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Human Medicines Division

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

Revolade

eltrombopag

Procedure no: EMEA/H/C/001110/P46/032

Note

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

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1. Introduction

On 12 April 2021, the MAH submitted a completed study including a subset of paediatric patients (Study CETB115B1401) for Revolade (eltrombopag), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Only 33 of 2019 total subjects in the safety analysis set of study CETB115B1401 were between 1 and 18 years.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

Eltrombopag is an orally bioavailable, small molecule thrombopoietin receptor agonist, approved for marketing in the EU through the centralised procedure on 15th March 2010.

Eltrombopag is currently indicated in the paediatric and adult population for the treatment of patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

Pursuant to Article 7 of Regulation (EC) No 1901/2006, as amended, the application included an EMA Decision on the agreement of a paediatric investigation plan (PIP) for the condition ITP, which included a waiver in all subsets of the paediatric population from birth to less than 1 years of age (P/0167/2016; EMEA-000170-PIP01-07-M04). All studies/measures agreed in this PIP were conducted in accordance with the PIP decision (EMEA-C-000170-PIP01-07-M03).

In accordance with Article 46 of the regulation (EC) No 1901/2006, Novartis Pharma AG hereby submits to the EMA a final study report for study CETB115B1401. This study was performed in Japan to meet a regulatory requirement of the Pharmaceuticals and Medical Devices Agency (PMDA) for market authorization (post-approval measure).

The MAH stated that study CETB115B1401 "Drug-use Results Surveillance of Revolade Tablets (Chronic Idiopathic Thrombocytopenic Purpura)" is a stand alone study. As such, a line listing is not provided.

1.2. Information on the pharmaceutical formulation used in the study

Two pharmaceutical formulations of eltrombopag for oral administration have been approved in the European Union:

- 12.5 mg, 25 mg, 50 mg or 75 mg film-coated tablets, and
- 25 mg powder for oral suspension (PfOS).

In the hereby submitted study, eltrombopag was administered orally in Japanese patients in the conditions of usual practice in Japan. Eltrombopag was approved in Japan on 27 October 2010 for the treatment of chronic ITP (cITP).

Study CETB115B1401 was a non-controlled study where all patients received eltrombopag as film-coated tablets in dosage strengths of 12.5 mg and 25 mg.

The formulations of eltrombopag used in the study were the same as the products approved in the EU. No new data were submitted for the pharmaceutical formulation used in the study CETB115B1401.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for study CETB115B1401: "Drug-use Results Surveillance of Revolade Tablets (Chronic Idiopathic Thrombocytopenic Purpura)"

Only 33 of 2019 total subjects in the safety analysis set of study CETB115B1401 were between 1 and 18 years.

1.3.2. Clinical study

Clinical study CETB115B1401: "Drug-use Results Surveillance of Revolade Tablets (Chronic Idiopathic Thrombocytopenic Purpura)"

Description

Study CETB115B1401 collected clinical data on long-term safety and effectiveness of eltrombopag under the Japanese real clinical setting after launching this product to meet a regulatory requirement of the Pharmaceuticals and Medical Devices Agency (PMDA) for market authorization (post-approval measure) in Japan.

This was an all-case, multicenter, central registration-based, non-controlled, observational, post-marketing survey conducted in Japanese adult and paediatric patients with chronic ITP who were administered eltrombopag (12.5 mg and 25 mg film-coated tablets) in accordance to locally approved prescribing information.

Methods

Objective

The primary objective of this study, performed in conditions of Japanese real-world setting under authorised indications of eltrombopag (as film-coated tablets in strengths of 12.5 mg and 25 mg), was to investigate its safety and effectiveness over long-term clinical use in patients with cITP.

No secondary or exploratory objectives were planned.

Study design

This was an all-case, multicenter, central registration-based, non-controlled, observational, post-marketing survey, performed in Japan for adult and paediatric patients with chronic ITP who administered eltrombopag (12.5 mg and 25 mg film-coated tablets) in accordance to locally approved prescribing information, to investigate its safety and effectiveness in conditions of a real-world setting.

The follow-up period for each patient was 1 year from the start of this drug with an additional 1-year extension in patients willing to continue in this study.

Study population /Sample size

This was an all-case study. Therefore, the study population included all cITP patients to whom eltrombopag was administered.

The target sample size for registration was 1,000 cITP patients.

Treatments

All patients received eltrombopag (12.5 mg and 25 mg film-coated tablets) in conditions of the Japanese real-world setting.

Outcomes/endpoints

In this observational study, case report form (CRF) data were entered by the investigator/subinvestigator based on routine medical records at the site were collected.

Variables considered in study CETB115B1401 were:

- Patient characteristics
- Data on eltrombopag use
- Data on use of concomitant drugs and therapies other than concomitant drugs
- History of prior treatments
- Effectiveness
    - Changes in platelet count
    - Bleeding tendency
    - Quality of Life (QoL)
    - Global improvement rating
- Laboratory tests
- Safety
    - Adverse events/reactions: adverse events (AE), serious adverse events (SAE), adverse reactions (AR), serious adverse reactions (SAR)
    - Priority variables: Thromboembolism (embolic and thrombotic events [SMQ])
- Other variables:
    - Site information (site name, department name, name of physician in charge)
    - Pre-treatment test (latest)
    - Changes in cITP diagnosis during the study
    - Willingness to cooperate in study continuation

Statistical Methods

In this study, only CRF data were used for statistical analyses.

The CRF consisted of multiple volumes, including CRF (I) (Volume 01: from the start of treatment to Month 6) and CRF (II) (Volume 02: from the start of treatment to the completion of the follow-up period at Month 12), and for patients in whom the follow-up period was extended by 1 year, CRF (III) (from the start of treatment to the completion of the follow-up period at Month 24) was used.

Safety analysis set

The safety analysis set consists of patients in the CRF-locked population who do not meet any of the following safety analysis exclusion conditions:

- Eltrombopag not administered
- Not within the contract term
- Beyond the contacted number of patients
- Multiple registration
- Previous volume not locked
- Physician's signature absent
- Off-label use

Effectiveness analysis set

Defined as patients in the safety analysis set, excluding patients in whom all of the effectiveness variables (i.e. platelet count, bleeding tendency, QoL and global improvement rating), are missing. Patients with results in any of the variables are included.

Results

Recruitment/ Number analysed

From the start date of study (December 10, 2010, market launch date) to the end date (October 16, 2020, database lock), a total of 5843 patients were registered at 1174 centers. Among them, CRFs were collected from 2163 patients at 686 centers.

A total of 2019 patients were included in the safety analysis set and 144 patients were excluded. Of these 2019 patients, 33 patients (1.63%) were reported to be under 18 years of age. A total of 2,018 patients are included in the effectiveness analysis set after excluding 1 patient for "evaluation not done" from the safety analysis set.

Baseline data

The majority of patients were female (59.88%, n=1209) and 40.12% (n=810) were male. Elderly patients (≥65 years) accounted for 51.46% (n=1039) and paediatric patients (<18 years) accounted for 1.63% (n=33). There were 4 pregnant women (0.33%).

Pre-treatment complications were reported in 1553 (76.92%) patients, including renal impairment (12.23%, n=247), hepatic impairment (20.01%, n=404), and other complications (72.36%, n=1461). Ninety-seven (4.80%) patients were predisposed to thromboembolism.

Effectiveness results

A patient was considered a responder if the last test in the CRF (laboratory tests/others – global improvement rating) was listed as "improved" and a non-responder if "unchanged", "worsened", or "others" was chosen.

The proportion of responders and non-responders were similar between the paediatric (<18 years) population and adult (≥18 years) population: 51.52% (17/33 paediatric patients) vs. 42.42% (14/33

paediatric patients) and 43.67% (862/1974 adult patients) vs. 45.80% (904/1974 adult patients), respectively (Table 1).

Table 1 Efficacy in paediatric population (efficacy analysis set)

Age, years	Number of patients	Responders (%)	Non-responders (%)	Odds ratios[a]	95% CI of odds ratio	
					Lower limit	Upper limit
Paediatric vs. adults						
<18	33	17 (51.52)	14 (42.42)	1.2728	0.6236	2.5979
≥18[b]	1974	862 (43.67)	904 (45.80)	-	-	-
Unknown/not specified	11	4 (36.36)	4 (36.36)	-	-	-
Paediatric sub-categories						
1-5	9	3 (33.33)	5 (55.56)	0.6292	0.1499	2.6410
6-11	6	2 (33.33)	3 (50.00)	0.6992	0.1165	4.1943
12-17	18	12 (66.67)	6 (33.33)	2.0972	0.7837	5.6126
≥18[b]	1974	862 (43.67)	904 (45.80)	-	-	-
Unknown/not specified	11	4 (36.36)	4 (36.36)	-	-	-

[a] Odds ratios were calculated excluding patients with unknown/not specified age groups and patients with unknown response.
[b] Bases of odds ratios.
Source: [Study B1401-Table 10-11]

Safety results

The median number of total treatment days on eltrombopag was 216 days (range from 1 to 728 days).

Of the 33 paediatric patients in the study, 7 patients (21.21%) experienced adverse reactions considered to be related to study drug compared to 24.71% (488/1975 patients, odds ratio: 0.8204, 95% CI: 0.3539-1.9019) in patients aged 18 years and above (Table 2). No deaths occurred in paediatric patients.

In the paediatric population, the adverse reactions considered related to study drug were headache (n=2), pharyngitis (n=1), neuroblastoma (n=1), alopecia (n=1), white blood cell count decreased (n=1) and platelet count increased (n=1). The events of pharyngitis and neuroblastoma occurred only in the paediatric patients. The pharyngitis in the patient was a non-serious adverse reaction and its outcome was resolved. The event of neuroblastoma was a serious adverse reaction reported in a 2-year-old boy. While the relationship of the event to eltrombopag was unknown/not recorded, this event was counted as an adverse reaction related to study drug (conservative approach). The outcome of the event was resolved 348 days after the date of occurrence.

There were no incidences of thromboembolic adverse reactions in the paediatric population.

Table 2 Data on occurrence of adverse reactions in the paediatric population (safety analysis set)

Age, years	Number of patients	Number of patients who reported ADRs (%)	Odds ratios[a]	95% CI of odds ratio	
				Lower limit	Upper limit
Paediatric vs. adults					
<18	33	7 (21.21)	0.8204	0.3539	1.9019
≥18[b]	1975	488 (24.71)	-	-	-
Unknown/not specified	11	2 (18.18)	-	-	-
Paediatric sub-categories					
1-5	9	2 (22.22)	0.8706	0.1803	4.2048
6-11	6	1 (16.67)	0.6102	0.0712	5.2309

Age, years	Number of	Number of patients who	Odds	95% CI of odds ratio	
12-17	18	4 (22.22)	0.8706	0.2852	2.6574
≥18[b]	1975	488 (24.71)	-	-	-
Unknown/not specified	11	2 (18.18)	-	-	-

ADR= adverse drug reaction
[a] Unknown/not specified category are excluded from odds ratio calculation.
[b] Bases of odds ratios.
Source: [Study B1401-Table 10-9]

Based on the available data, no differences were observed in the safety profile of eltrombopag in paediatric and adult patients in study CETB115B1401 as most adverse events that occurred in paediatric patients were generally observed in adults.

1.3.3. Discussion on clinical aspects

This Article 46 procedure of Regulation (EC) No1901/2006, as amended, concerns the submission of the stand-alone study CETB115B1401: "Drug-use Results Surveillance of Revolade Tablets (Chronic Idiopathic Thrombocytopenic Purpura)".

Study CETB115B1401, which is not part of a PIP, was performed in Japan to meet a regulatory requirement of the Pharmaceuticals and Medical Devices Agency (PMDA) for market authorization (post-approval measure).

The primary objective of this post-marketing Japanese study was to investigate the safety and effectiveness of eltrombopag (12.5 mg and 25 mg), administered orally as film-coated tablets, over long-term clinical use in patients with cITP. Despite the lack of a comparison group and the limitations expected to any observational study, the study design (all-case, multicenter, central registration-based, non-controlled, observational, post-marketing) is considered acceptable.

From the start date of study (December 10, 2010, market launch date) to the end date (October 16, 2020, database lock), a total of 5843 patients were registered at 1174 centers. Among them, CRFs were collected from 2163 patients at 686 centers.

Only 33 of 2019 total subjects (1.63%) in the safety analysis set of study CETB115B1401 were between 1 and 18 years.

Regarding the effectiveness results, the proportion of responders and non-responders patients were similar between the paediatric (<18 years) population and adult (≥18 years) population: 51.52% (17/33 paediatric patients) vs. 42.42% (14/33 paediatric patients) and 43.67% (862/1974 adult patients) vs. 45.80% (904/1974 adult patients), respectively.

With regard to safety data, 7 (21.21%) out of the 33 paediatric patients in the study experienced adverse reactions considered to be related to study drug compared to 24.71% (488/1975 patients, odds ratio: 0.8204,95% CI: 0.3539-1.9019) in patients aged 18 years and above. No deaths occurred in paediatric patients.

In the paediatric population, the adverse reactions considered related to study drug were headache (n=2), pharyngitis (n=1), neuroblastoma (n=1), alopecia (n=1), white blood cell count decreased (n=1) and platelet count increased (n=1). The events of pharyngitis and neuroblastoma occurred only in the paediatric patients. The pharyngitis in the patient was a non-serious adverse reaction and its outcome was resolved. The event of neuroblastoma was a serious adverse reaction reported in a 2-year-old boy. While the relationship of the event to eltrombopag was unknown/not recorded, this event was counted as an adverse reaction related to study drug (conservative approach). The outcome of the

event was resolved 348 days after the date of occurrence. However, the Applicant has not stated how the neuroblastoma was treated (chemotherapy, surgery or radiotherapy) to be solved.

There were no incidences of thromboembolic adverse reactions in the paediatric population.

Based on the available data, the effectiveness and safety profile observed in this study is consistent with the known safety profile of eltrombopag.

As the benefit risk assessment remains unchanged and positive, no further regulatory is action required.

2. Overall conclusion and recommendation

Results obtained in the study CETB115B1401 performed in Japan for patients with with cITP treated with eltrombopag (12.5 mg and 25 mg), administered orally as film-coated tablets under the real clinical setting after launching these formulations, are consistent to the EU summary product characteristics (SmPC) and not modify the risk/benefit profile of eltrombopag 12.5 mg and 25 mg film-coated tablets.

Paediatric population in that study was very limited (N=33) and the long-term results of effectiveness and safety were similar to that shown in adults.

☒ **Fulfilled:**

No regulatory action required.