Adempas® (riociguat) is a soluble guanylate cyclase (sGC) stimulator, the first member of a novel class of compounds, discovered and developed by Bayer as an oral treatment to target a key molecular mechanism underlying pulmonary hypertension (PH). Riociguat is being investigated as a new and specific approach to treat different types of PH.\(^1,2\) PH is a severe, progressive, life-changing and life-threatening disorder of the heart and lungs in which the blood pressure in the pulmonary arteries is above normal and which can lead to heart failure and death.\(^3,4\) Research suggests that nitric oxide (NO) deficiency, accompanied by endothelial dysfunction, lies at the heart of the problem of PH and is linked to disease progression and death.\(^5,6\)

There are five types of PH; each can affect the patient in a different way and every patient may have a different etiology and manifestation of PH.\(^7\) Based on the findings of an extensive clinical trial program, riociguat is the first and only drug approved for the treatment of two types of PH: chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH).\(^10\) It is the first and only drug that has consistently demonstrated robust and sustained clinical efficacy in two separate PH indications.\(^10,11\)

**PH is associated with increased pulmonary artery pressure and endothelial dysfunction**

In PH, blood pressure in the pulmonary arteries (the arteries that take de-oxygenated blood to the lungs from the heart) is above normal.\(^3,4\) Abnormal functioning of the inner lining of the blood vessels (endothelial dysfunction) contributes to the elevated blood pressure in the pulmonary artery that is associated with PH. Tightening and thickening of the pulmonary artery wall (vascular remodelling) lead to a further increased pulmonary blood pressure.
As a result, the right side of the heart has to work harder to pump blood through the arteries. Eventually, this part of the heart becomes enlarged and consequently is less able to pump blood through the lungs, leading to heart failure and death.\textsuperscript{3, 4}

**Nitric oxide (NO) is insufficiently available when endothelial dysfunction occurs**

- Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of NO and insufficient stimulation of sGC.\textsuperscript{1}
- In people whose blood vessel linings function in a healthy way (normal endothelial function), NO produced by cells of the blood vessel lining (endothelial cells) causes the smooth muscle cells of the blood vessel to relax and become wider.
- This means that the blood can flow more easily through the blood vessel. The endothelial cells do this by increasing the production of a chemical messenger (signalling molecule) called cyclic guanosine monophosphate (cGMP) through activation of a key biological catalyst (enzyme) called soluble guanylate cyclase (sGC).\textsuperscript{13}
- cGMP plays a pivotal role in controlling the way in which the endothelium in the blood vessel works, to avoid:
  - the tightening and thickening of the blood vessel walls (vascular tone)
  - the narrowing and loss of elasticity of vessels (fibrosis)
  - the rapid and excessive growth of cells and inflammation (proliferation)\textsuperscript{13}

**Riociguat is developed to restore the NO-sGC-cGMP pathway and, in doing so, decrease endothelial dysfunction**

Riociguat is developed to address endothelial dysfunction and works through the NO-sGC-cGMP signalling pathway, both sensitizing the sGC enzyme to the body’s own NO and also stimulating sGC independently of NO – enabling it to work in two ways (giving it a unique mode of action).\textsuperscript{1, 2, 13}

- As such riociguat is the first member of a new class of compounds, known as the sGC-stimulators.\textsuperscript{1, 2}
- Riociguat addresses the issue of NO deficiency by restoring the NO-sGC-cGMP pathway leading to increased generation of cGMP.\textsuperscript{1}
- Through this unique way of working, riociguat decreases blood pressure within the pulmonary arteries that take blood from the heart to the lungs, reducing pressure on the heart leading to improved patient outcomes and bringing a much needed new treatment option to PH specialists.
Riociguat stimulates sGC independently of NO

- The ability of riociguat to directly stimulate sGC independently of NO while also increasing the sensitivity of sGC to NO is fundamentally important in PH as endothelial dysfunction associated with the condition can be related to low levels of NO which is linked to mortality in CTEPH and PAH.¹, ⁵, ⁶
- Low levels of NO potentially reduce the ability of other PH therapies, such as phosphodiesterase 5 (PDE5) inhibitors*, to work effectively as these treatments rely on the body’s natural production of NO.¹

Riociguat aims to address areas of high unmet medical need

Although the prognosis for patients with PH has improved in recent years, there is still a high unmet need for more efficient therapies.¹⁴ With its novel mode of action, riociguat has the potential to overcome a number of limitations of other approved PAH therapies, such as PDE5-inhibitors*, including NO dependence, and is the first drug which has shown clinical benefits in CTEPH, where, until the approval of riociguat, no approved pharmacological treatment was available.¹, ¹⁰, ¹²

* Concomitant use of Riociguat with PDE5-inhibitors (such as sildenafil, tadalafil, and vardenafil) is contraindicated.
The development program for riociguat across different forms of PH demonstrates Bayer’s commitment to understanding this severe and life-threatening condition with a high unmet medical need to improve the lives of people with PH.

References


