Challenging the 2015 PH Guidelines and annual G6 meeting

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European Heart House

Sophia-Antipolis

France

EU Regulatory Perspective

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Disclaimer: Any viewpoints represented in this talk are not necessarily those of **EMA** or the Dutch **MEB**.

Data presented are available on public websites.

Content

- **New medicinal products**

Indications ??

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- PAH drugs investigated in other PH subtypes
- Paediatric development

New medicinal products

Riociguat (2015)

Chronic thromboembolic pulmonary hypertension (CTEPH)

adult patients with WHO FC II to III with

- inoperable CTEPH,
- persistent or recurrent CTEPH after surgical treatment

to improve exercise capacity (see section 5.1).

Pulmonary arterial hypertension (PAH)

as monotherapy or in combination with ERA, is indicated for the

- treatment of adult patients with PAH with WHO FC II to III to improve exercise capacity.

Efficacy has been shown in a PAH population including idiopathic or heritable PAH or PAH associated with CTD (see section 5.1).

ESC Guideline: I B

Selexipag (2016)

- Uptravi is indicated for the long-term treatment of PAH in adult patients with WHO (FC) II–III, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies.

- Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).

ESC Guideline: I B (same as macitentan)

(g): not approved by EMA at time of publication

Table 11-2 Summary of type of first CEC-confirmed MM event up to 7 days after last study drug intake in AC-065A302 treatment period, FAS

	Selexipag N=574 n	Selexipag N=574 %	Placebo N=582 n	Placebo N=582 %
Patients with morbidity/mortality event	140	24.4%	212	36.4%
First morbidity/mortality event:				
Death	25	4.4%	16	2.7%
DEATH	25	4.4%	15	2.6%
HOSPITALIZATION-PAH / DEATH	0		1	0.2%
Hospitalization for PAH worsening	71	12.4%	96	16.5%
HOSPITALIZATION-PAH	51	8.9%	68	11.7%
DIS. PROGR. / HOSPITALIZATION-PAH	15	2.6%	19	3.3%
INIT. OF CHRONIC OXY. THERAPY / HOSPITALIZATION-PAH	4	0.7%	5	0.9%
INIT. OF PARENTERAL PROST. THERAPY / HOSPITALIZATION-PAH	1	0.2%	2	0.3%
DIS. PROGR. / INIT. OF CHRONIC OXY. THERAPY / HOSPITALIZATION-PAH	0		2	0.3%
PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	1	0.2%	2	0.3%
NEED FOR LUNG TX.	1	0.2%	2	0.3%
Parenteral prostanoid therapy or chronic oxygen therapy	11	1.9%	14	2.4%
INIT. OF PARENTERAL PROST. THERAPY	7	1.2%	8	1.4%
INIT. OF CHRONIC OXY. THERAPY	4	0.7%	4	0.7%
DIS. PROGR. / INIT. OF CHRONIC OXY. THERAPY	0		2	0.3%
Disease Progression	32	5.6%	84	14.4%
DIS. PROGR.	32	5.6%	84	14.4%

Drug Combinations

Labelling does not address sequential or upfront combination.

1. **Ambrisentan** is indicated for PAH in adult patients of WHO FC II to III, including use in combination treatment (see section 5.1)…

Section 4.2 (Posology)

Dose titration in case of combined therapy

Section 5.1 (Pharmacodynamics and description of Clinical Studies)

Description of the AMBITION study.

2. **Macitentan** as monotherapy or in combination, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III.

3. **Riociguat** as monotherapy or in combination with ERA……

4. **Selexipag** either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies

Drugs Not Centrally Registered

(*by EMA***)**

Vardenafil

Iloprost IV

Treprostinil, inhaled and oral

Beraprost

❑ Other Regulatory Challenges

1. PAH authorised products for other PH subtypes

ESC GL: Use of drugs approved for PAH is not recommended in patients with PH due to lung diseases

Contraindication for Ambrisentan

Idiopathic pulmonary fibrosis (IPF), with or without secondary pulmonary hypertension (see section 5.1).

Based on results of ARTEMIS-IPF study

Ongoing assessment: Riociguat

Riociguat authorised in PH group 1 and 4, was investigated in in PH associated with idiopathic interstitial pneumonias (group 3).

RISE IIP
Terminated study with **145 PH-IIP** patients treated with either riociguat or placebo.

PEP: 6 MWT after 26 weeks.

Interim assessment: **21 deaths**: 17 patients on riociguat and 4 patients on placebo.

Serious AEs: respiratory disease or lung infections

Preliminary data indicated no clinical benefit for PH-IIP patients.

2. Paediatric Development

- Labelling only for sildenafil, PK data for bosentan.
- ***ESC GL acknowledges the limited RCT; refers to adult algorithm***
- Paediatric investigation plan PIP, obligatory for all new products
- Paediatric addendum for regulatory guidance on drug development
- Re-discussion regarding required data to support paediatric use
- Challenges with recruitment and feasible efficacy or PD parameters in paediatrics e.g RHC

Thank You