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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cosentyx

secukinumab

Procedure no: EMEA/H/C/003729/P46/013

Note

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

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1. Introduction

On 19 October 2022, the MAH submitted a clinical study report for a non-interventional clinical study (study number CAIN457A1402) for Cosentyx. In principle, the completed study was not a paediatric study, but since a single adolescent patient (aged 16 years) had been enrolled into the study, the clinical study report was submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided. It briefly summarises the study results in the overall population as well as for the single adolescent patient.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CAIN457A1402, titled "Special drug-use investigation for Cosentyx subcutaneous injection", is part of the development program to support the registration of Cosentyx in pustular psoriasis in Japan and completed on 19 April 2022. As part of the post-marketing surveillance request from the Japanese Health Authority to evaluate the long-term safety and efficacy of Cosentyx subcutaneous injection in pustular psoriasis patients in Japan, the study enrolled 99 patients, including 1 paediatric patient aged < 18 years.

The results of the study were submitted to the CHMP as a stand-alone submission. According to the MAH, the submitted data from the single paediatric patient do not warrant any update of the currently approved product labelling. Notably, within the EU, Cosentyx is currently not authorised for pustular psoriasis.

2.2. Information on the pharmaceutical formulation used in the study

The study was a post-marketing surveillance study. The following presentations are listed in the study report as having been used:

(1) Cosentyx 150 mg Syringe for Subcutaneous Injection

(2) Cosentyx 150 mg for Subcutaneous Injection

(3) Cosentyx 150 mg Pen for Subcutaneous Injection

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a Clinical Study Report for:

- Study CAIN457A1402, titled "Special drug-use investigation for Cosentyx subcutaneous injection"

2.3.2. Clinical study

Study CAIN457A1402, titled "Special drug-use investigation for Cosentyx subcutaneous injection"

Description

The study was a post-marketing surveillance conducted as requested by the Japanese regulatory authorities at approval to collect safety and efficacy data of Cosentyx subcutaneous injection (hereafter called Cosentyx) in clinical use in the newly approved indication.

Methods

The study was an open-label, multicentre, uncontrolled, single-arm, prospective observational surveillance in Japanese patients with pustular psoriasis receiving Cosentyx for the first time since the approval of a supplemental application for this new indication. The study was to be conducted at around 30 Japanese dermatology departments and other sites that have dermatologists familiar with the diagnosis and treatment of pustular psoriasis and that had adopted Cosentyx or to which Cosentyx had been delivered.

The observation period was 52 weeks from the start of treatment with Cosentyx. The follow-up period was 2 years from the end of the observation period (156 weeks from the start of treatment with Cosentyx).

Study participants

Patients with pustular psoriasis who are not adequately responding to conventional therapies, and who were receiving Cosentyx for the first time since the approval of a supplemental application for this new indication were registered in this surveillance. Patients had to meet all of the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria

1. Patients who provide written consent to cooperate with this surveillance before registration
2. Patients who meet either of the following
    a. Patients not adequately responding to ultraviolet light therapy and other conventional systemic therapies (other than biological drugs) and whose eruption covers 10% of the body surface area or more
    b. Patients with refractory eruption, joint symptoms, or pustules

Exclusion criteria

1. Patients previously treated with secukinumab or a product containing the same active ingredient as Cosentyx (either as an investigational drug or in a post-marketing clinical study)
2. Patients who will be treated with a product containing the same active ingredient as Cosentyx (in a post-marketing clinical study)

Treatments

Being a non-interventional surveillance, there was no binding treatment strategy, and patients were treated in accordance with approved labelling. For Japan, the usual Cosentyx psoriasis dose for adults

is 300 mg by subcutaneous injection at weeks 0, 1, 2, 3 and 4 followed by administration of 300 mg every 4 weeks. According to body weight, 150 mg can be administered.

Objective

The stated objective of the surveillance was to evaluate the long-term safety and efficacy of Cosentyx subcutaneous injection in clinical use in Japanese pustular psoriasis patients.

Outcomes/endpoints

Primary Endpoint

- Incidence of adverse events during the 52-week observation period in patients treated with Cosentyx

Secondary endpoints

- Number of patients with incidences of serious infections and malignant tumours occurring during the total 156 weeks of the observation period
- PASI 50/75/90/100 response rates at Week 16 and Week 52
- Percent change in PASI from baseline to different time points until Week 52
- DLQI score improvement to 0 or 1 at Week 16 and Week 52
- Changes in DLQI total score from baseline to Week 16 and Week 52
- Pustular psoriasis severity scores at each timepoint and changes from baseline, based on the generalized pustular psoriasis severity criteria of the JDA
- Number and proportion of patients in each of the 3 pustular psoriasis severity categories (mild, moderate, or severe) at each assessment time point
- Number and proportion of patients with global impression of change grades (complete response, partial response, no response, progression, and not evaluable) at each assessment time point

There were no binding treatment steps or visit schedule. Routine medical practice was followed for the visit frequency and tests to be performed, and only these data were collected as part of the surveillance.

Events considered as identified risks or potential risks in the Cosentyx risk management plan were separately defined as priority investigation items for purposes of the surveillance. The priority investigation items included: serious infections, tuberculosis, neutropenia, fungal infections, hypersensitivity reactions, malignant tumours, inflammatory bowel disease, and cardiovascular/cerebrovascular events.

Sample size

The target sample size of the safety analysis set in this surveillance was set at 100 patients and the target number of patients to be registered was set at 110 patients, expecting that some patients would be excluded from the safety analysis set.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Presentation of data is based on descriptive statistics.

Results

Recruitment and numbers analysed

The first patient was registered and FPFV occurred on 25 February 2016. The end date of registration period (LPFV) was on 5 December 2018, and the end date of the surveillance period (LPLV) was on 24 November 2021.

During the recruitment period for this surveillance (up to 30 November 2018), 99 patients were enrolled at 71 sites, and the surveillance form data were locked for 96 patients on 19 April 2022 (database lock) at 69 sites. Of these patients, 95 were included in the safety analysis set after excluding 1 ineligible patient. A total of 82 patients were included in the efficacy analysis set after excluding 13 patients in the safety analysis set who were not evaluable for efficacy.

Baseline data

In the safety analysis set, 42 patients (44.2%) were male, and 53 patients (55.8%) were female. Mean (SD) age at the start of treatment with Cosentyx was 56.9 (16.0) years. Most patients (61 patients, 64.2%) were aged ≥ 15 years and < 65 years, and 34 patients (35.8%) were aged ≥ 65 years. One of these patients, a single female patient aged 16 years at enrolment, was considered a paediatric patient per EU definition. Mean (SD) body weight was 61.3 (13.9) kg and mean (SD) BMI was 24.0 (4.8) kg/m2.

The most common total psoriasis duration was ≥ 10 years to < 20 years (22 patients, 23.2%), followed by ≥ 30 years (19 patients, 20.0%) and ≥ 20 years to < 30 years (15 patients, 15.8%). The most common pustular psoriasis duration was < 1 year (30 patients, 31.6%) followed by ≥ 1 year to < 5 years (15 patients, 15.8%), and ≥ 10 years to < 20 years and ≥ 20 years to < 30 years in 13 patients (13.7%) each. At baseline, 44 patients (46.3%) had PASI ≤ 20 and 17 patients (17.9%) had PASI > 20. Most patients had been previously treated with non-biological products (85 patients, 89.5%), with the most common being corticosteroids for topical use (50 patients, 52.6%). Biological products were used for the treatment of psoriasis or other reasons in 38 patients (40.0%) and for the treatment of psoriasis in 37 patients (38.9%).

Paediatric patient

As stated above, the single paediatric patient was a 16-year-old female. She had psoriasis for ≥ 10 years and <20 years, a BMI of 22 kg/m2, and a 1st degree family history of psoriasis. She had received previous biological and non-biological drugs for psoriasis.

Efficacy results

The changes in PASI score were evaluated in the 59 patients with PASI score results among the 82 patients in the efficacy analysis set. The mean (SD) PASI scores were 17.3 (16.0) at the start of treatment with Cosentyx, 3.6 (4.8) at Week 4, and 1.2 (2.0) at Week 16, showing decreases over time from Week 1 of treatment. The mean PASI score was maintained from Week 16 to Week 52 without major changes and was 0.8 (1.1) at Week 52. The mean (SE) percentage changes in PASI score were −28.1 (7.8) at Week 1, −54.8 (5.2) at Week 2, −73.5 (4.3) at Week 3, −75.2 (3.6) at Week 4, −90.2 (3.1) at Week 16 and −85.2 (5.1) at Week 52. The mean percentage change in PASI score decreased over time until Week 16 and was stable thereafter.

The PASI response rates were evaluated in 59 patients for which PASI scores were available at the start of treatment with Cosentyx and at the last evaluation. The PASI response rate showed increases from Week 1 of treatment to Week 16 and until Week 52. At Week 16, the PASI 75 response rate was 89.2% (33/37 patients), the PASI 90 response rate was 75.7% (28/37 patients), and the PASI 100 response rate was 45.9% (17/37 patients). At Week 52, the PASI 75 response rate was 76.9% (20/26 patients), the PASI 90 response rate was 65.4% (17/26 patients) and the PASI 100 response rate was 46.2% (12/26 patients).

The changes in DLQI total score were evaluated in 47 patients for which DLQI total scores were available at the start of treatment with Cosentyx and at the last evaluation. For clarity, higher DLQI scores represent higher impairment in health-related quality of life. The mean DLQI total scores (SD) were 8.7 (7.0) at the start of treatment with Cosentyx, 4.8 (4.1) at Week 4, 3.3 (4.7) at Week 16 and 1.9 (2.1) at Week 52, showing decreases over time. The proportion of patients with a DLQI total score of 0 or 1 (no impairment) increased over time and was 17.0% (8/47 patients) at the start of treatment with Cosentyx, 30.8% (12/39 patients) at Week 4, 51.7% (15/29 patients) at Week 16, and 57.1% (8/14 patients) at Week 52.

Severity assessments were based on the generalised pustular psoriasis severity criteria of the Japanese Dermatological Association (JDA). By JDA total score (category), the proportions of patients at the start of treatment with Cosentyx were: no symptom (remission) in 3.4% (2/59 patients), mild symptoms in 59.3% (35/59 patients), moderate symptoms in 23.7% (14/59 patients) and severe symptoms in 13.6% (8/59 patients). The proportion of patients without symptoms (remission) increased from 22.2% (8/36 patients) at Week 4 of treatment, to 36.7% (11/30 patients) at Week 16 and to 47.8% (11/23 patients) at Week 52. The proportion of patients with mild symptoms were 77.8% (28/36 patients) at Week 4, 63.3% (19/30 patients) at Week 16 and 52.2% (12/23 patients) at Week 52. At Week 12 and later, no patient was classified as moderate or severe. The mean JDA total score (SD) was 5.5 (4.0) at the start of treatment with Cosentyx and showed decreases over time from Week 1 to 1.7 (1.5) at Week 4 and 1.1 (1.2) at Week 16, with a further decrease to 0.8 (1.2) at Week 52.

For global impression of change, patients started showing response (defined as "complete response" or "partial response") at Week 1 of treatment. The response rate at Week 4 was 93.8% (60/64 patients), including 43.8% (28/64 patients) who achieved "complete response" and 50.0% (32/64 patients) who achieved "partial response". The response rate at Week 16 was 94.4% (51/54 patients), including 55.6% (30/54 patients) who achieved "complete response" and 38.9% (21/54 patients) who achieved "partial response". The response rate at Week 52 was 90.0% (36/40 patients), including 65.0% (26/40 patients) who achieved "complete response" and 25.0% (10/40 patients) who achieved "partial response".

Paediatric patient

According to the MAH, the single paediatric patient enrolled into the study was not evaluable for efficacy, and no efficacy data has therefore been presented. For clarity, "not evaluable for efficacy" was defined as a patient who either had no global impression of change at all or who was not evaluable for global impression of change at all time points.

Safety results

The mean (SD) observation duration in the safety analysis set (n = 95) was 346 (65) days, and the observation durations were longer than 48 weeks in 87 patients (91.6%). The mean (SD) duration of treatment with Cosentyx was 278 (120) days and the median (min-max) was 344 (8-365) days.

Treatment duration was > 4 weeks for 87 patients (91.6%), > 16 weeks for 80 patients (84.2%), and > 48 weeks for 58 patients (61.1%).

The initial dose of Cosentyx per administration was 300 mg in 90 patients (94.7%), and the most commonly used dose per administration was 300 mg in 92 patients (96.8%). The mean (SD) total number of Cosentyx doses was 13.1 (4.3). Self-administration was performed at least once in 44 patients (46.3%) during the observation period.

Most patients completed the observation period (52 weeks) and entered the follow-up period. The mean (SD) total observation duration including the follow-up period was 991 (278) days. Patients completed observation duration as follows: >52 weeks (87 patients, 91.6%), >104 weeks (85 patients, 89.5%), and >156 weeks (81 patients, 85.2%).

In the safety analysis set, 9 patients (9.5%) discontinued the surveillance period for reasons including "failure to return before completion (including a hospital transfer)" in 5 patients (5.3%), "withdrawal of consent by the patient" in 3 patients (3.2%), and death in 1 patient (1.1%). The death occurred in a patient who developed hepatocellular carcinoma 149 days after the start of treatment with Cosentyx and died 1234 days (about 3.5 years) after the occurrence; the causal relationship with Cosentyx was considered not related by the investigator.

Adverse events were reported in 49 patients (51.6%). The most commonly affected system organ class was Infections and Infestations, with an incidence of 16.8% (16 patients). Common AEs (≥ 3%) were reported as follows: pustular psoriasis (verbatim events: worsening of the underlying disease) in 9 patients (9.5%), and folliculitis, oral candidiasis, interstitial lung disease, upper respiratory tract inflammation, rash and pyrexia in 3 patients (3.2%) each. The only AE reported in ≥ 3% of patients before Week 12 from the start of treatment was pyrexia in 3 patients (3.2%).

The incidence of adverse events that led to Cosentyx discontinuation was 16.8% (16 patients). The adverse events that led to treatment discontinuation were pustular psoriasis (verbatim: worsening of the underlying disease) in 4.2% (4 patients), nasopharyngitis, pneumonia staphylococcal, sepsis, hepatocellular carcinoma, interstitial lung disease, liver disorder, drug eruption, erythema, pruritus, rash, drug ineffective, therapeutic response decreased, neutrophil count decreased, white blood cell count decreased, and KL-6 increased in 1.1% (1 patient) each. The outcomes were resolved or resolving except for hepatocellular carcinoma, for which the outcome was death (see above).

Serious AEs were reported in 12 patients (12.6%). There was no event that occurred in ≥ 2 patients, and the serious AEs included oral candidiasis, pneumonia staphylococcal, sepsis, septic shock, tonsillitis, breast cancer stage II, pancreatic carcinoma recurrent, hepatocellular carcinoma, adrenal insufficiency, colitis ulcerative, intestinal obstruction, erythema, pruritus and pyrexia in 1 patient (1.1%) each. The outcomes of the serious AEs were resolved or resolving except for hepatocellular carcinoma (death; see above for details), breast cancer stage II, pancreatic carcinoma recurrent, and intestinal obstruction (unknown).

For this study, adverse reactions were defined as AEs suspected by the investigator to be related to Cosentyx. Adverse reactions were reported in 34 patients (35.8%). The most frequently reported adverse reactions (≥ 3%) were as follows: pustular psoriasis (verbatim events: worsening of the underlying disease) in 4 patients (4.2%), and oral candidiasis and rash in 3 patients (3.2%) each.

In the 34 patients with adverse reactions, the most common time of the first occurrence was "≤ 4 weeks" in 11 patients, followed by "> 4 weeks to ≤ 16 weeks" in 6 patients. Thus, adverse reactions first occurred within 16 weeks from the start of treatment in approximately half of the patients. There was no adverse reaction that occurred uniquely in one specific time category.

Serious adverse reactions (serious AE suspected by the investigator to be related to Cosentyx) were reported in 6 patients (6.3%). They included oral candidiasis, pneumonia staphylococcal, sepsis, septic shock, breast cancer stage II, colitis ulcerative, erythema and pruritus in 1 patient each (1.1%).

Occurrence of adverse events and adverse reactions of the priority investigation items in the safety analysis set (n = 95) during the observation period are summarised in Table 2.3.2.1.

Table 2.3.2.1 Data on the occurrence of priority investigation items (adverse events and adverse reactions) (by priority investigation item, PT) (safety analysis set)

	Safety analysis set N = 95	
	Adverse events	Adverse reactions
Priority investigation items PT	Number of applicable patients (%)	Number of applicable patients (%)
Total	24 (25.26)	18 (18.95)
Serious infections	4 (4.21)	3 (3.16)
Oral candidiasis	1 (1.05)	1 (1.05)
Pneumonia staphylococcal	1 (1.05)	1 (1.05)
Sepsis	1 (1.05)	1 (1.05)
Septic shock	1 (1.05)	1 (1.05)
Tonsillitis	1 (1.05)	0 (0.00)
Fungal infections	8 (8.42)	6 (6.32)
Oral candidiasis	3 (3.16)	3 (3.16)
Skin candida	2 (2.11)	1 (1.05)
Malassezia infection	1 (1.05)	0 (0.00)
Tinea infection	1 (1.05)	1 (1.05)
Candida infection	1 (1.05)	1 (1.05)
Tuberculosis	0 (0.00)	0 (0.00)
Neutrophil count decreased	2 (2.11)	2 (2.11)
Neutrophil count decreased	2 (2.11)	2 (2.11)
White blood cell count decreased	2 (2.11)	2 (2.11)
Hypersensitivity reactions	6 (6.32)	5 (5.26)
Rash	3 (3.16)	3 (3.16)
Drug eruption	2 (2.11)	1 (1.05)
Conjunctivitis allergic	1 (1.05)	0 (0.00)
Urticaria	1 (1.05)	1 (1.05)
Malignant tumors	3 (3.16)	1 (1.05)
Breast cancer stage II	1 (1.05)	1 (1.05)
Pancreatic carcinoma recurrent	1 (1.05)	0 (0.00)
Hepatocellular carcinoma	1 (1.05)	0 (0.00)
Inflammatory bowel disease	1 (1.05)	1 (1.05)
Colitis ulcerative	1 (1.05)	1 (1.05)
Cardiovascular/cerebrovascular events	2 (2.11)	2 (2.11)
Hypertension	2 (2.11)	2 (2.11)

Source: Data on file
Multiple episodes of an event (PT) in the same patient are counted only once.
Priority investigation items (order of listing in surveillance form), PT: shown in the descending order of the incidences of adverse events→PT codes
MedDRA/J version 24.1

Adverse events and adverse reactions of "serious infections" were reported in 4 patients (4.2%) and 3 patients (3.2%), respectively. Median (min-max) time to onset (first occurrence) was 54 (11-170) days. The outcomes in these 3 patients were resolved or resolving and the median (min-max) time to resolved or resolving was 33 (28-129) days. During the follow-up period, a "serious infection" occurred, which was pneumonia aspiration (1 patient). This event occurred at 1.006 days

from the start of treatment (986 days from the most recent dosing) and was resolving at 18 days after the occurrence following hospitalisation/prolongation of existing hospitalisation. This event was assessed to be serious, but not causally associated with Cosentyx.

Adverse events and adverse reactions of "neutropenia" (comprising events of neutrophil count decreased and white blood cell count decreased) were reported in 2 patients (2.1%); times to onset were 29 and 32 days. Both events were reported as resolved or resolving, and times to resolved or resolving were 67 and 237 days.

Adverse events and adverse reactions of "fungal infections" were reported in 8 patients (8.4%) and 6 patients (6.3%), respectively. Median (min-max) time to onset (first occurrence) was 142 (92-337) days. The outcomes in these 6 patients were resolved or resolving, with a median (min-max) time to resolved or resolving of 85 (15-162) days.

Adverse events and adverse reactions of "hypersensitivity reactions" were reported in 6 patients (6.3%) and 5 patients (5.2%), respectively. Median (min-max) time to onset (first occurrence) was 132 (8-311) days. The outcomes in these 5 patients were all resolved or resolving, with a median (min-max) time to resolved or resolving of 24 (8-71) days (population for calculation: 4 patients).

Adverse events and adverse reactions of "malignant tumours" were reported in 3 patients (3.2%) and 1 patient (1.1%), respectively. The adverse reaction (breast cancer stage II) occurred 21 days from the start of treatment with Cosentyx (1 day from the most recent dosing) and was assessed to be serious. The outcome following actions (follow-up, changes made to concomitant drugs etc., hospitalisation/prolongation of existing hospitalisation) was unknown. Cosentyx was not resumed after follow-up and the total number of doses was 4 times. During the follow-up period, an event of "malignant tumours" (small intestine carcinoma) occurred, in the same patient that developed breast cancer stage II during the observation period. This event occurred at 374 days from the start of treatment with Cosentyx (354 days from the most recent dosing). The outcome following actions (changes made to concomitant drugs etc., hospitalisation/prolongation of existing hospitalisation) was unknown. This event was assessed by the investigator as serious and related to Cosentyx.

The adverse event and adverse reaction of "inflammatory bowel disease" was colitis ulcerative reported in 1 patient (1.1%). Time to onset (first occurrence) was 54 days, the outcome was resolved and the number of days to resolved was 40 days.

The adverse event and adverse reaction of "cardiovascular/cerebrovascular events" were both hypertension in 2 patients (2.1%). Times to onset (first occurrence) were 1 day and 227 days, the outcomes for both were reported as resolving and the numbers of days to resolving were 29 days and 99 days.

A factorial analysis of adverse event and adverse reaction data based on various baseline characteristics (such as age, sex, body weight, disease duration, medical history, prior use of biologicals) identified no particular trends.

Paediatric patient

The 16-year-old paediatric patient initiated treatment with Cosentyx at 300 mg with no dose increases or reductions. The patient had an administration duration of 344 days and received 16 doses of Cosentyx with no self-administration. According to the MAH, no AEs were reported for this paediatric patient during the surveillance period.

2.3.3. Discussion on clinical aspects

The study reported within the current submission was a non-interventional surveillance study developed and carried out by the MAH to collect safety and efficacy data from the patient population that received Cosentyx after the approval of a supplemental application for the new indication of pustular psoriasis. The study design and execution in themselves seem typical for a non-interventional surveillance study, with no unusual features. For purposes of assessment from the perspective of Article 46, the overall relevance of the study is very limited, as it primarily enrolled an adult population in accordance with the authorised use. No patients under the age of 15 years (Japanese definition of paediatric patients) were enrolled, but one 16-year-old patient was enrolled and was thus considered a paediatric patient as per the EU definition.

The reported study was a small, uncontrolled non-interventional survey, and as such, very limited conclusions can overall be drawn from the results. Moreover, pustular psoriasis is not an authorised indication for secukinumab in the EU. Recognising these inherent limitations, it can nevertheless be generally noted that the reported results are broadly consistent with previous results from controlled clinical studies with secukinumab in other indications, and there are no new findings or observations of concern. The safety findings are also appropriately addressed in existing EU Product Information for secukinumab, and no updates are warranted. In terms of paediatric use, the reported survey assessed adult patients, and no conclusions relevant to Article 46 can be made based on a single treated adolescent patient. Overall, the results of the study do not change the benefit-risk profile of secukinumab.

The MAH has concluded that the surveillance results do not show any new safety concerns for Cosentyx in long-term treatment. In addition, because Cosentyx showed long-term efficacy in patients with pustular psoriasis also in clinical use, additional safety measures are considered unnecessary. The MAH's conclusion is endorsed.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.