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Procedure Management and Committees Support Division

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

Glivec

imatinib

Procedure no: EMEA/H/C/000406/P46/194

Note

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

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Administrative information

Invented name of the medicinal product:	Glivec
INN (or common name) of the active substance(s):	Imatinib
MAH:	Novartis
Currently approved Indication(s)	See SmPC
Pharmaco-therapeutic group (ATC Code):	L01XE01
Pharmaceutical form(s) and strength(s):	50-100 mg Capsule, hard 100-400 mg Film-coated tablet

Introduction

On February 2015, the MAH submitted completed paediatric studies for Glivec, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Glivec and that no consequential regulatory action is required.

Scientific discussion

Information on the development program

The MAH stated that study titles and numbers are a stand alone studies.

Information on the pharmaceutical formulation used in the studies

Study STI571AJP03 use a formulation of Glivec® 100 mg Capsules in two patients with chronic myeloid leukaemia (CML)

Study CSTI571I1401 use a formulation of Glivec® l00mg tablets in six patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ALL)

Clinical aspects

1. Introduction

The MAH submitted an overview and the Japanese final reports for:

- CSTI571AJP03 (last patient last visit on December 31, 2009), Implementation Outline of Special Investigation (Long-Term Use) of Glivec® 100 mg Capsules in two patients with chronic myeloid leukaemia (CML)
- CSTI571I1401 (last patient last visit on February 28, 2010), Special Drug Use Observational Investigation (long-term use) Glivec® l00mg tablets in six patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ALL)

Novartis is submitting the results of these clinical trials to the CHMP in accordance with Article 46 of Regulation (EC) No 1901/2006 which requires that any marketing authorization holder sponsored study which involves the use in the paediatric population of a medicinal product covered by a marketing authorization, whether or not they are conducted in compliance with an agreed paediatric investigation plan, is to be submitted to the competent authority.

Imatinib is approved in the following indications in paediatric population in Europe at a recommended dose of 340 mg/m2 daily:

- Paediatric patients with newly diagnosed Ph+ CML for whom bone marrow transplantation is not considered as the first line of treatment
- Paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in blast crisis or accelerated phase
- Paediatric patients with newly diagnosed Ph+ ALL integrated with chemotherapy

As in adults, imatinib was rapidly absorbed after oral administration and showed a 1.7-fold accumulation at steady state in paediatric patients. Plasma concentrations at steady state in children following once daily dosing with 260 mg/m2 and 340 mg/m2 were comparable to the exposure in adults at daily doses of 400 mg and 600 mg, respectively.

Comparison of the relationship between dose based either on body surface area (BSA) (m^2) or body weight (kg) and area under the curve (AUC) at steady state showed that dosing based on body weight (kg) did not reduce interpatient variability of AUC compared to dosing based on BSA (m^2). Therefore, the conventional approach of dosing based on BSA is appropriate in paediatric patients (Champagne 2004).

The analysis confirmed that exposure of imatinib in paediatric patients receiving 260 mg/m^2/d (not exceeding 400 mg/d) or 340 mg/m2/d (not exceeding 600 mg/d) were similar to those in adult patients who received imatinib 400 mg/d or 600 mg/d.

2. Clinical studies

Study CSTI571AJP03 was carried out in Japan only. This study was an observational study to confirm the safety and efficacy of Glivec capsules in Ph+ chronic myeloid leukaemia (CML) patients during long-term use, 5 years, and report on the actual use of the drug in medical practice. This study included 326 adult and paediatric patients in total. The safety analysis included 324 patients, 304 were included in the analysis of haematological effects, and 291 were included in the analysis of cytogenetic effects. Two paediatric patients participated in this study. For patients in the chronic phase (CP) of CML (CML-CP), the imatinib dose was 400 mg once daily, with a maximum dose of 600 mg once daily in the adult population. For the accelerated or blastic phase of CML, the imatinib dose was 600 mg once daily, with the maximum daily dose of 800 mg (400 mg twice daily) in the adult population. The paediatric dose of imatinib was defined based on the standard of care for Ph+ CML paediatric patients in Japan. The dose was adjusted depending on the patient's haematological findings, age and symptoms.

Efficacy evaluation was performed in 304 patients for the analysis of haematological endpoints and 291 patients for the analysis of cytogenetical endpoints.

The haematological efficacy rate was 94.4% (287/304 patients), and the cytogenetic efficacy rate was 87.6% (255/291 patients). The efficacy rates in study CSTI571AJP03 were comparable to the response rate in clinical trials supporting the approval of Glivec which had demonstrated a rate of complete haematological remission (93.8%) and a rate of cytogenetical effects (40.6%) in a Japanese clinical study (phase II part of Study 1201) involving patients with Philadelphia chromosome-positive (Ph+) CML-CP and a rate of complete haematological remission (88.0%) and a rate of cytogenetical effects (33.3%) in a clinical study (Study 0110) not conducted in Japan in patients with CML-CP.

Efficacy evaluation for paediatric patients was not performed separately in this study

In study CSTI571AJP03 a total of 2143 AEs were reported in 294 patients (adults and paediatric patient population). The incidence of any AEs in any patient was 91% (294/324 patients).

Two (2) paediatric patients with Ph+ CML participated in the study.

No deaths were reported during this study among paediatric patients. None of the paediatric patient experienced AE leading to treatment discontinuation.

Both paediatric patients experienced AEs. The only SOC for the AEs was blood and lymphatic system disorders.

The most frequently reported AEs were anaemia and neutropenia.

One (1) paediatric patient completed study treatment and 1 paediatric patient discontinued due to logistic reasons.

Study CSTI571I1401 was carried out in Japan. This study was an observational study to determine the safety and efficacy of Glivec 100 mg tablets in long-term use for Ph + acute lymphoblastic leukaemia (Ph+ ALL) and was used as part of the re-examination of the application dossier for data generated in actual medical practice. This study included 162 adult and paediatric patients in total. The safety analysis included 161 patients, 136 were included in the analysis of anti-leukaemia effects, and 130 were included in the analysis of cytogenetic effects. Six paediatric patients participated in the study. The dose of imatinib was 600 mg once daily. The dose of imatinib could be decreased based on hematologic findings, age and symptoms of the patient. The paediatric dose of imatinib was defined based on the standard of care for Ph+ ALL paediatric patients in Japan.

Efficacy evaluation was performed in 136 patients included in the analysis of anti-leukaemia endpoints and 130 patients included in the analysis of cytogenetical endpoints.

For efficacy evaluation based on anti-leukaemia endpoints, patients achieving complete haematological remission (CHR) and complete marrow remission/partial haematological remission were regarded as responders. For efficacy evaluation based on cytogenetical endpoints, patients achieving complete cytogenetical remission (CCyR) and major cytogenetical remission (MCyR) were regarded as responders.

The anti-leukaemia efficacy rate was 96.32% (131/136 patients) and the cytogenetic efficacy rated was 96.92% (126/130 patients). The efficacy rates were not markedly different from the efficacy rate that had been determined in the Japanese clinical studies conducted for the approval of Glivec, both for anti-leukaemia efficacy rate (100.00% [8/8 patients]) and cytogenetical efficacy rate (87.5% [7/8 patients]).

Efficacy evaluation for paediatric patients was not performed separately.

In CSTI571I1401 study a total of 381 AEs were reported in 108 patients (adults and paediatric patient population). The incidence of any AE in a patient was 67.1% (108/161 patients).

A total of 6 paediatric patients with Ph+ ALL participated in the study. No deaths were reported during this study among paediatric patients.

The incidence of any AEs occurring in paediatric patients was 66.6% (4/6 patients). The SOCs with the highest incidence were:

☐ Gastrointestinal disorders with 4/6 patients (66.6%)

☐ General disorders and administration site conditions with 3/6 patients (50%).

The PTs with the highest incidence were face oedema and nausea (33.3% of the patients each).

Two (2) paediatric patients (33.3%) discontinued study treatment because of haematopoietic stem cell transplantation (HSCT); 2 paediatric patients (33.3%) completed study treatment,1 paediatric patient (16.6%) discontinued due to disease progression, and 1 paediatric patient (16.6%) experienced AEs leading to treatment discontinuation.

The safety profile was consistent with that reported in other imatinib studies conducted in paediatric population with Ph+ ALL; there were no new safety signals.

Rapporteur's overall conclusion and recommendation

Overall conclusion

Two clinical studies have been submitted within the framework of article 46. These two studies were carried out in Japan, being the purpose of these trials to provide post-marketing surveillance data in Japanese patients.

The first one, study CSTI571AJP03 investigated the use of glivec in CML patients, whereas the second one, study CSTI571I1401 was designed in order to provide data in Ph+ALL patients.

Few data can be obtained from these two clinical trials, since only 2 and 6 paediatric patients were recruited in these studies. Given the low number of subjects the MAH has submitted only a clinical overview for both studies (with the CSR in Japanese). This strategy even though debatable a priori, has eventually no impact on the final conclusions that can be drawn from these studies, seeing as on the one hand there were very few paediatric subjects and on the other hand, data from children were not performed separately.

Overall, efficacy and safety data in these two clinical trials are in line with those previously reported.

The conclusions from these two Japanese studies do not modify the benefit-risk conclusion of glivec, both in CML and Ph+ALL.

Recommendation

☒ **Fulfilled –**

No regulatory action required

Additional clarifications requested

Not applicable