Off-label use of PAH-targeted medications approved for adults and their financial coverage by health insurances are vital for children with pulmonary hypertension

Pulmonary hypertension (PH) is a progressive disease defined by chronic elevation of pulmonary artery pressure. The underlying causes of PH are diverse and include pathological changes in the pulmonary vessels, the pulmonary parenchyma or interstitium and small or dysfunctional left-sided heart structures. Over the last two decades, echocardiography, the primary diagnostic tool in paediatric PH, has developed into an advanced imaging technology with usually great image quality and prognostic impact.1–10 Prior to the modern area of PH therapy, the average life expectancy after diagnosis has been 10 months for children with pulmonary arterial hypertension (PAH).11 The development and availability of new, so-called “targeted” or “advanced” therapies, which are approved for adults with PAH, have significantly improved quality of life and life expectancy of paediatric PAH patients as well.12,13 The pathogenesis of pulmonary hypertensive vascular disease, however, in most cases, is still chronically progressive: In end-stage PH, defined as advanced pulmonary vascular disease (PVD) and severe right ventricular (RV) dysfunction,14–18 bilateral lung transplantation remains the only treatment option.19–21

1.1 Phenotyping paediatric PH patients–there is a lot to unpack

According to the World Symposium Pulmonary Hypertension (WSPH, 2018), PH is classified into five different groups (Group 1-5 PH).22 Obviously, children are not simply young adults and PAH in children differs from PAH in adults.23,24 The first WSPH article dedicated to paediatric PH was published in 2013.25 Especially in children, but also in adults >40 years of age, overlapping group assignments are frequently indicated; for example, a child may be assigned to have both heritable pulmonary arterial hypertension (HPAH)26 and PH due to (developmental) lung disease,27 or PAH associated with congenital heart disease (CHD)24,28 plus either of the former PH subgroup phenotypes.24,29,30

1.2 Medications approved for use in children with PAH

Currently, only the phosphodiesterase-5 inhibitor sildenafil and the endothelin receptor antagonist bosentan (age >12 months) have been approved by the European Medicines Agency (EMA) for the treatment of PAH (WSPH Group1) in children. In the United States, only bosentan (in children >12 months of age) has been approved by the Food and Drug Administration (FDA) for paediatric use while sildenafil is not approved. Nevertheless, the mainstay of therapy worldwide for two of the most common forms of PH in childhood, that is, PH associated with bronchopulmonary dysplasia in preterm infants (BPD-PH)27 and PH associated with congenital heart disease,31 is the oral phosphodiesterase-5 (PDE5) inhibitor sildenafil, either as monotherapy or in combination with an endothelin receptor antagonist (ERA).

1.3 Medications approved for use in adults with PAH

For adults, various other drugs beyond sildenafil and bosentan have received approval for PAH treatment by the EMA and FDA32,33 (Table 1). Pursuant to the 2018 WSPH recommendations, medium- to high-risk adult PAH patients should receive a combined therapy consisting of 2 or 3 of these substance classes.32 All of these medications primarily lead to a reduction of the pulmonary vascular tone by vasodilation via various mechanisms. Similarly, the current 2018 WSPH paediatric PH recommendations advise a...
combination therapy of at least two oral PAH medications in children at medium to high-risk PAH. In severe disease, oral PAH medications should be further combined with parenteral prostacyclin analog (PCA) therapy (inhalation, intravenous infusion).\(^{29,32,33}\) Besides their vasodilatory effects, some of the PAH-targeted drugs also have anti-proliferative and anti-inflammatory effects,\(^{34-36}\) aiming to prevent or at least slow down pulmonary vascular remodelling, which would lead to elevated pressure and resistance in the pulmonary circulation and right heart failure.\(^{35}\)

After the first PAH medications had become available for paediatric use (bosentan, sildenafil), the most common treatment strategy has been starting with monotherapy, followed by combination pharmacotherapy (usually a PDE5 inhibitor plus endothelin receptor antagonist). However, it has been increasingly recognized that early combination and upfront combination PAH-targeted pharmacotherapy is more effective in adults with PAH (AMBITION RCT),\(^{37-39}\) and also most likely in children, according to a retrospective multicenter observational study.\(^{40}\) With respect to the progression of symptoms in the course of the disease, an early combination of therapy has favourable effects on PAH and seems to increase long-term survival,\(^{9,11,32,41-43}\) as it has been previously demonstrated for childhood cancers such as acute lymphocytic leukaemia.\(^{44}\)

Since there are only very few randomized, controlled trials in children with P(A)H, the current therapeutic algorithm for paediatric PH\(^{29}\) is primarily based on data of studies from adult PH patients.\(^{32,33}\) In children with moderate-to-severe PAH and more than half-systemic pressure, the EPPVDN recommends upfront oral combination pharmacotherapy (PDE5 inhibitor plus endothelin receptor antagonist) in most treatment-naïve cases, although exceptions may apply (e.g., sildenafil monotherapy in BPD-PH, calcium channel blocker use in select cases, upfront oral triple therapy or upfront intravenous prostacyclin analog therapy).\(^{29}\)

One of the main reasons for the lack of prospective/randomized controlled studies in paediatric PAH is that pulmonary hypertensive vascular disease, although underestimated, is a rare disease, particularly in children.\(^{24,45,46}\) For that reason, randomized controlled studies with sufficiently high patient numbers and statistical power cannot be expected in the near future,\(^{24,45,46}\) and however, pharma-sponsored prospective paediatric PH studies are ongoing.\(^{47}\)

For the prostacyclin receptor (IP-) agonist selexipag, the GRIPHON trial did not demonstrate a significant benefit in survival in adults with PAH already on concomitant PAH-medications.\(^{28}\) However, there was significant improvement of the primary combined clinical endpoint ‘mortality or PAH-associated event’ (i.e., hospitalization, start of parenteral prostacyclin or oxygen therapy, balloon atrioseptostomy).\(^{48}\) Indeed, selexipag appears to be relatively well tolerated in adults and to slow down the progression of PAH.\(^{38,49}\)

### Key points

- **Pulmonary Hypertension is currently an incurable condition in adults and children.**
- **Several PAH-targeted medications, alone or in combination, have been proven effective in PAH randomized controlled trials, resulting in approval of such pharmacotherapy for adult PAH.**
- **Clinical drug trials in pediatric PH patients are more difficult to do for several reasons, including challenging patient recruitment, and will likely take several years to complete. Thus, the pediatric use of several medications is considered ‘off label’ and currently is not regularly reimbursed by health insurances.**
- **Withholding ‘off label’ drugs for pediatric patients until clinical trials are completed leaves them without alternative therapeutic options, resulting in poor quality of life, hospital admissions and high mortality.**
- **We propose careful use of ‘off label’ medications under the guidance of pediatric PH experts for selected patients, while completion of clinical trials in the pediatric population is ongoing, since such an approach provides a compassionate alternative that can improve quality of life and prolong survival.**
- **Reimbursement of ‘off label’ medications for children with PH by health insurances will remove the barrier to their use; reporting of the resulting clinical experience will complement the results of clinical trials, thus advancing the pediatric PH field more rapidly.**

Today, there is several years of experience in paediatric PH centres with the oral PAH-targeted medications, for example macitentan,\(^{43,50}\) riociguat\(^{51,52}\) and selexipag,\(^{29,48,53}\) or parenteral prostacyclin analogs (PCA: epoprostenol, treprostinil, iloprost), all of which are not (yet) approved for children. Accordingly, it can be assumed that ‘off-label’ combination therapy will reduce morbidity and re-hospitalization rates due to PAH exacerbation, and likely mortality, but this has not been shown in clinical studies in the current era of combination therapy. The aim of combination pharmacotherapy is to allow PH patients to live independently if possible, with an acceptable or good quality of life.\(^{9,25}\) Postponing the listing for lung transplantation\(^{19}\) in patients at higher risk can be safely achieved by combination therapy.
There are currently no large, randomized prospective study data sets on childhood PAH combination therapy available. Due to heterogeneity and relatively low incidence of PAH and persistent regulatory hurdles, it cannot be assumed that such data based on sufficient study sizes will be generated and published in the foreseeable future. The ongoing, pharma-sponsored ‘Study to Assess Whether Macitentan Delays Disease Progression in Children With Pulmonary Arterial Hypertension (PAH)’ (TOMORROW, NCT 02932410) plans to enrol 300 children >2 years of age, with an estimated study completion by July 2022. Moreover, a pharma-sponsored prospective study entitled ‘A Clinical Study to Confirm the Doses of Selexipag in Children With Pulmonary Arterial Hypertension’ (PATENT-CHILD, NCT02562235) has an estimated completion in 2031 despite only 24 subjects planned to be enrolled. While these studies are important in establishing safety, tolerability and pharmacokinetics, it will take several years before they are completed, and a large number of patients will die in the interim. Thus, one may question whether it is ethically justified to withhold these efficient but nonapproved therapies from PH children for whom trial participation is not feasible who are not responding to the 1-2 approved PAH medications available. We propose that careful use of these ‘off-label’ therapies under the close monitoring of an expert in selected cases and with the intention to report all observations is useful. Such an approach will yield important knowledge, complementary to the knowledge gained by RCTs, but will more rapidly advance the field.
In order to address this dilemma, the EPPVDN conducted and recently published two small but comprehensive investigator-initiated prospective observational studies on the use of oral, add-on, off-label PAH-targeted medications in children with PH: The first prospective study of macitentan pharmacotherapy in infants and children with PH <12 years of age showed that macitentan treatment was well tolerated and associated with improvements in invasive hemodynamics, longitudinal systolic RV function (TAPSE) and serum NT-proBNP levels. The other EPPVDN investigator-initiated multicenter study on add-on selexipag in children with PAH demonstrated that oral selexipag is well tolerated and safe when closely monitored. Add-on selexipag therapy improved several outcome-relevant, hemodynamic and clinical variables in about 50% of patients and prevented disease progression in an additional 27% of patients. Of note, ‘off-label’ use, although widely practised, should not be regarded as an alternative to the generation of sufficient safety and efficacy data by RCT. In contrast, we believe that publication of results from off-label use provides a timely addition to classic RCTs (with their inherent limitations as outlined above). Patients’ and guardians’ attitude towards informed use of ‘off-label’ medication is usually positive. In addition, most indications in paediatric PH/PAH drug therapy will still remain ‘off-label’, when RCT data become available as for several rare disease entities execution of sufficiently powered RCTs is unlikely and even for already approved drugs (sildenafil, bosentan) several indications are still ‘off-label’ (BPD-PH, infants below 1 year of age, certain congenital heart disease-associated PH entities, etc.). Thus, we believe that there is a moral obligation to offer off-label treatment (and to publish observational results) to patients who are unlikely to survive until RCT data will become available.

### 1.5 Catheter-based interventional and intravenous drug device therapies

In addition to pharmacotherapy, a catheter interventional or surgical procedure, such as the establishment of a reverse Potts shunt or an atrial septostomy, may also be considered for selected PAH patients, although they carry a considerable risk of procedure-related death or morbidity. In addition, off-label subcutaneous implantation of an intravenous treprostinil pump for continuous drug delivery has been reported in very few adolescents (Lenus Pro: 20mL, 40mL). Even after successful implementation of one of these invasive measures, only bilateral lung transplantation (LuTx) remains a therapeutic option in the far advanced stages of PAH and associated RV failure. However, allograft rejection is common and organ half-life is rather short after LuTx compared to other organ transplantations.

### 1.6 Off-label use of PAH-targeted medications is vital for children with pulmonary hypertension

There is an urgent need for advanced pharmacotherapy in children with progressive, life-limiting PH. For this reason, the following measures are proposed as next steps:

1. To avoid withholding PAH-targeted medications (approved for adults) from children with PH, the ‘off-label use’ and its reimbursement by health insurances are required. In the majority of cases, children with more than mild PH do not sufficiently respond to the 1-2 medications approved for paediatric use (Table 1). Any refusal of reimbursement of advanced PAH medications by health insurance companies is ethically not justifiable, given the published safety and efficacy data and the grim prognosis of the disease, especially with suboptimal treatment. The coverage of costs for ‘off-label’ PAH medications is imperative if—according to expert opinion—the agent (Table 1) can have a positive impact on the course of the disease.

2. The decision on the specific therapy for PH with the possibility of combining drugs of all substance classes—including ‘off-label pediatric formulations’—should be made by a PH expert with sufficient experience in the treatment of children with pulmonary hypertension—and especially with vasoactive drugs (Table 1). Given the heterogeneous drug response depending on the aetiology of paediatric PH/PVD, it is highly advisable to build interdisciplinary teams and networks in paediatric PH centres that are dedicated to provide close outpatient follow-up and tailored treatment, including objective and structured assessments of positive effects. Of note, the qualification ‘PH-expert’ is currently not formally regulated in most countries. The definition of expert status by national regulatory agencies should be based on objective criteria, such as patient volume and outcome. A potential framework has been outlined in the recent AEPC training recommendations on pulmonary hypertension which propose institutional and personal requirements for a specialty training in paediatric and congenital PH.

3. Paediatric formulations of PAH-targeted drugs must be developed and produced in the future, but this is not a mandatory pre-requisite for ‘off-label’ use of such medications in children. In two prospective studies, children with PH tolerated add-on macitentan or add-on selexipag well.

4. The lack of approval of available PAH drugs for use in children and the limited published paediatric study data, should not prevent the healthcare provider (HCP) with
solid PH expertise from being able to offer these therapies to young PH patients, given the very limited treatment alternatives and grim prognosis in patients not responding to approved pharmacotherapy.

To achieve therapeutic success in the young, treatment with the above-mentioned PAH-targeted drugs—‘off-label’ in children (Table 1; currently, e.g., selexipag, macitentan, riociguat, iloprost, treprostinil, epoprostenol), usually in combination with 1-3 other PAH medications—is necessary.29,32,33 Affected children without access to such advanced pharmacotherapy will likely have greater—and presumably more rapid—disease progression. The latter is associated with loss of exercise capacity and quality of life, and often severe adverse events, including syncope, resuscitation, hospitalization and death. Quality of life for paediatric patients with pulmonary hypertension is rated lower by parents and patients than quality of life associated with congenital heart disease or paediatric cancer.62 Especially in the young, clinical deteriorations in the context of pulmonary hypertensive vascular disease and associated RV dysfunction usually lead to an increased number of outpatient contacts, and to costly, hospital admissions, frequently requiring intensive care monitoring and therapy. Thus, even from an economic standpoint, health insurance coverage of off-label combinatory pharmacotherapy for paediatric PH is likely a worthwhile financial commitment.

KEYWORDS
children, macitentan, off-label, pulmonary hypertension, riociguat, selexipag

CONFLICT OF INTEREST
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