NEWS RELEASE

NIPPON SHINYAKU CO., LTD.

December 27, 2024

MHLW approval of Uptravi® tablets 0.2 mg and 0.4 mg for the Treatment of Pediatric PAH and Uptravi® tablets for pediatric 0.05 mg

Kyoto, Japan, December 27, 2024 - Nippon Shinyaku Co., Ltd. (Nippon Shinyaku; Headquarters, Kyoto; President, Toru Nakai) announced that it has obtained approval from the Ministry of Health, Labor and Welfare (MHLW) in Japan for Uptravi® tablets 0.2 mg and 0.4 mg for the additional indication of pediatric pulmonary arterial hypertension (PAH), as well as for a new drug application for Uptravi® tablets for pediatric 0.05 mg.

PAH is a disease with a poor prognosis characterized by abnormally high blood pressure in the pulmonary artery. It is classified into idiopathic PAH, heritable PAH and PAH associated with various diseases such as connective tissue disease and congenital heart disease. Because the disease pathology of PAH is similar between pediatric and adult patients, combination therapy of prostacyclin pathway drug, endothelin receptor antagonist and phosphodiesterase-5 inhibitor, is also recommended for pediatric PAH patients. However, treatment options for pediatric PAH are limited in Japan. Particularly, in the case of prostacyclin pathway drug, only an injectable formulation requiring continuous intravenous infusion is available. Therefore, there has been an unmet need for oral formulations of prostacyclin pathway drug.

Uptravi® is an oral prostacyclin receptor (IP receptor) agonist with high selectivity for the IP receptor among prostacyclin pathway drugs. Uptravi® is believed to reduce pulmonary arterial pressure by binding to the IP receptors on vascular smooth muscle cells and increasing cAMP production, thereby leading to vasodilation and inhibition of vascular smooth muscle proliferation.

The optimal dose of Uptravi® for each patient is determined by dose titration. The new 0.05 mg tablet allows for finer dosing for pediatric patients, but some patients may need to take a larger number of tablets at one time. To support patents and healthcare professionals who take and dispense the drug, we developed a new pill case especially for the pediatric formulation. (the figure on the right; Download image click here). With the dedicated filler for the case, healthcare professionals can dispense the correct number of tablets simply by filling the case. Then, patients can take the correct number of tablets by dispensing them in a single row from the case each time they take the drug.

Nippon Shinyaku focuses on rare and intractable diseases as a key area and continues to make further efforts to develop new treatments and provide product information. With the recent approval of Uptravi® for pediatric use, we hope to contribute to pediatric patients suffering from PAH, their families, and healthcare providers.

Summary of Uptravi® tablets 0.2 mg and 0.4 mg (Main additions to the package insert)

<table>
<tr><td>Dosage and administration</td><td>< Pulmonary arterial hypertension >
For pediatric patients aged two years or older, the starting dose in the table below are usually administered orally twice daily after meals. While confirming the tolerability, the maintenance dose is determined by increasing the dosage to the maximum tolerated dose according to the table below at intervals of 7 days or more. It is not allowed to exceed the maximum dose in the table below. In any dose, and oral administration is performed twice daily after meals at each dose.
<table>
<tr><th>Body weight (kg)</th><th>Starting dose (per dose)</th><th>Increasing dose (per dose)</th><th>Maximum dose (per dose)</th></tr>
<tr><td>≥9kg to <25kg</td><td>0.1mg</td><td>0.1mg</td><td>0.8mg</td></tr>
<tr><td>≥25 to <50 kg</td><td>0.15mg</td><td>0.15mg</td><td>1.2mg</td></tr>
<tr><td>≥50 kg</td><td>0.2mg</td><td>0.2mg</td><td>1.6mg</td></tr>
</table></td></tr>
<tr><td>Precautions concerning dosage and administrations (excerpt of items)</td><td>This drug should not be used in combination with pediatric 0.05mg tablets.

When administering selexipag to children weighing less than 50 kg, pediatric 0.05mg tablets should be used until the maintenance dose is reached. If the maintenance dose can be adjusted using 0.2mg and 0.4mg tablets, switching to these tablets is permissible.</td></tr>
</table>

Summary of Uptravi® tablets for pediatric 0.05 mg

<table>
<tr><td>Generic name</td><td>Selexipag</td></tr>
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