Report ZEPOSIA® ozanimod

Product & Mechanism of action

Substance:ozanimod

Brand Name: Zeposia

Originator/licensee: Bristol-Myers Squibb Pharma EEIG

Classification:NI

ATC code:L04AA38

OrphanStatus:
Eu: No
Us: No

Mechanism of action:
Ozanimod is a S1P receptor modulator, which binds selectively to S1P receptor subtypes 1 and 5. Ozanimod causes lymphocyte retention in lymphoid tissues[1].

Authorized indications Licensing status

Authorized Indication:
EMA: Ozanimod is indicated for the treatment of adult pts with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent [2].

FDA: Ozanimod is a S1P receptor modulator indicated for the treatment of moderately to severely active UC in adults [3].

Route of administration: OS

Licensing status
EU CHMP P.O. date:14/10/2021
FDA M.A. date: 27/05/2021

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

ABBREVIATIONS:
ACG: American Gastroenterological Association
AEs: Adverse Events
ALT: alanine aminotransferase
CHMP: Committee for Medicinal Products for Human Use
GGT: γ-glutamyltransferase
MA: Marketing Authorization
MCS: Mayo Clinical Score
OS: Oral Administration
PO: Positive Opinion
Pts: Patients
QD: Once Daily
SAEs: Serious Adverse Events
S1P: Sphingosine 1-Phosphate
TNF: Tumor Necrosis Factor
UC: Ulcerative Colitis
vs.: versus

Essential therapeutic features

Summary of clinical EFFICACY:
NCT02435992 is a multicenter, randomized clinical study aiming to determine the efficacy of ozanimod as induction and maintenance therapy in adults with moderately to severely active UC. Pts were required to have received stable doses of oral aminosalicylates or glucocorticoids (prednisone at a dose of ≤20 mg per day orbudesonide) or both for at least two weeks before screening endoscopy and to continue receiving the same dose for the duration of the induction period; the glucocorticoid dose had to be tapered once the patient entered the maintenance period. Pts were excluded from the trial if they had not had a response to induction therapy with at least two biologic agents approved for the treatment of UC, had a clinically relevant cardiac condition, or had a historyof uveitis or macular edema.

- **Induction study:** Pts were divided in two cohorts: those who had previous exposure with TNF antagonists were assigned in cohort one and, once their percentage reached 30% in cohort one, they were assigned to cohort two. Pts without prior TNF antagonist exposure were allocated in cohort one until enrollment was closed, at that time such pts were assigned to cohort two.

Cohort One: Subjects (*n*=645) were randomized 2:1 to either ozanimod 0.92 mg (*n*=430) given orally QD or placebo (*n*=216) for 10 weeks, in a double-blind fashion, beginning with a dosage titration.
Cohort Two: Subjects (*n*=367) received open-label ozanimod 0.92 mg orally QD for 10 weeks.
The primary endpoint was the proportion of pts in clinical remission based on components of MCS*at week 10. The proportion of pts meeting clinical remission in the ozanimod arm was 18% vs. 6% in the placebo arm. The difference between treatments was 12% (95% CI, 8-17; p<0.001) [3-5].

- **Maintenance study:** a total of 457 pts who received ozanimod in either the double-blind or open-label arm and achieved clinical response at week 10 were re-randomized 1:1 and were treated with either ozanimod 0.92 mg (*n*=230) or placebo (*n*=227) in a double-blind fashion for 42 weeks, for a total of 52 weeks of treatment.

Pts without a clinical response during induction period could enter an open-label extension trial at week 10, whereas pts who were included in the maintenance period could enter the extension trial at week 52 or after disease relapse.
The primary endpoint was the proportion of pts in clinical remission based on components of MCS* at week 52.
The proportion of pts meeting clinical remission in the ozanimod arm was 37% vs. 19% in the placebo arm. The difference between treatments was 19% (95% CI11-26; p<0.001) [3-5].

**Clinical remission, assessed through the MCS, isdefined as follows: a rectal-bleeding subscore of 0; a stool-frequency subscore of 1 or less, with a decrease of at least 1 point from baseline; an endoscopy subscore of 1 or less (all on scales from 0 to 3 [most severe]).*

Summary of clinical SAFETY[4,5]**:**

	Induction period		Maintenance period	
	Placebo	Ozanimod	Placebo	Ozanimod
AEs	38.0%	39.9%	36.6%	49.1%
SAEs	3.2%	5.0%	7.9%	5.2%
AEs leading to discontinuation	3.2%	3.5%	2.6%	1.3%
Anemia	5.6%	4.3%	1.8%	1.3%
Nasopharyngitis	1.4%	3.1%	1.8%	3.0%
Headache	1.9%	3.0%	0.4%	3.5%
Increase of ALT	0	2.1%	0.4%	4.8%
Arthralgia	1.4%	1.9%	2.6%	3.0%
Increase of GGT	0	1.4%	0.4%	3.0%
Infections	11.6%	11.6%	11.9%	23.0%

Ongoing studies:
- ***For the same indication:***Yes
- ***For other indications:***Yes

Discontinued studies (for the same indication): No

NHS impact

Cost of therapy:
The Italian price for a one-month therapy with ozanimod 0.92 mg is 1,855.62 €* [6].
**Retail price including VAT.*

Epidemiology:
In Italy, the available incidence estimates are generally based on relatively small populations. A review basedon 16 studies reported for the early 2010s incidence rates of UC as 10-15 cases per 100,000inhabitants per year [7].

POSSIBLE PLACE IN THERAPY
In pts with moderately to severely active UC, the ACG Clinical Guidelines recommend anti-TNF therapy using adalimumab, golimumab, or infliximab for induction of remission. For pts who have previously failed anti-TNF therapy, tofacitinib is recommended for induction of remission [8].

OTHER INDICATIONS IN DEVELOPMENT: Yes(Multiple Sclerosis, Crohn Disease) [4].

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: No**.**

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION: Yes(Ontamalimab, Visilizumab, Efavaleukin alfa) [4].
*Service reorganization Y/N: No
*Possible off label use Y/N: Yes

References:
1.https://www.ema.europa.eu/en/documents/overview/zeposia-epar-medicine-overview_en.pdf
2.https://www.ema.europa.eu/en/medicines/human/summaries-opinion/zeposia-0
3.https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209899s001lbl.pdf
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