Taiwan Food and Drug Administration

Assessment Report

Trade Name： **Brilinta Film-coated Tablets 90mg**

Active Ingredient：Ticagrelor

License Number：DOH-PI 025691

Applicant：AstraZeneca Taiwan

Approval Date：101/07/30

Indication ： Brilinta, co-adminstered with aspirin, can reduce atherothrombotic events in patients with acute coronary syndrome (includes unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction). Compared with Clopidogrel, Brilinta can reduce cardiovascular death and myocardial infarction, but there was no difference in stroke. In patients treated with PCI, Brilinta also reduces the rate of stent thrombosis. When Brilinta used in combination with aspirin, avoid maintenance doses of aspirin above 100mg daily.

1. Background Information

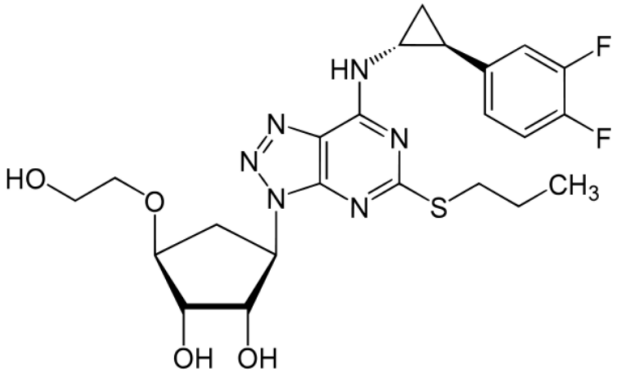
Trade Name	Brilinta Film-coated Tablets 90mg
Active Ingredient(s)	Ticagrelor
Applicant	**AstraZeneca Taiwan**
Dosage Form & Strengths	Film-coated Tablets 90 mg
Indication	”Brilinta, co-adminstered with aspirin, can reduce atherothrombotic events in patients with acute coronary syndrome(includes unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction). Compared with Clopidogrel, Brilinta can reduce cardiovascular death and myocardial infarction, but there was no difference in stroke. In patients treated with PCI, Brilinta also reduces the rate of stent thrombosis. When Brilinta used in combination with aspirin, avoid maintenance doses of aspirin above 100mg daily.
Posology	N/A
Pharmacological Category **ATC Code**	

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, ticagrelor, is chemically designated as (1S,2S,3R,5S)-3-[7-{ [(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino }-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol， has the following structure:



The structure contains six chiral centers and all stereo centers are controlled in the proposed starting materials which configurations are same as those of drug substance to yield specific enantiomer. It has four polymorphs; batch analyses confirm that the proposed polymorphic form is not conversion to other crystalline forms. The empirical formula and the molecular weight are C23H28F2N6O4S and 522.57 g/ mol, respectively. The structure of ticagrelor is confirmed by UV,IR, mass, nuclear magnetic resonance spectrum (1H-NMR, 13C-NMR, 19F-NMRand 15N-NMR)and single-crystal X-ray crystallography. Adequate information on characterization of the drug substance has been provided.

The specification includes tests for appearance, identity, assay, structural related substances, potential genotoxic impurity, residual solvents, heavy metals, catalytic residues, sulphated ash, particle size and polymorphic form. The results of pre-clinical and clinical batches demonstrate minimal inter-batch variability and fully supportive of the justification of specification

2.1.2 Drug product

Ticagrelor drug product (Brilinta) in 90 mg is a round, biconvex, yellow film-coated tablet. The excipients except for ferric oxide used in the formulation are all compendial materials and compatible with ticagrelor drug substance. Excipients are neither novel nor of animal origin. The manufacturing process has been developed and optimized by the principles described in ICH Q8. Critical parameters affecting the tablet performance have been established.

Adequate release and shelf-life specification have been presented for the Brilinta tablet and test items include description, identification, assay, degradation products, content uniformity and dissolution. The specification is consistent with the principle of ICH Q6A guidance. The results of batch analysis are all complied with the specification. For non-pharmacopoeia methods, validations are performed and accepted in terms of linearity, accuracy, repeatability, intermediate precision and robustness.

Primary stability studies under long-term(25℃/60% RH and 30℃/75% RH)and accelerated conditions (40℃/75% RH) have been carried out. The products are packaged in the container closure system intended for marketing. Up to 24months of long-term and 6 months of accelerated stability data are submitted. The available results showed that water content is slightly increased, but others show no significant changes at both conditions. The shelf life of Brilinta®90 mg tablets can be granted for 24 months under the storage condition of 30℃.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Ticagrelor binds at a separate P2Y12 sub-receptor that non-competitively blocks

ADP activation, which ultimately leads to thrombin generation and platelet aggregation, through inactivating the receptor, this reversible binding leaves the receptor intact. A comprehensive program of *in vivo* and *in vitro* non-clinical studies has been conducted to evaluate the safety and toxicological profile of ticagrelor in support of its administration to humans.

2.2.2 Toxicological Studies

Consistent observations across species in repeat dose studies are seen primarily in the gastrointestinal tract, but were inconsistent with respect to the location, severity, and type of the observations. Indications of subclinical bleeding were also observed across species. Increased liver weight at high doses occurred in rodents. In rats, this was accompanied by centrilobular hypertrophy and induction of cytochrome P450 liver enzymes. Adrenal weights increased at higher doses in the repeat dose studies in rodents, and were reversible upon withdrawal of treatment. The results from the reproductive toxicity studies do not indicate reproductive risk to the fetus, suckling neonate or to adults at tolerated exposures. Ticagrelor and the active metabolite AR-C124910XX do not demonstrate any genotoxic potential. Ticagrelor was not carcinogenic in the male or female mouse or male rat. In female rats at the high dose used in the carcinogenicity study, a change in tumor spectrum was seen, notably an increase in the incidence of uterine tumors, a reduction in mammary tumors, and a reduction in combined anterior pituitary tumors and hyperplasias. These observations are considered to be the result of a prolonged pattern of hormonal imbalance. The tumor effects seen in the rat would not be expected in primates，including humans, leading to the conclusion that ticagrelor does not represent a carcinogenic risk to man. A modest increase in the incidence of liver tumors in high dose females occurred, reflecting a modest enzyme induction response. The observation of a slight increase in hepatic adenomas was considered not to be relevant for humans because the incidence was low, occurred at the high dose in females only, and they are considered secondary to the adaptive hepatic enzyme induction response.

In conclusion, the technical data submitted by sponsor is acceptable. This NDA (Brilinta, ticagrelor 90 mg) is recommended to be approved from the preclinical pharmacological and toxicological point of view.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following oral administration, ticagrelor was rapidly absorbed. Ticagrelor showed linear pharmacokinetics and the bioavailability was approximately 36%. The effect of high-fat food on ticagrelor and its active metabolite, AR-C124910XX, was not significant. Therefore, ticagrelor could be administered with or without food. The

steady-state volume of distribution of ticagrelor is 87.5 L with a high protein binding rate (>99.7%). CYP3A4 is the major enzyme responsible for ticagrelor metabolism, and the formation of AR-C124910XX. The systemic exposure of active metabolite, AR-C124910XX, is around 30%~40% of ticagrelor exposure. The total recovery of radioactivity was 84.3%, including 57.8% in feces and 26.5% in urine. The unchanged form of ticagrelor and AR-C124910XX are 0.02% and 0.04% of the dose in urine. The mean half-life of ticagrelor and its active metabolite was 6.9 hr and 8.6 hr, respectively.

2.3.2 Interaction Studies

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Ticagrelor was not an inhibitor of CYP1A2, 2B6, 2C8, 2C19, and 2E1.

The co-administration with ticagrelor and CYP3A4 inhibitor and inducer should be avoided. Avoid simvastatin and lovastatin doses greater than 40 mg. Monitor digoxin levels with initiation of or any change in ticagrelor therapy. No significantly drug-drug interaction was observed with moderate CYP3A4 inhibitor, atorvastatin, levonorgestrel, ethnyl estradiol, tolbutamide, desmopressin, heparin and enoxaparin.

2.3.3 Special Populations

Age, gender, body weight, race, renal impairment and mild hepatic impairment did not significantly affect pharmacokinetic parameters of ticagrelor. It should be cautioned when given ticagrelor to patients with moderate hepatic impairment. Ticagrelor is contraindicated to patients with severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

One active-controlled Phase III study (PLATO) was reviewed to evaluate the efficacy of Brilinta (ticagrelor) 90 mg indicated for prevention of thrombotic events (cardiovascular [CV] death, myocardial infarction [MI] and stroke) in patients with non-ST or ST elevation acute coronary syndromes (ACS). In the study, eligible patients were randomized in a 1:1 ratio to receive ticagrelor 90 mg twice a day (n=9333) or clopidogrel 75 mg once daily (n=9291), in combination with acetylsalicylic acid (ASA). The primary efficacy endpoint was the composite of first occurrence of CV death, MI (excluding silent MI), or stroke.

Study PLATO demonstrated that Brilinta was significantly superior to clopidogrel in reducing the risk of the primary composite event (CV death, MI [excluding silent MI] and stroke) with HR (hazard ratio) of 0.84 (95% CI= [0.77, 0.92], p=0.0003). Brilinta, compared to clopidogrel, significantly reduced the risk of CV death (HR=0.79, 95%

CI= [0.69, 0.91]; p=0.0013) and of MI (excluding silent MI) (HR=0.84, 95% CI= [0.75, 0.95]; p=0.0045), but not that of stroke (HR=1.17, 95% CI= [0.91, 1.52]; p=0.2249). Brilinta also resulted a significantly reduced risk of all-cause mortality (HR=0.78, 95% CI= [0.69, 0.89]; p=0.0003), compared to clopidogrel. Among 11289 patients with PCI (percutaneous coronary intervention) during PLATO, there was a lower risk of stent thrombosis than with clopidogrel (HR=0.67, 95% CI= [0.50, 0.91]; p=0.0091).

The PLATO protocol did not limit the daily aspirin dose. Further analysis with regard to aspirin dosage showed that overall results favored Brilinta when used with low maintenance doses (≦100mg) of aspirin.

In summary, the submitted data provided sufficient evidence to support the efficacy of Brilinta (ticagrelor) for the claimed indication.

2.4.2 Safety Results

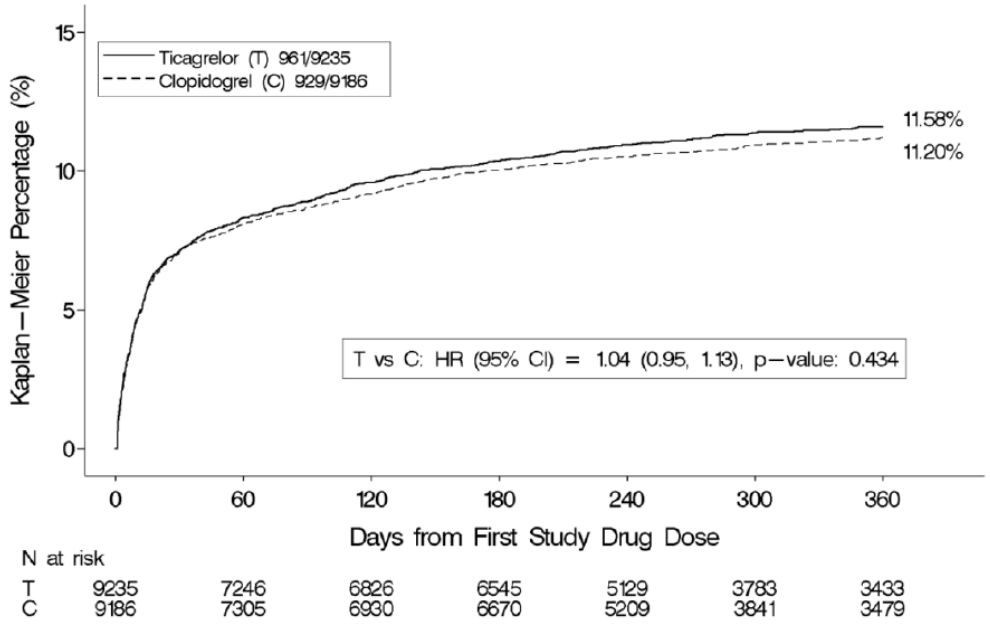
BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

With regard to bleeding, PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding
- Major bleed-other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding.
- Minimal bleed. All others not requiring intervention or treatment

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI (percutaneous coronary intervention), CABG (coronary artery bypass graft), and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1. Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days. BRILINTA was associated with slightly higher risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

Table 1. Non-CABG related bleeds (KM%)

	Brilinta N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were similar for BRILINTA and clopidogrel.

Table 2. CABG bleeds (KM%)

	Patients with CABG	
	Brilinta N=770	Clopidogrel N=814
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel.

Table 3 lists non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more in either group. Dyspnea was reported in 13.8% of patients treated with BRILINTA and in 7.8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment

Table 3. Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	Brilinta N=9235	Clopidogrel N=9186
Dyspnea	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Backpain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

* Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Overall, the safety of BRILINTA for claimed indication is acceptable.

2.5 Bridging Study Evaluation

Ticagrelor is administered by oral route. Ticagrelor has a linear PK profile in the dose range from 50 to 300 mg in healthy subjects and patients. It is not a drug with narrow therapeutic range and not a prodrug. CYP3A4 contributes for majority of metabolism and is responsible to form the active metabolite, AR-C124910XX. The inter-subject variation in bioavailability is moderate. Food does not significantly affect the pharmacokinetics of ticagrelor. There are significantly systemic exposure difference between Japanese, Chinese, and Caucasian. Due to the exposure difference of active metabolite between Japanese, Chinese and Caucasian following the administration of 90mg ticagrelor. The exposure difference of active metabolite between Chinese and Caucasian is up to 36-50%(not corrected by body weight). The impact of differences in clinical should be judged. Considering the differences between Asian and non-Asian populations is shown, no additional pharmacokinetic study is required in Taiwanese from PK perspective.

In the pivotal study “PLATO”, the overall population consisted of 18624 subjects which included 1056 Asians. With regard to efficacy and safety, the results were similar between Asians and overall population. However, the number of Taiwan subjects was relative small so it was difficult to perform adequate analyses.

2.6 Conclusion

The submitted CMC, PT, PK, clinical efficacy and safety data was acceptable. Therefore, Brilinta is approved with the following indication ”Brilinta, co-adminstered with aspirin, can reduce atherothrombotic events in patients with acute coronary syndrome(includes unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction). Compared with Clopidogrel, Brilinta can reduce cardiovascular death and myocardial infarction, but there was no difference in stroke. In patients treated with PCI, Brilinta also reduces the rate of stent thrombosis. When Brilinta used in combination with aspirin, avoid maintenance doses of aspirin above 100mg daily.

3. Post-Marketing Requirements

A Phase IV commitment study should be conducted.