Report RINVOQ® - Upadacitinib

Product & Mechanism of action

Substance: upadacitinib

Brand Name: Rinvoq

Originator/licensee: AbbVie Deutschland GmbH & Co. KG

Classification: NI

ATC code: L04AA44

Orphan Status:
Eu: No
Us: -

Mechanism of action: Upadacitinib is a selective and reversible JAK inhibitor. It preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2. JAK1 is important in inflame-matory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function [1].

Authorized indications Licensing status

Authorized Indication:
EMA: upadacitinib is indicated for the treatment of MSAD in adults and adolescents 12 years and older who are candidates for systemic therapy [1].

Route of administration: OS

Licensing status
EU CHMP P.O. date: 24/06/2021
FDA M.A. date: -

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: -

ABBREVIATIONS:
AD: atopic dermatitis
AE: adverse event
CHMP: Committee for Medicinal Products for Human Use
EASI: composite index with scores ranging from 0 to 72, based on four AD disease characteristics and the body area of AD involvement
JAK: Janus Kinases
M.A.: Marketing Authorization
MSAD: Moderate-to-Severe Atopic Dermatitis
PCPE: plasma creatine phosphokinase elevation
P.O.: Positive Opinion
Pts: patients
URTI: upper respiratory tract infection
SAE: serious adverse event
TEAE: treatment-emergent AE

Essential therapeutic features

Summary of clinical EFFICACY:

Measure Up 1 and Measure Up 2 (NCT03569293 and NCT03607422) were replicate multicenter, randomized, double-blind, placebo-controlled, phase 3 trials that enrolled pts aged 12 to 75 years with MSAD. Pts were randomly assigned (1:1:1) to receive upadacitinib 15 mg, 30 mg or placebo once daily for 16 weeks. Pts were required to discontinue topical corticosteroids [2].

AD Up (NCT03568318) was a randomized, double-blind, placebo-controlled, phase 3 trial that enrolled pts aged 12 to 75 years with MSAD. Pts were randomly assigned (1:1:1) to receive upadacitinib 15 mg, 30 mg or placebo once daily, all in combination with topical corticosteroids, for 16 weeks [3]. Coprimary endpoints were the proportion of pts who had achieved at least 75% improvement in EASI score from baseline (EASI-75) and the proportion of pts who had achieved a vIGA-AD* response at week 16 [2,3]. Results are reported in Table 1. All these clinical trials are ongoing and further results will be published [2,3].

Table 1: Coprimary efficacy endpoint results at week 16

Coprimary endpoints	Measure Up 1		Measure Up 2		AD Up	
	Upadacitinib 15 mg (n=281)	Upadacitinib 30 mg (n=285)	Upadacitinib 15 mg (n=276)	Upadacitinib 30 mg (n=282)	Upadacitinib 15 mg (n=300)	Upadacitinib 30 mg (n=297)
EASI-75 at week 16						
Adjusted % difference vs placebo (95% CI)	53,3 (46,4 - 60,2); p<0.0001	63,4 (57,1 - 69,8); p<0.0001	46,9 (39,9 - 53,9); p<0.0001	59,6 (53,1 - 66,2); p<0.0001	38,1 (30,8 - 45,4); p<0.0001	50,6 (43,8 - 57,4); p<0.0001
vIGA-AD response at week 16						
Adjusted % difference vs placebo (95% CI)	39,8 (33,2 - 46,4); p<0.0001	53,6 (47,2 - 60,0); p<0.0001	34,0 (27,8 - 40,2); p<0.0001	47,4 (41,0 - 53,7); p<0.0001	28,5 (22,1 - 34,9); p<0.0001	47,6 (41,1 - 54,0); p<0.0001

*defined as a vIGA-AD score of 0 [clear] or 1 [almost clear] with ≥2 grades of reduction from baseline. vIGA-AD is based on a 5-point scale ranging from 0 (clear) to 4 (severe).

Summary of clinical SAFETY:

Safety results are summarized in Table 2. The most frequently reported TEAEs in Measure Up 1 and 2 were acne (10% in the upadacitinib 15 mg group, 16% in the 30 mg group and 2% in the placebo group), URTI (8% vs 10% vs 6%), nasopharyngitis (7% vs 9% vs 5%), headache (6% vs 7% vs 4%), elevation in plasma creatine phosphokinase levels (4% vs 5% vs 2%) and worsening of AD (3% vs 1% vs 9%). The most frequently reported TEAEs in AD Up were acne (10% vs 14% vs 2%), nasopharyngitis (12% vs 13% vs 11%), URTI (7% vs 8% vs 7%), oral herpes (3% vs 8% vs 2%), elevation in plasma creatine phosphokinase levels (4% vs 6% vs 2%), headache (5% vs 5% vs 5%) and worsening of AD (4% vs 1% vs 7%). No deaths were reported [2,3].

Table 2: TEAEs in the safety population

	Upadacitinib 15 mg			Upadacitinib 30 mg			Placebo		
	Measure Up 1 (n=281)	Measure Up 2 (n= 276)	AD Up (n=300)**	Measure Up 1 (n=285)	Measure Up 2 (n= 282)	AD Up (n=297)**	Measure Up 1 (n=281)	Measure Up 2 (n= 278)	AD Up (n=303)**
Any TEAE	176 (63%)	166 (60%)	200 (67%)	209 (73%)	173 (61%)	215 (72%)	166 (59%)	146 (53%)	190 (63%)
SAE	6 (2%)	5 (2%)	7 (2%)	8 (3%)	7 (3%)	4 (1%)	8 (3%)	8 (3%)	9 (3%)
Drop-out due to AEs	4 (1%)	11 (4%)	4 (1%)	11 (4%)	7 (3%)	4 (1%)	12 (4%)	12 (4%)	7 (2%)

**Combination with topical corticosteroids

Ongoing studies:

- ***For the same indication:*** Yes (NCT03738397, NCT04195698, NCT03661138).
- ***For other indications:*** Yes

Discontinued studies (for the same indication): Yes (NCT04666675, withdrawn prior to enrollment)

References:
[1]. https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf
[2]. Guttman-Yassky E., Teixeira H.D., et al.: Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet 2021; 397:2151-68.
[3]. Reich K., Teixeira H.D., et al.: Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021; 397:2169-81.
[4].https://gallery.farmadati.it/Home.aspx
[5]. Langan S.M., Irvine A.D., et al.: Atopic dermatitis. Lancet 2020; 396: 345–60.
[6].https://www.nice.org.uk/guidance/ta681/resources/baricitinib-for-treating-moderate-to-severe-atopic-dermatitis-pdf-82609375014853
[7].https://www.ema.europa.eu/en/documents/product-information/adtralza-epar-product-information_en.pdf
[8]. https://adisinsight.springer.com/drugs/800037410
[9].https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=Upadacitinib&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=
[10].https://adisinsight.springer.com/search
[11].https://clinicaltrials.gov/ct2/results?cond=Atopic+Dermatitis&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=

NHS impact

Cost of therapy:
28 sustained release tablets of upadacitinib 15 mg cost € 722,00 (ex-factory price) [4].

Epidemiology:
AD is one of the most common inflammatory disorders, affecting up to 20% of children and 10% of adults in high-income countries [5].

POSSIBLE PLACE IN THERAPY
A typical MSAD treatment pathway involves emollients and topical corticosteroids (1st-line), topical calcineurin inhibitors (2nd-line), phototherapy (3rd-line, for adults only) and systemic immunosuppressant therapies (4th-line). Dupilumab (for pts ≥12 years of age) and baricitinib (for adults) are recommended for the treatment of MSAD in pts that have not responded to at least one systemic therapy (5th-line) [6]. Tralokinumab has recently been approved for the treatment of MSAD in adult pts who are candidates for systemic therapy [7].

OTHER INDICATIONS IN DEVELOPMENT
Crohn's disease, giant cell arteritis, ulcerative colitis, vasculitis, axial spondyloarthritis [8,9].

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: /

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION
Delgocitinib, ruxolitinib, abrocitinib, lebrikizumab, ustekinumab, tezepelumab, nemolizumab [10,11].

*Service reorganization: No
*Possible off label use: Yes