27 June 2019
EMA/399654/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of marketing authorisation and a variation of marketing authorisation

Imraldi

International non-proprietary name:adalimumab

Procedure No. EMEA/H/C/004279/X/0019/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AS	ankylosing spondylitis
CCIT	Container Closure Integrity Testing
CCP	Critical Controlled Parameters
CD	Crohn's disease
CHO	Chinese Hamster Ovary
CIPC	Critical In-Process Control
CIPT	Critical In-Process Test
CQA	Critical Quality Attribute
DP	Drug Product
DS	Drug substance
ERA	Enthesitis-related arthritis
GCP	Good Clinical practice
GMP	Good manufacturing practice
HS	hidradenitis suppurativa
IgG1	immunoglobulin G1
IPC	In-Process Controls
IPM	In-Process Measurement
IPT	In-Process Tests
JIA	Juvenile idiopathic arthritis polyarticular
KCP	Key controlled parameter
mAb	monoclonal antibody
MCB	Master Cell Bank
N-KCP	Non-key Controlled Process Parameters
PFP	Pre-Filled Pen
PFS	Pre-Filled Syringe
PPQ	Process performance qualification
PsA	psoriatic arthritis
PsO	psoriasis
PVR	Process validation rug

QC	Quality Control
RA	rheumatoid arthritis
SBL	Samsung BioLogics
TNF-α	Tumour Necrosis Factor alpha
UC	ulcerative colitis
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

Samsung Bioepis NL B.V. submitted on 12 November 2018 a group of variation(s) consisting of an extension of the marketing authorisation and the following variations:

Variation(s) requested		Type
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	IB

The MAH applied for the addition of a new strength of 40 mg/0.8 ml solution for injection in a vial, to allow the administration to paediatric patients requiring less than a full 40mg dose.
In addition, the MAH proposed to update the Product Information for the pre-filled syringe (EU/1/17/1216/001-004) and pre-filled pen (EU/1/17/1216/005-008) presentations in line with the dosage regimen changes introduced with the extension application.
The RMP (version 3.0) is updated in accordance.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: N/A

The application was received by the EMA on	12 November 2018
The procedure started on	29 November 2018

The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 February 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	21 Feburay 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 March 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	28 March 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	26 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Imraldi on	27 June 2019

2. Scientific discussion

2.1. Problem statement

Imraldi is a biosimilar adalimumab with the EU Humira as the reference medicinal product. Imraldi was approved by the European Commission in August 2017. Adalimumab is a genetically engineered recombinant human immunoglobulin IgG1 monoclonal antibody. Imraldi is currently available only as single dose 40 mg prefilled syringe (PFS) or pen. However, in accordance with the reference medicinal product Humira Imraldi was also authorised in paediatric indications for which doses lower than 40mg should be given. Therefore, the introduction of the vial presentation that allows dosing lower than 40 mg dose is justified from a clinical point of view.

There are no changes to the pharmaceutical form, route of administration, and proposed indications compared to the currently licensed strengths. Therefore no additional nonclinical or clinical studies have been performed.

The Product Information (PI) is revised for pre-filled syringe and pre-filled pen to be in the line with the line extension application so that dosing instructions to the paediatric patients are included.

2.1.1. Disease or condition

The line extension for 40 mg solution for injection vial presentation of Imraldi applies to the following indications:

- Juvenile idiopathic arthritis polyarticular (JIA):

- Paediatric plaque psoriasis
- Paediatric Crohn's disease
- Adolescent Hidradenitis suppurativa (HS)
- Paediatric uveitis.

2.1.2. Epidemiology

No new data were submitted in this application.

2.1.3. Biologic features

Adalimumab neutralises the biological function of both soluble and transmembrane forms of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF receptors and modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.

2.1.4. Clinical presentation, diagnosis

TNF-α has been shown to be elevated in several disease states, including rheumatoid arthritis (RA), psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), axial spondyloarthritis without radiographic evidence of AS, Crohn's disease (CD), ulcerative colitis (UC), and hidradenitis suppurativa (HS). In addition, elevated serum TNF-α levels seem to be positively correlated with recurrent episodes of uveitis of idiopathic origin. Biological therapies have well-documented efficacy, rapid onset of action, and good acute tolerability.

2.1.5. Management

About the product

Imraldi, a biosimilar to Humira, is currently indicated in rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa (HS), Crohn's disease, paediatric Crohn's disease, ulcerative colitis and uveitis. The extension of indication in paediatric uveitis has been recently approved in February 2019 for Imraldi (EMEA/H/C/004279/IB/0020).

The active substance of Imraldi is adalimumab, a chimeric human immunoglobulin G1 (IgG1) monoclonal antibody. It binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Imraldi is authorised for two single dose 40 mg solution for injection presentations, as a pre-filled syringe since initial marketing authorisation granted in August 2017 and as a pre-filled pen since September 2018 (EMEA/H/C/004279/II/0002/G).

The current application is an extension application to the marketing authorisation for Imraldi (EMEA/H/C/004279) to add a new strength of 40 mg/0.8 ml solution for injection (in vial). The product will be administered via s.c. injection.

Type of Application and aspects on development

Imraldi is a biosimilar product to the EU-approved Humira reference medicinal product. The marketing authorisation for Imraldi was granted in September 2017 under Article 10 (4) of Directive 2001/83/EC as amended by Directive 2004/27/EC and Article 3(3) of Regulation 726/2004/EC, with reference to Humira 40 mg solution for injection (EU/1/03/256/001) and Humira 40 solution for injection in pre-filled syringe (EU/1/03/256/003,005). Imraldi is currently marketed as 40 mg solution for injection in pre-filled syringe and 40 mg solution for injection in pre-filled pen.

The purpose of the present application is to seek approval for Imraldi 40 mg/0.8 ml solution for injection in vial to allow dosing in paediatric patients.

2.2. Quality aspects

2.2.1. Introduction

Imraldi, also referred to as SB5, is a recombinant fully human monoclonal antibody, adalimumab, directed against tumour necrosis factor alpha (TNF-α). It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. From cell banking up to the manufacturing process of SB5 active substance and finished product, materials of animal origin were used only during early cell line development.

SB5 finished product is a clear to opalescent, colourless to pale brown, sterile and preservative-free solution for injection. SB5 is currently presented as a single-use pre-filled syringe (PFS) or single-use pre-filled pen (PFP) containing 40 mg adalimumab in 0.8 mL to be administered via subcutaneous injection.

The scope of this line extension application is to add a new strength of 40 mg/0.8 mL solution for injection in vial, to allow the administration to paediatric patients that require less than a full 40 mg dose. The excipients remain unchanged: sodium citrate, citric acid monohydrate, histidine, histidine hydrochloride monohydrate, sorbitol, polysorbate 20 and water for injections.

This new presentation is presented as one pack of 2 boxes each containing 1 vial (0.8 ml sterile solution), 1 empty sterile injection syringe, 1 needle, 1 vial adapter and 2 alcohol pads.

Additionally, within this application, the marketing authorisation holder (MAH) would like to register a manufacturing/Quality Control testing site for the Imraldi 40 mg/0.8 mL vial finished product.

The MAH also submitted a Type IB variation together with the line extension application to update the Product Information for pre-filled syringe and pre-filled pen to be in the line with the line extension application.

Only data supportive of the proposed extension application is submitted. For all other sections, reference is made to the currently approved dossier of Imraldi.

2.2.2. Active Substance

In section 3.2.S.4.5, only contents describing the finished product container closure has been updated from “per syringe” to “per container” since glass vial has been added as Imraldi finished product container closure. The other sections of Module 3.2.S remain unchanged.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Manufacturing process development

A thorough pharmaceutical development was conducted by exploring the changes needed for finished product manufacturing site transfer and by comparing the changes needed for in-process controls (IPC) and in-process tests. The MAH presented process changes proposed for facility fit and container closure difference. In addition some changes are introduced in the IPC tests. The process changes were confirmed by validation and considered as technical adaptation of the equipment and facility.

The MAH compared the finished product physicochemical and biological characteristics after the transfer. The MAH demonstrated comparability of the vial product to PFS product. The results show that the finished product manufacturing site addition and vial filling process do not impact product quality in terms of physicochemical and biological attributes.

It is confirmed that the new facility is capable of producing a finished product comparable to the finished product from the already approved manufacturing sites.

Manufacture of the product and process controls

The vial manufacturing process involves thawing, pooling, and mixing of the active substance, followed by sterile filtration and aseptic vial filling, stopper placement, and capping. The SB5 vial finished product contains formulated SB5 active substance at a nominal concentration of 50 mg/mL. The only processing that occurs between active substance and finished product is sterile filtration and aseptic filling into vials, and thus the composition of the finished product is identical to the composition of the active substance.

The manufacturing process is adequately described and it was demonstrated that the controls in place are sufficient to produce a product of acceptable quality. The control strategy defining the critical and non-critical process steps is agreed. Both critical process parameters (CPPs) and key process parameter (KPPs) have operating ranges and action limits because they can respectively affect product quality or process performance or consistency. The non-KPPs are unlikely to affect either process performance or product quality, and as such only have operating ranges. Likewise critical in-process controls (CIPCs) and critical in-process tests (CIPTs) are the subset of IPCs and IPTs which have action limits or in-process specifications. In-process measurements are used to assess process consistency and/or measured to evaluate process scale-up, but do not have action limits.

The presented validation of the manufacturing steps has been successfully completed, meeting the defined specifications. The proposed validation ranges are appropriate for control of product and ensure no adverse impact on the critical quality attributes (CQAs).

Container closure

The primary packaging materials for SB5 vial presentation are a sterile Type I borosilicate glass vial, a sterile chlorobutyl rubber stopper and an aluminium crimping cap. The glass vial and the stopper are of compendial quality. The container closure system is adequately presented and all components have a CE-mark and declaration of conformity. In these certificates the supplier of the device is stated. The information is included in the dossier Section 3.2.P.7 as well. In addition the sterilisation method for primary packaging components is presented in detail.

Extractables and leachables studies were performed on the vial presentation, which demonstrate compatibility of SB5 with the container closure system.

The new vial presentation was demonstrated to be safe and to fulfill the requirements set for the container closure. The MAH addressed the risk of trace element impurities as required by ICH Q3D.

Product specification

The release and shelf life specifications for the SB5 finished product are presented and include control of identity, purity and impurity, biological activity and other general tests.

Batch analysis

Details of batches including batch size, manufacturing site and conditions, and use in SB5 development were presented together with the results. All the batches complied with the specifications.

Stability of the product

Stability data provided in this submission for the vial presentation are available at long-term, at accelerated, and at stress storage conditions.. All results met the acceptance criteria.

It can be concluded that the vial presentation does not change the stability of the finished product substantially and hence the proposed shelf life for the vial finished product of 36 months when stored at 5 ± 3°C is acceptable. The vial should be kept in the outer carton in order to protect it from light.

In accordance with EU GMP guidelines (*6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union*), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Adventitious agents

Module 3.2.A.2 is not affected by this application.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant adequately addressed the three minor issues identified during the procedure.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, CHMP considers that this line extension application is approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

No new non-clinical data has been generated for the 40 mg/0.8 ml vial.

2.3.1. Ecotoxicity/environmental risk assessment

As Imraldi is a biosimilar product to Humira having adalimumab as the active substance, the absence of formal ERA is justified given the nature of the product and the expected exposure, in accordance with the EMA guideline

on the Evironment risk assessment of medicinal products for human use.

2.3.2. Conclusion on the non-clinical aspects

No non-clinical data has been provided for this submission and justification was provided for absence of ERA.

2.4. Clinical aspects

No new clinical data has been generated for the 40 mg/0.8 ml vial.

2.5. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB); Reactivation of hepatitis B; Pancreatitis; Lymphoma; Hepatosplenic T-cell lymphoma (HSTCL); Leukaemia; Non-melanoma skin cancer (NMSC); Melanoma; Merkel cell carcinoma (Neuroendocrine carcinoma of the skin); Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS] and optic neuritis); Immune reactions (including lupus-like reactions and allergic reactions); Sarcoidosis; Congestive heart failure (CHF); Myocardial infarction (MI); Cerebrovascular accident (CVA); Interstitial lung disease (ILD); Pulmonary embolism; Cutaneous vasculitis; Stevens-Johnson syndrome (SJS); Erythema multiforme; Worsening and new onset of psoriasis (PsO);

Summary of safety concerns	
	Haematologic disorders; Intestinal perforation; Intestinal stricture in Crohn's disease (CD); Liver failure and other liver events; Elevated alanine aminotransferase (ALT) levels; Autoimmune hepatitis; Medication errors and maladministration
Important potential risks	Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma); Vasculitis (non-cutaneous); Progressive multifocal leukoencephalopathy (PML); Reversible posterior leukoencephalopathy syndrome (RPLS); Amyotrophic lateral sclerosis (ALS); Adenocarcinoma of colon in ulcerative colitis (UC) patients; Infections in infants exposed to adalimumab in utero; Off-label use
Missing information	Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications; Pregnant and lactating women; Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in PsO, CD, UC and juvenile idiopathic arthritis (JIA); Long-term safety information in the treatment of adults with HS; Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD and pedERA; Long-term safety data in the treatment of adults and children with uveitis

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				
Category 3 - Required additional pharmacovigilance activities				
ARTIS - Anti-rheumatic Therapies In Sweden Planned	A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, JIA, and other rheumatic disease patients treated with adalimumab.	Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB; Merkel cell carcinoma; elevated ALT levels; autoimmune hepatitis; pregnant and lactating women; remission-withdrawal-retreatment nr-axSpA data and episodic treatment in PsO and JIA	Protocol submission	2017 1Q
			Study start	2019 2Q (planned)
			Study finish	2024 (planned)
			Final report	2025 (planned)
BIOBADASER - Spanish Registry of Adverse Events of Biological Therapies Planned	1. To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence 2. To identify unexpected adverse events 3. To identify relevant adverse events that occur following the suspension of the treatment 4. To estimate the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to	Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB; Merkel cell carcinoma; elevated ALT levels; autoimmune hepatitis; pregnant and lactating women; remission-withdrawal-retreatment nr-axSpA data and episodic treatment in PsO and JIA	Protocol submission	2017 1Q
			Study start	2019 2Q (planned)
			Study finish	2024 (planned)
			Final report	2025 (planned) Annual interim reports will be submitted during the study period and until submission of the final report.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	those not exposed to these treatments 5. To identify risk factors for suffering adverse reactions with these treatments 6. To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment			

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB	<Routine risk minimisation measures> SmPC section 4.3, 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Alert Card HCP Educational Programme (including Imraldi Safety Monograph and TB screening and checklist brochure)	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> Registry: ARTIS, BIOBADASER
Reactivation of hepatitis B	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	measures> None proposed	activities> None
Pancreatitis	<Routine risk minimisation measures> SmPC section 4.8 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Lymphoma	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2 Prescription-only medication <Additional risk minimisation measures> Patient Alert Card HCP Educational Programme	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
HSTCL	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> Patient Alert Card HCP Educational Programme	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Leukaemia	<Routine risk minimisation measures> SmPC section 4.4; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Alert Card HCP Educational Programme	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
NMSC	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2 Prescription-only medication <Additional risk minimisation measures> Patient Alert Card HCP Educational Programme	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Melanoma	<Routine risk minimisation	<Routine pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Alert Card HCP Educational Programme	activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Merkel cell carcinoma (neuroendocrine carcinoma of the skin)	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> Patient Alert Card HCP Educational Programme	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> Registry: ARTIS, BIOBADASER
Demyelinating disorders (including MS, GBS, and optic neuritis)	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> Patient Alert Card HCP Educational Programme	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Immune reactions (including lupus-like reactions and allergic reactions)	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Sarcoidosis	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
CHF	<Routine risk minimisation measures> SmPC section 4.3, 4.4, 4.8; PL section 2	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection>

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Prescription-only medication <Additional risk minimisation measures> Patient Alert Card HCP Educational Programme	None <Additional pharmacovigilance activities> None
MI	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
CVA	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
ILD	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Pulmonary embolism	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Cutaneous vasculitis	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures>	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None proposed	activities> None
SJS	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Erythema multiforme	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Worsening and new onset of PsO	<Routine risk minimisation measures> SmPC section 4.8 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Haematologic disorders	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Intestinal perforation	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Intestinal stricture in CD	<Routine risk minimisation measures>	<Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.4 Prescription-only medication <Additional risk minimisation measures> None proposed	reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Liver failure and other liver events	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Elevated ALT levels	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> Registry: ARTIS, BIOBADASER
Autoimmune hepatitis	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> Registry: ARTIS, BIOBADASER
Medication errors and maladministration	<Routine risk minimisation measures> SmPC Section 4.2 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma)	<Routine risk minimisation measures> SmPC section 4.4, 4.8; PL section 2, 4 Prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	<Additional risk minimisation measures> Patient Alert Card HCP Educational Programme	<Additional pharmacovigilance activities> None
Vasculitis (non-cutaneous)	<Routine risk minimisation measures> SmPC section 4.8; PL section 4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
PML	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
RPLS	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
ALS	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Adenocarcinoma of colon in UC patients	<Routine risk minimisation measures> SmPC section 4.4 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infections in infants exposed to adalimumab in utero	<Routine risk minimisation measures> SmPC section 4.6 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Off-label use	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications	<Routine risk minimisation measures> SmPC section 4.4; PL section 2 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Pregnant and lactating women	<Routine risk minimisation measures> SmPC section 4.6; PL section 2 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> Registry: ARTIS, BIOBADASER
Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in PsO, CD, UC and juvenile idiopathic arthritis (JIA)	<Routine risk minimisation measures> SmPC section 4.6 Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> Registry: ARTIS, BIOBADASER
Long-term safety information in the treatment of adults with HS	<Routine risk minimisation measures>	<Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD and pedERA	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Long-term safety data in the treatment of adults and children with uveitis	<Routine risk minimisation measures> None proposed Prescription-only medication <Additional risk minimisation measures> None proposed	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Humira 40mg/0.8ml solution for injection. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

Imraldi is authorised in all indications in accordance with its reference medicinal product Humira. For paediatric indications doses lower than 40mg should be given to patients 10kg to <30kg but Imraldi was so far only available as single dose 40 mg prefilled syringe (PFS) or pen. The present line extension is to add a new strength Imraldi 40 mg/0.8 ml solution for injection in a vial to allow weight adapted dosing in paediatric patients requiring less than a full 40mg dose.

The review of the quality data indicates that the extension of marketing authorisation is approvable. No clinical or non-clinical data were submitted.

Accordingly the PI for Imraldi is updated to add the strength 40mg/0.8ml solution for injection in a vial and to include dosing instructions pertaining to the paediatric patients for whom lower dose than 40mg based on body weight can be needed. The product information has been updated to include also the recently approved paediatric uveitis indication (IB/0023). Minor additional amendments to the SmPC and PL are also made to align the PI with Humira (the reference product).

The RMP v3.0 has been updated to include the new strength 40mg/0.8ml solution for injection in a vial and to align with the latest approved version for Humira.

3.1. Conclusions

The overall B/R of Imraldi is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, the CHMP considers by consensus that the benefit-risk balance of Imraldi new strength is favourable in the following indications:

- Juvenile idiopathic arthritis polyarticular (JIA):
- Paediatric plaque psoriasis
- Paediatric Crohn's disease
- Adolescent Hidradenitis suppurativa (HS)
- Paediatric uveitis.

The CHMP therefore recommends the extension of the marketing authorisation for Imraldi subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Imraldi in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including distribution modalities, and any other aspects of the programme, with the National Competent Authority. The educational program consists of a Patient Reminder Card.

The Patient Reminder Cards should contain the following key elements:

- serious infections
- tuberculosis
- cancer
- nervous system problems
- vaccinations

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations approved		**Type**	**Annexes affected**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type IB	I and IIIB

Extension application to introduce a new strength of 40 mg/0.8 ml solution for injection in a vial, to allow the administration to paediatric patients requiring less than a full 40mg dose.
C.I.z - To update the Product Information for the pre-filled syringe (EU/1/17/1216/001-004) and pre-filled pen (EU/1/17/1216/005-008) presentations in line with the dosage regimen changes introduced with the extension application. Minor additional amendments to the SmPC and PL are also made to align the PI with Humira (the reference product).
The RMP (version 3.0) is updated in accordance.