

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, granules for oral suspension.
Each sachet contains 125 mg ataluren.

Translarna 250 mg, granules for oral suspension.
Each sachet contains 250 mg ataluren.

Translarna 1000 mg, granules for oral suspension.
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 2 years and older (see section 5.1).

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 impairment

No dosage adjustment is required for patients with mild or moderate renal impairment. Treatment of patients with severe renal impairment (eGFR <30 ml/min) or end-stage renal disease is not recommended (see sections 4.4 and 5.2).

Hepatic impairment

No dosage adjustment is required for patients with mild, moderate or severe hepatic impairment (see section 5.2).

Paediatric population

Paediatric patients with body weight ≥ 12 kg are treated as per the dosing recommendations by body weight range (see above dosing table). The recommended dose is the same for all age ranges, i.e. 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).

The safety and efficacy of Translarna in children < 12 kg and aged 6 months to 2 years have not yet been established. No data are available.

Non-ambulatory

Efficacy has not been demonstrated in non-ambulatory patients.

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 (yoghurt or apple sauce). 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 sections 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.

Renal impairment

An increase in ataluren exposure and in ataluren metabolite has been reported in patients with severe renal impairment (eGFR < 30 ml/min). The toxicity of the metabolite is unknown. Higher ataluren exposure was associated with potential decrease in efficacy. Therefore, patients with severe renal impairment or end-stage renal disease should be treated with ataluren only if the anticipated clinical benefit outweighs the potential risk, and should be closely monitored for possible metabolite toxicity and decrease in efficacy. A lower ataluren dose should be considered.

Treatment should not be initiated in previously untreated patients with eGFR < 30 ml/min (see sections 4.2 and 5.2).

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 nonsense mutation Duchenne muscular dystrophy (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 corticosteroids, 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 studies 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 inducers of UGT1A9, or substrates of OAT1 or OAT3 (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. Co-administration of rifampicin, a strong inducer of metabolic enzymes including UGT1A9, decreased ataluren exposure by 29%. The significance of these findings for humans is unknown. Caution should be exercised when ataluren is co-administered with medicinal products that are inducers of UGT1A9 (e.g. rifampicin).

Effect of ataluren on pharmacokinetics of other medicinal products

Based on *in vitro* studies, ataluren has the potential to inhibit UGT1A9, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3) and organic anion transporting polypeptide 1B3 (OATP1B3).

Co-administration of ataluren with mycophenolate mofetil in healthy subjects did not affect the exposure of its active metabolite, mycophenolic acid (a substrate of UGT1A9).

No dose adjustment is required when ataluren is co-administered with medicinal products that are substrates of UGT1A9.

In a clinical study to evaluate the potential for ataluren to inhibit the OATP1B3 transport system using a single-dose of 80 mg telmisartan, an *in-vitro* selective OATP1B3 substrate, ataluren increased the exposure to telmisartan by 28%. This effect is considered clinically not relevant. However, the magnitude of this effect could be larger for the 40 mg dose of telmisartan. Therefore caution should be exercised when ataluren is co-administered with medicinal products that are substrates of OAT1 or OATP1B3 because of the risk of increased concentration of these medicinal products (eg, oseltamivir, aciclovir, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin). Caution should also be exercised when ataluren is co-administered with OAT3 substrates (eg, ciprofloxacin), especially those OAT3 substrates with a narrow therapeutic window. In a clinical study, the extent of exposure for ciprofloxacin was 32% higher in the presence of ataluren. In a separate clinical study, the extent of exposure for adefovir was 60% higher in the presence of ataluren. Caution should be exercised when ataluren is co-administered with adefovir.

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, on cycling, or on 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

The safety profile of ataluren is based on pooled data from two randomised, double-blind, 48-week placebo-controlled studies conducted in a total of 232 male patients with Duchenne muscular dystrophy (nmDMD) caused by a nonsense mutation treated at the recommended dose of 40 mg/kg/day (10, 10, 20 mg/kg; n=172) or at a dose of 80 mg/kg/day (20, 20, 40 mg/kg; n=60), as compared to placebo-treated patients (n=172).

The most common adverse reactions in the 2 placebo-controlled studies were vomiting, diarrhoea, nausea, headache, upper abdominal pain, and flatulence, all occurring in $\geq 5\%$ of all ataluren-treated patients. In both studies, 1/232 (0.43%) patients treated with ataluren discontinued due to an adverse reaction of constipation and 1/172 (0.58%) placebo patients discontinued treatment due to an adverse reaction of disease progression (loss of ambulation).

An open-label study was performed including patients aged 2-5 years (n=14) to evaluate the PK and safety of ataluren. A higher frequency of malaise (7.1%), pyrexia (42.9%), ear infection (28.6%), and rash (21.4%) were reported in patients aged 2-5 years compared with patients 5 years of age and older. However, these conditions are reported more frequently in the younger children in general. Safety data from 28 weeks of therapy showed a similar safety profile of ataluren in patients 2-5 years as compared with patients aged 5 years and older.

Adverse reactions were generally mild or moderate in severity, and no treatment-related serious adverse events were reported among ataluren-treated patients in these 2 studies.

Tabulated list of adverse reactions

The adverse reactions reported in patients with nmDMD treated with the recommended daily dose of 40 mg/kg/day ataluren in the 2 placebo-controlled studies are presented in Table 1. Adverse reactions reported in >1 patient in the 40 mg/kg/day group at a frequency greater than that of the placebo group are presented by MedDRA System Organ Class, Preferred Term, and frequency. Frequency groupings are defined to the following convention: very common ($\geq 1/10$) and common ($\geq 1/100$ to $< 1/10$).

Table 1. Adverse reactions reported in >1 ataluren-treated patients with nmDMD at a frequency greater than placebo in the 2 placebo-controlled studies (pooled analysis)

System Organ Class	Very common	Common	Frequency not known
Metabolism and nutrition disorders		Decreased appetite hypertriglyceridaemia	Change in lipid profile (increased triglycerides and cholesterol)
Nervous system disorders		Headache	
Vascular disorders		Hypertension	
Respiratory, thoracic, and mediastinal disorders		Cough, epistaxis	

System Organ Class	Very common	Common	Frequency not known
Gastrointestinal disorders	Vomiting	Nausea, upper abdominal pain, flatulence, abdominal discomfort, constipation	
Skin and subcutaneous tissue disorders		Rash erythematous	
Musculoskeletal and connective tissue disorders		Pain in extremity, musculoskeletal chest pain	
Renal and urinary disorders		Haematuria, enuresis	Change in renal function tests (increased creatinine, blood urea nitrogen, cystatin C)
General disorders and administration site conditions		Pyrexia, weight decreased	

In a 48-week open-label extension study in patients with nmDMD patients who were ambulant or non-ambulant demonstrated a similar safety profile. Long term safety data is not available.

Description of selected adverse reactions (laboratory abnormalities)

Serum lipids

An increase in serum lipids, i.e. cholesterol and triglycerides, was observed. There have been cases reported where this increase to abnormal high values was already observed after 4 weeks.

Renal function tests

During the randomised, placebo-controlled studies, small increases in mean serum creatinine, BUN, and cystatin C were observed. The values tended to stabilize early in the study and did not increase further with continued treatment.

Reporting of suspected adverse reactions

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: <https://sideeffects.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: Other drugs for disorders of the musculo-skeletal system,
ATC code: M09AX03

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 readthrough with a bell-shaped (inverted-U shaped) concentration-response relationship. It is hypothesised that the *in vivo* dose response 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.

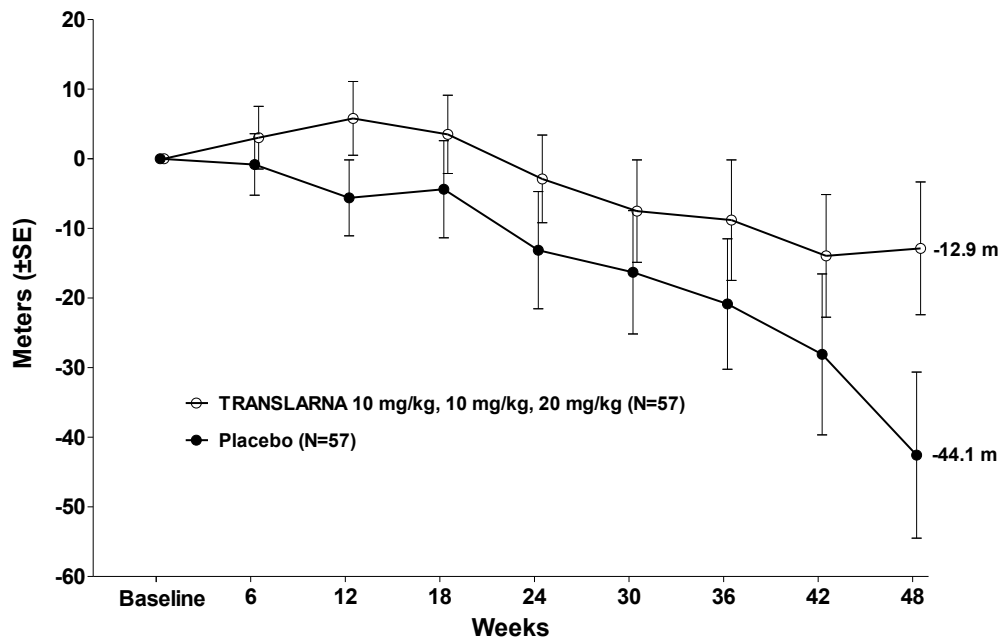
Nonclinical *in vitro* studies suggest that continuous exposure to ataluren may be important for maximizing activity and that effects of the active substance on ribosomal read-through of premature stop codons reverse shortly after withdrawal of ataluren.

Clinical efficacy and safety

The efficacy and safety of Translarna were assessed in 2 randomised, double-blind, placebo-controlled, trials in nmDMD. The primary efficacy endpoint in both trials was change in 6 Minute Walk Distance (6MWD) at Week 48. Other endpoints included in both trials were time to persistent 10% worsening in 6MWD, change in time to run/walk 10 meters at Week 48, change in time to climb 4 stairs at Week 48, and change in time to descend 4 stairs at Week 48. Patients were required to have documented confirmation of the presence of a nonsense mutation in the dystrophin gene as determined by gene sequencing.

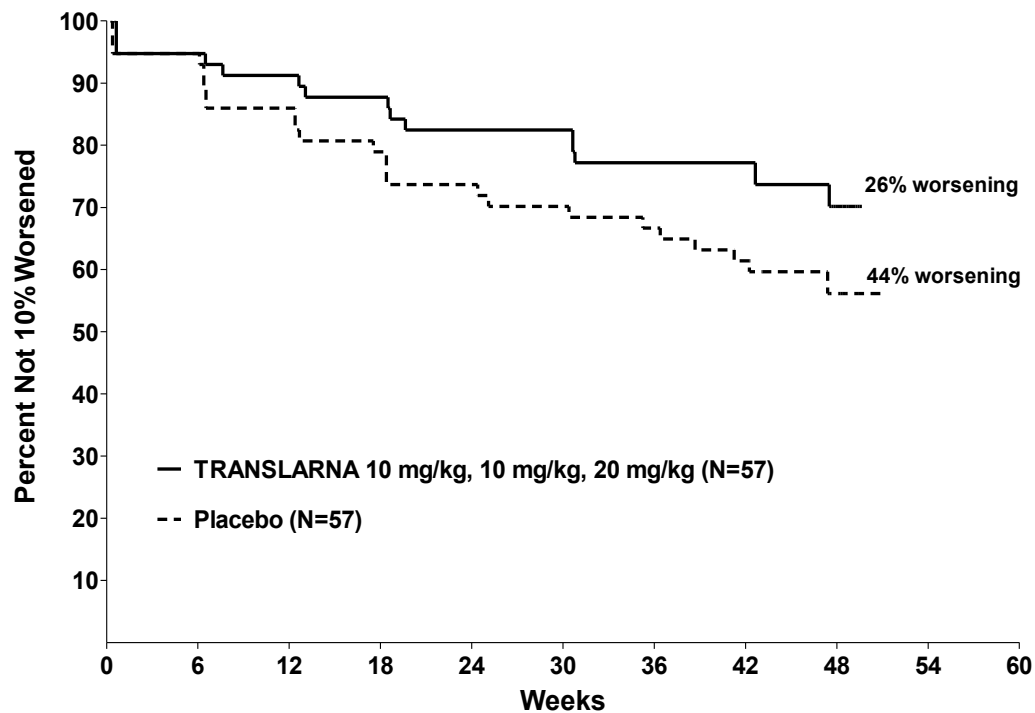
Study 1 evaluated 174 male patients, aged 5 to 20 years. All patients were required to be able to walk ≥ 75 meters without the need for assistive devices during a screening 6 -Minute Walk Test (6MWT). The majority of patients in all treatment groups were Caucasian (90%). Patients were randomised in a 1:1:1 ratio and received ataluren or placebo 3 times per day (morning, midday, and evening), with 57 receiving ataluren 40 mg/kg/day (10, 10, 20mg/kg), 60 receiving ataluren 80 mg/kg/day (20, 20, 40 mg/kg), and 57 receiving placebo. In Study 1, a post hoc analysis of the primary endpoint showed that from baseline to Week 48, patients receiving ataluren 40 mg/kg/day 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 40 mg/kg/day 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 80 mg/kg/day and placebo. These results indicate that ataluren 40-mg/kg/day slows the loss of walking ability in nmDMD patients.

Figure 1. Mean Change in 6-Minute Walk Distance (Study 1)



A post-hoc analysis of time to persistent 10% worsening in 6MWD showed that 26% of patients in the ataluren 40mg/kg/day arm had progressed at Week 48 compared to 44% in the placebo group ($p=0.0652$) (Figure 2). There was no difference between ataluren 80 mg/kg/day and placebo. These results indicate that fewer patients receiving ataluren 40 mg/kg/day worsened in 6MWD over 48 weeks.

Figure 2. Kaplan-Meier Curve of Time to Persistent 10% 6MWD Worsening (Study 1)

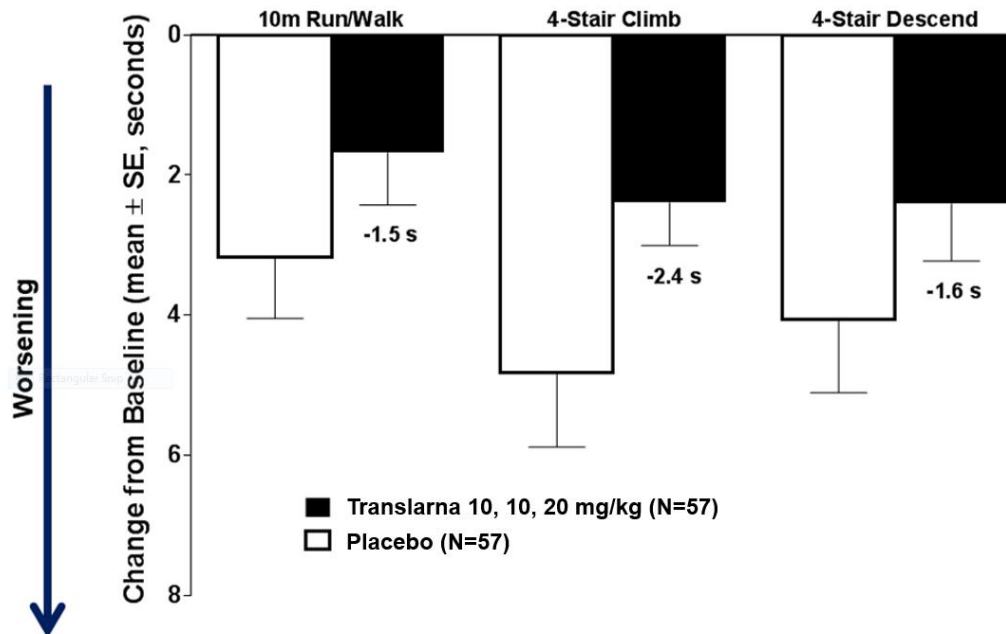


In timed function tests (TFTs), tests of time to run/walk 10 meters, time to climb 4 stairs, and time to descend 4 stairs, ataluren-treated patients demonstrated smaller increases in the time it takes to

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 40mg/kg/day arm than placebo in time to run/walk 10 meters (better by 1.5 seconds), 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 (Study 1)



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 40mg/kg/day arm than in the placebo arm ($p=0.0053$).

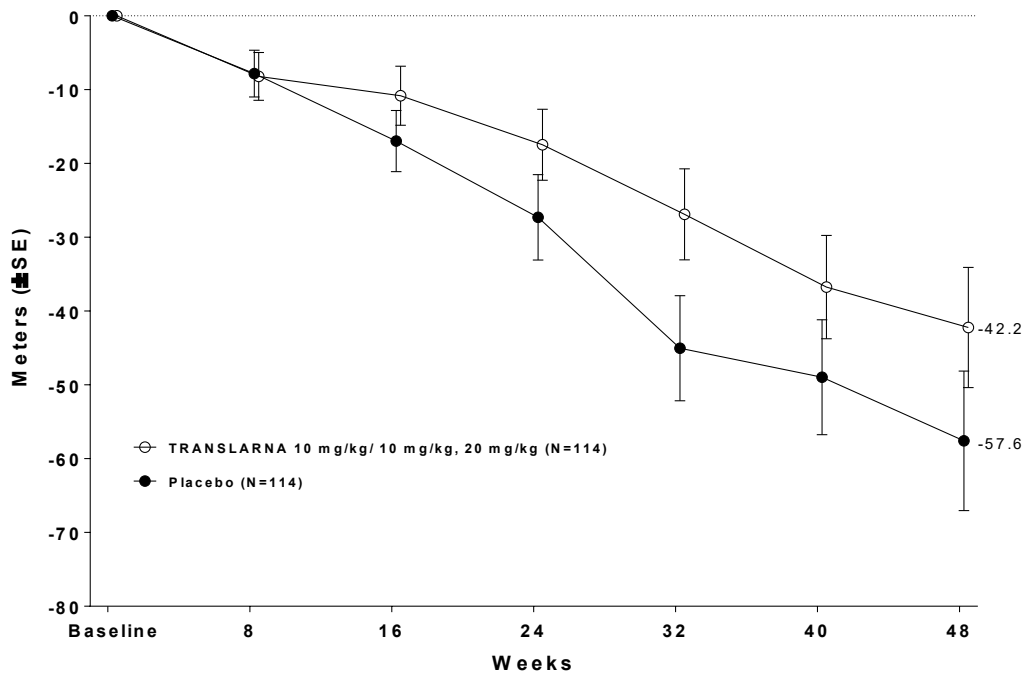
In these patients, the mean change in timed function tests from baseline to Week 48 was better in the ataluren 40mg/kg/day arm than placebo in time to run/walk 10 meters (better by 3.5 seconds), time to climb 4 stairs (better by 6.4 seconds), and time to descend 4 stairs (better by 5.0 seconds).

Study 2 evaluated 230 male patients, ages 7 to 14 years. All patients were required to be able to walk ≥ 150 meters and less than 80% predicted without the need for assistive devices during a screening 6MWT. The majority of patients in both treatment groups were Caucasian (76%). Patients were randomised in a 1:1 ratio and received ataluren 40 mg/kg/day ($n=115$) or placebo ($n=115$) 3 times per day (morning, midday, and evening).

Ataluren-treated patients experienced clinical benefit as measured by numerically favorable differences versus placebo across the primary and secondary efficacy endpoints. As the primary endpoint (change in 6MWD from baseline to Week 48) did not reach statistical significance ($p \leq 0.05$), all other p-values should be considered nominal.

In the ITT population, the difference between the ataluren and placebo arms in mean change in observed 6MWD from baseline to Week 48 was 15.4 meters better in the ataluren 40 mg/kg/day arm than in the placebo arm. In a statistical based model the estimated mean difference was 13.0 meters ($p=0.213$), Figure 4. Separation between ataluren and placebo was maintained from Week 16 through the end of the study.

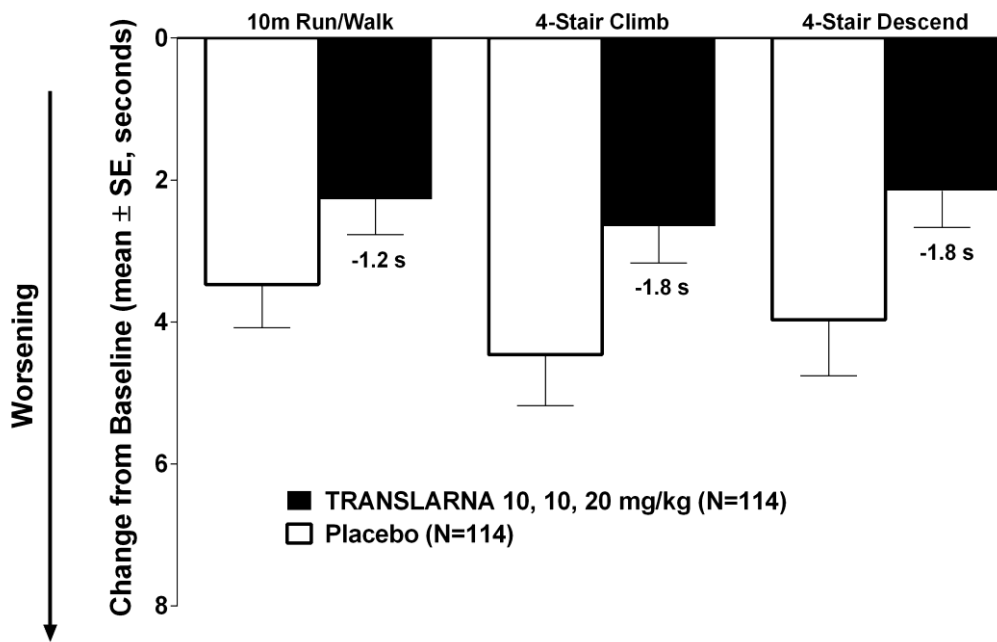
Figure 4. Mean Change in 6-Minute Walk Distance (Study 2)



Over 48 weeks, ataluren-treated patients showed less decline in muscle function, as evidenced by smaller increases in the time to run/walk 10 meters, climb 4 steps, and descend 4 steps in the ataluren-treated group relative to placebo. The differences favoring ataluren versus placebo in mean changes in timed function tests at Week 48 in the ITT population reached the threshold for a clinically meaningful difference (changes ~1 to 1.5 seconds).

The mean change in timed function tests from baseline to Week 48 was better in the ataluren 40 mg/kg/day arm than placebo in observed time to run/walk 10 meters (better by 1.2 seconds, $p=0.117$), time to climb 4 stairs (better by 1.8 seconds, $p=0.058$), and time to descend 4 stairs (better by 1.8 seconds, $p=0.012$), Figure 5.

Figure 5. Mean Change in Timed Function Tests (Study 2)



Time to 10% worsening in 6MWD was defined as the last time that 6MWD was not 10% worse than baseline. In the ITT population, the hazard ratio for ataluren versus placebo was 0.75 ($p=0.160$), representing a 25% reduction in the risk of 10% 6MWD worsening.

Paediatric population

The safety, pharmacokinetics and exploratory effectiveness of Translarna were assessed in an open-label study in children between 2 and 5 years of age with nmDMD. The efficacy of Translarna in children aged 2 - 5 years has been established on extrapolation from patients aged >5years.

In the clinical program investigating the efficacy and safety of monotherapy ataluren in patients with nonsense mutation cystic fibrosis, no statistically significant effect was observed in the primary and key secondary clinical outcome measures (ppFEV1 and pulmonary exacerbation rate) in adults and children aged 6 years and older.

An open-label exploratory study (Study 045) was conducted in 20 subjects with nonsense mutation Duchenne muscular dystrophy (nmDMD) aged 2 to 7 years to explore quantitative levels of dystrophin in muscle tissue before and after 40 weeks of treatment with ataluren. Dystrophin was measured using the electrochemiluminescence (ECL) and immunohistochemistry (IHC) assays. From each subject, 3 needle biopsies were taken from the gastrocnemius and the tibialis anterior at baseline and at the end of the treatment. Study 045 also included assessment of functional outcomes (i.e., the revised North Star Ambulatory Assessment [rNSAA] and Timed Function Tests [TFTs]).

The baseline median dystrophin levels as measured by ECL was 0.42% of normal (range 0.00% to 41.85%). At the end of the study, the median dystrophin level was 0.33% of normal (range 0.04% to 48.55%).

For IHC, the median percentage of positive fibres at baseline was 73% (range 0.42% to 99.6%). At the end of the study, the median percentage of positive fibres was 66% (range 0.51% to 99.77%).

At the end of the study, the mean (median) worsening from baseline on the rNSAA was 0.1 (1.0) points in total score and the mean (median) change from baseline for the time to stand, to

run or walk 10 meters, climb 4 stairs, and descend 4 stairs was -1.56 (-0.6), -0.41 (-0.35), -1.09 (-0.5), and -2.43 (-0.7) seconds, respectively.

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 radiolabelled ataluren, the oral bioavailability of ataluren is estimated to be $\geq 55\%$. 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, intestine and kidney.

In vivo, the only metabolite detected in plasma after oral administration of radio-labelled ataluren was the ataluren-O-1 β -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 renal glucuronidation of ataluren followed by renal and hepatic excretion of the resulting glucuronide metabolite.

After a single oral dose of radiolabelled 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 2 years to 57 years, there is no apparent effect of age on ataluren plasma exposure. Age-adjusted dosing is not required.

The pharmacokinetics of ataluren has been evaluated in study PTC124-GD-030 over a duration of 4 weeks. Ataluren plasma concentrations in patients from 2 to less than 5 years old were consistent with those seen in patients above the age of 5 years receiving the 10/10/20 mg/kg dose regimen.

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 UGT1A9 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 UGT1A9 in other ethnic groups.

Renal impairment

No dosage adjustment is required for patients with mild or moderate renal impairment. In a pharmacokinetic study in subjects with varying degrees of renal impairment, following a single dose administration, ataluren plasma exposure changed by -13%, 27%, and 61% for the mild, moderate and severe groups, respectively, and 46% for the end-stage renal disease group compared with the normal renal function group. In addition, a 3 to 8 fold increase in ataluren metabolite has been reported in patients with severe renal impairment (eGFR <30 ml/min). Following multiple dosing, the increase in ataluren and ataluren metabolite is anticipated to be higher in patients with severe renal impairment and end-stage renal disease when compared with patients with normal renal function at steady state. Patients with severe renal impairment (eGFR <30 ml/min) or end-stage renal disease should be treated with ataluren only if the anticipated clinical benefit outweighs the potential risk (see sections 4.2 and 4.4).

Hepatic impairment

Based on a pharmacokinetic assessment conducted in groups with either mild, moderate or severe hepatic impairment versus a control group of healthy subjects, no dose adjustment is required for patients with any degree of hepatic impairment. No apparent differences of the total ataluren exposure in the control, mild, and severe hepatic impairment groups were observed. An approximately 40% decrease of mean total ataluren exposure in the moderate hepatic impairment group versus the control group was noted probably due to the small sample size and variability.

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 non-ambulatory.

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 (40 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 $\leq 27\%$ 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 adrenocorticotrophic 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 40 mg/kg/day 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.

No adverse findings, including in the adrenal gland, were observed in a 3-month study in neonatal dogs (1-week old) followed by a 3-month recovery period up to steady state systemic exposures equivalent to the steady state AUC in patients. In preliminary studies in neonatal dogs (1-week old), initial systemic exposures equivalent to 5-10 times the steady state AUC in patients were not tolerated in some animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Polydextrose

Polyethylene glycol 3350

Crospovidone

Poloxamer 407

Hydroxyethyl cellulose

Colloidal silicon dioxide
Magnesium stearate
Artificial vanilla flavour

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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 (colouring and polyester/foil bond), aluminium 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 (yoghurt or apple sauce). 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
Unit 1, 52-55 Sir John Rogerson's Quay,
Dublin 2, D02 NA07
Ireland

8. LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach St.,
POB 7090 Petach Tikva
Israel

9. REGISTRATION NUMBERS:

Translarna 125 mg: 154-26-34264-00

Translarna 250 mg: 154-27-34266-00

Translarna 1000 mg: 154-28-34267-00

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