxicity of intravenous aminoglycosides is not known, concomitant use of other nephrotoxic medicinal products with ataluren is not recommended. If this is unavoidable (e.g. vancomycin to treat MRSA) careful monitoring of renal function is advised (see section 4.5)

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglycosides

Ataluren should not be co-administered with intravenous aminoglycosides, based on cases of decreased renal function observed in a clinical trial in patients with nmCF (see section 4.3).

Elevations of serum creatinine occurred in several nmCF patients treated with ataluren and intravenous aminoglycosides together with other antibiotics for cystic fibrosis exacerbations. The serum creatinine elevations resolved in all cases, with discontinuation of the intravenous aminoglycoside, and either continuation or interruption of Translarna. These findings suggested that co-administration of Translarna and intravenous aminoglycosides may potentiate the nephrotoxic effect of the aminoglycosides. Therefore, if treatment with intravenous aminoglycosides is necessary the treatment with Translarna should be stopped and can be resumed 2 days after administration of the aminoglycoside has ended. The effect of co-administration of ataluren with other nephrotoxic medicinal products is unknown.

Dehydration may be a contributing factor in some of these cases. Patients should maintain adequate hydration while taking ataluren. See section 4.4

Effect of other medicinal products on ataluren pharmacokinetics

Based on *in vitro* studies, ataluren is a substrate of UGT1A9 and breast cancer resistant protein (BCRP). Caution should be exercised when ataluren is co-administered with

medicinal products that are inducers of UGT1A9 (e.g. mycophenolate mofetil), or inhibitors of BCRP (e.g. cyclosporine).

Effect of ataluren on pharmacokinetics of other medicinal products

Based on *in vitro* studies, ataluren is an inhibitor of UGT1A9, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3) and organic anion transporting polypeptide 1B3 (OATP1B3). Caution should be exercised when ataluren is co-administered with medicinal products that are substrates of UGT1A9, OAT1, OAT3, or OATP1B3 because of the risk of increase concentration of these medicinal products (eg, oseltamivir, acyclovir, ciprofloxacin, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin).
Based on the *in vitro* studies, ataluren is not expected to be an inhibitor of neither p-gp mediated transport nor of cytochrome P450 mediated metabolism. Similarly, ataluren is not expected *in vivo* to be an inducer of cytochrome P450 isoenzymes.

Coadministration of corticosteroids (deflazacort, prednisone, or prednisolone) with ataluren did not affect the plasma concentrations of ataluren. No clinically relevant change in the plasma concentrations of corticosteroids was seen with co-administration of ataluren. These data indicate no apparent drug-drug interaction between corticosteroids and ataluren, and no dose adjustments are required.

Medicinal products that affect the p-glycoprotein transporter

In vitro, ataluren is not a substrate for the p-glycoprotein transporter. The pharmacokinetics of ataluren are unlikely to be affected by medicinal products that inhibit the p-glycoprotein transporter.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of ataluren in pregnant women. Studies in animals have shown reproductive toxicity only at doses that resulted in maternal toxicity (see section 5.3).
As a precautionary measure**,** it is recommended to avoid the use of ataluren during pregnancy.

Breastfeeding

It is unknown whether ataluren/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of ataluren/metabolites in milk (see section 5.3). A risk to the breastfed new-borns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with ataluren.

Fertility

Non-clinical data revealed no hazard for humans based on a standard male and female fertility study in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

The effect of ataluren on driving, cycling, and using machines has not been tested. Patients who experience dizziness should use caution when driving, cycling or using machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials of patients with Duchenne muscular dystrophy (nmDMD) caused by a nonsense mutation, the most frequent adverse reactions at the recommended dose were nausea, vomiting, and headache. These adverse reactions generally did not require medical intervention, and no patients discontinued ataluren treatment due to any adverse reaction.

Tabulated list of adverse reactions

The adverse reactions reported in the clinical trial of predominantly paediatric patients with nmDMD treated at the recommended dose of 10-, 10-, 20 mg/kg are classified according to the System Organ Class of MeDRA and frequency. Frequency groupings are defined to the following convention: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions in Translarna in controlled study of nmDMD

System Organ Class	Very common	Common	Frequency not known
Metabolism and nutrition disorders		Decreased appetite	Change in lipid profile (increased triglycerides and cholesterol)
Nervous system disorders	Headache	Dizziness	
Vascular disorders		Hypertension	
Respiratory, thoracic, and mediastinal disorders		Cough, epistaxis	
Gastrointestinal disorders	Nausea, Vomiting	Upper abdominal pain, flatulence, diarrhoea, stomach discomfort, abdominal pain, constipation, regurgitation	
Skin and subcutaneous tissue disorders		Erythema	
Musculoskeletal and connective tissue disorders		Pain in extremity	
Renal and urinary disorders		Enuresis, renal cyst, pollakiuria, urine colour abnormal	Change in renal function tests (increased creatinine, blood urea nitrogen, cystatin C)

System Organ Class	Very common	Common	Frequency not known
General disorders and administration site conditions		Pyrexia, fatigue, weight decreased	

Description of selected adverse reactions

Serum lipids
During the controlled study of nmDMD, mean total cholesterol and triglycerides were normal at baseline and increased, reaching borderline high or high values. The values tended to stabilize early in the study and did not increase further with continued treatment.

Renal function tests
During the controlled study of nmDMD, small increases in mean serum creatinine, blood urea nitrogen (BUN), and cystatin C were observed. The values tended to stabilize early in the study and did not increase further with continued treatment.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

Healthy volunteers receiving a single oral dose of 200 mg/kg of ataluren experienced transient, low-grade symptoms of headache, nausea, vomiting, and diarrhoea. No serious adverse reactions were observed in these subjects. In the event of a suspected overdose, supportive medical care should be provided including consulting with a healthcare professional and close observation of the clinical status of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {group}, ATC code: not yet assigned
Mechanism of action

A nonsense mutation in DNA results in a premature stop codon within an mRNA. This premature stop codon in the mRNA causes disease by terminating translation before a full-length protein is generated. Ataluren enables ribosomal readthrough of mRNA containing such a premature stop codon, resulting in production of a full-length protein.

Pharmacodynamic effects

Nonclinical *in vitro* experiments in nonsense mutation cellular assays and fish larvae cultured in an ataluren solution have shown that ataluren enabled ribosomal readthroughwith a bell-

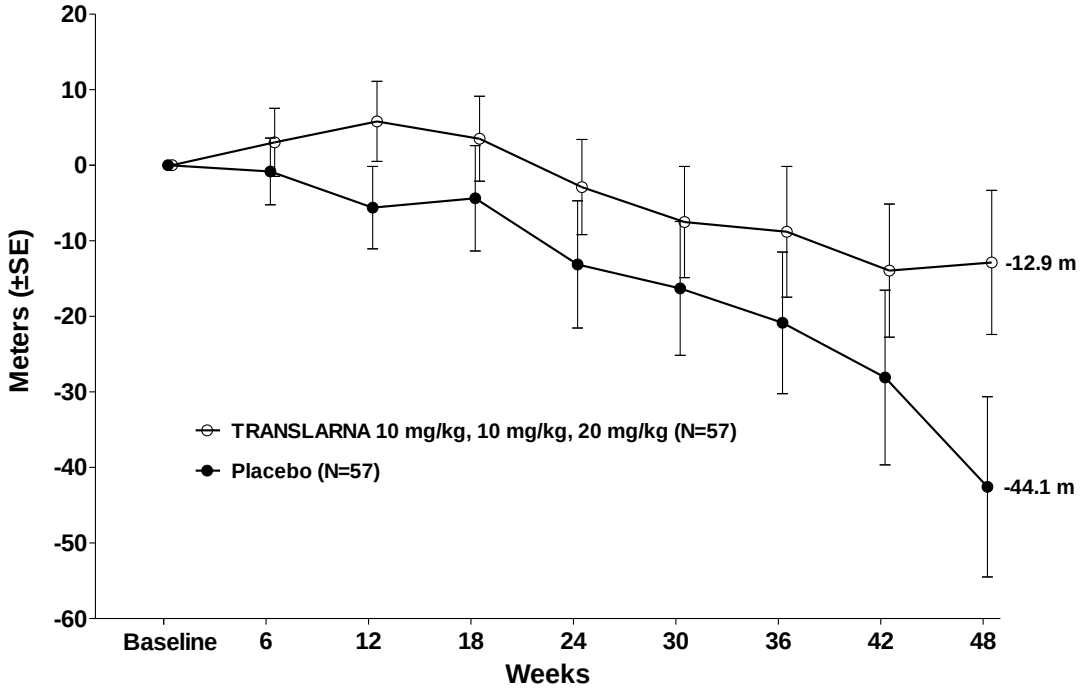
shaped (inverted-U shaped) concentration-response relationship. It is hypothetised that the *in vivo* dose reponse relationship may also be bell-shaped, but *in vivo* data were too limited to confirm this hypothesis in a mouse model for nmDMD and in humans.

Nonclinical *in vitro* studies suggest that continuous exposure to ataluren may be important for maximizing activity and that effects of the active substance on ribosomal read-through of premature stop codons reverse shortly after withdrawal of ataluren.

Clinical efficacy and safety

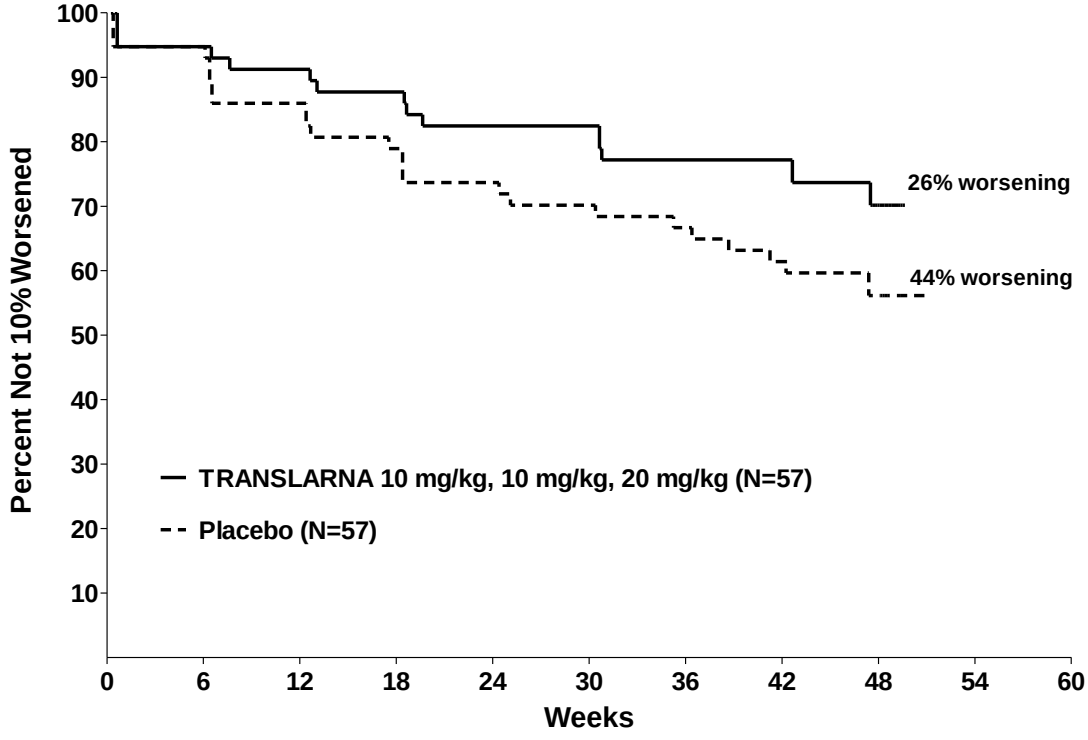
The safety and efficacy of Translarna were assessed in a randomized, double-blind, placebo-controlled, multicentre nonsense mutation Duchenne muscular dystrophy (nmDMD) study of 174 male patients ages 5 to 20 years. All patients were required to be ambulatory, defined as the ability to walk for ≥75 meters without the need for assistive devices during a screening 6-minute Walk Test (6MWT). Patients were also required to have documented confirmation of the presence of a nonsense mutation in the dystrophin gene as determined by gene sequencing. The majority of patients in all treatment groups were Caucasian (90%). Patients were randomized in a 1:1:1 ratio and received ataluren or placebo 3 times per day (morning, midday, and evening) for 48 weeks, with 57 receiving placebo, 57 receiving ataluren 10-, 10-, 20-mg/kg, and 60 receiving ataluren 20-, 20-, 40 mg/kg; 173 patients completed the study. The primary efficacy endpoint evaluated the effect of ataluren on ambulation as assessed by the change in distance (6MWD) walked during a 6MWT. The post hoc analysis showed that from baseline to Week 48, patients receiving ataluren 10-, 10-, 20-mg/kg had a 12.9 meters mean decline in 6MWD, and patients receiving placebo had a 44.1-meter mean decline in 6MWD (Figure 1). Thus, the mean change in observed 6MWD from baseline to Week 48 was 31.3 meters better in the ataluren 10-, 10-, 20-mg/kg arm than in the placebo arm ($p=0.056$). In a statistical based model the estimated mean difference was 31.7 meters (adjusted $p=0.0367$). There was no difference between ataluren 20-, 20-, 40 mg/kg and placebo. These results indicate that ataluren 10-, 10-, 20-mg/kg slows the loss of walking ability in nmDMD patients.

Figure 1. Mean Change in 6-Minute Walk Distance



A post-hoc analysis of time to persistent 10% worsening in 6MWD showed that 26% of patients in the ataluren 10-, 10-, 20-mg/kg arm had progressed at Week 48 compared to 44% in the placebo group (p=0.0652) (Figure 2). There was no difference between ataluren 20-, 20-, 40 mg/kg and placebo. These results indicate that fewer patients receiving ataluren 10-, 10-, 20-mg/kg worsened in 6MWD over 48 weeks.

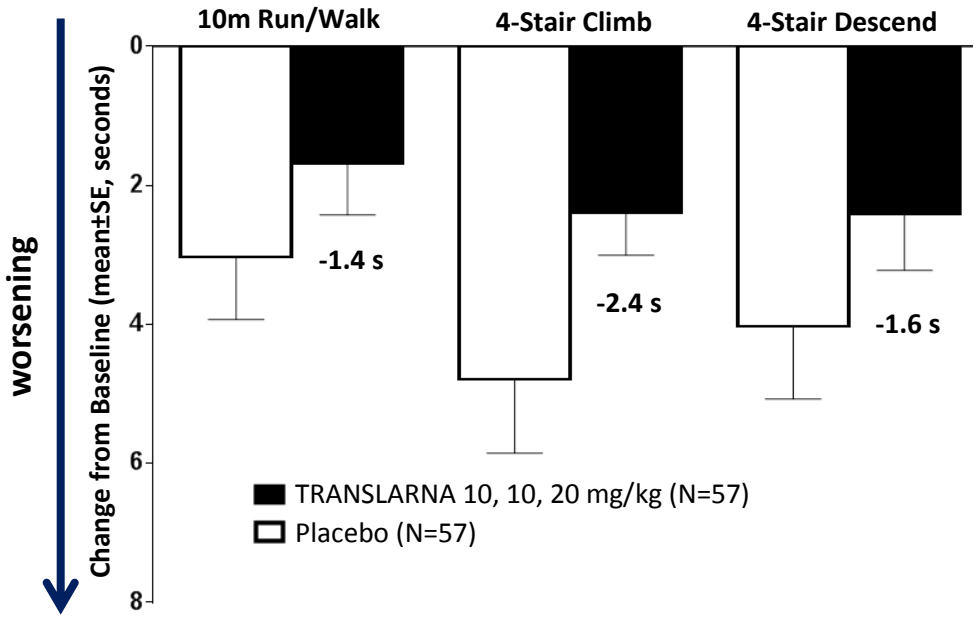
Figure 2. Kaplan-Meier Curve of Time to Persistent 10% 6MWD Worsening



In timed function tests (TFTs), tests of time to run/walk 10 meters, time to climb 4 stairs, and time to descend 4 stairs, ataluren-treated patients demonstrated smaller increases in the time it takes to run/walk 10 meters, climb 4 stairs, and descend 4 steps, indicating slowing of nmDMD progression relative to placebo.

The mean change in timed function tests from baseline to Week 48 was better in the ataluren 10-, 10-, 20-mg/kg arm than placebo in time to run/walk 10 meters (better by 1.5seconds), time to climb 4 stairs (better by 2.4 seconds), and time to descend 4 stairs (better by 1.6 seconds), Figure 3.

Figure 3. Mean Change in Timed Function Tests



6MWD Results in Patients with a Baseline 6MWD <350 meters

In patients with a baseline 6MWD < 350 meters, the mean change in observed 6MWD from baseline to Week 48 was 68 meters better in the ataluren 10-, 10-, 20-mg/kg arm than in the placebo arm (p=0.0053).

In these patients, the mean change in timed function tests from baseline to Week 48 was better in the ataluren 10-, 10-, 20-mg/kg arm than placebo in time to run/walk 10 meters (better by 3.5 seconds), time to climb 4 stairs (better by 6.4 seconds), and time to descend 4 stairs (better by 5.0 seconds).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ataluren in two subsets of the paediatric population from birth to less than 28 days and infants from 28 days to less than 6 months in nmDMD, as per Paediatric Investigation Plan (PIP) decision in the granted indication (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with ataluren in one subset of the paediatric population aged 6 months to less than 5 years old

in nmDMD, as per Paediatric Investigation Plan (PIP) decision in the granted indication (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Administration of ataluren on a body weight-adjusted basis (mg/kg) resulted in similar steady-state exposures (AUC) among children and adolescents with nmDMD over a broad range of body weights. Although ataluren is practically insoluble in water, ataluren is readily absorbed after oral administration as a suspension.

General characteristics of ataluren after administration

Absorption

Peak plasma levels of ataluren are attained approximately 1.5 hours after dosing in subjects who received medicinal product within 30 minutes of a meal. Based on the urinary recovery of radioactivity in a single-dose study of radiolabeled ataluren, the oral bioavailability of ataluren is estimated to be ≥55%. Ataluren plasma concentrations at steady state increase proportionally with increasing dose. Steady-state plasma concentrations are dose-proportional for ataluren doses between 10 and 50 mg/kg, and no accumulation is observed after repeated dosing.

Distribution

In vitro, ataluren is 99.6% bound to human plasma proteins and the binding is independent of plasma concentration. Ataluren does not distribute into red blood cells.

Biotransformation

Ataluren is metabolized by conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes, predominantly UGT1A9 in liver and intestine.

In vivo, the only metabolite detected in plasma after oral administration of radio-labelled ataluren was the ataluren-O-1β-acyl glucuronide; exposure to this metabolite in humans was approximately 8% of the plasma AUC of ataluren.

Elimination

Ataluren plasma half-life ranges from 2-6 hours and is unaffected either by dose or repeated administration. The elimination of ataluren is likely dependent on hepatic and intestinal glucuronidation of ataluren followed by renal excretion of the resulting glucuronide metabolite.

After a single oral dose of radiolabeled ataluren, approximately half of the administered radioactive dose is recovered in the faeces and the remainder was recovered in the urine. In

the urine, unchanged ataluren and the acyl glucuronide metabolite account for <1% and 49%, respectively, of the administered dose.

Linearity/non-linearity

Steady-state plasma concentrations are dose-proportional for ataluren doses between 10 and 50 mg/kg, and no accumulation is observed after repeated dosing. Based on data in healthy volunteers, the relative bioavailability of ataluren is approximately 40% lower at steady-state than after the initial dose. The onset of reduction in relative bioavailability is estimated to occur approximately 60 hours after the first dose. The steady-state is established after approximately two weeks of thrice daily dosing.

Characteristic in specific groups of subjects or patients

Age
Based on data from subjects ranging in age from 5 years to 57 years, there is no apparent effect of age on ataluren plasma exposure. Age-adjusted dosing is not required.

Gender
Females were not studied in nmDMD clinical trials. However there were no apparent effects of gender on ataluren plasma exposure in other populations.

Race
It is unlikely that the pharmacokinetics of ataluren are significantly affected by UTG1A9 polymorphisms in a Caucasian population. Due to the low number of other races included in the clinical studies, no conclusions can be drawn on the effect of UTG1A9 in other ethnic groups.

Renal or hepatic impairment
No studies have been conducted with Translarna in patients with renal or hepatic impairment. Patients with renal or hepatic impairment should be monitored closely.

Non-ambulatory
There were no apparent differences in either steady-state relative bioavailability or apparent clearance due to loss of ambulation. No dosing adjustment is needed for patients who are becoming nonambulatory.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and genotoxicity.

A standard package of reproduction toxicity studies was available. No effects on male and female fertility were observed, but effects of early juvenile treatment on fertility during adulthood were not investigated. In rats and rabbits embryo-foetal toxicity (e.g. increased early resorptions, post-implantation loss, decreased viable foetuses) and signs of delayed development (increased skeletal variations) were found in the presence of maternal toxicity. Exposure at the no observed adverse effect level (NOAEL) was similar to (rabbit) or 4 times (rat) the systemic exposure in humans (10, 10, 20 mg/kg/day). Placental transfer was shown of radiolabelled ataluren in rats. At a single tested, relatively low, maternal dose of 30 mg/kg,

the concentration of foetal radioactivity was ≤ 27% of the maternal concentration. In the rat pre/postnatal developmental toxicity study, at exposure about 5 times human exposure, significant maternal toxicity as well as effects on offspring body weight and development of ambulatory activity were observed. The maternal systemic exposure at the no observed effect level (NOEL) for neonatal toxicity was about 3 times human exposure. At a single, relatively low, maternal dose of 30 mg/kg radiolabelled ataluren, the highest measured concentration of radioactivity in rat milk was 37% of the maternal plasma concentration. Presence of radioactivity in pup plasma confirmed absorption from the milk by the pups.

Renal toxicity (nephrosis in the distal nephron) occurred in repeat oral dose studies in mice at systemic exposure equivalent to 0.3 times the steady state AUC in patients administered Translarna at respective morning, midday, and evening doses of 10-, 10-, 20-mg/kg and higher.

In a 26-week transgenic mouse model for carcinogenicity, no evidence of carcinogenicity was found. In a 2-year rat carcinogenicity study, one case of hibernoma was found. In addition, at exposure much higher than in patients an increase of (rare) urinary bladder tumours was found. Significance of the urinary bladder tumours for humans is considered unlikely.

One out of two 26-week rat repeat dose studies, initiated in 4-5 weeks old rats, showed a dose related increase of the incidence of malignant hibernoma, a rare tumour in rats. In addition, one case of malignant hibernoma was found at the highest dose in a 2-year rat carcinogenicity study. Background incidence of this tumour type in rats as well as humans is very low and the mechanism causing these tumours in the rat studies (including its relation to ataluren treatment) is unknown. The significance for humans is not known.

A 1-year study in 10-12 weeks old dogs demonstrated findings in the adrenal gland (focal inflammation and degeneration in the glucocorticoid-producing regions of the cortex) and a mild compromise of cortisol production after exogenous stimulation with adrenocorticotropic hormone. These findings were seen in dogs at systemic exposure equivalent to 0.8 times the steady state AUC in patients administered Translarna at respective morning, midday, and evening doses of 10-, 10-, 20-mg/kg and higher. In a rat distribution study a high adrenal concentration of ataluren was observed.

In addition to the above mentioned effects, several other less adverse effects were found in the repeat dose studies; in particular decreased body weight gain, food intake and increased liver weight without a histological correlate and of unclear clinical significance. Also rat and dog studies showed changes in plasma lipid (cholesterol and triglycerides) suggestive of changes in fat metabolism.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polydextrose
Polyethylene glycol 3350
Poloxamer 407
Mannitol
Crospovidone
Hydroxyethyl cellulose
Artificial vanilla flavour
-colloidal silicon dioxide

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

Each prepared dose is best administered immediately after preparation. The prepared dose should be discarded if not consumed within 24 hours of preparation if kept refrigerated (2 - 8°C), or within 3 hours at room temperature (15-30 °C).

6.4 Special precautions for storage

Store below 30 C°
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Heat-sealed laminated aluminium foil sachet: polyethylene terephthalate (child resistance), polyethylene (coloring and polyester/foil bond), aluminum foil (moisture barrier), adhesive (polyurethane class), copolymer of ethylene and methacrylic acid (sealant resin for packaging integrity).
Pack of 30 sachets.

6.6 Special precautions for disposal and other handling

Sachets should only be opened at the time of dose preparation. The full contents of each sachet should be mixed with at least 30 ml of liquid (water, milk, fruit juice), or 3 tablespoons of semi-solid food (yogurt or applesauce). The prepared dose should be mixed well before administration. The amount of the liquid or semi-solid food can be increased based on patient preference.

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

7. MANUFACTURER

PTC Therapeutics International Limited
77 Sir John Rogerson's Quay
Dublin
Ireland

8. LICENSE HOLDER

Medison Pharma Ltd.
POB 7090 Petach Tikva
Israel

This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in.02.2016