Taiwan Food and Drug Administration

Assessment Report

Trade Name：ENSPRYNG 120 mg for SC Injection

Active Ingredient：Satralizumab

License Number：MOHW-BI 001143

Applicant：台灣中外製藥股份有限公司

Approval Date：2020/11/09

Indication：
適用於治療水通道蛋白 4 自體抗體陽性[anti-aquaporin-4 (AQP4) antibody positive]的泛視神經脊髓炎(Neuromyelitis optica spectrum disorder, NMOSD)之成人及 12 歲以上青少年病人。

Enspryng is indicated for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients aged 12 years and older who are anti-aquaporin-4 (AQP4) antibody positive.

Background Information

Trade Name	ENSPRYNG 120 mg for SC Injection
Active Ingredient(s)	Satralizumab
Applicant	台灣中外製藥股份有限公司
Dosage Form & Strengths	Injection 120 mg
Indication	適用於治療水通道蛋白 4 自體抗體陽性[anti-aquaporin-4 (AQP4) antibody positive]的泛視神經脊髓炎(Neuromyelitis optica spectrum disorder, NMOSD)之成人及 12 歲以上青少年病人。 Enspryng is indicated for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients aged 12 years and older who are anti-aquaporin-4 (AQP4) antibody positive.
Posology	The recommended loading dosage of ENSPRYNG for the first three administrations is 120 mg by subcutaneous injection at weeks 0, 2, and 4, followed by a maintenance dosage of 120 mg every 4 weeks. Enspryng can be used as a monotherapy or in combination with immunosuppressant therapy (IST), such as oral corticosteroids, azathioprine or mycophenolate mofetil. For patients under 12 years old or less than 40 kg, the efficacy and safety of Enspryng has not been established. 初始治療時，於第 0、2 及第 4 週(最初三次給藥)皮下注射 120 毫克，後續則每 4 週一次(120 毫克皮下注射)。Enspryng 可單獨使用或與免疫抑制療法(IST)併用，如:口服皮質類固醇、azathioprine 或 mycophenolate mofetil。對於未滿 12 歲或體重小於 40 公斤的病人，Enspryng 的療效與安全性尚未建立。
Pharmacological Category **ATC Code**	L04AC19

2. Summary Report

2.1Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

General Information

The drug substance “satralizumab” is a humanized monoclonal antibody based on a human immunoglobulin G2 (IgG2) framework and is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.

Satralizumab consists of two heavy chains (443 amino acid residues each) and two light chains (214 amino acid residues each) and the molecular weight is about 143 kDa. Satralizumab is designed to bind to human interleukin-6 (IL-6) receptors and thereby prevents IL-6-mediated signal transmission through these receptors. The binding of Satralizumab to IL-6R is pH-sensitive.

Manufacturing

Satralizumab is manufactured according to Good Manufacturing Practices (GMP). The drug substance manufacturing process consists of the cell culture process and the purification process. The cell culture starts from the vial thawing followed by cell expansion and the production culture. Following completion of the cell culture production stage, a multistep purification process including chromatography and filtration steps as well as virus inactivation are performed to purify Satralizumab from the culture harvest. The resulting staralizumab solution is concentrated, buffer exchanged and filtered into appropriate storage containers.

- Control of material

The adequate information regarding the raw materials used in the manufacturing process has been provided. No substances of human or animal origin are used in the drug substance manufacturing process. All materials used are tested and released according to established procedures.

Sufficient details of the cell substrate generation are described. Two tiered cell banking system including master cell bank (MCB) and working cell bank (WCB) were established. The cell banks as well as post-process cells (PPC) were tested for adventitious agents in accordance with regulatory guidelines. Cell substrate stability was also evaluated using MCB and PPC derived from WCB and the presented data support a maximum *in vitro* cell age.

- Control of critical steps and intermediates

The critical process steps, critical process parameters (CPPs), and in-process limits employed to control the quality of satralizumab during the manufacture have been provided. The

control of critical steps and intermediates has been sufficiently described and is found acceptable.

- Process validation

The process performance qualification (PPQ) has been conducted on serval consecutive full scale batches, manufactured using the proposed commercial process. The PPQ results demonstrate the process was validated to consistently deliver the intended performance and product quality.

The maximum hold times for the in-process pools were established based on the proven stability data obtained from PPQ and clinical batches.

Removal of process and product related impurities were also evaluated during PPQ. The results, regarding removal of impurities, from the PPQ data together with the batch analysis data from clinical trials batches were found acceptable.

- Manufacturing process development

The applicant has set up an enhanced development approach aimed at analyzing, categorizing, and ensuring appropriate mitigation and management of risk to product efficacy and safety related to the production process.

- Using CQA risk ranking and filtering tool (RRF) to identity critical quality attributes (CQAs) for drug substance and drug product.
- Identification of potential critical process parameters (pCPPs) from the process design studies with risk ranking and filtering tool. Analysis and categorization of study results to identify CPPs were refined continuously over the process development life cycle.
- Following a systematic approach that used a combination of testing and process controls, an overall control strategy was developed to ensure acceptable CQA levels.

The development history of drug substance manufacturing process, including a summary of changes has been provided. The analytical comparability assessment to evaluate the impact of these changes on product quality and process performance has been performed. The results demonstrated the comparability for materials produced using different manufacturing process.

Characterization

Sufficient data on the physicochemical (primary structure, post-translational modifications, higher-order structure, and variants), biological, and immunochemical characteristics (binding to IL-6Rs) of satralizumab has been provided.

The potential impurities have been analysed and are considered sufficiently controlled.

Control of drug substance

- Specification

The proposed drug substance specification includes appearance, pH, identity, protein content, purity/ impurities, potency and safety tests. The proposed commercial specification for drug substance is considered adequate and acceptable.

- Analytical methods

All analytical procedures used have been described (the methods common to releasing of drug substance and the drug product are described in the section P.5.2). These tests are performed either according to compendial methods or in-house analytical methods. The potency of satrazilumab is determined by cell based assay which is is designed to achieve its pharmacological effects by blocking the binding of human interleukin-6 (hIL-6) to hIL-6 receptor (hIL-6R).

All analytical methods used have been validated or verified.

- Batch analysis

Batch analysis results of drug substance batches used for non-clinical studies, clinical studies, development studies, stability and process validation studies have been provided. The results confirm consistency of the manufacturing process.

In addition, all available release data from drug substance batches produced during the process validation campaign met the acceptance criteria of the proposed commercial specification acceptance criteria.

Reference standards

The primary reference material and working reference material have been suitably manufactured and characterized for their purpose. A protocol for qualification of future reference materials has been described, listing the methods to be used.

Container closure system

Sufficient descriptions of the container closure have been provided. The risk assessment regarding extractables and leachables from container has been conducted and the results show that the container closure system is safe to use.

The drug substance stability data also support that container closure system used is suitable for the storage of satralizumab drug substance at the recommended conditions.

Stability

The stability studies have been performed according to ICH Q5C. Considering the totality of stability data, the proposed shelf life for drug substance is considered acceptable.

2.1.2 Drug product

Satralizumab drug product is a prefilled 1 mL polymer syringe containing a sterile, colorless to slightly yellow solution for subcutaneous injection with no preservatives. Each single-dose, 1 mL prefilled syringe (PFS) contains 120 mg (nominal) of satralizumab antibody at pH 6.0. The excipients used for the Satralizumab PFS are L-histidine, L-aspartic acid, L-arginine, polpxamer 188, and water for injection.

Pharmaceutical Development

The formulation development has been adequately described. The selected formulation has been shown to maintain the stability of drug product when stored as recommended and has been assessed in a multivariate formulation robustness study. The commercial drug product formulation is the same as the one used in clinical trials.

The drug product configurations used during clinical development and changes to the process over the course of development are summarized in the dossier. Analytical comparability exercises were conducted to evaluate the impact of changes on drug product. The presented data show that the manufacturing process changes had no impact on product quality attributes that could affect patient safety or drug efficacy.

Manufacture

The manufacturing process of satralizumab PFS consists of drug solution preparation, filtration and aseptic filling and stoppering. Each PFS is labeled, assembled with a plunger rod (PR) and needle safety device (NSD) followed by secondary packaging.

Controls

The CPPs and IPCs that control the critical steps and, thus, ensure appropriate routine control of the entire manufacturing process have been provided.

Process validation/qualification

The validation of satralizumab drug product manufacturing process included the manufacture of several process performance qualification (PPQ) batches representing the full range of batch sizes for commercial manufacturing.

Data from the PPQ batches showed

- All critical quality attributes (CQAs) met their acceptance criteria.
- In-process controls (IPCs) met their acceptable ranges or limits, respectively.

- All critical and non-critical process parameters (CPPs and non-CPPs) were maintained within their acceptable ranges
- Process performance was consistent between the PPQ batches

The filters used for bioburden reduction and sterile filtration have been validated.
The process of aseptic filling is validated by media fill.

Control of Drug Product

- Specification

The commercial release specification for satralizuma PFS includes appearance, identity, general tests, purity/impurities, potency assay and safety tests. The justification of specifications for satralizumab PFS has been provided and considered acceptable.

- Analytical procedures

Both pharmacopoeia-based and satralizumab-specific methods are used for releasing of satralizumab PFS. All analytical methods are satisfactorily described in the dossier and non-compendial methods have been validated.

- Batch analyses

The results of batch analyses meet the specifications that were in effect at the time of testing and releasing. In addition, all available release data from the satralizumab PFS batches produced during the process validation campaign also met the commercial release specification acceptance criteria. Overall, the results confirm consistency of the manufacturing process.

Control of excipients

All excipients used are tested according to compendial methods and released with compendial specifications. No excipients of human or animal origin are used to manufacture satralizumab PFS. No novel excipients are used to manufacture satralizumab PFS.

Reference materials

The reference standard used for the release of satralizumab PFS is the same as the one used for the release of satralizumab drug substance.

Container closure system

The primary packaging components for satralizumab drug product consist of a 1 mL colorless USP/Ph. Eur./JP compliant polymer syringe with a staked-in stainless steel needle, fitted with a rigid needle shield and sealed with a plunger stopper. All primary packaging materials are of pharmaceutical quality, suited for packaging sterile liquid products, and

comply with relevant pharmacopoeia requirements. The container closure is considered suitable for its intended use.

Stability of the product

The proposed drug product shelf life is 24 months when stored at the recommended temperature of 2-8℃, protected from light. The shelf life claim is based on the *real-time*/*real-temperature* stability data.

A temperature excursion study was also performed. The results of the temperature excursion study support unopened satralizumab PFS can be removed from and returned to the refrigerator and the total combined time out of refrigeration should not exceed 8 days at a temperature that does not exceed 30℃.

A photostability study was conducted in accordance with ICH Q1B and the results indicate the satralizumab is sensitive to light and should be protected from light.

Adventitious agents

Adequate information has been presented to support Satralizumab meets the requirements of complying to TSE/BSE.

All cell banks have been tested for non-viral and viral adventitious agents according to regulatory requirements. To ensure absence of adventitious agents, testing for non-viral and viral adventitious agents is conducted in the routine manufacture at different stages.

Viral clearance studies have been described. The viral clearance claim is based on unit operations that were validated at worst-case settings of process parameters as evaluated by a risk analysis. Data, regarding virus inactivation and removal, have been provided and confirms the viral clearance capacity of the purification process.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Satralizumab is an IL-6 receptor (IL-6R) inhibitor which is indicated for the treatment of patients with neuromyelitis optica spectrum disorder (NMOSD). IL-6 is a pleiotropic cytokine produced by a variety of cell types and is involved in diverse inflammatory processes including B-cell activation, differentiation of B-cells to plasmablasts and production of autoantibodies, Th17-cell activation and differentiation, T-regulatory cell inhibition, and changes in blood-brain-barrier permeability. IL-6 levels are increased in cerebrospinal fluid and serum of patients with NMOSD during periods of disease activity. Some IL-6 functions have been implicated in the pathogenesis of NMOSD, including

production of pathological autoantibodies against Aquaporin-4 (AQP4), a water channel protein mainly expressed by astrocytes in the CNS.

The precise mechanism by which satralizumab exerts therapeutic effects in NMOSD is unknown but is presumed to involve inhibition of IL-6-mediated signaling through binding to soluble and membrane-bound IL-6 receptors.

There is another IL-6R inhibitor drug, tocilizumab, which is indicated for the treatment of rheumatoid arthritis. The *in vitro* pharmacology studies indicated that satralizumab had a similar binding affinity in human and monkey IL-6R. The epitopes recognized by satralizumab and tocilizumab would overlap. Satralizumab blocked the binding of IL-6 to receptors and then blocked the signal transduction through gp130. However, satralizumab did not affect the other gp130-family cytokine receptors. Besides, satralizumab inhibited IL-6-induced T-cell proliferation and cytokine production, and was unlikely to induce PBMC-mediated ADCC or CDC. The *in vivo* study showed that satralizumab inhibited IL-6-stimulated CRP production in cynomolgus monkeys.

2.2.2 Toxicological Studies

The pivotal nonclinical repeated-dose toxicity studies included a 4-week IV, a 4-week SC, and a 26-week SC studies in cynomolgus monkeys. The endpoints of safety pharmacology, fertility, and local tolerance were also evaluated in the repeated-dose studies. There was no significant finding observed in the IV study (at up to 200 mg/kg QW) and SC studies (at up to 50 mg/kg QW).

The genotoxicity and carcinogenicity studies were not conducted since satralizumab was unlikely to interact with DNA directly and did not cross-react to rodent IL-6R. The embryo-fetal development, pre- and post-natal development, and juvenile toxicity were evaluated in an enhanced PPND study in the cynomolgus monkey. There was no significant toxicity in embryonic development and juvenile animals.

The human blood compatibility study indicated that no hemolytic or precipitation reaction was observed at 1.182 mg/mL. The risk of cytokine release syndrome of satralizumab was similar to tocilizumab.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following single 30 mg to 240 mg dose of satralizumab by subcutaneous injection, time to reach peak concentration ranged from 4.0 to 5.5 days. In healthy subjects, the PK of satralizumab was shown to be non-linear over the dose range of 30 mg to 240 mg. In adult

NMO (neuromyelitis optica) /NMOSD patients following subcutaneous administration, the absorption half-life was around 3 days at the recommended dose regimen. Steady state was achieved after the dose loading period (8 weeks). Population PK analysis estimated that the bioavailability was approximately 85%.

Satralizumab undergoes biphasic distribution. For a typical 60 kg patient, the estimated central volume of distribution was 3.46 L, and the peripheral volume of distribution was 2.07 L. Satralizumab is expected to be cleared principally by catabolism. The total clearance of satralizumab is concentration-dependent both linear and target-mediated elimination. Bodyweight was shown to be a significant covariate. The clearance and Vc for patients weighing 123 kg increased by 71.3% and 105%, respectively, compared to a 60 kg patient. Linear clearance (accounting for approximately half of the total clearance at steady state using the recommended dose in NMOSD patients) is estimated to be 0.0601 L/day. The associated terminal $t_{1/2}$ is approximately 30 days based on data pooled from the Phase 3 studies.

2.3.2 Interaction Studies

No formal drug-drug interaction studies have been performed with satralizumab. The population PK analysis did not show potential of drug interaction between satralizumab and immunosuppressive therapy such as oral corticosteroids, azathioprine, and mycophenolate mofetil. Since the expression of specific hepatic CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) is suppressed by cytokines such as IL-6 *in vitro* and *in vivo*, caution should be exercised when satralizumab is administered or discontinued in patients also receiving CYP450 substrates with a narrow therapeutic index.

2.3.3 Special Populations

Based on population PK analysis, age, gender, and race have no clinically meaningful effect on the PK of satralizumab in adult and adolescent patients with NMOSD. Body weight and the presence of anti-drug antibody (ADA) significantly influenced the PK of satralizumab. In NMOSD patients with either post-treatment ADA positive or higher body weight (75.0-151.0 kg), approximately 2-fold lower exposure was observed as compared to patients with ADA negative or lower body weight (57.3-75.0 kg). There was no dedicated PK study conducted in pediatric NMOSD patients with body weight lower than 40 kg. Only the simulated PK data was provided for this population. The results showed that the predicted steady-state exposures in patients with body weight range in 30 kg~40 kg were higher than that in adult and adolescent population based on Studies BN40898 and BN40900.

No dedicated PK study was conducted to evaluate the impact of renal or hepatic impairment on the PK of satralizumab. Patients with mild renal impairment (CCL<80 mL/min and ≥50

mL/min) were included in Studies BN40898 and BN40900. The PK of satralizumab in these patients was not significantly impacted based on population PK analysis.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Two Phase III clinical studies, Study BN40898 (SAkurasky) and Study BN40900 (SAkurastar), were provided and demonstrated the efficacy of ENSPRYNG® (Satralizumab) as monotherapy or in combination with immunosuppressive therapy for the treatment of adults and pediatric patients 12 years of age and older with neuromyelitis optica spectrum disorder (NMOSD).

Study BN40898 (SAkurasky) in adolescent and adult patients (age 12-74 years) with NMO and NMOSD had demonstrated that satralizumab 120 mg SC at Weeks 0, 2 and 4, and every 4 weeks (Q4W) thereafter was superior to placebo, in combination with immunosuppressive therapy such as oral corticosteroids, azathioprine, and mycophenolate mofetil, in time to first protocol-defined relapse (PDR) in the double-blind period [median: 120.6 weeks vs. NE; HR (95% CI): 0.38 (0.16, 0.88); p-value (2-sided; stratified log-rank)=0.0184]. The double-blind period ended when either the patient had a relapse or the total number of protocol-defined relapses judged by the Clinical Endpoint Committee (CEC) reached 26.

Study BN40900 (SAkurastar) in adult patients (age 18-74 years) with NMO and NMOSD had demonstrated that satralizumab 120 mg SC at Weeks 0, 2 and 4, and every 4 weeks (Q4W) thereafter was superior to placebo in time to first protocol-defined relapse (PDR) in the double-blind period [median: 128.3 weeks vs. NE; HR (95% CI): 0.45 (0.23, 0.89); p-value (2-sided; stratified log-rank) = 0.0184]. The double-blind period ended when either the patient had a relapse or the total number of protocol-defined relapses judged by the CEC reached 44, or when the last patient enrolled had been treated for 1.5 years since the date of randomization, whichever occurred first.

In the subgroup analysis, robustness of efficacy in the subgroup of AQP4 IgG seropositive NMOSD was shown. However, subgroup analysis of AQP4 IgG seronegative revealed inconsistent efficacy results in terms of time to first relapse or annualized relapse rate. Therefore, the benefit of satralizumab in treating AQP4 IgG seronegative NMOSD is uncertain according to currently available data.

2.4.2 Safety Results

Treatment emergent adverse events (TEAEs) included leukopenia, decreased platelet count, elevation of liver enzymes (AST and ALT), elevation of TG, headache, injection-related reactions, nausea, fatigue, rash, arthralgia and pain in extremity.

Satralizumab is an immunosuppressant through blocking IL-6 from binding to IL-6 receptor; opportunistic infections would be considered as potential risks.

It should be noted that subjects with active hepatitis B or C, latent TB without chemoprophylaxis and active TB were excluded in two pivotal studies. The sponsor provided an RMP which consisted of Medication Guide and Communication Plan; the content of Communication Plan is risk minimization measures for TB and hepatitis B/C, these measures are in line with the Official RMP for TNF-alpha inhibitors.

2.5 Bridging Study Evaluation

The impact of ethnic factor on the PK of satralizumab was evaluated based on data from a phase I Japanese study (SA-001JP) and two phase III clinical studies (SA-307JG and SA-309JG). Following single 120 mg dose of satralizumab by subcutaneous injection, satralizumab C_{max}, AUC_{last}, and AUC_{inf} in Japanese healthy subjects (N=12, 61 kg) was higher by 11%, 18%, and 18%, respectively, compared to Caucasians healthy subjects (N=10, 74 kg). As body weight is a significant covariate for satralizumab exposures, the PK parameters were adjusted per body weight. The ratio of AUC_{inf}, AUC_{last}, and C_{max} adjusted by body weight in Japanese and Caucasians was 0.973, 0.968 and 1.06, respectively. For East Asian patients with NMOSD (54~61 kg) in Studies SA-307JG and SA-309JG, satralizumab $C_{trough,ss}$ was approximately 18%~27% higher than non-East Asian patients (66~80 kg). The difference in exposure between East Asian and total subjects may attribute to difference in body weight. Based on the exposure-response analysis, the above observed exposure differences were not expected to translate into a clinically relevant impact on the efficacy and safety.

The clinical bridging data were generated based on the Asian subpopulation in the pivotal Phase III studies BN40898 and BN40900. There were a total of 43 East Asian subjects, including 16 Taiwanese subjects, 22 Japanese subjects, and 5 Korean subjects. Asian subjects accounted for 41.0% (34/83) of overall subjects in Study BN40898, 10.5% (10/95) in Study BN40900.

The Asian and non-Asian subpopulations demonstrated comparable efficacy and safety profile with satralizumab treatment in the pivotal studies, however, a slightly increased incidence rate of serious infection was observed in the Asian subpopulation when satralizumab was administered in combination with other immunosuppressants (mainly corticosteroids) [Study BN40898: AEs per 100 patient-year: Asian vs. Non-Asian: 8.64 vs. 1.31]. A risk-management plan (RMP) is required.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy was established and the safety profile was acceptable. Approval of ENSPRYNG® (Satralizumab) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients aged 12 years and older who are anti-aquaporin-4 (AQP4) antibody positive is recommended. Warning of uncertainty regarding safety and efficacy for patients with body weight <40 Kg should be put in label. Considering the potential risk of opportunistic infections, a risk management plan (RMP) is required to ensure that the benefits of the drug outweigh the risks.

3. Post-Marketing Requirements

1. Submit final study report of BN40898 and BN40900 once available.
2. Routine pharmacovigilance along with periodic RMP report.