Taiwan Food and Drug Administration

Assessment Report

Trade Name：

吉炎可膜衣錠 100 毫克 / Jyseleca 100 mg Film-Coated Tablets
吉炎可膜衣錠 200 毫克 / Jyseleca 200 mg Film-Coated Tablets

Active Ingredient：Filgotinib maleate

License Number： MOHW-PI 028208
MOHW-PI 028209

Applicant：香港商吉立亞醫藥有限公司台灣分公司

Approval Date： 2022.01.03

Indication：

可用於單一療法或與 methotrexate 合併使用，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。

Jyseleca 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). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX).

Background Information

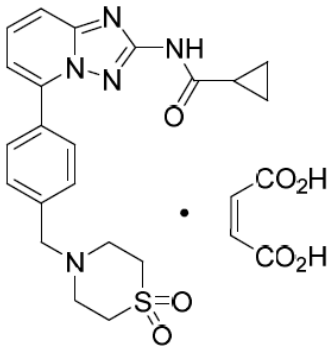
Trade Name	吉炎可膜衣錠 100 毫克 / Jyseleca 100 mg Film-Coated Tablets 吉炎可膜衣錠 200 毫克 / Jyseleca 200 mg Film-Coated Tablets
Active Ingredient(s)	Filgotinib maleate
Applicant	香港商吉立亞醫藥有限公司台灣分公司
Dosage Form & Strengths	膜衣錠 100 mg、200mg
Indication	可用於單一療法或與 methotrexate 合併使用，治療患有中至重度活動性類風濕性關節炎且對至少一種疾病緩解型抗風濕藥物(DMARDs)無法產生適當治療反應或無法耐受之成人病人。 Jyseleca 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). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX).
Posology	用於治療類風濕性關節炎成年病人的建議劑量為 200 毫克每日一次。 The recommended dose of filgotinib for adult patients with rheumatoid arthritis is 200 mg once daily.
Pharmacological Category **ATC Code**	L04AA45

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The chemical name of filgotinib maleate is *N*-(5-{4-[(1,1-dioxidothiomorpholin-4-yl)methyl]phenyl}[1,2,4]triazolo[1,5-a]pyridin-2-yl)cyclopropanecarboxamide (2*Z*)- but-2-enedioate. Filgotinib maleate is a white to off-white solid. The molecular formula and the molecular weight for filgotinib maleate are $C_{21}H_{23}N_5O_3S•C_4H_4O_4$ and 541.6 g/mol, respectively. It has the following structure:



The chemical structure of filgotinib maleate is elucidated by elemental analysis, mass spectroscopy, infrared spectrum, ultraviolet-visible spectrum, ^{1}H-NMR and ^{13}C-NMR.
The specification for filgotinib maleate includes tests for appearance, identification, insoluble particulates, water content, maleic acid content, assay, impurities, residual solvents, organic volatile impurities and particle size.

2.1.2 Drug product

The drug product is presented as film-coated tablets containing filgotinib maleate as drug substance, equivalent to 100 mg or 200 mg of filgotinib free base. The specifications for the excipients are adequate.

The specification for the drug product includes tests for appearance, identification, water content, assay, degradation products, uniformity of dosage units, dissolution and microbiological examination. Analytical methods are described and well validated.

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

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Filgotinib is a potent and selective ATP competitive inhibitor of JAK1. Data that support this conclusion include the following: 1) filgotinib binds JAK1 with high affinity; 2) filgotinib directly inhibited the JAK1 kinase activity; 3) in binding assays, kinase enzyme assays, and cell-based assays, filgotinib showed selective binding and inhibition of JAK1 compared to other kinases and receptors tested. The disproportionate human metabolite, GS-829845, exhibited the same *in vitro* and *in vivo* pharmacologic efficacy profile as filgotinib but lesser potency. GS-829845 did not show any meaningful inhibition of off-target kinases or receptors. In multiple rat CIA models, filgotinib dosed alone or combined with GS-829845 demonstrated efficacy in reducing clinical score, paw swelling, anti-Type II collagen antibody titers, the Larsen score (for bone erosion), and joint histopathology. Filgotinib and GS-829845 did not affect the central nervous system and respiratory function in rats at doses up to 180 mg/kg, the

highest dose evaluated. In the *in vitro* hERG assay, a low liability for delayed rectifier potassium current (Ikr) inhibition was seen with both filgotinib and GS-829845. In the cardiovascular study, oral administration of filgotinib was not associated with any adverse effects on hemodynamic, ECG parameters, or body temperature. GS-829845 was associated with slightly increased heart rate and decreased mean blood pressure at 100 mg/kg. The potential clinical relevance of increased heart rate and a slight decrease in blood pressure in dogs due to GS-829845 is unknown; however, these parameters were monitored in clinical trials with filgotinib and were not impacted.

2.2.2 Toxicological Studies

Repeated-dose toxicity studies were conducted in rats and dogs up to 26-week and 39-week, respectively. The primary target tissues identified for filgotinib were the lymphoid tissues and bone marrow, which were expected based on the pharmacology of JAK inhibition.

Filgotinib-related findings were observed in the male reproductive organs of rats and dogs and the incisor teeth of rats only. The dog was the most sensitive species for male reproductive organs findings. Effects on the male reproductive organs were not seen following oral administration of GS-829845. The severity of the male reproductive organs effects was dose-dependent. Effects on the lymphoid system were fully reversible. Testicular toxicity demonstrated partial reversibility; however, sperm counts remained low.

The metabolite GS-829845-related findings were similar to those of filgotinib; however, no testicular toxicity was noted following administration of GS-829845. Filgotinib and GS-829845 were both not genotoxic *in vitro* and *in vivo*. No treatment-related carcinogenicity was observed in the 6-month CB6F1-TgrasH2 transgenic mouse study at doses up to 150 mg/kg/day. In the 2-year rat carcinogenicity study, filgotinib treatment resulted in an increase in incidence and decrease in latency of benign Leydig cell tumors in testis at the highest dose of 45 mg/kg/day. Literature has demonstrated that benign Leydig cell tumors are considered to be of low relevance to humans. Administration of GS-829845 in the 26-week rat study did not result in increases in luteining hormone (LH) at any dose administered, and Leydig cell tumors were not observed following administration of GS-829845.

GS-829845 demonstrated a lack of carcinogenic potential in a 26-week study in CB6F1-TgrasH2 mice and a 2-year bioassay in SD rats at exposures that exceed human exposures at the therapeutic dose. Filgotinib did not affect female fertility, but impaired fertility was observed in male rats. GS-829845 did not have any effects on fertility parameters in either male or female rats. In rats and rabbits, filgotinib and GS-829845 caused visceral malformations in eyes, lung, cardiovascular, urinary system, and brain, skeletal malformations (primarily vertebral anomaly) and teratogenicity at all doses, with an increased number of early and late resorptions were noted together with a decreased number of viable fetuses. There were

no filgotinib-related adverse findings in the rat PPND study.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following oral administration, filgotinib was absorbed quickly and its median peak plasma concentration was observed 2 to 3 hours postdose after multiple dosing; the median peak plasma concentrations of its primary metabolite GS-829845 were observed 5 hours postdose after multiple dosing. Filgotinib and GS-829845 exposures (AUC) and C_{max} were similar in healthy adult subjects and patients with rheumatoid arthritis. Filgotinib and GS-829845 exposures (AUC) and C_{max} were dose-proportional over the therapeutic dose range. Steady-state concentrations of filgotinib were achieved in 2 - 3 days with negligible accumulation after once daily administration. Steady-state concentrations of GS-829845 were achieved in 4 days with approximately 2-fold accumulation after once daily dosing of filgotinib.

There were no clinically relevant differences in exposures when filgotinib was administered with a high-fat or low-fat meal as compared to a fasted state. Filgotinib can be administered with or without food.

Filgotinib and GS-829845 binding to human plasma proteins was low (55 - 59% and 39 - 44% bound, respectively). The blood-to-plasma ratio of filgotinib ranged from 0.85 to 1.1 indicating no preferential distribution of filgotinib and GS-829845 into blood cells. Filgotinib and GS-829845 are substrates of the P-gp transporter.

Filgotinib was extensively metabolized with approximately 9.4% and 4.5% of an orally administered dose recovered as unchanged filgotinib in urine and faeces, respectively. Filgotinib is primarily metabolized by CES2, and to a lesser extent by CES1. Both CES2 and CES1 form GS-829845, an active circulating metabolite that is approximately 10-fold less potent than the parent compound. In a clinical pharmacology study, filgotinib and GS-829845 accounted for the majority of radioactivity circulating in plasma (2.9% and 92%, respectively). No other major metabolites were identified. As both filgotinib and GS-829845 contribute to efficacy, their exposures were combined into a single parameter, AUC_{eff}. AUC_{eff} is the sum of the AUC of filgotinib and GS-829845, corrected for their respective molecular weights and potencies.

Approximately 87% of the administered dose was eliminated in the urine as filgotinib and its metabolites, while about 15% of the dose was eliminated in the faeces. GS-829845 accounted for approximately 54% and 8.9% of dose recovered in urine and faeces, respectively. The mean terminal half-lives of filgotinib and GS-829845 were approximately 7 and 19 hours, respectively.

2.3.2 Interaction Studies

In vitro studies indicated that filgotinib and GS-829845 were not inhibitors of OCT1, BSEP, OAT1, OAT3 or OAT4 at clinically relevant concentrations. *In vitro* data indicated that filgotinib and GS-829845 had the potential to inhibit OATP1B1, OATP1B3, OCT2, MATE1 (filgotinib only), and MATE-2K. While *in vitro* studies indicated that filgotinib was not an inhibitor of P-gp or BCRP, the results for GS-829845 were inconclusive and i*n vivo* inhibition of P-gp or BCRP by GS-829845 could not be excluded.

In vivo studies indicated that filgotinib was not considered a clinically relevant inhibitor or inducer of CYP3A, and it had no effect on the PK of ethinyl estradiol (EE)/levonorgestrel (LEVO). Filgotinib and GS-829845 were also not considered clinically relevant inhibitors of OCT2, MATE1, or MATE-2K.

In vivo studies, co-administration of gastric acid-reducing agents (ARAs) with filgotinib indicated that filgotinib exposure was not affected by gastric ARAs. Coadministration of P-gp inhibitor or P-gp inducer with filgotinib also resulted in a non-clinically relevant changes in the effective exposures (AUC_{eff}).

2.3.3 Special Populations

Bodyweight, gender, race, and age did not have a clinically relevant effect on the pharmacokinetics (AUC) of filgotinib or GS-829845. There were no clinically relevant differences in mean filgotinib and GS-829845 exposures (AUC and C_{max}) between older patients aged ≥ 65 years relative to adult patients aged < 65 years.

The pharmacokinetics of filgotinib and GS-829845 were unaffected in subjects with mild renal impairment (CrCl 60 to < 90 mL/min). Increases in exposures (AUC) of filgotinib, GS-829845, and combined AUC_{eff} (≤ 2-fold), were observed in subjects with moderate renal impairment (CrCl 30 to < 60 mL/min). In subjects with severe renal impairment (CrCl 15 to < 30 mL/min), filgotinib exposure (AUC) increased by 2.2-fold and GS-829845 exposure significantly increased by 3.5-fold leading to a 3-fold increase in AUC_{eff}. The pharmacokinetics of filgotinib has not been studied in subjects with end stage renal disease (CrCl < 15 mL/min).

No clinically relevant changes in the exposures (AUC) of filgotinib and GS-829845 individually, or their combined exposure (AUC_{eff}), were observed in subjects with moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of filgotinib has not been studied in subjects with severe hepatic impairment (Child-Pugh C)

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The sponsor provided two pivotal studies (Study [FINCH1] and [FINCH2]) and two supportive studies (Study [FINCH3] and [DARWIN2]) to support the efficacy of filgotinib for the claimed indication. It was noted that the study population in [FINCH3] and treatment background in [DARWIN2] are different from the claimed indication.

Study [FINCH1] (pivotal)

The study enrolled RA subjects with an inadequate response to MTX. Study treatment was administered on top of each subject's stable dose of MTX. The primary endpoint is ACR20 at Week 12. The ACR20 was 364/475 (76.6%) in filgotinib 200mg, 335/480 (69.8%) in filgotinib 100mg, 229/325 (70.5%) in adalimumab and 237/475 (49.9%) in placebo group. The difference between filgotinib 200mg and placebo group was 26.7%, 95% CI (20.6%, 32.8%), $p < 0.001$. The difference between filgotinib 100mg and placebo group was 19.9%, 95% CI (13.6%, 26.2%), $p < 0.001$.

Study [FINCH2] (pivotal)

The study enrolled RA subjects with an inadequate response to biological disease-modifying antirheumatic drugs (bDMARDs). Study treatment was administered on top of each subject's stable dose of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). The primary endpoint is ACR20 at Week 12. The ACR20 was 97/147 (66%) in filgotinib 200mg, 88/153 (57.5%) in filgotinib 100mg and 46/148 (31.1%) in placebo group. The difference between filgotinib 200mg and placebo group was 34.9%, 95% CI (23.5%, 46.3%), $p < 0.001$. The difference between filgotinib 100mg and placebo group was 26.4%, 95% CI (15.0%, 37.9%), $p < 0.001$.

Study [FINCH3] (supportive)

The study enrolled MTX-naïve subjects with RA. Study treatment was administered with or without MTX. The primary endpoint is ACR20 at Week 24. The ACR20 was 337/416 (81%) in filgotinib 200mg + MTX, 166/207 (80.2%) in filgotinib 100mg + MTX, 164/210 (78.1%) in filgotinib 200mg monotherapy and 297/416 (71.4%) in MTX monotherapy group. The difference between filgotinib 200mg + MTX and MTX monotherapy group was 9.6%, 95% CI (3.6%, 15.6%), $p < 0.001$. The difference between filgotinib 100mg + MTX and MTX monotherapy group was 8.8%, 95% CI (1.5%, 16.1%), $p = 0.017$. The difference between filgotinib 200mg monotherapy and MTX monotherapy group was 6.7%, 95% CI (-0.7%, 14.1%), $p = 0.058$.

Study [DARWIN2] (supportive)

This is a phase 2 dosing finding study. The study enrolled RA subjects with an inadequate response to MTX. Subjects currently treated with DMARDs or bDMARDs would be

excluded form the trial. The ACR20 is 50/69 (72.5%) in filgotinib 200mg, 46/70 (65.7%) in Filgotinib 100mg, 48/72 (66.7%) in filgotinib 50mg and 21/72 (29.2%) in placebo group. The ACR50 was 30/69 (43.5%) in filgotinib 200mg, 26/70 (37.1%) in filgotinib 100mg, 25/72 (34.7%) in filgotinib 50mg and 8/72 (11.1%) in placebo group.

2.4.2 Safety Results

Among pooled patients participating in phase 2/3 randomized controlled trials treated up to Weeks 12 and 24, the safety profile was similar between the filgotinib groups and the placebo group. In general, exposure-adjusted incidence rate of AEs for both filgotinib dose groups were similar to those of placebo, with exceptions of nausea, hypertension, and upper respiratory tract infection. The risks of filgotinib was comparable to the known risks related to other JAK inhibitor.

There were 29 TEAEs potentially related to male reproductive safety in 13 men(1.8%) treated with filgotinib in the Pooled Phase 2/3 Safety Population. Most of these events (27 events in 11 men) were reproductive hormones change and resolved over time. The change in hormones were related to changes in protocol mandated measures of specific reproductive hormones (decreases in free/total testosterone, increases in follicle stimulating hormone [FSH], and a single increase and decrease in luteinizing hormone [LH]). The majority of AEs identified occurred in the long-term Phase 2 open-label Study GLPG0634-CL-205 that incorporated protocol-mandated measures of male reproductive hormones. The majority of these events resolved over time. Moreover, measures of reproductive hormones in the broader Phase 2 study population in which these subjects participated demonstrate no clinically relevant changes in mean values of reproductive hormone measures. Furthermore, the long-term open-label extension study suggests long term stability of these reproductive hormones.In the integrated data from the randomized placebo-controlled studies to evaluate the potential effect of filgotinib (200 mg) treatment on male semen parameters, no meaningful difference was observed across the filgotinib and placebo treatments in the proportion of subjects who displayed a ≥ 50% decrease from baseline in sperm concentration at Week 13. The long-term follow up for subjects with decreased sperm concentration is ongoing.

2.5 Bridging Study Evaluation

Filgotinib and GS-829845 exposure (Cmax and AUC) was comparable between healthy Japanese and White subjects following multiple-dose administration. Population PK analysis also suggested that race (Taiwanese versus Non-Taiwanese, Asian versus Non-Asian) was not found to be a significant covariate on filgotinib and GS-829845 PK. Overall, there was no significant race/ethnicity difference in filgotinib and GS-829845 PK.

The sponsor provided Asian subgroup analyses in Study 0301, 0302 and 0303 for bridging study evaluation. Demographics and baseline disease characteristics were generally balanced between Asians and Non-Asians in the 3 parent Phase 3 studies. Lower body weight and BMI was noted in Asians comparing to Non-Asians. Efficacy results evaluating clinical response, low disease activity (LDA), and remission were generally consistent between Asian and non-Asian subjects in the MTX-IR (Study 0301), bDMARD-IR (Study 0302), and MTX naïve populations (Study 0303). The safety profile between the treatment group and the placebo group in Asians were similar to the non-Asians.

No obvious clinical impact caused by ethnicity was observed. Bridging study was waived.

2.6 Conclusion

Jyseleca® (filgotinib) for treating adults with moderate to severe rheumatoid arthritis demonstrated a favorable risk-benefit profile with adequate evidence to recommend regular approval.

Jyseleca® 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). Jyseleca® may be used as monotherapy or in combination with methotrexate (MTX).

A risk management plan (RMP) is required to ensure that the benefits of the drug outweigh the risks.

3. Post-Marketing Requirements

- Submit the updated data and final report of GS-US-418-4279(MANTA), GLPG0634-CL-227(MANTA-RAy) studies while available.
- Submit the final report of GS-US-417-0304、GLPG0634-CL-205 studies after study completion.