

Large-scale post-marketing surveillance of biological drugs for immune-mediated inflammatory diseases through an Italian distributed multi-database healthcare network: the VALORE project

Running head: Post-marketing surveillance of biological drugs through an Italian distributed multi-database healthcare network

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Supplementary materials

Supplementary table 1. Demographic information of underlying population of the regions participating in the VALORE project network

Regions	Population	Mean age ($\pm$ SD)	Sex distribution (F/M ratio)
Abruzzo	1,300,645	45.7 (23.5)	1.05
Apulia	3,975,528	44.2 (23.3)	1.06
Basilicata	558,587	45.3 (23.3)	1.03
Campania	5,740,291	42.1 (22.9)	1.05
Emilia-Romagna	4,459,453	45.8 (23.7)	1.06
Friuli Venezia Giulia	1,210,414	47.1 (23.6)	1.06
Lazio	5,773,076	44.7 (23.2)	1.07
Lombardy	10,010,833	44.8 (23.5)	1.04
Sardinia	1,622,257	46.4 (22.8)	1.03
Sicily	4,908,548	43.5 (23.3)	1.06
Tuscany	3,701,343	46.6 (23.7)	1.07
Umbria	873,744	46.5 (23.8)	1.07
Veneto	4,884,590	45.2 (23.4)	1.04

*The demographic information are related to the year 2019.

Supplementary table 2: Biological drugs approved for the treatment of immune-mediated inflammatory diseases during the study period in Italy

Mechanistic class	Active substance	ATC	NDC	Brand name	Originator/biosimilar	Date of reimbursement approval by NHS in Italy
Selective immunosuppressants	Abatacept	L04AA24	037989*	ORENCIA	Originator	22/11/2007
	Vedolizumab	L04AA33	043442019	ENTYVIO	Originator	15/04/2016
Tumor necrosis factor-alpha inhibitors	Etanercept	L04AB01	034675*	ENBREL	Originator	04/05/2001
			044691*	BENEPALI	Biosimilar	14/06/2016
			045451*	ERELZI		09/03/2018
	Infliximab	L04AB02	034528012	REMICADE	Originator	04/05/2001
			043010*	INFLECTRA	Biosimilar	15/11/2014
			044892*	FLIXABI		31/05/2017
			042942*	REMSIMA		01/01/2015
			046635*	ZESSLY		10/03/2019
	Adalimumab	L04AB04	035946*	HUMIRA	Originator	02/07/2004
			047088*	HULIO	Biosimilar	09/02/2019
			045616*	IMRALDI		19/09/2018
			047805*	IDACIO		04/02/2020
			046889*	HYRIMOZ		10/02/2019
			046888*	HALIMATOZ		12/02/2020
			045317*	AMGEVITA		08/08/2018
			046887*	HEFIYA		09/02/2020
	Certolizumab pegol	L04AB05	039539*	CIMZIA	Originator	16/10/2010
	Golimumab	L04AB06	039541*	SIMPONI	Originator	31/08/2010
Interleukin inhibitors	Anakinra	L04AC03	035607*	KINERET	Originator	02/03/2003
	Ustekinumab	L04AC05	038936*	STELARA	Originator	31/08/2010
	Secukinumab	L04AC10	043873*	COSENTYX	Originator	12/11/2016
	Ixekizumab	L04AC13	044863*	TALTZ	Originator	30/06/2017
	Brodalumab	L04AC12	045484*	KYNTHEUM	Originator	20/04/2019

	Guselkumab	L04AC16	045772*	TREMFYA	Originator	12/10/2018
	Sarilumab	L04AC14	045491*	KEVZARA	Originator	17/07/2018
	Tildrakizumab	L04AC17	047196*	ILUMETRI	Originator	12/02/2020
	Risankizumab	L04AC18	047821018	SKYRIZI	Originator	04/03/2020
	Tocilizumab	L04AC07	038937*	ROACTEMRA	Originator	20/03/2010

Legend: ATC= Anatomical Therapeutic Chemical classification system; NDC= National Drug Code; NHS= National Health Service.

Supplementary table 3: Major safety outcomes reported for TNF-alpha inhibitors, as reported on SmPC and RMP

Safety outcome	TNF-alpha inhibitors				
	Infliximab	Adalimumab	Golimumab	Etanercept	Certolizumab
Immune system disorders					
Hypersensitivity (incl. anaphylaxis or anaphylactoid reactions) ^{a,b}	•	•	•	•	•
Infections and infestations					
Tuberculosis ^{a,b}	•	•	•	•	•
Sepsis ^{a,b}	•	•	•	•	•
Pneumonia ^{a,b}	•	•	•		
Invasive fungal infections ^{a,b}	•	•	•	•	
Hepatitis B virus (HBV) reactivation ^{a,b}	•	•	•	•	•
Cardiac disorders					
Congestive heart failure ^{a,b}	•	•	•	•	•
Hepatobiliary disorders					
Worsening of hepatitis C ^a				•	
Autoimmune hepatitis ^a	•				
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)					
Lymphomas ^{a,b}	•	•	•	•	•
Leukaemia ^{a,b}	•	•	•	•	•
Melanoma ^{a,b}	•	•	•	•	•
Nonmelanoma skin cancer ^{a,b}		•	•	•	
Merkel cell carcinoma ^{a,b}	•	•	•	•	•
Colon cancer/dysplasia ^{a,c}	• ^α	• ^α	• ^α		
Cervical cancer ^b	•				
Lung Cancer ^a				•	
Breast Cancer ^a				•	
Blood and lymphatic system disorders					
Pancytopenia, leukopenia, neutropenia and thrombocytopenia ^{a,b}	•	•	•	•	•
Wegener's granulomatosis ^a				•	
Musculoskeletal and connective tissue disorders					
Lupus and lupus-like illness ^{a,b}	•	•	•	•	•
Nervous system disorders					
Guillain-Barré syndrome ^{a,b}	•	•		•	
Multiple Sclerosis ^{a,b}	•	•	•	•	•
Serious depression (including suicidality) ^c			•		

Optic neuritis ^b	•	•			
Progressive multifocal leukoencephalopathy (PML) ^c		•		•	
Reversible posterior leukoencephalopathy syndrome ^c		•			
Encephalitis/Leukoencephalomyelitis ^c				•	
Metabolism and nutrition disorders					
Hypoglycaemia ^a				• ^β	

^a Patients treated for diabetes

^a Paragraph 4.4 Special warnings and precautions for use, Summary of product characteristics.

^b Risk Management Plan, Important identified risk



^c Risk Management Plan, Important potential risk



Legend: RMP=risk management plan; SmPC= summary of product characteristic; TNF-alpha inhibitors= Tumor Necrosis Factor alpha inhibitors.

Supplementary table 4: Major safety outcomes reported for selective immunosuppressants, as reported on SmPC and RMP

Safety outcome	Selective immunosuppressants	
	Abatacept	Vedolizumab
Immune system disorders		
Hypersensitivity (incl. anaphylaxis or anaphylactoid reactions) ^{a,b}	•	•
Infections and infestations		
Tuberculosis ^{a,b}	•	
Sepsis ^a	•	
Pneumonia ^a	•	
Invasive fungal infection ^b	•	
Gastrointestinal infections ^c		•
Upper Respiratory Tract Infections ^b		•
Hepatitis B virus (HBV) reactivation ^a	•	
Nervous system disorders		
Progressive multifocal leukoencephalopathy (PML) ^{a,c}	•	•
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Non-melanoma skin cancers ^c		• ^α
Colon cancer ^c		• ^α

^aPatients with inflammatory bowel disease

^a Paragraph 4.4 Special warnings and precautions for use, Summary of product characteristics.

^b Risk Management Plan, Important identified risk ■

^c Risk Management Plan, Important potential risk ■

Legend: RMP=risk management plan; SmPC= summary of product characteristic

Supplementary table 5: Major safety outcomes reported for interleukin inhibitors, as reported on SmPC and RMP

Safety outcome	Interleukin inhibitors									
	Ustekinumab	Secukinumab	Tocilizumab	Anakinra	Brodalumab	Ixekizumab	Risankizumab	Tildrakizumab	Guselkumab	Sarilumab
General disorders and administration site conditions										
Hypersensitivity (incl. anaphylaxis or anaphylactoid reactions) ^{a,b,c}	•	•	•	•	•	•	•	•	•	•
Infections and infestations										
Tuberculosis ^{a,b,c}	•		•	•			•	•	•	•
Hepatitis B virus (HBV) reactivation ^{a,c}		•	•							
Diverticulitis aggravated ^{a,b}			•							
Upper Respiratory Tract Infections ^{a,b}						•				
Conjunctivitis ^{a,b}						•				
Fungal infections ^{a,b}						•				
Cardiac disorders										
Hyperlipidaemia ^a			•							
Major Adverse Cardiac Events (MACE) ^c	•	•	•			•	•	• ^α	• ^α	•
Blood and lymphatic system disorders										
Pancytopenia, leukopenia, neutropenia and thrombocytopenia ^{a,b}		•	•	•						•
Gastrointestinal disorders										
Inflammatory bowel disease (including Crohn's disease and		•			•	•		•		

ulcerative colitis) ^{a,b,c}										
Gastrointestinal perforation ^b										•
Investigations										
Transaminase elevations ^a			•	•					•	•
Increases in lipid parameters ^{a,c}			•							•
Metabolism and nutrition disorders										
Hyperlipidaemia ^a										•
Respiratory, thoracic and mediastinal disorders										
Eosinophilic pneumonia ^a	•									
Pulmonary alveolar proteinosis ^{a,c}				• ^β						
Pulmonary hypertension ^{a,c}				• ^β						
Interstitial lung disease ^{a,c}				• ^β						
Skin and subcutaneous tissue disorders										
Exfoliative dermatitis ^a	•									
Psoriasis ^b	•									
Nervous system disorders										
Facial palsy ^b	•									
Serious depression (incl. suicidality) ^{a,c}	•	•			•			• ^α		
Reversible posterior leukoencephalopathy syndrome ^c	•									
Vascular disorders										
Venous thromboembolism ^c	• ^γ									
Hepatobiliary disorders										
Acute liver failure ^{b,c}			•	• ^β						

Hepatitis ^{b,c}			•	• ^β						
Jaundice ^a			•							
Immuno system disorders										
Macrophage activation syndrome (MAS) ^{a,c}				• ^β						
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)										
Lymphoma ^{a,c}				•			• ^α			
Non-melanoma skin cancer ^c		•					• ^α			
Lung cancer ^c							• ^α			

^α Patients with psoriasis

^β Patients with Still's disease

^γ Patients with inflammatory bowel disease

^a Paragraph 4.4 Special warnings and precautions for use, Summary of product characteristics.

^b Risk Management Plan, Important identified risk



^c Risk Management Plan, Important potential risk



Legend: RMP=risk management plan; SmPC= summary of product characteristic