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To

Nämnden för bedömning av Läkemedelsinformation (NBL)

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2023-01-17

NBL case based on a complaint from the Swedish Medicines Agency (regarding commercial advertisement of Cimzia in the journal "Dagens Medicin")

Referring to NBL's email dated December 19th, 2022, with a letter from the Swedish Medicines Agency, the MPA (Läkemedelsverket) dated on November 8th, 2022, UCB Pharma AB would like to provide the following information:

The NBL case now at issue partly concerns the same claims as have already been assessed by the IGN 457 case, in which case the IGN accepted UCB´s arguments (see further in section 1.2)).

The following points from the MPA are being considered here below *(column 2 contains a summary of the MPA´s objections)*:

1) Claims about Cimzia's effect on uveitis

1.1) According to LER Article 11 (Chapter 1, Section 1), documentation must be relied on in a balanced and fair way. According to Article 11.5, the requirement for balanced and fair presentation means, among other, that the report of a study should not be cited or abstracted in such a way that the citation or abstract gives an inaccurate or misleading impression of the contents of the report and the conclusions stated therein.

The claim refers to Cimzia's SmPC (reference 1), as well as a paper by van der Heijde D, et al. which summarize results from the RAPID-axSpA study (reference 4) and a paper by van der Horst-Bruinsma, et al. which summarizes results from the C-VIEW study (reference 5).	The MPA considers that the reference to the Cimzia SmPC and the article by van der Heijde D, et al. in support of the statement "Significant improvement in extra-articular manifestations" gives a misrepresentation of the contents of the SmPC and the article by van der Heijde D, et al.	**UCB's response:** Uveitis, the most prevalent of extra-articular manifestations in axSpA, has indeed been studied in the RAPID-axSpA study, but the references should have been van der Heijde et al. Rheumatology 2017;56:1498-1509 and Rudwaleit et al. Arthritis Care Res 2016;68:838–844 *and is thus a reference typo. Reference 5 is correct though.* Although uveitis is the most prevalent of the extra-articular manifestations in axSpA patients, these also entail IBD and skin psoriasis, that have not been specifically studied in the referenced

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		studies. Therefore, we follow the MPA, that it would have been better to write *"Significant improvement in uveitis flares".* Extraarticular manifestations are clinical manifestations outside the musculoskeletal system in axSpA patients, which still are due to the disease. In the Cimzia SmPC the C-VIEW study is described in which Cimzia was studied in a 96-week open-label study in 89 axSpA patients with a history of documented anterior uveitis flares (Cimzia SmPC 4.8). The above mentioned references from the RAPID-axSpA study (van der Heijde et al. Rheumatology 2017; 56:1498-1509 and Rudwaleit et al. Arthritis Care Res 2016; 68:838–844) support the data from the SmPC, also describing similar findings in a post-hoc study based on a study also included in the SmPC. LER 1.1 article 2 says that the SmPC is the core base for information on medicine but also states that "In addition to information directly taken from the SmPC, or which can be derived from it, other information may be used. This is under the condition that such information supplements the SmPC, by confirming or specifying information in it, and that such supplementary information is in conformity with the information in the SmPC." Based on the above facts, UCB does not consider the statement being open for misinterpretation.

1.2) According to LER Article 2 (Chapter 1, Section 1) the summary of product characteristics (SmPC) that has been adopted for a medicinal product constitutes the factual basis for information about the medicinal product. In addition to information directly taken from the SmPC, or which can be derived from it, other information may be used. This is under the condition that such information supplements the SmPC, by confirming or specifying information in it, and that such supplementary information is in conformity with the information in the SmPC.

The current marketing includes claims about Cimzia's	The MPA considers that Cimzia's SmPC lacks	***UCB's response:***

effect on uveitis, among others with reference to the study C-VIEW.	information on Cimzia's effect on uveitis. The C-VIEW study is only briefly reproduced in SmPC section 4.8 Side effects.	Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis (axSpA), comprising: Ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (Cimzia SmPC 4.1). Uveitis is well-described in axSpA patients with up to half of patients having anterior uveitis as part of the axSpA, why this is relevant and of interest for the HCP. The Cimzia SmPC includes data from the axSpA registration studies (Cimzia SmPC 4.8): RAPID-axSpA (AS001), c-axSpAnd (AS0006), C-OPTIMISE, and C-VIEW. In the latter Cimzia was studied in a 96-week open-label study in 89 axSpA patients with a history of documented anterior uveitis flares (Cimzia SmPC 4.8). LER 1.1 article 2 says the SmPC is the core base for information on medicine and “In addition to information directly taken from the SmPC, or which can be derived from it, other information may be used. This is under the condition that such information supplements the SmPC, by confirming or specifying information in it, and that such supplementary information is in conformity with the information in the SmPC.” The Cimzia advertisement text: ”CIMZIA significantly reduced acute anterior uveitis flares in axSpA with a history of uveitis” and ”CIMZIA has a sustained impact on reducing uveitis flares in axSpA” does not include any claim on treating acute anterior uveitis without active axSpA, but is presented as an extraarticular manifestation of the condition. The data in the material is mentioned in the SmPC in section 4.8. Extraarticular manifestations are non-joint manifestations of rheumatic conditions which are not separate indications per se. To give another example: psoriatic arthritis is an arthritis condition which typically overlaps with psoriasis,

		where e.g. enthesitis and dactylitis are extraarticular manifestations, which are necessary for treating rheumatologists to know about, and are as such not considered as separate indications. It is UCB´s firm opinion that the advertisement text: ”CIMZIA significantly reduced acute anterior uveitis flares in axSpA with a history of uveitis” and ”CIMZIA has a sustained impact on reducing uveitis flares in axSpA” is compliant to article 2 as the text refers to a study mentioned in the SmPC and efficacy data is fully in line with other efficacy data from the studies AS001 and AS0006 mentioned above. Hence the data confirms and clarifies the information in the product summary. Therefore, we would like to stress that the Cimzia ad was made with the intention to bring relevant and requested information to health care professionals and we do our outmost to comply with the LER rules.

2) Early treatment claims

According to LER Article 4.2 (Chapter 1, Section 1) medicinal product information must be truthful and may not contain any presentation in words or pictures that directly or indirectly – by implication, omission, distortion, exaggeration or ambiguity – is intended to mislead. This entails, among other, that information regarding a medicinal product may not be so brief or incomplete that it could be misunderstood.

Treating early and to a stringent target with CIMZIA® may result in improved clinical outcomes and increased likelihood of achieving sustained remission (references 6, 14)	The MPA considers the claims to be scant and general in wording (Swe*: knapphändiga och allmänt hållna*). It is not clear what "early treatment" or "stringent target" means. The MPA also questions the use of the term "may result in", which may be interpreted as meaning that Cimzia could result in a certain effect.	***UCB's response:*** A. Regarding early treatment in axSpA, in clinical practice this refers to patients with either short disease duration (<5 years in C-OPTIMISE) or in an earlier disease state such as nr-axSpA, that has not progressed to an ankylosing spondylitis, (as studied in c-axSpAnd/AS006). Stringent targets refer to more high hurdle endpoints e.g. ASAS-PR, ASDAS-ID, and ASDAS-MI, than those used for regulatory purposes e.g. ASAS20. This nomenclature is usually well known to most rheumatologists. It is shown that early treatment results in improved clinical outcomes e.g.

		sustained remission and objectively decreased MRI signs of inflammation in the SI-joints and the spine (C-OPTIMISE study) and in ASDAS-MI (c-axSpAnd study) as compared with placebo, respectively (Cimzia SmPC). However, we agree with the MPA that the wording would have been more appropriate if clarifying that, in this advertisement, *the claim mainly refers to axSpA patients.* B. Furthermore the wording "may result in" was an unfortunate choice of words as the study shows that Cimzia treatment gave significant clinical responses. *UCB consider that this could have been better phrased but is not incorrect per se.*

3) Claims about continued treatment for women of childbearing age

According to LER Article 4.2 (Chapter 1, Section 1) medicinal product information must be truthful and may not contain any presentation in words or pictures that directly or indirectly – by implication, omission, distortion, exaggeration or ambiguity – is intended to mislead. This entails, among other, that information regarding a medicinal product may not be so brief or incomplete that it could be misunderstood.

Treatment continuity, if clinically needed* CIMZIA® offers treatment continuity for women of childbearing age, if clinically Needed (references 1-3, 13)	A. Together with the **headline** of the ad ("When considering a biologic for a woman with axSpA, PsA or RA, think CIMZIA") and the **picture** of a young woman, the MPA considers that these claims on a cursory reading give the impression that **Cimzia would be particularly suitable for women of childbearing age.** B. The MPA also notes that the asterisk in the claim **Treatment** **continuity, if clinically needed*** is not matched by any footnote in the ad that would be able to clarify the statement.	A. UCB's response: As a starting point UCB wishes to refer to the information and reasoning provided in case NBL 1079/20. In addition, the following should be noted. Through this ad, UCB is wishing to inform the treating physicians on varying scientific clinical study results with certolizumab pegol that could address varying unmet needs of their patients if clinically needed. UCB´s intention is not to claim that CIMZIA is particularly suitable for women of childbearing age. Instead UCB wants to inform that CIMZIA would be a treatment option for RA, axSpA, PsA patients, and also for women of childbearing age provided that it is clinically needed. The material is containing the approved indications of CIMZIA (ref CIMZIA SmPC indications section), and with the wording 'offers' and 'if clinically needed' UCB´s intention is to provide the information that CIMZIA

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		could be one of a treatment option if clinically needed. B. *UCB acknowledges that there is a footnote mistake and that the footnote linked to the asterisk (*) hasn't been printed on the material.* The asterisk should have been appearing as a footnote referring to the following text in the fertility, pregnancy and breastfeeding section of the abbreviated product information under the ad: "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. CIMZIA should only be used during pregnancy if clinically needed".

We continue to do our outmost to comply with the applicable rules for promotion.

In the meantime, we are looking forward to hearing back from you.

Sincere regards,

DocuSigned by:
Berling Patric
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Patric Berling

Managing Director of UCB Pharma AB

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