MEDISON

We are **Always Ahead** | We **Grow as One** | We **Care**
2023 אוגוסט

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

הריני להודיעכם על שינוי במשטר המינון של התכשירים הבאים:

Translarna 125 mg	**טרנסלרנה 125 מ"ג**
Translarna 250 mg	**טרנסלרנה 250 מ"ג**
Translarna 1000 mg	**טרנסלרנה 1000 מ"ג**

GRANULES FOR ORAL SUSPENSION

מרכיב פעיל : ataluren

התוויה מאושרת :

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. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.

להלן העדכונים בעלון לרופא (מסומנים בכחול**):**

העלון לרופא והעלון לצרכן נמצאים בקישור, וכן מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

4.2 Posology and method of administration

[…]

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).
~~Safety and efficacy of ataluren in patients with renal impairment has not been established (see section 4.4).~~

[…]

4.4 Special warnings and precautions for use

~~renal~~ 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

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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).~~Patients with renal impairment should be closely monitored.~~

[…]

5.1 Pharmacodynamic properties

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

[…]

Biotransformation

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

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~~ 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.

[…]

Renal impairment
No dosage adjustment is required for ~~studies have been conducted with Translarna in~~ 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).~~Patients with renal impairment should be monitored closely.~~

להלן העדכונים בעלון לצרכן המהווים החמרות (מסומנים בכחול):

אזהרות מיוחדות הנוגעות לשימוש בתרופה:
[...]
- אם אתה סובל מבעיות כליות חמורות (eGFR <30ml/min) או אם אתה מטופל בדיאליזה בגלל חוסר תפקוד של הכליות (מחלת כליות סופנית) הרופא שלך יקבע אם הטיפול בטרנסלרנה מתאים לך.

בברכה,

מדיסון פארמה בע"מ

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