Taiwan Food and Drug Administration

Assessment Report

Trade Name：銳虎持續性藥效錠 15 毫克 / Rinvoq Extended-Release Tablets 15 mg

Active Ingredient：Upadacitinib

License Number：MOHW-PI 027902

Applicant：瑞士商艾伯維藥品有限公司台灣分公司

Approval Date：2020/07/27

Indication：

治療患有中至重度活動性類風濕性關節炎且對至少一種疾病緩解型抗風濕藥物(DMARDs)無法產生適當治療反應或無法耐受之成人病人。可用於單一療法或與 methotrexate 合併使用。

RINVOQ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).
RINVOQ may be used as monotherapy or in combination with methotrexate.

Background Information

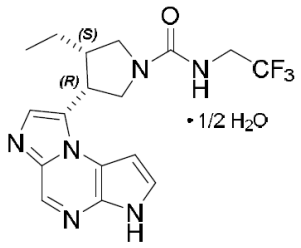
Trade Name	銳虎持續性藥效錠 15 毫克 / Rinvoq Extended-Release Tablets 15 mg
Active Ingredient(s)	Upadacitinib
Applicant	瑞士商艾伯維藥品有限公司台灣分公司
Dosage Form & Strengths	持續性藥效錠 15 毫克
Indication	治療患有中至重度活動性類風濕性關節炎且對至少一種疾病緩解型抗風濕藥物 (DMARDs) 無法產生適當治療反應或無法耐受之成人病人。可用於單一療法或與 methotrexate 合併使用。 RINVOQ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate.
Posology	The recommended dose of upadacitinib is 15 mg once daily.
Pharmacological Category **ATC Code**	L04AA44

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, upadacitinib, is chemically designated as (3*S*,4*R*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-*N*-(2,2,2-trifluoroethyl) pyrrolidine-1-carboxamide hydrate (2:1) and has the following structure:



It is a crystalline white to light brown powder. The molecular formula and the molecular weight are $C_{17}H_{19}F_3N_6O$ • ½ H_2O and 389.38 g/mol, respectively. It is non-hygroscopic. The structure of upadacitinib is confirmed by IR spectrum, mass spectrum, nuclear magnetic

resonance spectrum, elemental analysis, and single crystal X-ray crystallography.

The specification of drug substance includes tests for description, identification, crystal form, assay, impurities, water content, particle size distribution, and microbial limit test.

2.1.2 Drug product

Rinvoq Extended-Release Tablets 15 mg contains 15 mg of anhydrous upadacitinib (15.4 mg of upadacitinib hemihydrate). The excipients used in the drug product comply with the compendial monographs.

Specifications have been presented for Rinvoq Extended-Release Tablets 15 mg and the test items include description, identification, assay, degradation products, water content, dissolution, and uniformity of dosage units. Analytical methods are described and validated.

Stability studies of drug product under long term condition (25 °C/60% RH and 30 °C/75% RH) and accelerated condition (40 °C/75% RH) have been performed.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Upadacitinib is a potent and selective JAK1 inhibitor, demonstrating efficacy in rat models of RA. Peripheral NK cell count is a convenient, mechanistically relevant pharmacodynamic biomarker. Based on JAK1 and JAK2 independent cellular assays and in vivo rat experiments, upadacitinib demonstrated minimal impact on JAK2 at efficacious drug levels.

In terms of safety pharmacology, upadacitinib inhibited the hERG channel with an IC_{50} of 39.5 μg/mL. In a neurobehavioral study, upadacitinib decreased motor activity in rats at the highest oral dose of 100 mg/kg. In a cardiovascular study in conscious dogs, upadacitinib produced a moderate decrease in mean arterial pressure at an oral dose equal to or greater than 1.5 mg/kg and increased heart rate at 5 mg/kg. These effects were produced at plasma concentrations higher than those in relevant clinical studies. No effects were observed in a respiratory study in rats.

2.2.2 Toxicological Studies

Pivotal nonclinical toxicology studies of upadacitinib were conducted in rats and dogs. Upadacitinib-related effects in rats and dogs included decreases in circulating lymphocytes and decreased cellularity of lymphoid tissues as well as suppression of erythropoiesis with resultant decreases in RBC mass and/or reticulocytes. These findings are consistent with the expected effects of inhibition of JAK enzyme activity and the known roles of JAK-dependent cytokines on the immune system. With chronic dosing in dogs, nonclinical findings were

attributed to immunosuppression, and reflective of the pharmacologic properties of upadacitinib. No adverse findings were noted in a chronic rat study and in a chronic dog study at dose levels resulting in exposure 13 and 2 times higher than the proposed clinical dose, respectively.

There is no evidence of genotoxicity, phototoxicity, or carcinogenicity of upadacitinib. The studies in animals have shown reproductive toxicity. Adverse effects attributed to upadacitinib were observed in the rat fertility (increased post-implantation loss and reduced live fetuses per litter), rat EFD (skeletal malformations), and rabbit EFD (cardiac malformations, post-implantation loss, decreased fetal body weights) studies. No adverse findings were noted in the PPND study. Administration of upadacitinib to juvenile rats resulted in pharmacologic effects similar to those observed in adult rats.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Upadacitinib median T_{max} was 2 to 4 hours after administration of the extended-release (ER) formulation and the terminal $t_{1/2}$ ranged from 9 to 14 hours. Upadacitinib C_{max} and AUC were approximately dose-proportional over 7.5-45 mg dose ranges using the ER formulation. Following repeated dosing, steady state was achieved within 4 days with minimal accumulation. High-fat and high-caloric meal increased upadacitinib C_{max} and $AUC_{0\text{-}inf}$ by 39% and 29%, respectively.

Based on population PK analysis, subjects with RA are estimated to have 25% lower CL/F compared to healthy subjects. Upadacitinib is approximately 52% bound to human plasma proteins. For a typical patient with RA with body weight of 74 kg, Vd at steady state is estimated to be 224 L.

Upadacitinib is metabolized by CYP3A4 with a potential minor contribution from CYP2D6. In the mass balance study, approximately 53% and 43% of the administered dose was excreted in feces and urine, respectively. Upadacitinib was eliminated predominantly as the unchanged parent drug in feces (38%) and urine (24%), and approximately 34% of upadacitinib dose was excreted as metabolites.

2.3.2 Interaction Studies

When co-administered with a strong CYP3A4 inhibitor, upadacitinib exposure increased by 75% for $AUC_{0\text{-}inf}$ and 70% for C_{max}. When co-administered with a strong CYP3A4 inducer, upadacitinib exposure decreased by 61% for $AUC_{0\text{-}inf}$ and 51% for C_{max}, which may result in inefficacious concentrations and consequently decrease the efficacy.

From population PK analysis, CYP2D6 metabolic phenotype had no effect on upadacitinib PK, indicating that inhibitors of CYP2D6 have no clinically relevant effect on upadacitinib exposures. The pH modifying medications are not expected to affect upadacitinib plasma exposures based on *in vitro* assessments and population PK analysis. When co-administered with midazolam (a CYP3A4 substrate), caffeine (a CYP1A2 substrate), dextromethorphan (a CYP2D6 substrate), S-warfarin (a CYP2C9 substrate), omeprazole (a CYP2C19 substrate), bupropion (a CYP2B6 substrate), or potential co-administered drugs, there was no clinically relevant effects of upadacitinib on the PK of these co-administered drugs.

2.3.3 Special Populations

Population PK analysis showed that body weight, gender, race, ethnicity, and age did not have a clinically meaningful effect on upadacitinib exposures.

In hepatic impairment study (M13-539), upadacitinib AUC was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function. Upadacitinib C_{max} was similar in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal hepatic function.

In renal impairment study (M13-551), upadacitinib C_{max} remained similar while AUC was 18%, 33% and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In summary, five phase 3, randomized, double-blind studies were evaluated:

- Two monotherapy studies (Study M13-545 and Study M15-555): MTX-naïve subjects were studied in Study M13-545; MTX- inadequate response (IR) subjects were studied in Study M15-555.
- Three add-on studies (Studies M14-465, Study M13-549 and Study M13-542): MTX-IR subjects were studied in Studies M14-465, csDMARD-inadequate response (IR) subjects were studied in Study M13-549 and bDMARD-IR subjects were studied in Study M13-542.

The Studies M13-545 and M15-555 evaluated upadacitinib 15 mg QD and 30 mg QD as monotherapy in MTX-naïve and MTX-IR subjects, respectively. The Phase 3 Study M14-465 evaluated upadacitinib 15 mg QD in combination with background MTX in MTX-IR subjects. The Phase 3 Studies M13-549 and M13-542 evaluated upadacitinib 15 mg QD and 30 mg QD in combination with background csDMARDs in csDMARD-IR and bDMARD-IR

subjects, respectively.

The applicant's primary analyses were different in US FDA and EMA, including ACR20 and CR/LDA based on DAS28 at their efficacy time points. For US FDA version, the primary endpoints are ACR20 for Studies M15-555 (Week 14), M13-549 (Week 12), M13-542 (Week 12), Study M14-465 (Week 12), and ACR50 for Study M13-545 (Week 12). For EU version, clinical Remission (CR) and low disease activity (LDA) based on DAS28 (CRP) are primary endpoints: CR in Study M13-545 (Week 24) and Study M14-465 (Week 12), LDA in M13-549 (Week 12), Study M15-555 (Week 14), M13-542 (Week 12).

- In the monotherapy studies :
  - ***Study M13-545***: the primary endpoint for US FDA version was the proportion of subjects achieving ACR50 response at Week 12. The primary endpoint for EMA version was the proportion of subjects achieving CR at Week 24.Statistically significant improvements in the upadacitinib 15 mg and 30 mg groups compared with the MTX group were observed for all pre-specified primary endpoints at Week 12 or Week 24.
  - ***Study M15-555***: the primary endpoint for US FDA version was the proportion of subjects achieving ACR20 at Week 14. The primary endpoint for EMA version was the proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 14. Statistically significant improvements in the upadacitinib 15 mg and 30 mg groups compared with the cMTX group were observed for all pre-specified primary endpoints at Week 14.
- In add-on studies:
  - ***Study M13-549***: the primary endpoint for US FDA version was the proportion of subjects achieving ACR20 response at Week 12. The primary endpoint for EMA version was the proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12. Statistically significant improvements in both the upadacitinib 15 mg and 30 mg groups compared with the placebo group were observed for all pre-specified primary endpoints.
  - ***Study M14-465***: the primary endpoint for US FDA version was the ACR20 response at Week 12. The primary endpoint for EMA version was the proportion of subjects achieving CR based on DAS28 (CRP) < 2.6 at Week 12. At Week 12, treatment with upadacitinib 15 mg QD demonstrated a statistically significantly improvement of subjects achieving an ACR20 response and CR based on DAS28 (CRP) < 2.6 compared with the placebo group.
  - ***Study M13-542***: the primary endpoint for US FDA version was the proportion of subjects achieving ACR20 response at Week 12. The primary endpoint for EMA version was the proportion of subjects achieving LDA based on DAS28 (CRP) ≤

3.2 at Week 12. Statistically significant improvements in both the upadacitinib 15 mg and 30 mg groups compared with the placebo group were observed for all pre-specified primary endpoints at Week 12.

Dose selection:

There was only slight treatment difference between upadacitinib 15mg and 30mg group. In other words, there was no obvious incremental effect for dose increment to 30mg. Higher incidence of AEs, especially laboratory data abnormality, was observed for upadacitinib 30mg group than upadacitinib 15mg group. It's reasonable to propose upadacitinib 15mg rather than 30mg as the proper dose.

Monotherapy and combination therapy

In general, both versions of primary analyses were supportive of the proposed upadacitinib 15 mg QD in the monotherapy or in combination therapy for subjects who had inadequate response to MTX, csDMARD, or bDAMRD.

Efficacy data on upadacitinib with non-MTX-csDMARD are limited due to small sample size. Safety data for this subgroup showed numerically more AEs and SAEs than upadacitinib with MTX population. Considering the insufficiency of efficacy information and uncertainty of safety profile, the combination therapy is restricted to upadacitinib with MTX.

2.4.2 Safety Results

The most frequent AEs in upadacitinib 15 mgQD group were urinary tract infection, upper respiratory tract infection, nasopharyngitis, nausea, headache, and bronchitis. Serious infections, malignancy, gastrointestinal perforations, thrombosis, cytopenia (lymphopenia, neutropenia, anemia), and lipid elevations are important safety signals for drugs in this class. Upadacitinib showed similar safety signals to other JAK inhibitors. In the upadacitinib clinical trials, the incidence of these important AEs were generally consistent with other JAK inhibitors. A dose-dependent lipid increase was observed with upadacitinib treatment. Generally, the safety profile of upadacitinib 15mg dose is acceptable.

2.5 Bridging Study Evaluation

The effect of ethnic factor on upadacitinib PK was evaluated via cross study comparison and population PK analysis. Upadacitinib dose-normalized exposure parameters following multiple doses administration using ER formulation in healthy Chinese subjects (Study M15-558, 15 mg, 30 mg, and 45 mg QD) were compared to Western subjects (Study M14-680, 15 mg and 30 mg QD). Upadacitinib dose-normalized C_{max} and AUC_{0-24} at steady-state in Chinese subjects were 32% and 26% higher, respectively, compared to Western subjects. A population PK analysis which included a total of 4,170 subjects (96%

with RA, and 4% healthy) was conducted. Asian subjects in this analysis were from Japan, China, Hong Kong, Taiwan, and Korea. The results indicated that race had no significant effect on upadacitinib PK parameters. Model-estimated upadacitinib exposures (C_{max}, C_{ave}, and C_{trough}) at steady-state are comparable between Asian and non-Asian subjects with RA. Overall, race is not a sensitive factor on upadacitinib PK.

There were 243 East Asian subjects enrolled in five pivotal trials during upadacitinib development program. These Asian subjects mainly came from Korea, Taiwan, Hong Kong, China, and Japan. The Asian subjects presented similar baseline demographic and disease characteristics to non-Asian subjects. The efficacy results were also similar between Asian and non-Asian subjects, in terms of ACR20 response, ACR50 response, and CR/LDA based on DAS28 (CRP). The common AEs on Asian subjects were urinary tract infection, upper respiratory tract infection, nasopharyngitis, nausea, AST elevation, ALT elevation, and CPK elevation. The incidence of herpes zoster and CPK elevation were higher in Asian population than non-Asian. Generally, the efficacy and safety data on Asian population and non-Asian population were comparable. The ethnic difference of upadacitinib in RA treatment is insignificant.

In summary, bridging study for upadacitinib in RA treatment could be waived.

2.6 Conclusion

The overall benefit-risk of upadacitinib is favorable. Based on the review of data on CMC, non-clinical pharmacology, clinical pharmacology, to approve upadacitinib for following indication is suggested:

Indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have inadequate response to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

RINVOQ may be used as monotherapy or in combination with methotrexate.

3. Post-Marketing Requirements

Post marketing risk management plan is required to mitigate the risk of serious infection, opportunistic infection, tuberculosis reactivation, virial hepatitis reactivation, malignancy, thrombosis, GI perforation, lipid profile abnormality, and liver enzyme abnormality.