LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Elsa Willebrand
Apotek och receptfri detaljhandel

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Dnr: 6.2.9-2022-091080

Nämnden för bedömning av
Läkemedelsinformation (NBL)
LIF
BOX 17608
118 92 Stockholm

Marknadsföring av Cimzia

Läkemedelsverket har uppmärksammat UCB Pharma AB:s marknadsföring av Cimzia genom en annons som publicerats i tidskriften Dagens Medicin (se bilaga 1). Läkemedelsverket anser att marknadsföringen står i strid med Läkemedelsbranschens etiska regelverk.

Tillämpliga bestämmelser

Kapitel 1, avdelning 1, artikel 2, 4.2 och 11.5 Läkemedelsbranschens etiska regelverk (LER).

Marknadsföringen och Läkemedelsverkets motivering

Den aktuella annonsen har rubriken *When considering a biologic for a woman with axSpA, PsA or RA, think CIMZIA®[1].* I annonsen förekommer bland annat en bild på en ung kvinna som drar en väska och flera påståenden om Cimzia med hänvisningar till olika kliniska studier.

Påståenden om Cimzias effekt på uveit

I annonsen förekommer bland annat följande påståenden:

> **Significant improvement in extra-articular manifestations[1,4-5]**
> CIMZIA® significantly reduced acute anterior uveitis flares in axSpA with a history of uveitis[4-5]
> CIMZIA® has a sustained impact on reducing uveitis flares in axSpA[4-5]

Påståendena presenteras tillsammans med en stiliserad bild på ett öga och hänvisningar till RAPID-axSpA[4] och C-VIEW[5].

Enligt LER artikel 11 (kapitel 1, avdelning 1) ska dokumentation åberopas på ett nyanserat och rättvisande sätt. Enligt artikel 11.5 innebär kravet på nyansering och rättvisande presentation bland annat att rapport från undersökning ej får citeras eller refereras på sådant sätt att citatet eller referatet ger en felaktig eller missvisande bild av rapportens innehåll och slutsatser.

Angående påståendet ”**Significant improvement in extra-articular manifestations**” noterar Läkemedelsverket att marknadsföringen inte innehåller en uttrycklig förklaring till begreppet extraartikulära manifestationer, men att texten under det fetstilade påståendet enbart refererar till uveit, samt att påståendena presenteras tillsammans med en bild på ett öga. Läkemedelsverket förstår därför påståendet om signifikant förbättring av extraartikulära manifestationer som att det handlar om uveit.

Påståendet refererar till Cimzias produktresumé (referens 1), samt en artikel av van der Heijde D, et al. som sammanfattar resultat från studien RAPID-axSpA (referens 4) och en artikel av van der Horst-Bruinsma, et al. som sammanfattar resultat från studien C-VIEW (referens 5).

Cimzias produktresumé saknar information om läkemedlets effekt på uveit. Läkemedelsverket noterar också att artikeln av van der Heijde D, et al. (referens 4), inte innehåller någon information om Cimzias effekt på uveit. Läkemedelsverket anser att åberopandet av Cimzias produktresumé och artikeln av van der Heijde D, et al. som stöd för påståendet ”**Significant improvement in extra-articular manifestations**” ger en missvisande bild av innehållet i produktresumén och artikeln av van der Heijde D, et al. Läkemedelsverket anser även av åberopandet av artikeln av van der Heijde D, et al. efter påståendena ”CIMZIA® significanly reduced acute anterior uveitis flares in axSpA with an history of uveitis[4-5]” och ”CIMZIA® has a sustained impact on reducing uveitis flares in axSpA[4-5]” ger en missvisande bild av innehållet i artikeln, eftersom den saknar information om Cimzias effekt på uveit. Läkemedelsverket anser därför att marknadsföringen inte uppfyller kravet i LER artikel 11.5 att rapport från undersökning ej får citeras eller refereras på sådant sätt att citatet eller referatet ger en felaktig eller missvisande bild av rapportens innehåll och slutsatser.

I LER artikel 2 (kapitel 1, avdelning 1) anges att den produktresumé som fastställts för ett läkemedel utgör den sakliga utgångspunkten för informationen om läkemedlet. Vidare anges att utöver uppgifter direkt hämtade ut produktresumén, eller som kan härledas ut den, kan också andra uppgifter användas i informationen. Detta under förutsättning att sådana uppgifter kompletterar produktresumén, genom att bekräfta eller precisera uppgifter i den, och att uppgifterna är förenliga med informationen i produktresumén.

Den aktuella marknadsföringen innehåller påståenden om Cimzias effekt på uveit, bland annat med hänvisning till studien C-VIEW. Cimzias produktresumé saknar information om Cimzias effekt på uveit. Studien C-VIEW förekommer endast kort återgiven i produktresuméns avsnitt 4.8 Biverkningar. I dokumentet Cimzia Procedural steps taken and scientific information after the authorisation (se bilaga 2) finns ytterligare information om C-VIEW och CHMPs bedömning av studien. På sidan 3 i dokumentet står bland annat att resultaten från studien indikerar en minskning av skov av främre uveit som skulle kunna vara kliniskt relevant men att CHMP ansåg att uppskattningarna av effekt var överdrivna, på grund av studiens begränsningar (till exempel avsaknad av samtidig kontroll). Effektdata ansågs därför inte tillräckligt robusta och övertygande för att reflekteras i produktresuméns sektion 5.1. Däremot inkluderades en kort beskrivning av studiens säkerhetsprofil i sektion 4.8.

Marknadsföringen hänvisar således till en studie vars resultat bedömts inte vara tillräckligt övertygande för att rymmas i Cimzias produktresumé. Läkemedelsverket anser därför att annonsen inte är förenlig med informationen i Cimzias produktresumé i avseende av följande påståenden:

> **Significant improvement in extra-articular manifestations[1,4-5]**
> CIMZIA® significanly reduced acute anterior uveitis flares in axSpA with an history of uveitis[4-5]
> CIMZIA® has a sustained impact on reducing uveitis flares in axSpA[4-5]

Marknadsföringen uppfyller inte kravet i LER artikel 2 att den produktresumé som fastställts för ett läkemedel utgör den sakliga utgångspunkten för informationen om läkemedlet.

Påståenden om tidig behandling

Enligt LER artikel 4 (kapitel 1, avdelning 1) ska läkemedelsinformation vara vederhäftig och får ej innehålla framställning i ord eller bild som direkt eller indirekt – genom t.ex. antydningar, utelämnande, förvrängningar, överdrifter eller oklart framställningssätt – är ägnad att vilseleda. Enligt artikel 4.2 innebär kravet på vederhäftighet bland annat att uppgift om läkemedlet ej får vara så knapphändig eller ofullständig att den kan missförstås.

Bredvid en stiliserad bild på en spruta och en klocka förekommer i annonsen följande påstående:

> **Early treatment to a stringent target**
>
> Treating early and to a stringent target with CIMZIA® may result in improved clinical outcomes and increased likelihood of achieving sustained remission[6,14]

Läkemedelsverket anser att påståendena är knapphändiga och allmänt hållna. Det framgår inte vad ”early treatment” eller ”stringent target” innebär. Läkemedelsverket ställer sig också frågande till användningen av begreppet ”may result in”, vilket får tolkas som att Cimzia skulle *kunna resultera* i en viss effekt.

Påståendena refererar till artiklar som sammanfattar resultat från studierna C-OPTIMISE och C-axSpAnd (referens 6 respektive 14). Studien C-axSpAnd utvärderade Cimzias effekt i patienter med axSpA. Studiens primära syfte var att utvärdera Cimzias effekt på symtom hos patienter med aktiv, icke-radiografisk axSpA som tidigare blivit behandlade med minst två NSAID. I den angivna referensen finns ingen information om att det skulle röra sig om patienter med tidig axSpA. Enligt referens 14 rekryterade studien C-OPTIMISE visserligen patienter med tidig axSpA, men studiens huvudsakliga syfte var att utvärdera effekten av en minskad underhållsdos av Cimzia jämfört med oförändrad underhållsdos eller placebo.

Läkemedelsverket anser att de aktuella påståendena är så knapphändiga och ofullständiga att marknadsföringen kan missförstås. Påståendena ger sken av att tidig behandling med Cimzia har resulterat i statistiskt säkerställda kliniska förbättringar och ökad sannolikhet för bibehållen remission i jämförelse med att inte initiera behandling med Cimzia tidigt, och att detta skulle ha säkerställts i studier vars syfte var att utvärdera just detta. Utan ytterligare kvalificering anser Läkemedelsverket att de aktuella påståendena strider mot LER artikel 4.2.

Läkemedelsverket vill också framhålla att de aktuella påståendena inte specificerar att det handlar om patienter med axSpA. I stället ges intrycket av att påståendena skulle gälla samtliga indikationer som annonsen berör (axSpA, PsA och RA). Enligt Läkemedelsverkets bedömning är påståendena även i detta avseende så knapphändiga och ofullständiga att de kan missförstås, i strid med LER artikel 4.2.

Påståenden om fortsatt behandling för kvinnor i fertil ålder

I annonsen, bredvid en stiliserad bild på en kvinna, förekommer följande påståenden:

> **Treatment continuity, if clinically needed***
>
> CIMZIA® offers treatment continuity for women of childbearing age, if clinically needed[1-3, 13]

Tillsammans med annonsens rubrik (”When considering a biologic for a woman with axSpA, PsA or RA, think CIMZIA”) och bilden på en ung kvinna, anser Läkemedelsverket att dessa påståenden vid en flyktig läsning ger intrycket att Cimzia skulle vara särskilt lämplig för kvinnor i fertil ålder. Läkemedelsverket noterar även att asterisken i påståendet **Treatment continuity, if clinically needed*** inte motsvaras av någon fotnot i annonsen som skulle kunna förtydliga påståendet.

Detta intryck kan ställas mot information om graviditet och amning i Cimzias produktresumé (avsnitt 4.6 Fertilitet, graviditet och amning). Där står bland annat följande:

> Användning av ett effektivt preventivmedel ska övervägas för kvinnor i fertil ålder. För kvinnor som planerar att skaffa barn kan fortsatt användning av preventivmedel övervägas i 5 månader efter den sista Cimziadosen p.g.a. dess elimineringshastighet (se avsnitt 5.2), men kvinnans behov av behandling bör även tas i beaktande (se nedan).
>
> […]
>
> Prospektivt insamlade data från över 1 300 gravida kvinnor som exponerats för Cimzia, och där utfallen från graviditeterna är kända, inklusive över 1 000 gravida kvinnor som exponerats under den första trimestern, tyder inte på någon missbildande effekt av Cimzia. Ytterligare data samlas in eftersom de tillgängliga kliniska erfarenheterna fortfarande är för begränsade för att man ska kunna dra slutsatsen att det inte finns en ökad risk förknippad med administrering av Cimzia under graviditet.
>
> […]
>
> Cimzia ska endast användas under graviditet om det finns ett kliniskt behov.

Mer ingående information finns visserligen i finstilt text i annonsens nedre del, men Läkemedelsverket anser inte att det kompenserar för det intryck som annonsen ger vid en flyktig läsning. Marknadsföringens påståenden om fortsatt behandling för kvinnor i fertil ålder är vagt formulerade. Utan ytterligare kvalificering och tillsammans med annonsens rubrik och bildsättning ger påståenden som ”Cimzia® offers treatment continuity” sken av att användning av Cimizia är särskilt lämplig för kvinnor i fertil ålder. Enligt Läkemedelsverkets bedömning är annonsens framställning vilseledande och så knapphändig att den riskerar att missförstås, i strid med LER artikel 4.2.

Läkemedelsverket emotser NBL:s bedömning.

På Läkemedelsverkets vägnar

Elsa Willebrand

Utredare Marknadsföringstillsyn

Bilagor:

1. Annons för Cimzia publicerad i Dagens Medicin, nr 37 onsdag 14 september 2022

2. Cimzia Procedural steps taken and scientific information after the authorization, tillgänglig via https://www.ema.europa.eu/en/medicines/human/EPAR/cimzia

cimzia
(certolizumab pegol)

When considering a biologic for a woman with axSpA, PsA or RA, think CIMZIA®[1]

CIMZIA® has a package of clinical trials supporting early treatment, if clinically needed[6,14]

C-OPTIMISE[6] C-axSpAnd[14]

Early treatment to a stringent target

Treating early and to a stringent target with CIMZIA® may result in improved clinical outcomes and increased likelihood of achieving sustained remission[6,14]

C-OPTIMISE[6]

Dose reduction after sustained remission[a]

CIMZIA® is the only biologic with a label allowing for a reduced maintenance dose in axSpA[1,6-12]

RAPID-axSpA[4] C-VIEW[5]

Significant improvement in extra-articular manifestations[1,4-5]

CIMZIA® significantly reduced acute anterior uveitis flares in axSpA with a history of uveitis[4-5]

CIMZIA® has a sustained impact on reducing uveitis flares in axSpA[4-5]

CRIB[3] CRADLE[2] CZP Pregnancy Outcomes[13]

Treatment continuity, if clinically needed*

CIMZIA® offers treatment continuity for women of childbearing age, if clinically needed[1-3,13]

Cimzia® (certolizumabpegol), 200 mg injektionsvätska, lösning i förfylld spruta, förfylld injektionspenna och kassett för dosdispenser. R_x. immunsuppressiva medel, TNF-alfa hämmare (L04AB05). ***Indikationer:*** *Reumatoid artrit:* Cimzia, i kombination med metotrexat (MTX), är indicerat för: - behandling av måttlig till svår aktiv reumatoid artrit (RA) hos vuxna patienter när behandling med sjukdomsmodifierande antireumatiska läkemedel (DMARD) inklusive metotrexat är otillräcklig. Cimzia kan ges som monoterapi vid intolerans mot metotrexat eller om fortsatt behandling med metotrexat är olämplig. - behandling av svår, aktiv och progredierande reumatoid artrit (RA) hos vuxna som inte tidigare behandlats med metotrexat eller andra sjukdomsmodifierande antireumatiska läkemedel (DMARD). Cimzia har visats minska progressionshastigheten av ledskador mätt med röntgen och förbättra fysiska funktioner när det ges tillsammans med metotrexat. *Axial spondylartrit:* Cimzia är indicerat för behandling av vuxna patienter med svår aktiv axial spondylartrit, innefattande: *Ankyloserande spondylit (AS) (även kallad radiografisk axial spondylartrit):* Vuxna med svår aktiv ankyloserande spondylit som haft ett otillräckligt svar på, eller är intoleranta mot behandling med icke-steroida antiinflammatoriska läkemedel (NSAID). *Axial spondylartrit utan radiografiska tecken på AS (även kallad icke-radiografisk axial spondylartrit):* Vuxna med svår aktiv axial spondylartrit utan radiografiska tecken på AS men med objektiva tecken på inflammation genom förhöjt CRP och/eller MR, som haft ett otillräckligt svar på, eller är intoleranta mot NSAID.Cimzia studerades också i en 96 veckors öppen studie med 89 axSpA patienter med dokumenterade skov av främre uveit i anamnesen. *Psoriasisartrit:* Cimzia, i kombination med metotrexat, är indicerat för behandling av aktiv psoriasisartrit hos vuxna patienter när behandling med sjukdomsmodifierande antireumatiska läkemedel (DMARD) haft otillräcklig effekt. Cimzia kan ges som monoterapi vid intolerans mot metotrexat eller om fortsatt behandling med metotrexat är olämplig. *Plackpsoriasis:* Cimzia är indicerat för behandling av måttlig till svår plackpsoriasis hos vuxna patienter som behöver systemisk behandling. ***Kontraindikationer:*** Överkänslighet mot den aktiva substansen eller mot något hjälpämne. Aktiv tuberkulos eller andra svåra infektioner såsom sepsis eller opportunistiska infektioner. Måttlig till svår hjärtsvikt (NYHA klass III/IV). ***Varningar:*** Behandling med Cimzia får inte initieras hos patienter med en kliniskt signifikant aktiv infektion, inklusive kroniska eller lokala infektioner, tills infektionen är under kontroll. Patienter måste övervakas noggrant med avseende på tecken och symtom på infektioner, inklusive tuberkulos före, under och efter behandling med Cimzia. Patienter ska testas för HBV-infektion innan behandling med Cimzia påbörjas. För patienter som testats positivt för HBV-infektion rekommenderas konsultation hos läkare som är specialist på behandling av hepatit-B. Hematologiska biverkningar, inklusive medicinskt signifikant cytopeni (leukopeni, neutropeni, lymfopeni), har rapporterats med Cimzia. Eftersom tumörnekrosfaktor (TNF) medierar inflammation och modulerar cellulär immunrespons, finns risken att TNF-antagonister, inklusive Cimzia, orsakar immunsuppression som påverkar värdförsvaret mot infektioner och maligniteter. Levande vacciner ska inte ges samtidigt med Cimzia. Kombination av certolizumabpegol och anakinra eller abatacept rekommenderas ej. ***Fertilitet, graviditet och amning***: Användning av ett effektivt preventivmedel ska övervägas för kvinnor i fertil ålder. För kvinnor som planerar att skaffa barn kan fortsatt användning av preventivmedel övervägas i 5 månader efter den sista Cimziadosen p.g.a. dess elimineringshastighet, men kvinnans behov av behandling bör även tas i beaktande. Prospektivt insamlade data från över 1 300 gravida kvinnor som exponerats för Cimzia, och där utfallen från graviditeterna är kända, inklusive över 1 000 gravida kvinnor som exponerats under den första trimestern, tyder inte på någon missbildande effekt av Cimzia. Ytterligare data samlas in eftersom de tillgängliga kliniska erfarenheterna fortfarande är för begränsade för att kunna dra slutsatsen att det inte finns en ökad risk förknippad med administrering av Cimzia under graviditet. I en klinisk studie behandlades 16 kvinnor med certolizumabpegol under graviditeten. Plasmakoncentrationerna av certolizumabpegol som mättes hos 14 spädbarn vid födseln låg under detektionsgränsen i 13 prover; ett låg på 0,042 mikrog/ml med ett förhållande mellan spädbarn och moderplasma på 0,09 % vid födseln. Vid vecka 4 och vecka 8 låg koncentrationen hos alla spädbarnen under detektionsgränsen. Den kliniska betydelsen av låga nivåer av certolizumabpegol för spädbarn är okänd. I en klinisk studie med 17 ammande kvinnor som behandlats med Cimzia observerades minimal överföring av certolizumabpegol från plasma till bröstmjölk. Följaktligen kan Cimzia användas under amning. ***Beredningsform och förpackning:*** Injektionsvätska, lösning, 200 mg/ml i förfylld spruta. Varje förpackning innehåller 2 sprutor à 1 ml och 2 desinfektionsservetter. Injektionsvätska, lösning 200 mg/ml i förfylld injektionspenna. Varje förpackning innehåller 2 pennor à 1 ml och 2 desinfektionsservetter. Injektionsvätska, lösning, 200 mg i kassett för dosdispenser. Varje förpackning innehåller 2 kassetter à 1 ml och 2 desinfektionsservetter. Behandling ska initieras och övervakas av specialistläkare med erfarenhet av diagnostisering och behandling av de sjukdomstillstånd som Cimzia är indicerat för. ***Särskilda förvaringsanvisningar:*** Förvaras i kylskåp (2-8 °C). Kan förvaras vid rumstemperatur (högst 25 °C) under en enda period på högst 10 dagar med skydd mot ljus. Måste användas eller kasseras i slutet av denna period.***Förmån:*** 2 förfyllda sprutor, 2 förfyllda injektionspennor, 2 kassetter för dosdispenser: F. ***Begränsningar i förmån:*** Cimzia subventioneras endast när behandling med etanercept eller adalimumab inte är lämpligt. 5x2 förfyllda injektionspennor: EF. ***Datum för översyn av produktresumé:*** Juli 2022. För fullständig information, varningsföreskrifter och aktuella priser se www.fass.se

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Inspired by **patients.**
Driven by **science.**

References

1. CIMZIA® EU Summary of Product Characteristics. Available at <https://www.ema.europa.eu/en/documents/productinformation/cimzia-epar-product-informationen.pdf>. Accessed April 2022.
2. Clowse ME, et al. Ann Rheum Dis. 2017;76(11):1890-96.
3. Mariette X, et al. Ann Rheum Dis. 2018;77(2):228-33.
4. Van der Heijde D, et al. Ann Rheum Dis. 2018;77(5):699-705.
5. Horst-Bruinsma et al. Ther Adv Musculoskelet Dis . 2021 Mar 29;13:1759720X211003803.
6. Landewé RBM, et al. Ann Rheum Dis. 2020;79(7):920-28. doi:10.1136/annrheumdis-2019-216839.
7. Enbrel® EU Summary of Product Characteristics. Available at <http://www.ema.europa.eu/docs/enGB/documentlibrary/EPAR-ProductInformation/human/000262/WC500027361.pdf>.Accessed April 2022.
8. Humira® EU Summary of Product Characteristics. Available at <http://www.ema.europa.eu/docs/enGB/documentlibrary/EPAR-ProductInformation/human/000481/WC500050870.pdf>. Accessed April 2022.
9. Cosentyx® EU Summary of Product Characteristics.Available at <http://www.ema.europa.eu/docs/enGB/documentlibrary/EPAR-ProductInformation/human/003729/ WC500183129.pdf>. Accessed April 2022.
10. Taltz® EU Summary of Product Characteristics. Available at <http://www.ema.europa.eu/docs/enGB/documentlibrary/EPAR-ProductInformation/human/003943/WC500205804.pdf>. Accessed April 2022.
11. Simponi® EU Summary of Product Characteristics. Available at https://www.ema.europa.eu/en/documents/productinformation/simponi-epar-product-informationen.pdf. Accessed April 2022.
12. Remicade® EU Summary of Product Characteristics. Available at <https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_en.pdf>. Accessed April 2022.
13. Clowse MEB et al. Arthritis Rheum. 2018;70(9):1399-1407.
14. Deodhar, A. et al., 2019. A Fifty-Two-Week, Randomized, Placebo-Controlled Trial of Certolizumab Pegol in Nonradiographic Axial Spondyloarthritis. Arthritis & Rheumatology, 71(7), pp.1101-1111.

SE-P-CZ-axSpA-2200008, September 2022, Coolgray

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Cimzia

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0101	C.I.4: Update of section 4.6 of the SmPC in order to update information on pregnancy based on non-interventional data from the UCB Global Safety Database on prospective Cimzia-exposed pregnancies with known outcomes. The MAH also took the opportunity to make some editorial updates in Annex IIIA and IIIB.	23/06/2022		SmPC, Labelling and PL	Data from more than 1300 prospectively collected pregnancies exposed to Cimzia with known pregnancy outcomes, including more than 1000 pregnancies exposed during the first trimester, does not indicate a malformative effect of Cimzia. Further data are being collected as the available clinical experience is still limited to conclude that there is no increased risk associated with Cimzia administration during pregnancy.

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				For more information, please refer to the Summary of Product Characteristics.
IB/0104/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	30/03/2022	n/a		
IB/0103/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	07/02/2022	n/a		
IB/0102	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	06/01/2022	n/a		
IB/0100/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	06/09/2021	n/a		

	material/intermediate/reagent - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0098	Update of section 4.8 of the SmPC in order to update the safety information on active axial spondyloarthritis based on study AS0007 (C-VIEW); this is a multicenter, open-label study to assess the effects of certolizumab pegol on the reduction of anterior uveitis flares in axial spondyloarthritis subjects with a history of anterior uveitis. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/09/2021	02/12/2021	SmPC and PL	Final results of Study AS0007 (C-VIEW) were submitted by the MAH upon request by CHMP in procedure EMEA/H/C/001037/II/0087. While the overall results indicated that there is a reduction of anterior uveitis flare that could be clinically relevant, the CHMP considered that due to the limitations of the study (e.g. absence of concurrent control), the efficacy estimates were overestimated. Thus, the efficacy data were not considered robust and compelling enough to be reflected in SmPC section 5.1. Nevertheless, a short description of the study and information regarding the safety profile was included in SmPC section 4.8.
II/0099	Submission of the final report from study (RA0020 - RABBIT) listed as a category 3 study in the RMP. This is a nationwide prospective observational cohort study in Germany on the long-term safety and effectiveness of bDMARDs in rhumatoid arthritis (RA). In addition, this submission includes a safety analysis across the 4 completed RA registries (ARTIS, NDB, BSRBR and RABBIT) as requested by EMA/PRAC in the final assessment report of Procedures EMEA/H/C/001037/II/0072,	10/06/2021	n/a		The results of the RABBIT study showed a higher risk for serious hospitalised infections and nonmelanoma skin cancer (NMSC) for Cimzia compared to csDMARDs and a significantly reduced risk for all-cause mortality. The elevated infection risk and risk for NMSC was not confirmed by the sensitivity analysis. However, it was not possible to distinguish if this effect was caused by the reduced number of events or by elimination of residual confounding factors. Due to low numbers of patients with NMSC, these results are not conclusive and would need to be evaluated in larger

	EMEA/H/C/001037/II/0081, and EMA/H/C/001037/II/0087. Based on this, revisions to the RMP summary of safety concerns and consequently the pharmacovigilance plan are proposed in line with GVP Module V Rev.2. An updated RMP version 19.1 is included. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				studies. The risk of infection and NMSC are is already covered in the SmPC of Cimzia and other TNF-inhibitors. Overall, the results are in line with the known safety profile of Cimzia and suggest that the use of Cimzia for the treatment of RA patients in daily rheumatologic care is a safe and generally well tolerated option.
IB/0097	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	12/03/2021	02/12/2021	SmPC	
IB/0096	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/01/2021	n/a		
IB/0095	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	22/12/2020	n/a		
PSUSA/624/202003	Periodic Safety Update EU Single assessment - certolizumab	29/10/2020	n/a		PRAC Recommendation - maintenance
IAIN/0094	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/10/2020	02/12/2021	SmPC and PL	

IB/0093/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	23/10/2020	n/a		
IB/0092	B.I.z - Quality change - Active substance - Other variation	09/09/2020	n/a		
IA/0091/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number	10/08/2020	n/a		
II/0087	Update of sections 4.2, 4.8, 5.1 of the SmPC in order to introduce a change in posology for axial spondyloarthritis (axSpA) and to update the safety and efficacy information based on the results of the study AS0005 (C-OPTIMISE) listed as a category 3 study in the RMP; this is a multicentre, open-label	25/06/2020	27/07/2020	SmPC and PL	Cimzia was studied in patients with axial spondyloarthritis (axSpA) (including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)) in a clinical study for up to 96 weeks, which included a 48-week open-label run-in phase (N=736) followed by a 48-week placebo-controlled phase (N=313) for patients in sustained

	(part A) followed by a randomised, double-blind, parallel-group, placebo-controlled study (part B) to evaluate maintenance of remission in subjects with active axSpA receiving either certolizumab pegol 200mg q2w or 200mg q4w as compared to placebo. The package leaflet is updated accordingly. The RMP version 17.0 has also been updated to reflect the completion of study AS0005 and update to list of safety concerns. In addition, the interim study reports AS0006 and AS0007 have been submitted to include additional pooled safety data in the SmPC. Study AS0006 is a phase 3, multicenter, randomised, placebo-controlled, double-blind study to evaluate efficacy and safety of certolizumab pegol in subjects with active axSpA without x-ray evidence of ankylosing spondylitis and objective signs of inflammation. Study AS0007 is a multicenter, open-label study to assess the effects of certolizumab pegol on the reduction of anterior uveitis flares in aSpA subjects with a history of anterior uveitis (C-view). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				remission (C-OPTIMISE). The study evaluated the efficacy and safety of dose reduction and treatment withdrawal in patients in sustained remission. The percentage of patients who achieved sustained remission at Week 48 was 43.9% for the overall axSpA population, and was similar in the nr axSpA (45.3%) and AS (42.8%) subpopulations. Among the patients who were randomised in the second part of the study (N=313), a statistically significant (p <0.001, Non-responder Imputation (NRI)) greater proportion of patients did not experience a flare when continuing treatment with Cimzia 200 mg every 2 weeks (83.7%) or Cimzia 200 mg every 4 weeks (79.0%) compared with treatment withdrawal (20.2%). The difference in time to flare between the treatment withdrawal group and either of the Cimzia treatment groups, was statistically significant (p<0.001 for each comparison) and clinically meaningful. In the placebo group, flares started approximately 8 weeks after Cimzia was withdrawn, with the majority of flares occurring within 24 weeks of treatment withdrawal. Patients who were in sustained remission at Week 48 had no or very low inflammation, and no meaningful increase in inflammation was observed at Week 96 irrespective of their treatment group. In the second part of the study, 70% (73/104) placebo-treated patients, 14% (15/105) patients treated with Cimzia 200 mg every 4 weeks and 6.7% (7/104) patients treated with Cimzia 200 mg every 2 weeks experienced a flare and were subsequently treated with Cimzia 200 mg every 2 weeks. Based on the results from C-OPTIMISE, a dose reduction

					(200 mg every 4 weeks) in patients in sustained remission after one year of treatment with Cimzia may be considered. Withdrawal of Cimzia treatment is associated with a high risk of flare. Results from C-OPTIMISE also indicated that a reduction of the dose to Cimzia 200 mg every 4 weeks did not change immunogenicity outcomes. No new safety signal was identified with this study.
IB/0089	B.IV.z - Quality change - Change in Medical Devices - Other variation	08/05/2020	n/a		
IB/0088/G	This was an application for a group of variations. B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product A.7 - Administrative change - Deletion of manufacturing sites	06/05/2020	n/a		
II/0084/G	This was an application for a group of variations. Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information following the final results from studies PS0002 (CIMPASI-2), PS0003 (CIMPACT) and PS0005 (CIMPASI-1) listed as category 3 studies in the RMP; these are results from the open label treatment periods assessing the safety and efficacy of long term use of certolizumab pegol in psoriasis. The RMP version 16.0 has also been updated. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD	17/04/2020	26/06/2020	SmPC, Annex II and Labelling	The information about maintenance of response for plaque psoriasis is updated as follows in the SmPC: In an integrated analysis of two placebo-controlled studies (CIMPASI-1 and CIMPASI-2), among patients who were Psoriasis Area and Severity Index 75% (PASI 75) responders at Week 16 and received Cimzia 400 mg every 2 weeks (N=134 of 175 randomised subjects) or Cimzia 200 mg every 2 weeks (N=132 of 186 randomised subjects), the maintenance of response at Week 48 was 98.0% and 87.5%, respectively. Among patients who were Physician Global Assessment (PGA) clear or almost clear at Week 16 and received Cimzia 400 mg every 2 weeks (N=103 of 175) or Cimzia 200 mg every 2 weeks (N=95 of

	template version 10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				186), the maintenance of response at Week 48 was 85.9% and 84.3% respectively. After an additional 96 weeks of open-label treatment (Week 144) the maintenance of response was evaluated. Twenty-one percent of all randomised subjects were lost to follow-up before Week 144. Approximately 27% of completer study subjects who entered the open-label treatment between weeks 48 to 144 on Cimzia 200 mg every 2 weeks had their dose increased to Cimzia 400 mg every 2 weeks for maintenance of response. In an analysis in which all patients with treatment failures were considered non-responders, the maintenance of response of the Cimzia 200 mg every 2 weeks treatment group, for the respective endpoint, after an additional 96 weeks of open-label therapy, was 84.5% for PASI 75 for study subjects who were responders at Week 16 and 78.4% for PGA clear or almost clear. The maintenance of response of the Cimzia 400 mg every 2 weeks treatment group, who entered the open-label period at Cimzia 200 mg every 2 weeks, was 84.7% for PASI 75 for study subjects who were responders at Week 16 and 73.1% for PGA clear or almost clear. In addition, the following information about quality of life, immunogenicity and safety are added in the SmPC: Improvements in Dermatology Life Quality Index score were sustained or slightly decreased through Week 144. First occurrences of antibody positivity in the open-label treatment period were observed in 2.8% (19/668) of patients. The long-term safety profile of Cimzia 400 mg every 2 weeks and Cimzia 200 mg every 2 weeks was generally similar and consistent with previous experience with

					Cimzia.
II/0086	Submission of the final report from study (UP0038) listed as a category 3 study in the RMP. This is a non-interventional post-authorisation safety study with the aim to evaluate the effectiveness of Cimzia risk minimisation educational materials for healthcare professionals and patients. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/02/2020	n/a		The overall objective of the post-authorisation safety study (UP0038) was to evaluate the effectiveness of the educational material risk minimisation measures being implemented in the EU in healthcare professionals (HCP) respondents who were prescribing and/or administering Cimzia and in patient respondents who were prescribed Cimzia. The focus of this review was the patient reminder card as the prescriber guide was removed from the educational material in January 2019. Of the 169 HCPs who completed the survey (147 rheumatologists, 22 rheumatology nurses), 113 (67%) indicated they received the patient reminder card. Of these, 107/113 (96%) read the patient card and 94/113 (83%) provided it to their patients. Among patients eligible for participation, 69/95 (73%) received the patient reminder card. Although the potential for selection bias must be acknowledged (i.e. only those receiving the patient card answering the survey), this is considered to be an acceptable proportion. Of the respondents, the majority read the patient card (63/69 patients, 91%) and understood its content (61/63 patients, 97%). All respondents considered the patient reminder card to be helpful in some way (somewhat, very or extremely). The survey also included a section capturing the patient recall of important safety information. This indicated that the patients were well aware of the most important safety concerns with Cimzia, such as infections (61/63 patients, 97% were aware of the need to contact their doctor in case of persistent fever or infection). To conclude, the number of healthcare professionals

					receiving the patient reminder card is considered rather low. However, the matter is not be further pursued given the recent revision of the educational material with the removal of the prescriber guide. An acceptable proportion of responding patients received, read and understood the content of the patient reminder card.
II/0085/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	13/02/2020	26/06/2020	Annex II	

II/0079/G	This was an application for a group of variations. B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	26/09/2019	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change				

	to an approved stability protocol B.I.e.2 - Introduction of a post approval change management protocol related to the AS B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IB/0082	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	19/09/2019	n/a		
IB/0083	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	18/09/2019	n/a		
II/0081	Submission of the final report from study (British Society for Rheumatology Biologics Register (BSRBR), RA0022) listed as a category 3 study in the	05/09/2019	n/a		Interim report of the German biologics register RABBIT (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie)

	RMP. This is a UK registry which aims to monitor the long term safety of TNF-α drugs and other targeted therapies in rheumatoid arthritis patients. Submission of the interim report from study (RABBIT registry, RA0020) listed as a category 3 study in the RMP. This is a Germany biologic registry, long-term observational cohort study of the safety and effectiveness of biologic agent in rheumatoid arthritis. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				The interim results showed a 1.5-fold higher risk for serious hospitalized infection for Cimzia compared to csDMARD treated patients. Moreover, a 2.4-fold risk increase for lung cancer was revealed for Cimzia treatment compared receiving csDMARDs. Due to low numbers of patients with lung cancer, these results need to be confirmed in larger studies. Overall, the use of Cimzia for the treatment of patients with RA in daily rheumatologic care appears as a safe and well tolerated option. Final report British Society Rheumatology (BSRBR) Registry The BSRBR final data show, that compared to non-biologic controls, Cimizia treatment was associated with lower rates of cardiac events and death. This must be interpreted cautiously and could suggest insufficient control of confounding. In addition, as moderate to severe heart failure is a contraindication for all anti-TNF-treatments, this finding is not surprising. When compared to other anti-TNF-α treatments, Cimizia treatment was associated with a lower rate of serious infections. For malignancies there was a slight increase in the rate reported for Cimzia compared to other anti-TNF-α treatments (14.2 vs 11.9 per 1,000 patient-years respectively), though it is noted that the 95% Confidence Intervals associated with these estimates overlapped, and that the highest reported rate for malignancies associated with the non-biologic control group was 24.4 per 1,000 patient-years. The risk of malignancy will continue to be closely monitored via pharmacovigilance activities as indicated in the RMP. The comparison to other anti-TNF-α should be interpreted with caution. All these outcomes would from a mechanistic perspective be expected to be class effects if there is a causal relation. Overall, no impact on the established safety profile of

					Cimzia is identified from these comparisons.
II/0075	Update of section 4.1 of the SmPC to add more clarity to the axial spondyloarthritis (axSpA) indication statement in particular with regard to the terms radiographic versus non-radiographic axSpA. Update of sections 4.8 and 5.1 of the SmPC to reflect the availability of additional safety information from the phase 3 clinical study designed to evaluate the safety and efficacy of certolizumab in subjects with active axSpA without X-ray evidence of ankylosing spondylitis and objective signs of inflammation (AS0006). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/06/2019	26/06/2020	SmPC	The efficacy and safety of Cimzia were assessed in a 52 weeks multicenter, randomised, double-blind, placebo-controlled study (AS0006) in 317 patients ≥18 years of age with adult-onset axial spondyloarthritis and back pain for at least 12 months. Patients had to fulfil ASAS criteria for nr-axSpA (not including family history and good response to NSAIDs), and have had objective signs of inflammation indicated by C-reactive protein (CRP) levels above the upper limit of normal and/or sacroiliitis on magnetic resonance imaging (MRI), indicative of inflammatory disease [positive CRP (> ULN) and/or positive MRI], but without definitive radiographic evidence of structural damage on sacroiliac joints. Patients had active disease as defined by the BASDAI ≥4, and spinal pain ≥4 on a 0 to 10 NRS. Patients must have been intolerant to or had an inadequate response to at least two NSAIDs. Patients were treated with placebo or a loading dose of Cimzia 400 mg at Weeks 0, 2 and 4 followed by 200 mg of Cimzia every 2 weeks. Utilisation and dose adjustment of standard of care medication (SC) (e.g., NSAIDs, DMARDs, corticosteroids, analgesics) were permitted at any time. The primary efficacy variable was the Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) response at Week 52. ASDAS-MI response was defined as an ASDAS reduction (improvement) ≥ 2.0 relative to baseline or as reaching the lowest possible score. ASAS 40 was a secondary endpoint. At baseline, 37 % and 41% of patients had high disease activity (ASDAS ≥2.1, ≤3.5) and 62% and 58% of patient had very high disease activity (ASDAS >3.5) in the CIMZIA

					group and placebo group respectively. At Week 52, a statistically significant greater proportion of patients treated with Cimzia achieved ASDAS-MI response compared to patients treated with placebo. Cimzia-treated patients also had improvements compared to placebo in multiple components of axial spondyloarthritis disease activity, including CRP. At both Week 12 and 52, ASAS 40 responses were significantly greater than placebo. At Week 52, the percentage of patients achieving ASDAS inactive disease (ASDAS < 1.3) was 36.4 % for the Cimzia group compared to 11.8 % for the placebo group. At Week 52, patients treated with Cimzia showed a clinical meaningful improvement in the MASES compared to placebo (LS mean change from baseline -2.4; -0.2 respectively).
IB/0080	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/06/2019	n/a		
II/0074/G	This was an application for a group of variations. Submission of the final report from studies (RA0021 and RA005) listed as a category 3 studies in the RMP. Study RA0021 (ARTIS registry) is to provide short- and long-term safety data from the use of certolizumab pegol (CZP) in Sweden for rheumatoid arthritis (RA) patients. Study RA005 (NBD registry) is to obtain safety and outcome data on RA patients receiving CZP and other RA treatments. In addition, the MAH submitted interim results for two ongoing registries studies (RA0020/RABBIT and	16/05/2019	n/a		Based on the real-world data from these 4 registries (ARTIS, NDB, RABBIT, and BSRBR), no new safety concerns for certolizumab pegol (CZP) have been identified. Final data from the ARTIS and NDB registries included in this annual status report inform the investigation of safety concerns with CZP related to infections, congestive heart failure, hypersensitivity reactions, malignancies, demyelinating-like disorders, lupus, hepatobiliary events, and cardiac and cerebrovascular ischemia. Collectively, these final data from ARTIS and NDB, interim data provided from BSRBR and RABBIT, are consistent with the established safety profile and risk characterisation of CZP,

	RA0022/BSRBR). Study RA0020/RABBIT is a German long-term observation of biologics/ DMARD in RA. Study RA0022/BSRBR is a longitudinal observational study of patients with RA treated with biologic agents, and prospective surveillance study for adverse events. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				and support the benefit-risk profile and pharmacovigilance activities outlined in the EU risk management plan (RMP).
IAIN/0078	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	22/03/2019	n/a		
IAIN/0077	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2019	17/04/2019	SmPC and PL	
IB/0076	B.II.g.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	12/03/2019	n/a		
II/0072	Submission of an updated RMP (version 14.1) in order to revise it in line with the new RMP template (GVP Module V rev.2) including the update of the important identified risks, important potential risks and missing information, to stop the distribution of	17/01/2019	17/04/2019	SmPC, Annex II and PL	In the risk management plan (RMP), the summary of safety concerns is updated to remove “Aplastic anaemia, neutropenia, thrombocytopenia, pancytopenia and leukopenia”, “Sarcoidosis” and “New onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and

	prescriber guide, to update the protocol of UP0038 study and to rename patient alert card by patient reminder card. The SmPC, Annex II and package leaflet are updated accordingly. In addition, the MAH took the opportunity to make some administrative changes in the RMP. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				related conditions" from the list of important identified risks; to remove "Cardiac ischemia and cerebrovascular ischemia" and "Serious bleeding events" from the list of important potential risks; and to remove "Children and adolescents" from the list of missing information. Based on the experience with the use of certolizumab and the knowledge about the safety profile, the distribution of the prescriber guide to rheumatologists will cease. In addition, based on the experience with the use of other TNF-inhibitors in psoriasis and an adequate level of understanding of the potential risks and management, the distribution of the prescriber guide to dermatologists will also cease. Finally, the Patient Alert Card has been re-named Patient Reminder Card throughout the RMP and the product information.
IB/0073/G	This was an application for a group of variations. B.I.a.z - Change in manufacture of the AS - Other variation B.I.d.z - Stability of AS - Other variation	05/10/2018	n/a		
II/0068/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	19/07/2018	17/04/2019	SmPC and PL	

	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol				
IB/0071/G	This was an application for a group of variations. B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.IV.z - Quality change - Change in Medical Devices - Other variation	11/07/2018	n/a		
II/0065	Extension of indication for the treatment of moderate to severe plaque psoriasis in adult patients who are candidate to systemic therapy. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/04/2018	07/06/2018	SmPC and PL	Three phase 3 studies (CIMPASI 1, CIMPASI 2 and CIMPACT) were submitted to support an indication for Cimzia in moderate to severe plaque psoriasis. All three studies met their primary end-points; to demonstrate superiority vs. placebo with respect to PASI75 response and PGA Clear or almost clear (with at least 2-category improvement) response at Week 16 in the CIMPASI studies (co-primary end-points) and to demonstrate superiority vs. placebo for PASI75 response at Week 12 in study CIMPACT. Both CZP dose regimens studied (400 mg Q2W and 200 mg Q2W after three initial loading doses of 400 mg) were superior to placebo. In study CIMPACT, the anti TNF alfa antibody etanercept (Enbrel®) was included as active comparator. Superiority

					vs. etanercept could be concluded for PASI75 at Week 12 for the higher 400 mg CZP dose (66.7% vs. 53.3%, p=0.0152) and non-inferiority for the 200 mg dose (61.3% vs. 53.3%; 8% difference, 95% CI: -2.9; 18.9). For PGA response at Week 12 in CIMPACT (secondary end-point), there was no difference in response for this variable for the 200 mg CZP dose vs. ETN (40% vs. 39%) while the 400 mg CZP dose showed a larger response (50%) than ETN. The safety profile of Cimzia 400 mg every 2 weeks and Cimzia 200 mg every 2 weeks were generally similar. In conclusion, the submitted clinical studies support an update of sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC. The Package leaflet is updated accordingly.
IB/0070	B.II.e.6.z - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Other variation	26/05/2018	17/04/2019	SmPC and PL	
IAIN/0069/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	23/03/2018	n/a		

PSUSA/624/201703	Periodic Safety Update EU Single assessment - certolizumab	09/11/2017	08/01/2018	SmPC and PL	Please refer to Cimzia PSUSA/00000624/201703 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0060	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/12/2017	07/06/2018	SmPC and PL	
IA/0066	B.I.d.1.b.1 - Stability of AS - Change in the storage conditions - Change to more restrictive storage conditions of the AS	08/12/2017	n/a		
IB/0067	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	06/12/2017	n/a		
IAIN/0064/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR	11/08/2017	n/a		
II/0061/G	This was an application for a group of variations. B.I.a.4.d - Change to in-process tests or limits	13/07/2017	n/a		

	applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS				
IA/0063	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	07/07/2017	08/01/2018	Annex II	
II/0057/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	21/04/2017	08/01/2018	SmPC, Labelling and PL	

	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
II/0058/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.c.z - Container closure system of the AS - Other variation B.I.d.z - Stability of AS - Other variation B.I.d.z - Stability of AS - Other variation	06/04/2017	n/a		
IA/0059	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	27/01/2017	n/a		
II/0055	Final clinical study report for study PsA001 is submitted to provide data on long-term use of Cimzia in psoriatic arthritis subjects up to 216 weeks of treatment. Sections 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) are revised in order to update the efficacy and safety information (Week 216) for study PsA001. The package leaflet remains unchanged. A revised RMP (version 11) is also submitted.	15/12/2016	28/04/2017	SmPC	For the current data from the overall study (combined double-blind, dose-blind and open-label treatment periods, it is similarly considered that the efficacy of certolizumab pegol (CZP) in reducing signs and symptoms of active PsA, in those subjects who remained in the study, was maintained (up to Week 216). Findings were similar for physical function and health-related outcomes. Inhibition of progression of structural damage in subjects who remained in the study was sustained with long-term (up to 216 weeks) CZP treatment.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Taken together, it is considered that the efficacy of CZP treatment in active PsA in subjects who remained in the study is sustained with long-term (up to 216 weeks) CZP treatment. Overall, it is considered that the incidence and type of AEs observed in the study is consistent with existing knowledge of CZP and anti-TNFα therapy in general and the open-label data from patients with PsA treated with CZP for up to 216 weeks is consistent with the previous study data. The "Long-term use in psoriatic arthritis" identified as a safety concern has been removed from the Risk Management Plan.
II/0054	To submit the final clinical study report for study AS001. Sections 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) are revised in order to update the efficacy and safety information (Week 204) for study AS001. Minor changes to the Package Leaflet have been implemented. A revisedTo submit the final clinical study report for study AS001. Sections 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) are revised in order to update the efficacy and safety information (Week 204) for study AS001. Minor changes to the Package Leaflet have been implemented. A revised RMP (version 11.1) is also submitted. RMP (version 11.1) is also submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	28/04/2017	SmPC and PL	The complete week 204 data in subjects with Active Axial Spondyloarthritis (axSpA) shows that certolizumab pegol (CZP) had an effect on disease activity, function and inflammation assed by MRI during treatment up to 4 years for patients remaining in the study. Accordingly, there are no major concerns regarding CZP's long term efficacy in axSpA patients. The final results of this study are reflected in section 5.1 of the SmPC. The long-term safety profile of CZP from the completed week 204-study, is consistent with the known safety profile of CZP and no new safety concerns have been identified. Section 4.8 of the SmPC reflects that the safety profile for axial spondyloarthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis also in the long term study. The "Long-term use in axial spondyloarthritis" identified as a safety concern has been removed from the Risk Management Plan.

IA/0056	A.7 - Administrative change - Deletion of manufacturing sites	22/11/2016	n/a		
II/0052/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	28/04/2017	SmPC, Annex II, Labelling and PL	
IA/0053	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	27/07/2016	n/a		

II/0049/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	28/04/2016	28/04/2017	Annex II	
IB/0050	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	17/03/2016	n/a		
IB/0051	B.I.a.z - Change in manufacture of the AS - Other variation	10/03/2016	n/a		
II/0048	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	04/02/2016	n/a		
II/0045	Extension of indication to include treatment of severe, active and progressive rheumatoid arthritis in adults not treated previously with methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs); as a consequence, sections 4.1 and 5.1 of the SmPC are revised in order to update the efficacy and safety information. The Package Leaflet	19/11/2015	16/12/2015	SmPC and PL	Please refer to the scientific discussion Cimzia EMEA/H/C/001037/II/0045

	is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0047	A.7 - Administrative change - Deletion of manufacturing sites	09/09/2015	n/a		
II/0046	Update of the SmPC section 5.1 with information on frequency of antibody development over time in subjects treated with CZP based on analysis of data from OLE studies C87028 and C87051. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	08/10/2015	SmPC	In this variation the MAH updated the PI with additional information on the frequency of development of anti-certolizumab antibodies in patients treated with Cimzia based on 2 long-term (up to 5 years of exposure) open-label studies. Antibodies detectable on at least one occasion were present in 13% of patients (8.4% of the overall patients had transient formation of antibodies and an additional 4.7% had persistent formation of antibodies). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 9.1%. Similar to the placebo-controlled studies, antibody positivity was associated with reduced efficacy in some patients.
II/0043/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	22/01/2015	n/a		

	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)				
PSUV/0041	Periodic Safety Update	23/10/2014	16/12/2014	SmPC and PL	Please refer to Cimzia-PSUV41 EPAR: Scientific conclusions and grounds recommending the variation of the terms of the marketing authorisation.
IB/0044/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	27/10/2014	08/10/2015	SmPC, Labelling and PL	
II/0042	change to the manufacturing process of the active substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	25/09/2014	n/a		
II/0037/G	This was an application for a group of variations.	25/09/2014	n/a		

	Change to DS, DP specifications control methods B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
II/0032/G	This was an application for a group of variations. Changes to active substance manufacturing process and in-process testing B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol B.I.a.4.b - Change to in-process tests or limits	26/06/2014	n/a		

	applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
R/0040	Renewal of the marketing authorisation.	20/03/2014	16/05/2014	SmPC, Annex II, Labelling and PL	Based on the review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and, therefore, considered that the benefit risk of Cimzia continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation with unlimited validity.
II/0036/G	This was an application for a group of variations. B.I.a.1.e) Change of quality control testing site of drug substance B.II.b.2.c) Change to batch release and quality control testing of the finished product B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a	23/01/2014	n/a		

	biological/immunological product B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method				
IB/0039/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	03/01/2014	n/a		
IA/0038/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	25/11/2013	n/a		
II/0027	Extension of indication to include the treatment of	24/10/2013	25/11/2013	SmPC and PL	Please refer to the scientific discussion Cimzia

	active psoriatic arthritis in adults patients when the response to previous DMARD therapy has been inadequate. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated accordingly as well as the package leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				EMEA/H/C/001037/II/27 for further information.
II/0026	Update of sections 4.2 and 5.1 of the SmPC in order to add an alternative dose regimen (400 mg every 4 weeks [Q4W]) to the current approved dose regimen (200 mg every 2 weeks [Q2W]) in the treatment of patients with rheumatoid arthritis. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	25/11/2013	SmPC and PL	The option of switching to a CZP 400mg Q4W maintenance dose regimen once clinical response is confirmed was assessed in Study C87077. The results demonstrated that efficacy was maintained after switching from a dose regimen of CZP 200mg Q2W to CZP 400mg Q4W. The results showed that for the maintenance of the clinical response, both regimen CZP 200mg Q2W and CZP 400mg Q4W with MTX demonstrated significance compared to placebo with MTX for ACR20, ACR50, and ACR70 (CZP 400mg Q4W + MTX only) response. The responses compared to placebo were similar for the 2 CZP maintenance dose regimens. The long-term use of the CZP 400mg Q4W dose regimen was followed in Study C87015. This supportive extension study was primarily a safety study. Its open label design without control group did not allow for any robust conclusions on long term efficacy. However, the provided figure on ACR 20/50/70 response generally supported the continued clinical benefits of CZP 400mg Q4W treatment with improvements in clinical response maintained over time up to 6.5 years. As additional supportive information, 1-year interim results

					from the open-label studies C87071 (with MTX) and RA0007 (without MTX) indicated comparable maintenance of clinical response and continued inhibition of structural damage progression (mTSS) by the CZP 200mg Q2W and the CZP 400mg Q4W dose regimens in Japanese subjects following 52 weeks of open-label treatment. In conclusion, based on these study results, CZP 400mg Q4W is considered effective as an alternative dosing option to the currently recommended CZP 200mg Q2W treatment regimen in sustaining the clinical benefit of CZP in subjects with moderate to severe RA once clinical response is achieved. No new safety concern has been identified from the studies submitted. The safety profile of CZP 400mg Q4W was consistent with the known safety profile of CZP.
II/0029	Extension of Indication to include the treatment of adult patients with severe active axial spondyloarthritis, comprising: ankylosing spondylitis (AS): adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs); and Axial spondyloarthritis without radiographic evidence of AS: adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated accordingly as well as the package leaflet. C.I.6.a - Change(s) to therapeutic indication(s) -	19/09/2013	18/10/2013	SmPC and PL	Please refer to the scientific discussion Cimzia EMEA/H/C/001037/II/29 for further information.

	Addition of a new therapeutic indication or modification of an approved one				
II/0034/G	This was an application for a group of variations. Approval of additional quality control testing site. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.II.b.2.b.3 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and one of the test methods is a biol/immunol/immunochemical method	19/09/2013	n/a		
IB/0033/G	This was an application for a group of variations. B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	12/08/2013	18/10/2013	SmPC, Labelling and PL	

II/0030	Change to active substance manufacturing process. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	27/06/2013	n/a		
II/0031	Update of section 4.4 of the SmPC in order to add the risk of hepatosplenic T cell lymphoma (HSTCL). Information in sections 4.8 and 5.1 of the SmPC is also updated based on the integrated summary of rheumatoid arthritis safety data. The package leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	18/10/2013	SmPC and PL	A post-marketing case of HSTCL concomitant with certolizumab pegol (CZP) use was reviewed. Although the time to onset of the event was short and a previous extended immunosuppressive treatment (including other anti-TNF agents) was a confounding factor, the contribution of CZP cannot be totally excluded. Therefore, in line with the wording for other anti-TNF agents, a warning concerning HSTCL is added to section 4.4 to inform healthcare professionals that a risk for the development of HSTCL in patients treated with Cimzia cannot be excluded. A cumulative safety review for the RA population studies showed that the incidence and the pattern of AEs presented are consistent with previous experience with CZP and with those expected for RA subjects treated with an anti-TNFα agent. Sections 4.8 and 5.1 are therefore updated concerning the number of patients exposed in RA clinical trials, the proportion of patients who discontinued due to an adverse drug reaction and the incidence rates for infections, malignancies and lymphoproliferative disorder, injections site reactions and antibodies to CZP.
II/0028	Update of sections 4.4 and 4.8 of the SmPC in order to add Merkel cell carcinoma (MCC) as a new adverse event with unknown frequency. This update is based on a review of post-marketing and clinical trials	21/03/2013	18/10/2013	SmPC, Annex II and PL	The MAH presented a cumulative review of cases of MCC associated with certolizumab pegol (CZP), supported by a literature review and disproportionality analyses. Two cases of MCC were retrieved from the cumulative review. Both

	cases, a literature search and disproportionality analysis. The package leaflet is updated in accordance. Furthermore, the PI is being brought in line with the latest QRD template version 8.3. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				reports were post marketing cases. No MCC cases were observed clinical trials. Both described cases lacked evidence of causal attribution to CZP. One of the cases had a short time to onset and was confounded by prior medications; the other case could not be completely disregarded. No cases of MCC associated with CZP were identified in the literature however the data presented strongly supports the suspicion of a class effect of TNF-blockers on development of MCC. The presented disproportionality analysis also supports the suspicion of a class effect. Overall, although it is not clear whether the appearance of MCC in patients receiving CZP might be due to a number of factors such as other TNF inhibitor therapy, the underlying autoimmune diseases, the patient's age, the exposure to other non-biologic immunosuppressant therapy, the possible contribution of CZP use to the risk cannot be excluded. Therefore MCC is added to section 4.8 'Undesirable effects' of the SmPC, with a frequency category of "not known". The severity and seriousness of the event of MCC also justify its addition to section 4.4 'Special warnings and precautions for use' to warn the prescribing physicians that cases of MCC have been reported in patients treated with TNF-antagonists including CZP and to recommend periodic skin examination, particularly for patients with risk factors for skin cancer.
II/0024	Update of section 4.4 of the SmPC to add information related to hypersensitivity reactions occurring after the first injection. The Package Leaflet is updated accordingly. Furthermore, Annex II is being brought in line with the latest QRD template version.	13/12/2012	18/10/2013	SmPC and PL	A cumulative analysis of hypersensitivity-related events was presented in PSUR 5 covering from 07 September 2011 to 06 March 2012. Results identified 112 cases of hypersensitivity of which 37 cases concerned patients treated with Cimzia for rheumatoid arthritis, 56 for Crohn's disease and 19 for other or unspecified indications.

	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				Approximately one third of hypersensitivity reactions occurred acutely after the first administration of Cimzia. This trend was even more pronounced for the global anaphylactic reactions for which 16 of the 25 hypersensitivity reactions were observed after the first administration. Although hypersensitivity (including anaphylactic shock) is already listed in section 4.8 and hypersensitivity is discussed in section 4.4 of the SmPC, the fact that these events may occur after the first injection of Cimzia is considered clinically important information and is therefore added in section 4.4 of the SmPC.
IG/0222	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/11/2012	n/a		
IB/0023/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	14/09/2012	n/a		
IB/0022/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters	13/08/2012	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0020	The MAH proposed the update of section 4.8 of the SmPC in order to add nausea as an adverse event, following the CHMP assessment of PSUR 3. The Package Leaflet was proposed to be updated in accordance. Furthermore, the MAH proposed this opportunity to make two minor editorial changes in section 4.3 and 4.8 of the SmPC. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	24/05/2012	27/06/2012	SmPC and PL	Following CHMP's assessment of PSUR 3, the MAH has reviewed the adverse event of nausea in the pooled RA placebo-controlled studies and in all pooled RA clinical studies including open-label extension studies in order to determine the frequency of the event of nausea occurring in the RA patient population; since there is at least a reasonable possibility for a causal relationship between nausea and treatment with CZP. As a result, nausea was included in section 4.8 of the SmPC as a common adverse drug reaction and the PL was updated in accordance.
II/0018	Update of section 4.6 of the SmPC and the related pre-clinical safety data in 5.3 to reflect the results of CSR CR0001 (Semen quality - FUM 003) and data on lack of active placental transfer. The package leaflet has been udpated accordingly. C.I.4 - Variations related to significant modifications	24/05/2012	27/06/2012	SmPC and PL	As part of their post-approval commitment, the MAH submitted the results from study CR0001, a randomized, placebo-controlled Phase 1 study evaluating the effect of certolizumab pegol treatment on semen quality. When a single dose of 400 mg certolizumab pegol was given subcutaneously to healthy males, no adverse effects on the semen quality parameters studied were observed compared

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				to placebo. Additionally, clinical and non-clinical studies that characterised the placental transfer of certolizumab pegol were submitted. Results from an in vitro study using a human placental transfer model showed only low levels of transfer to the foetal compartment. Furthermore, clinical data from an investigator-initiated study evaluating plasma levels in infants of mothers treated with certolizumab pegol in late pregnancy was submitted. The study results were considered insufficiently robust to support the claim of a lack of placental transfer. Due to the limited clinical data and the fact that infants from mothers who received certolizumab pegol during pregnancy might be at increased risk for infection, CHMP recommended not to expose these infants to live vaccines up to 5 month after the mother having received the last certolizumab pegol administration during pregancy.
II/0017	The MAH proposed the update of section 4.4 of the SmPC in order to reflect results from vaccination study RA0017 (FUM 004). The Package Leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to include editorial changes related to the information on risk of infections in section 4.4 of the SmPC and corresponding section of the PIL and to add the name of the manufacturer responsible for batch release. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.0.	24/05/2012	27/06/2012	SmPC, Annex II, Labelling and PL	As part of their post-approval commitment, the MAH submitted the results from vaccination study RA0017, a multicenter, Phase 4 study conducted in both a 6-week Single-Blind Period and an Open-Label Period in adult subjects with RA. This study evaluated the immune response to vaccination in RA patients trated with Cimzia. In this study a similar antibody response between Cimzia and placebo treatment were observed when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with Cimzia. Patients receiving Cimzia and concomitant methotrexate had a lower humoral response compared with patients receiving Cimzia alone; however, the clinical significance of this is

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				unknown.
II/0014/G	This was an application for a group of variations. Addition of alternative drug substance manufacturing site and changes to the manufacturing process. Administrative changes. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol A.7 - Administrative change - Deletion of manufacturing sites	21/06/2012	21/06/2012	Annex II	
IB/0019	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	22/03/2012	n/a		
IB/0015/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or	15/12/2011	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IB/0016	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	21/11/2011	21/06/2012	SmPC, Labelling and PL	Update to the Hepatitis B Virus reactivation warning in section 4.4 of the SmPC in line with the requested wording as specified in PSUR 3 assessment report. The PIL has been updated accordingly. The MAH also corrected section IIIA on the packaging of the multipack to clearly differentiate between the outer and intermediate carton and included a statement on the intermediate carton. The MAH aligned the PIL with the SmPC in terms of the wording used for rare vascular disorder side effects. The MAH additionally made typographical corrections to the Spanish and Portuguese local representatives contact details and took the opportunity to make linguistic corrections to the Greek, Finnish, French, Italian, Latvian, Norwegian and Polish annexes.
II/0010/G	This was an application for a group of variations. Additional testing site. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a	19/05/2011	19/05/2011		

	biological/immunological product B.II.b.2.b.3 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and one of the test methods is a biol/immunol/immunochemical method				
II/0009	Update of section 4.8 of the SmPC as requested by the CHMP following assessment of PSUR 1. The PIL has been amended accordingly and the list of local representatives is being updated. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	16/12/2010	09/02/2011	SmPC and PL	This Type II variation to update section 4.8 of the SmPC and the corresponding section of the PIL, was submitted following the assessment of the first PSUR for Cimzia in the EU. In support of the proposed changes, the MAH has made a thorough review of the available data and provided well founded justifications for the addition of ADR terms to the PI, as well as for those ADRs not to be included in section 4.8.
II/0001	Changes to drug substance manufacturing process. Quality changes	23/09/2010	29/09/2010		
IA/0008/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	27/08/2010	n/a	Annex II	

	C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0006	Update of SmPC section 4.4 and 4.8 to include information related to cases of leukaemia and paediatric malignancies associated with the use of TNF-antagonists. The PIL is updated accordingly. In addition, the MAH has taken the opportunity to introduce changes related to the new QRD template (Annexes I, II and IIIB), to make minor linguistic changes to the translations of the PI and to add the date of first authorisation and marketing authorisation numbers (I, IIIA). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/06/2010	26/08/2010	SmPC, Annex II, Labelling and PL	From the data presented by the MAH on leukaemias and paediatric malignancies, it is agreed that there are a number of uncertainties regarding whether there is a causal association between anti-TNF agents and leukaemias or paediatric malignancies or not. Nevertheless, given the mechanism of action of these agents, the possible risks for the development of such malignancies with use of agents of this class cannot be excluded. By addressing these risks in the product information, and with the ongoing follow up activities, the benefit/risk balance for Cimzia remains positive.

II/0005	B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS	22/04/2010	29/04/2010		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2009	n/a	Labelling	