Report Adcirca® - Tadalafil

Product & Mechanism of action

Substance: Tadalafil

Brand Name: Adcirca®

Originator/licensee: Eli Lilly Nederland B.V.

Classification: NI

ATC code:G04BE08

OrphanStatus:
Eu: No
Us: No

Mechanism of action:
Tadalafil is an inhibitor of PDE5, the enzyme responsible for the degradation of cGMP. PAH is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by Tadalafil increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed [1].

Authorized indications Licensing status

Authorized Indication:

EMA: Tadalafil is indicated for the treatment of paediatric pts aged 2 years and above with PAH classified as WHO functional class II and III [2].

FDA: -

Route of administration: OS

Licensing status
EU CHMP P.O. date: 15.12.2022
FDA M.A. date: -

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: -

ABBREVIATIONS:
AE= Adverse event
cGMP= Cyclic guanosine monophosphate
EP= Endpoint
ERA= Endothelin receptor antagonist
HW= Heavy-weight
LW= Lightweight
MW= Middle-weight
PAH = Pulmonary arterial hypertension
PDE5= Phosphodiesterase type 5
PDE5i= Phosphodiesterase type 5 inhibitor
pt= patient
PVR= Pulmonary vascular resistance
6MWD= Six-minute walk distance
TEAE= Treatment-emergent adverse event
WHO= World Health Organization

Essential therapeutic features

Summary of clinical EFFICACY:
NCT01824290 is a phase-3, international, randomized, multicenter, two-period (Period 1: 24 weeks, double-blind, placebo-controlled period;Period 2: 2-year, open-labeled extension period), add-on (i.e. in addition to the pts' current ERA) study aimed to assess the efficacy and safety of Tadalafil in a pediatric population. Eligibility criteria included pts aged ≥6 months to <18 years who had established PAH by a pulmonary artery pressure ≥25 mmHg, pulmonary artery wedge pressure≤15 mmHg, and PVR ≥3 Wood unit via right heart catheterization. Pts had also a WHO functional class value of II or III and had been receiving an ERA with no change in dose for at least 12 weeks prior to the study.
A total of 35 pediatric pts were enrolled and randomly (1:1) assigned to Tadalafil 40mg or 20mg based on their weight (respectively HW: 40kg, MW: 25 to <40kg) or placebo orally for 24 weeks in the Period 1. In the current study there were no pts enrolled in LW cohort (<25kg).
The primary EP of the study was change from baseline in 6MWD (meters; m) in pts aged ≥6 years at week 24 (end of Period 1). Of the 35 pts enrolled into the study, 33 pts (placebo N=16; Tadalafil N=17) were included in the primary analysis. Two enrolled pts who were ≥6 years aged were excluded from the primary analysis due to either unmet study entry criteria or lack of post baseline 6MWD data. The least square (LS) mean (SE) changes from baseline in 6MWD at week 24 was numerically greater with Tadalafil vs placebo [60.48 (20.41) m vs 36.60 (20.78) m; placebo-adjusted mean difference (SD) 23.88 (29.11)]. However, the statistical significance testing was not performed between the treatment groups due to low sample size [3].

Summary of clinical SAFETY:
Safety was evaluated in all pts who received at least one dose of study medication. Safety data refer to the Period 1 of the study and they are summarized in the table below.

	Tadalafil N=15	Placebo N=15
≥1 TEAEs	15 (100%)	8 (53.3%)
Headache	29.4%	11.1%
Upper respiratory tract infection	17.6%	5.6%
Influenza	17.6%	0.0%
Arthalgia	11.8%	5.6%
Epistaxis	11.8%	5.6%
AE leading to study discontinuation	1 (6.7%)	1 (6.7%)
Serious AE	0	0
Death	0	0

Headache was the most commonly reported TEAE considered by the investigator to be related to the study medication. One pt in each treatment group discontinued the study due to clinical worsening based on investigator's report [3].

Ongoing studies:
- ***For the same indication:***Yes
- ***For other indications:***Yes

Discontinued studies (for the same indication): No

References:
[1]https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022332Orig1s011lbl.pdf
[2]https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-adcirca-ii-58-g_en.pdf
[3]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8226239/
[4]https://gallery.farmadati.it/Home.aspx
[5]https://www.osservatoriomalattierare.it/malattie-rare/ipertensione-polmonare
[6] https://www.orpha.net
[7]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6771736/

NHS impact

Cost of therapy:
The cost of Tadalafil 20 mg is 978.41 € for a supply of 56 tablets [4].

Epidemiology:
PAH is a respiratory rare disease that affects about 2,000 pts in Italy [5]. This disease usually affects adult pts and rarely pediatric pts [6].

POSSIBLE PLACE IN THERAPY
There are various therapies aimed to treat PAH in children and most of them are founded on adult evidence based data [3]. Initiation of PAH-targeted therapy is based on the level of risk, with low-risk pts receiving an oral ERA or PDE5i (as first-line treatments, with the option of combination of both classes in those who deteriorate on ERA or PDE5i alone) or an oral or inhaled prostacyclin analog (prostanoid).
High-risk pts shouldreceiveaninjectableprostanoidaloneorincombinationwithotherdrugs.However, there are no definitive trials in children to support the combination therapy.Tadalafil could be used as a possible treatment in the first-line treatment in children [7].

OTHER INDICATIONS IN DEVELOPMENT
Acute kidney injury; Benign prostatic hyperplasia; Neck squamous cell carcinoma; Cerebrovascular disorders.

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:-

OTHER DRUGS IN DEVELOPMENT FOR THE SAME INDICATION
Macitentan

*Service reorganization No
*Possible off label use Yes

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