North America Medical Information
medinfoUS@takeda.com
www.takeda.com

04/01/2020

Joseph Roche
[redacted]
United States

Dear Mr. Roche,

Re: Your medical information request, Ref: 00062830

Thank you for your medical information request regarding FIRAZYR® (Icatibant).

Please find the enclosed package in response to your request for medical information:

- Firazyr and COVID-19-Treatment of Pulmonary Involvement or Acute Respiratory Distress Syndrome
- A Product Summary Document containing information about the indications and important safety information for FIRAZYR®
- The Full Prescribing Information for FIRAZYR®

The attached information is provided as a professional courtesy in response to your inquiry. It is intended to provide pertinent data to assist you in forming your own conclusions in order to make healthcare decisions. Takeda does not advocate the use of its products outside of approved labeling or the use of investigational drugs not approved by the U.S. Food and Drug Administration. Please refer to the full Prescribing Information.

If you have additional questions, or to report an adverse reaction please contact Takeda Medical Information at 1 800 828 2088 or medinfoUS@takeda.com.

Sincerely,

Tangela Battle
Takeda Medical Information
Shire is now part of Takeda

In order to respond to your request, Takeda processes your personal information. The Information will be processed in accordance with applicable data protection laws. It may be necessary to share your personal information with Takeda affiliates, partners and regulatory authorities located within and outside your home country. All the information provided will be retained for as long as necessary to fulfil the purposes for which the information was provided unless a longer period is required or permitted by law. For more detailed information about Takeda's privacy practices, please visit our website at www.takeda.com/privacy-notice. If you have questions, or would like additional information regarding our privacy practices, you may contact us at privacyoffice@takeda.com.

This document is part of a response package from Takeda Medical Information to an unsolicited request for medical information and it must be read with and in the context of all documents that are part of the response package, including the Full Prescribing Information

Firazyr and COVID-19 - Treatment of Pulmonary Involvement or Acute Respiratory Distress Syndrome (ARDS)

Firazyr (icatibant) is not indicated for the treatment of pulmonary involvement or acute respiratory distress syndrome (ARDS) associated with COVID-19 (SARS-Cov-2) infection. In addition, a search of the medical literature did not identify any information relevant to your request.

Takeda has not systematically evaluated the use of Firazyr for treatment of pulmonary involvement or ARDS associated with COVID-19 infection and, more generally, in viral infections.

Takeda does not recommend the use of Firazyr beyond the approved labeling. Any decisions regarding the usage of Firazyr beyond the approved labeling is left to the discretion of the treating healthcare professional.

A search of the medical literature identified publications related to kallikrein-kinin system activation and the pathogenesis of ARDs and publications of pre-clinical data and human case studies related to contact system involvement in ARDS. Please see the list of articles below.

Takeda is unable to suggest individualized treatment approaches or to provide advice or recommendations for the management of patients. Decisions regarding the management of patients must be made by the healthcare professional, based on the medical history and clinical status of the patient.

LOCAL LABEL INFORMATION

Indications and Clinical Use

Firazyr is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older (Firazyr PI).

Clinical Pharmacology

Mechanism of Action

Icatibant is a competitive antagonist selective for the bradykinin B2 receptor, with an affinity similar to bradykinin. Hereditary angioedema is caused by an absence or dysfunction of C1-esterase-inhibitor, a key regulator of the Factor XII/kallikrein proteolytic cascade that leads to bradykinin production. Bradykinin is a vasodilator which is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Icatibant inhibits bradykinin from binding the B2 receptor and thereby treats the clinical symptoms of an acute, episodic attack of HAE.

Pharmacodynamics

Following bradykinin challenge, intravenous administration of Firazyr caused dose and time-dependent inhibition of development of bradykinin-induced hypotension, vasodilation, and reflex tachycardia in healthy young subjects. Firazyr intravenous doses of 0.4 and 0.8 mg/kg infused over 4 hours inhibited response to bradykinin challenge for 6 to 8 hours following completion of the infusion. Based on exposure-response analysis, a subcutaneous dose of 30 mg Firazyr is

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predicted to be effective against bradykinin challenge for at least 6 hours. The clinical significance of these findings is unknown.

The effect of Firazyr 30 and 90 mg following a single subcutaneous injection on QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 72 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern. The dose of 90 mg is adequate to represent the high exposure clinical scenario.

Kinin System and Pathogenesis of ARDS

Evidence from experimental animal models and findings from *in vitro* and human studies suggest that the kinin system may be involved in the pathogenesis of ARDS and that the kinin system and bradykinin may contribute to the increased vascular permeability as well as sustain the inflammatory cascade by inducing recruitment of inflammatory cells and release of proinflammatory mediators by infiltrating cells (de Oliveira et al. 1988, Fuhrer et al. 1989, Carl et al. 1996, Hess et al. 2017).

The mechanisms through which coronaviruses lead to ARDS have not been fully elucidated but evidence suggests that a dysregulation of the mechanisms physiologically maintaining bradykinin levels under control in the pulmonary environment may be involved. Angiotensin-converting enzyme 2 (ACE2) is a protease expressed in the lungs that converts angiotensin II to angiotensin (1-7) inhibiting the degradation of bradykinin by ACE1 and that was shown to protect from ARDS in animal studies (Imai Y et al. 2005, Wösten-van Asperen RM et al. 2011). Coronaviruses bind to ACE2 as their cellular receptor and downregulate it (Li et al. 2002, Kuba et al 2005, Wan et al. 2020): downregulation of ACE2 leads to a reduced degradation/excess of bradykinin (Li et al. 2002, Kuba et al. 2005).

PUBLISHED DATA- PRECLINICAL AND HUMAN CASE STUDIES

A search of the medical literature identified the following preclinical data and human case studies related to Contact System involvement in ARDS:

- Akbary et al. Efficacy and tolerability of catibant (Hoe 140) in patients with moderately severe chronic bronchial asthma. *Immunopharmacology.* 1996;33(1-3):238-42.
- Folkerts et al. Virus- and bradykinin-induced airway hyperresponsiveness in guinea pigs. *Am J Respir Crit Care Med.* 2000;161(5):1666-71.
- Guerrero et al. Endotoxin-induced pulmonary dysfunction is prevented by C1-esterase inhibitor. *J Clin Invest*. 1993;91(6):2754-60.[Web Link]
- Persson K et al. Severe lung lesions caused by Salmonella are prevented by inhibition of the contact system. *J Exp Med*. 2000;192(10):1415-1424. [Web Link].
- Uchiba et al. Effects of plasma kallikrein specific inhibitor and active-site blocked factor VIIa on the pulmonary vascular injury induced by endotoxin in rats. *Thromb Haemost.* 1997;78:1209-1214.
- Vaheri et al. Pathophysiology of a severe case of Puumala hantavirus infection successfully treated with bradykinin receptor antagonist icatibant. Antiviral Research. 2014;111: 23-25.

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- Van Diepen et al. A case of acute respiratory distress syndrome responsive to methylene blue during a carcinoid crisis. *Can J Anaesth*. 2013;60(11):1085-8.
- Vangerow et al. Effects of C1 inhibitor and r-SP-C surfactant on oxygenation and histology in rats with lavage-induced acute lung injury. *Intensive Care Med*. 2001;27**:**1526-1531.
- Wygrecka et al. Antihistone Properties of C1 Esterase Inhibitor Protect against Lung Injury. *Am J Respir Crit Care Med. 2017;*196**:**186-199.

Please note that *in vitro* activity/in *vivo* studies cannot be used to draw clinical efficacy or safety conclusions. Caution should be applied when extrapolating preclinical data to humans.

REFERENCES

Carl VS, Moore EE, Moore FA, et al. Involvement of bradykinin B_1 and B_2 receptors in human PMN elastase release and increase in endothelial cell monolayer permeability. *Immunopharmacology* 1996;33:325-329.

de Oliveira GG, de Oliveira MP. Adult respiratory distress syndrome (ARDS): the pathophysiologic role of catecholamine-kinin interactions. *J Trauma* 1998;28(2):246-53.

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Fuhrer G, Heller W, Junginger W, et al. Components of the kallikrein-kinin system in patients with ARDS. *Prog Clin Biol Res* 1989;308:737-742.

Hess R, Wujak L, Hesse C, et al. Coagulation factor XII regulates inflammatory responses in human lungs. *Thromb Haemost* 2017;17(10):1896-1907.

Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme protects from severe acute lung failure (Letter). *Nature* 2005;436:112-116.

Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury (Letter). *Nat Med* 2005;11:875-879.

Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus (Letter). *Nature* 2003;426:450-454.

Wösten-van Asperen RM, Lutter R, Specht PA, et al. Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE-2 activities and is prevented by angiotensin-(1-7) or angiotensin II receptor antagonist. *J Pathol* 2011; 255:618-627.

Wan J, Shang J, Graham R, et al. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARs coronavirus. *J Virol* 2020;94(7):e00127-20.

March 2020

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Firazyr Product Summary from the FDA-Approved Prescribing Information

This summary does not include all the information needed to use Firazyr® (icatibant) safely and effectively. Shire does not advocate the use of its products outside of the U.S. Food and Drug Administration (FDA)-approved prescribing information.

See the enclosed FDA-approved full prescribing information for more information.

INDICATIONS AND USAGE

Firazyr (icatibant) is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older (Firazyr PI).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Laryngeal Attacks

Given the potential for airway obstruction during acute laryngeal HAE attacks, patients should be advised to seek medical attention in an appropriate healthcare facility immediately in addition to treatment with Firazyr.

REFERENCE

FIRAZYR® [package insert]. Lexington, MA: Shire Orphan Therapies LLC.

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