NOVARTIS

Regulatory Affairs

Cosentyx®/- SensoReady®/- UnoReady®

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Secukinumab
Product(s) concerned (brand name(s)):	Cosentyx
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Cosentyx®/- SensoReady®/- UnoReady® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Cosentyx®/- SensoReady®/- UnoReady® in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Cosentyx®/- SensoReady®/- UnoReady®.

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Summary of the risk management plan for Cosentyx (secukinumab)

This is a summary of the risk management plan (RMP) for Cosentyx. The RMP details important risks of Cosentyx, and how these risks can be minimized, and how more information will be obtained about Cosentyx's risks and uncertainties (missing information).

Cosentyx's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cosentyx should be used.

This summary of the RMP for Cosentyx should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cosentyx RMP.

I. The medicine and what it is used for

Cosentyx is authorized for:

- Psoriasis (adults)

The treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

- Psoriasis (pediatrics)

The treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

- Psoriatic arthritis

The treatment of active psoriatic arthritis in adult patients as a single agent or in combination with methotrexate, when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

- Ankylosing Spondylitis

The treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

- Non-radiographic axial spondyloarthritis (nr-axSpA)

The treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to nonsteroidal antiinflammatory
drugs (NSAIDs). (See SmPC for the full indication).

- Juvenile Idiopathic Arthritis (JIA)
    - Enthesitis-Related Arthritis (ERA)
      The treatment of active enthesitis-related arthritis in patients 6 years of age and older as a single agent or in combination with methotrexate (MTX), when the disease has responded inadequately to, or who cannot tolerate, conventional therapy.
    - Juvenile Psoriatic Arthritis (JPsA)

The treatment of active juvenile psoriatic arthritis in patients 6 years of age and older as a single agent or in combination with methotrexate (MTX), when the disease has responded inadequately to, or who cannot tolerate, conventional therapy. (See SmPC for the full indication).

It contains secukinumab as the active substance and it is given by subcutaneous injection [powder for solution for injection, solution for injection in pre-filled syringe or solution for injection in pre-filled pen]

Further information about the evaluation of Cosentyx's benefits can be found in Cosentyx's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage. https://www.ema.europa.eu/en/medicines/human/EPAR/cosentyx

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Cosentyx, together with measures to minimize such risks and the proposed studies for learning more about Cosentyx risks, are outlined below.
Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

If important information that may affect the safe use of Cosentyx is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Cosentyx are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered/taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cosentyx. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 13-1 List of important risks and missing information

Important identified risks	Infections and infestations Hypersensitivity
Important potential risks	Malignant or unspecified tumors Major Adverse Cardiovascular Events (MACE) Hepatitis B reactivation Suicidal ideation and behavior
Missing information	Fetal exposure in utero Long-term safety data

II B: Summary of important risks

Table 13-2 Important identified risk: Infections and infestations

Evidence for linking the risk to the medicine	As with any immunomodulator, secukinumab has the potential to increase the risk of infections. In clinical studies, an increased risk for infections have been observed, mostly mild or moderate, responsive to usual treatment and not requiring discontinuation. A similar pattern of events have been identified in the post-marketing setting and medical literature (Blauvelt 2016)
Risk factors and risk groups	Severe psoriasis is recognized as a risk factor for infections (Wakkee et al 2011). Other predictors for multiple infectious diseases were the use of anti-diabetic drugs, and COPD/anti-asthmatic drugs (Wakkee et al 2011). The use of systemic psoriasis therapies does seem to increase the risk of infections, although the individual long-term safety profiles are still being investigated in real-world use. Spondyloarthropathies can be associated with an increased risk for infections with incidence rates of infection around 5.3 per 100 PY (Perez-Sola et al 2011; Grijalva et al 2011). In a recent systematic review of randomized trials, the risk of serious infections among patients with AS was 0.4 per 100 PY, while in those treated with TNF blockers the incidence was 2.2 per 100 PY (Fouque-Aubert et al 2010). In JIA, an increased risk for bacterial infections has been described (Beukelmann et al 2012). Whether treatment with biologic agents further increases the risk is not clear (Aeschlimann 2019). Using claims data, Beukelman et al found that the rate of infections requiring hospitalization was not increased in patients with JIA treated with MTX or anti-TNF, but was increased with high-dose glucocorticoids (Beukelmann et al 2012).
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8 **Additional risk minimization measures** No risk minimization measures

Table 13-3 Important identified risk: Hypersensitivity

Evidence for linking the risk to the medicine	Hypersensitivity events, including rare cases of anaphylactic reactions have been observed in clinical studies. The majority of evens were mild to moderate. A similar pattern of events have been identified in the post-marketing setting and medical literature, although secukinumab displayed a minimal immunogenicity potential in pooled Phase 3 trials (Reich et al 2017)
Risk factors and risk groups	Patients with prior allergic reactions are at increased risk.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8 **Additional risk minimization measures** No risk minimization measures

Table 13-4 Important potential risk: Malignant or unspecified tumors

Evidence for linking the risk to the medicine	This is a therapeutic-class risk potentially associated with drugs with different mechanisms of action (e.g. TNF-inhibitors); an increased risk of malignant and unspecified tumors have not been demonstrated in patients treated with secukinumab in clinical trials and in the post-marketing setting.
Risk factors and risk groups	**Psoriasis:** Patients of older age, with previous skin cancer or actinic damage, family history of skin cancers, concurrent or history of immunosuppressive therapies or therapies known to increase skin cancer risk (i.e., cyclosporine, phototherapy especially PUVA) are reported to be at increased risk of NMSC. It is possible that an increased reporting of NMSC with biologics may be attributable to increased detection of skin cancer rather than increased development; however, studies comparing NMSC in patients on biologics with control patients also demonstrated increased rates of NMSC (Kamangar et al 2012). **Psoriatic Arthritis** The subset of PsA patients treated with DMARDS may be at increased risk of lymphoma. Evidence based conclusions cannot be reached with regard to risk groups/risk factors for NMSC in PsA patients, but it is possible that in PsA patients with plaque psoriasis, the risks may be shared with the overall psoriasis population. **Ankylosing Spondylitis** No specific risk groups or risk factors have been identified for malignancy in this patient population. **JIA** Slightly increased risk of lymphoproliferative, but not of other malignancies, has been reported, but there was no sign that the risk increased further after the introduction of DMARDs (Horne et al 2019).
Risk minimization measures	No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Corrona Psoriasis Registry: See section II.C of this summary for an overview of the post-authorisation development plan

Table 13-5 Important potential risk: MACE

Evidence for linking the risk to the medicine	This is a therapeutic-class risk potentially associated with drugs with different mechanisms of action (e.g. TNF-inhibitors); an increased risk of MACE have not been demonstrated in patients treated with secukinumab in clinical trials and in the post-marketing setting.
Risk factors and risk groups	**Psoriasis and Psoriatic Arthritis:** The increased cardiovascular risk in psoriasis and PsA patients is partly due to the association of psoriasis with factors that are known predictors of cardiovascular risk, including hyperlipidemia, obesity, hypertension, and diabetes. Whether an increased risk may also be linked to an independent role of psoriasis as a cardiovascular risk predictor over and above the association with these factors is still controversial, and robust data of a cause-effect relationship are lacking. The common role of a chronic inflammatory pathway seems plausible and it is supported by some studies in the medical literature. **Ankylosing Spondylitis:** Evidence suggests that AS patients may be at a slightly increased risk of MACE, although some studies have failed to identify any increase. No specific risk groups or risk factors have been identified within the overall population. The common role of a chronic inflammatory pathway as a contributing factor to any increased risk seems plausible and it is supported by some studies in the medical literature. Similarly in JIA, although several CVD risk factors are increased, no increase in CVD events was shown in patients, up to 29 years following disease onset when compared to the general population (Anderson et al 2016).
Risk minimization measures	No risk minimization measures.

Table 13-6 Important potential risk: Hepatitis B reactivation

Evidence for linking the risk to the medicine	This is a therapeutic-class risk potentially associated with immunomodulating drugs.
Risk factors and risk groups	The risk factors for HBV reactivation during immunosuppression include history of prior inactive or resolved HBV infection. Reactivation is also more common in men, younger patients, and patients co-infected with hepatitis C virus (Motaparthi et al 2014).
Risk minimization measures	No risk minimization measures.

Table 13-7 Important potential risk: Suicidal ideation and behavior

Evidence for linking the risk to the medicine	This is a therapeutic-class risk potentially associated with drugs with different mechanisms of action (e.g. brodalumab); and no increased risk of suicidality has been identified in clinical trials and in the post-marketing settings
Risk factors and risk groups	Although no particular 'at-risk' patient subset has been identified, some studies suggest a higher risk of depression and SIB in patients with more severe forms of disease (Gupta and Gupta 1998, Kurd et al 2010, McDonough et al 2014, Jensen et al 2016).
Risk minimization measures	No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Corrona Psoriasis Registry: See section II.C of this summary for an overview of the post-authorisation development plan

Table 13-8 Missing information: Fetal exposure in utero

Evidence for linking the risk to the medicine	There are no adequate data from the use of secukinumab in pregnant women. Animal reproduction studies are not always predictive of human response.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.6 **Additional risk minimization measures**

Table 13-9 Missing information: Long-term safety data

Evidence for linking the risk to the medicine	Long-term safety data (> 6 years) continues to be collected in two ongoing trials in pediatric patients (age ≥ 6 years) with PsO and in a 2-year extension study in pediatric patients with JIA (age 2-6 years). In addition, long-term safety data continues to be collected in the ongoing Corrona registry in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy.
Risk minimization measures	No risk minimization measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Corrona Psoriasis Registry: See section II.C of this summary for an overview of the post-authorisation development plan **CAIN457F2304E1:** See section II.C of this summary for an overview of the post-authorisation development plan

II C: Post-authorization development planII.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation for Cosentyx.

II.C.2. Other studies in post-authorization development plan

Table 13-10 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Corrona Psoriasis Registry	The primary goal of the registry is to assess the incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on Cosentyx therapy.
CAIN457F2304E1 Secukinumab long-term efficacy, safety and tolerability in JPsA and ERA up to 4 years	The primary objective of this study is to evaluate the long-term efficacy of subcutaneously administered secukinumab (provided as pre-filled syringes) with respect to JIA ACR30 response over time up to Week 308 visit in patients with active JPsA and ERA subtypes of JIA and who completed the Phase III study CAIN457F2304