Remibrutinib RHAPSIDO in Chronic Spontaneous Urticaria (CSU)
National Drug Mini-Monograph

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VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AAS7, angioedema activity score over past 7 days (range 0-105, higher scores indicate greater severity); ADEs, adverse drug events; DB, double-blind; H1 AH, H_1 antihistamine; DLQ Index Score, dermatology life quality index score (range 0-30, higher scores indicate greater severity); HSS7, hives severity score over the past 7 days; ISS7, itch severity score over past 7 days (range 0-21; higher scores indicate greater severity); LS, least squares mean; MC, multicenter; PBO, placebo; PC, placebo-controlled; QOL, quality of life; R, randomized, RCT, randomized clinical trial; UAS7, TEAE, treatment emergent adverse event; TESAE, treatment emergent serious adverse event; urticaria activity score over past 7 days (range 0-42; higher scores represent greater severity);

FDA PRESCRIBING INFORMATION[1]	
Description / MOA	Remibrutinib is a small molecule kinase inhibitor, inhibiting Bruton's tyrosine kinase (BTK). Bruton's tyrosine kinase is an intracellular protein expressed in various cells including mast, basophils, B cells, macrophages and thrombocytes. Remibrutinib prevents BTK mediated degranulation of mast cells and basophils and blocks release of histamine and other proinflammatory mediators that lead to itch, hives and/or angioedema. It also inhibits BTK-related kinases tec protein tyrosine kinase (TEC) and non-receptor tyrosine kinase (BMX).
Indication Under Review	Treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite use of H1 AH treatment
Dosage Regimen	25 mg by mouth twice daily
Dosage Forms Under Review	25 mg tablet

EFFICACY CONSIDERATIONS[2]	
Trial	**REMIX-1 and REMIX-2 (Phase 3 trials-published in single publication)**
Design	R (2:1), DB, MC, PC (REMIX 1 and 2 had the same design) x 24 weeks of DB treatment followed by unblinded treatment for all patients (all patients received remibrutinib) x 28 weeks and finally an additional 4 weeks of no treatment. Planned treatment period was 52 weeks. Patients who withdrew from the trial or continued in the extension trial were not included in the final 4 week follow up. *H1 AH were required to be used throughout the studies at the locally approved standard dose and not maximized as recommended in clinical practice guidelines. However, rescue medication could be used (a different H1 AH, up to 4x the usual dose) for flare-ups during screening, treatment and follow-up.*
Population	Adults with CSU diagnosed ≥ 6 months that remained symptomatic despite use of H1 AH. Symptomatic disease on H1 AH was defined as itch and hives for at least 6 consecutive weeks before screening and included the following during the 7 days prior to randomization: UAS7 ≥ 16; ISS7 ≥ 6; HSS7 ≥ 6
Key Baseline Characteristics	(see table below)

	REMIX-1	REMIX-2
Age (years)	45	42
Female sex (%)	69	65
UAS7 (0-42)	30 (63.4% UAS7 ≥ 28)	30 (59.1% UAS7 ≥ 28)
ISS7 (0-21)	15	14
HSS7 (0-21)	16	16
AAS7 (0-105)	26	22
DLQ Index Score (0-30)	14	14
Positive for angioedema (%)	50	46
Past exposure to anti-IgE biologics (%)	32	31

Higher scores within the range () indicate greater severity for all measures.

Intervention	Remibrutinib 25 mg twice daily for 24 weeks (open label remibrutinib in all patients after 24 weeks)
Comparator	Placebo twice daily for 24 weeks (open label remibrutinib in all patients after 24 weeks)

Results

REMIX-1 and REMIX-2

Outcome*	Remi (n=309)	PBO (n=153)	Remi (n=297)	PBO (n=153)	Comments
Change UAS7 to week 12 (primary)	-20 LS vs. PBO: 6.2 (-8.5 to -4); p<0.001	-13.8	-19.4 LS vs. PBO: 7.7 (-9.9 to -5.5); p<0.001	-11.7	
Change ISS7 to week 12	-9.5 LS vs. PBO: 2.6; p<0.001	-6.9	-9 LS vs. PBO: 303; p<0.001	-5.7	
Change HSS7 to week 12	-10.5 LS vs. PBO: 3.6; p<0.001	-6.9	-10.5 LS vs. PBO: 4.5; p<0.001	-6	
UAS7 ≤ 6 at week 2	33% OR: 15.5, (6.2-39.8); p<0.001	3.3%	30.5% OR: 7.9, (3.7-16.9); p<0.001	5.9%	
UAS7 ≤ 6 at week 12	49.8% OR: 3.1 (2-4.8); p<0.001	24.8%	46.8% OR: 3.8 (2.4-6.2); p<0.001	19.6%	
UAS7 = 0 at week 12	31.1% OR: 3.8 (2.2-6.8); p<0.001	10.5%	27.9% OR: 5.8 (2.8-11.8); p<0.001	6.5%	
UAS7 = 0 at week 24 (EXPLORATORY)	36.6%	19.6%	35.7%	15.7%	Exploratory, no statistics applied
Rescue Medication	-----	----	----	----	Not reported

Sources: [2]

All changes are from baseline; UAS7 MCID=0.9-10.5 (vs. PBO)

Early withdrawal was similar between groups: REMIX-1 (Remi: 12.5% vs. PBO: 12.7%); REMIX-2 (Remi: 12.7% vs. PBO: 15.5%), withdrawal was primarily due to patient decision and not due to lack of efficacy or ADEs.

Although DLQ Index Score (assesses quality of life) was reported as baseline, it was not included as an outcome measure nor was any information provided on change from baseline.

Authors' Conclusions

Results of the REMIX-1 and REMIX-2 trials support the safety and efficacy of remibrutinib in adult patients with CSU who remain symptomatic despite use of H1 AH.

SAFETY CONSIDERATIONS	
Boxed Warnings	None
Contraindications	None
Other Warnings	Risk of bleeding: monitor for signs and symptoms of bleeding. Remibrutinib should be stopped if bleeding occurs and temporarily interrupted 3-7 days before and after surgery, depending upon the type of surgery and bleeding risk. Concomitant use with antithrombotic drugs may increase bleeding risk. Avoid live or live-attenuated vaccines in patients receiving remibrutinib (lack of data on effect of remibrutinib on these vaccines).
Top 5 AEs	Nasopharyngitis (11% vs. 9%); bleeding (9% vs. 2%; m*ostly petechiae and contusion, no serious bleeding reported)*; headache (7% vs. 6%); nausea (3% vs. 2%) and abdominal pain (3% vs. 2%). Remibrutinib vs. placebo, respectively. Bleeding leading to discontinuation (0.5% Remi vs. 0% PBO).
Drug Interactions	Strong or moderate CYP3A4 Inhibitors: Avoid use with remibrutinib; Remi is a substrate for CYP3A4 Strong or moderate CYP3A4 Inducers: Avoid use with remibrutinib; Remi is a substrate for CYP3A4 P-glycoprotein substrates (P-gp): Remibrutinib is a P-gp inhibitor. For those P-gp substrates where minimal changes in concentration can lead to serious ADEs (e.g., digoxin), closer monitoring is recommended. Antithrombotic drugs: Risks and benefits of concomitant use should be considered. Lack of data on concomitant use of remibrutinib with anticoagulants since patients on anticoagulants were excluded from REMIX-1 and REMIX-2. Use of antiplatelet drugs (e.g., acetylsalicylic acid up to 100 mg or clopidogrel up to 75 mg) was permitted in the trials.
Hepatic Impairment	Remibrutinib exposure is increased in patients with any degree of liver impairment. Avoid use in patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B and C).
Renal Impairment	There is no clinically significant effect on the pharmacokinetics of remibrutinib in patients with mild, moderate or severe renal impairment.
Pregnancy	Data on the use of remibrutinib during pregnancy are lacking to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcome. There is a pregnancy exposure registry that monitors pregnancy outcomes in pregnant women. The manufacturer encourages participation for women exposed to remibrutinib during their pregnancy.
Lactation	No data. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for remibrutinib and any potential ADE on the breastfed child or from the mother's underlying condition.
Trial Safety Results[2-4]	REMIX-1 and 2: No difference in percentage reporting at least 1 ADE; serious ADE were reported in 3.3% Remi vs. 203% PBO (none were considered related to study treatment); petechiae were reported in 3.8% Remi vs. 0.3% PBO, other ADEs were similar between groups. No deaths were reported.[2] Phase 2b R, DB, PC trial x 12 weeks of treatment: ADEs do not appear to be dose-dependent (10 daily to up to 100 mg twice daily were studied). Discontinuation due to ADEs were reported in 2.6% Remi vs. 0% PBO. Incidence of mild, moderate and severe ADEs were higher with Remi vs. PBO; Remi: 38.6%, 16.9% and 2.6% vs. PBO: 33.3%, 9.5% and 0%, respectively. Higher rates of skin/subcutaneous ADEs were reported with Remi 16.9% vs. PBO 4.8%. Most were related to symptoms of CSU during periods of non-treatment (Remi 6% vs. PBO 2.4%. No deaths were reported.[3] Phase 2b single arm extension study (52 weeks): Remibrutinib 100 mg twice daily: Summary of clinically significant ADEs include patients with at least one TEAE 71.6%; patients with TESAE 3.1% and discontinuation due to the TEAE or TESAE.[4]

OTHER CONSIDERATIONS	
FDA Review	CSU is a nonprogressive, self-limited disorder in most patients, with a 1-year spontaneous remission rate of 30 to 50% and an average duration of 2 to 5 years. Although some patients may have more persistent disease.[5] Reviewers conclude that remibrutinib has a favorable benefit/risk ratio and offers patients with CSU another option for treatment.
ICER Review	None
NICE Review	Evaluation planned, not yet complete.
Other	Phase 2b dose-ranging and 52-week single arm extension trial.[3-4] Improvements in UAS7 were greater for all doses of remibrutinib vs. PBO. In the 52-week extension all patients received Remi 100 mg twice daily for the duration of the extension trail to 52 weeks, response was maintained. REMIX-1 and 2 exploratory measures of response at 24 weeks, response was maintained.[6] Although several systematic reviews/meta-analyses have noted improvement in QOL referring to the DLQ index score, the information was not found in the studies. Authors note that change in urticaria activity correlate with improvement in QOL

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY

DRUG	VANF	CFU	FDA	GUIDELINES[7-8]
Omalizumab	PA-F	Yes	Approved in patients with inadequately controlled CSU despite H1 AH.	2nd line for patients remaining symptomatic on H1 AH (up to 4x daily dose)
Dupilumab	NF	Yes-draft	Approved in patients with inadequately controlled CSU despite H1 AH.	SR concludes that Oma and Remi are most effective, but safety remains less certain for Remi.[8] Dup impact on QOL and angioedema activity is uncertain.
Cyclosporine ***Very low to low doses - 1-5 mg/kg/d***	F	No	Off-label use in patients with refractory disease/symptoms despite use of H1 AH and omalizumab	3rd line for patients remaining symptomatic on H1 AH (up to 4x daily dose) + omalizumab

POTENTIAL PLACE IN THERAPY OF ——

1. As an alternative to omalizumab or dupilumab in patients who remain symptomatic despite maximized H1 AH to up to 4 times the approved daily dose. The choice of “second line” agent to H1 AH may be guided by the presence of comorbidities such as chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, atopic dermatitis, etc. *However, omalizumab is the preferred 2nd line after inadequate response to H1 AH up to 4 times the approved dose.*
2. Maximum doses of H1 AH should be continued in combination with second line therapies.
3. Low dose cyclosporine may be considered as a third line agent in patients with more refractory symptoms/disease.
4. Therapy can be stepped down by reducing doses or extending dosing intervals when the urticaria control test (UCT) is equal to 16.

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References

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