PDL DRUG REVIEW

Proprietary Name: Ruconest®
Common Name: C1 esterase inhibitor
PDL Category: Hereditary Angioedema Agents

Comparable Products	Preferred Drug List Status
Firazyr	Preferred with Conditions

Summary

Pharmacology/Usage: Ruconest® is a recombinant analogue of human complement component 1 esterase inhibitor. It is purified from the milk of transgenic rabbits, and the skimmed milk goes through a screening process for contaminants prior to further manufacture. The manufacturing process has been validated to demonstrate adequate capacity for removal and/or inactivation of viruses. C1 esterase inhibitor (C1-INH) is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins). The main function of C1-INH is to regulate the activation of the complement and contact system pathways. Regulation of these systems is performed through the formation of complexes between the protease and the inhibitor, resulting in inactivation of both and consumption of the C1-INH. C1-INH exerts its inhibitory effect by irreversibly binding several proteases (target proteases) of the contact and complement system. The effect of Ruconest® on the following target proteases was assessed *in vitro*: activated C1s, kallikrein, factor XIIa and factor XIa.

Hereditary angioedema patients have absence or low levels of endogenous or functional C1-INH. While the events that induce attacks of angioedema in hereditary angioedema (HAE) patients are not well defined, it has been suggested that contact system activation and resulting increased vascular permeability lead to the clinical manifestation of HAE attacks. Suppression of contact system activation by C1-INH through the inactivation of plasma kallikrein and factor XIIa is thought to modulate vascular permeability by preventing the generation of bradykinin. Administration of Ruconest® replaces the missing or malfunctioning C1-INH protein and increases plasma levels of functional C1-INH activity.

Indications: For the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE). Effectiveness was not established in HAE patients with laryngeal attacks.

This is a pregnancy category B medication. The safety and efficacy of use in the pediatric population have been studied in 17 adolescent patients aged 13 to 17 years of age.

Dosage Forms: Lyophilized powder for reconstitution for injection in a single-use 25ml vial; 2100U of recombinant C1-INH (rhC1-INH)

Recommended Dosage: Ruconest® is for IV use after reconstitution only. Start treatment under the supervision of a qualified healthcare professional experienced in the treatment of HAE. Appropriately trained patients may

self-administer with recognition of an HAE attack. Start at 50U/kg (with body weight <84kg) with a maximum of 4200U (if body weight ≥84kg) to be administered as a slow IV injection over about 5 minutes. If the attack symptoms persist, a second dose can be given. Do not exceed 4200U per dose and no more than 2 doses should be administered in a 24-hour period.

Studies have not been conducted to assess the pharmacokinetics of Ruconest® with renal or hepatic impairment.

Drug Interactions: There were no drug interactions listed with Ruconest®.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ruconest® 50U/100U) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included headache (0%/6%), sneezing (2%/0%), angioedema (0%/3%), erythema marginatum (2%/0%), skin burning sensation (2%/0%), back pain (3%/0%), C-reactive protein increased (2%/0%), fibrin D-dimer increased (2%/0%), vertigo (0%/3%), procedural headache (2%/0%), and lipoma (2%/0%).

Serious arterial and venous thromboembolic (TE) events have been reported at the recommended dose of plasma derived C1 esterase inhibitor products in patients with risk factors. Risk factors may include the presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives or certain androgens, morbid obesity, and immobility. It is recommended to monitor patients with known risk factors for TE events during and after Ruconest® treatment.

Contraindications: In patients with a history of allergy to rabbits or rabbit-derived products; In patients with a history of life-threatening immediate hypersensitivity reactions to C1 esterase inhibitor preparations, including anaphylaxis.

Manufacturer: Pharming Healthcare Inc

Analysis: The safety and efficacy of Ruconest® were assessed in a randomized, double-blind, placebo-controlled study which included an open-label extension phase and was supported by the results of 2 additional randomized controlled trials (RCTs) and 2 additional open-label studies.

Study 1 included 75 adult and adolescent patients with HAE to assess Ruconest® in the treatment of acute attacks. Patients ranged in age from 17 to 69 years, while 63% were female and 96% were Caucasian. The primary endpoint was the time to beginning of relief of symptoms, assessed using patient-reported responses to 2 questions from a Treatment Effect Questionnaire (TEQ). The TEQ required patients to assess the severity of their attack symptoms at each affected anatomic location, using a 7-point scale (‘much worse’ to ‘much better’ [TEQ question 1]) and whether their symptoms had begun to decrease notably since receiving the medication (‘yes’ or ‘no’ [TEQ question 2]). To achieve the primary endpoint, a patient had to have a positive response to both questions along with persistence of improvement at the next assessment time (i.e. the same or better response).

Rescue treatment with Ruconest® was available for patients who did not experience the beginning of relief at 4 hours after study drug administration, or earlier to patients who experienced life-threatening oropharyngeal-laryngeal angioedema symptoms. In the RCT phase, the median time to beginning of relief of symptoms was statistically significantly shorter in patients treated with Ruconest® 50U/kg as compared with patients treated with placebo, as assessed by the TEQ. Results can be seen in the table below, which was adapted from the prescribing information.

Time to beginning of relief of symptoms, minutes	Ruconest® 50 U/kg (N=44)	Placebo (N=31)
Median	90	152
p-value	0.031	

Of several planned subgroup analyses, statistics demonstrated that in US patients a median time to beginning of relief of symptoms with persistence at the primary attack location (based on TEQ) was 98 minutes for those receiving Ruconest® and 90 minutes for those receiving placebo. The hazard ratio (HR) for time to the beginning of relief of symptoms in this subpopulation was 1.20 for patients receiving Ruconest® as compared with placebo. Non-US patients receiving Ruconest® had a median time to beginning of relief of 90 minutes and non-US patients receiving placebo had a median time to beginning of relief of 334 minutes. The HR for the non-US subgroup was 4.82 for patients receiving Ruconest® as compared to placebo.

Gender subgroups suggested a larger treatment effect in men than women. For women receiving Ruconest®, the median time to beginning of relief was 113 minutes and for women receiving placebo the median time was 105 minutes (HR 1.22). For men receiving Ruconest®, the median time to beginning of relief was 75 minutes and for men receiving placebo the median time was 480 minutes (HR 3.94).

Of patients who achieved relief within 4 hours, there were 4 (27%) in the placebo group who had a relapse of their symptoms within 24 hours as compared with 1 (3%) in the Ruconest® group. The proportion who received Ruconest® as rescue medication was greater in patients randomized to placebo (13 of 31 patients, 42%) than in patients randomized to Ruconest® (5 of 44, 11%).

The efficacy of Ruconest® 50U/kg for different anatomical locations of HAE attacks is summarized in the table below, which was adapted from the prescribing information.

Attack type	Ruconest® 50 U/kg	Placebo
Abdominal	14/16 (88%)	7/12 (58%)
Facial	3/6 (50%)	0/2 (0%)
Peripheral (extremities)	17/20 (85%)	7/14 (50%)

In the open-label extension (OLE) phase of study 1, patients were treated with open-label Ruconest® 50U/kg for repeated attacks. There were 44 patients who completed the RCT phase and enrolled into the OLE phase and were treated for a total of 170 attacks. In this phase, the median time to beginning of relief of symptoms was 75 minutes, consistent with the results of the RCT phase of the study. Results were comparable across attacks, suggesting that the efficacy of Ruconest® 50U/kg was maintained over repeated attacks of HAE. In the OLE phase of study 1, 3% (5/170) of attacks received a second dose of Ruconest® 50U/kg

In study 2 (North America RCT), patients were randomized to receive a single dose of either Ruconest® 50U/kg (N=12), Ruconest® 100U/kg (N=13), or placebo (N=13). Patients ranged in age from 17 to 66 years, 74% were female and 92% were Caucasian. In study 3 (European TCR), patients were randomized to receive a single administration of either Ruconest® 100U/kg (N=16) or placebo (N=16). Patients ranged in age from 17 to 71 years, 53% were female, and 100% were Caucasian. Patients scored their symptoms using a visual analogue scale (VAS) ranging from 0 to 100mm. A VAS decrease of ≥20mm compared with baseline with persistence of the improvement at 2 consecutive time points was considered the onset of relief in studies 2 and 3.

In study 2 and 3, the efficacy of Ruconest® in the treatment of acute angioedema attacks was demonstrated by significantly shorter times to beginning of relief of symptoms based on the VAS. In open-label extension

studies of study 2 and 3, 119 patients were treated with Ruconest® for a total of 362 acute angioedema attacks. As observed in study 1, the efficacy of Ruconest® was maintained for repeat attacks.

Place in Therapy: Ruconest® is a C1 esterase inhibitor (recombinant) indicated for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema. Effectiveness was not established in hereditary angioedema patients with laryngeal attacks. While this is for IV use, appropriately trained patients may self-administer upon recognition of a hereditary angioedema attack. In a phase 3 study, the median time to beginning of relief of symptoms was statistically significantly shorter in those treated with Ruconest® 50U/kg as compared with placebo. In addition, a greater number of those receiving Ruconest® achieved abdominal, facial, and peripheral symptom relief within 4 hours as compared with placebo.

Ruconest® is a cost effective alternative for the treatment of acute HAE attacks. It is therefore recommended that Ruconest® be made preferred and require prior authorization to confirm diagnosis of use.

PDL Placement: ☒ **Preferred with Prior Authorization**
☐ **Non-Preferred**

References

[1] Ruconest [package insert]. Bridgewater, NJ: Pharming Healthcare; 2018.