Annex II

Scientific conclusions

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An application was submitted under the decentralised procedure Daruph and Anafezyn and associated names, 16 mg, 40 mg, 55 mg, 63 mg, 79 mg, 111 mg, film-coated tablet on 31 August 2020.

The legal basis under which the application was submitted is: Article 10(3) of directive 2001/83/EC.

The application was submitted to the reference Member State (RMS): Sweden and the concerned Member States (CMS): DE, HU, IT, PL, RO, SK (SE/H/2098/01–06/DC) and for the duplicate application DE, FR, IE, PT (SE/H/2099/01–06/DC).

The reference medicinal product (RefMP) is Sprycel (dasatinib monohydrate) authorised in Europe since 2006.

The decentralised procedure (SE/H/2098/01–06/DC) and (SE/H/2099/01–06/DC) started on 29 October 2020.

On day 210, major issues on safety, bioequivalence/bioavailability, raised by IT and DE, remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by Sweden on21 October 2021. The CMDh 60-day procedure was initiated on 24 October 2021.

Day 60 of the CMDh procedure was on 22 December 2021 and as no agreement could be reached the procedure was referred to the CHMP.

On 23 December 2021 the RMS Sweden therefore triggered a referral under Article 29(4) of Directive 2001/83/EC with a subsequent revision on 14 January 2022. IT, DE and SK raised objections in relation to lack of bioequivalence in accordance to product specific guideline, differences in warnings compared to the reference product regarding the concomitant use of proton pump inhibitors (PPI) and histamine 2 (H2) antagonists and the potential risk of medication errors associated with the products. These issues raised were considered to constitute a potential serious risk to public health.

Overall summary of the scientific evaluation by the CHMP

Three issues were raised in the referral procedure which pertained to: 1) further justify the bridging of the medicinal product applied for to the reference medicinal product required; 2) the potential risk of medication errors and its impact on the benefit/risk balance; 3) the difference in warnings on the concomitant use of PPI/H2 antagonists compared to the warnings listed for the reference medicinal product.

With regard to the first point, the CHMP discussed the **studies 744/19** and **753/19** provided by the applicant to support the hybrid application for Daruph/Anafezyn:

- In **study 744/19**, where the reduced strength of the test product was compared with the reference product in the fasting state, standard bioequivalence criteria were fulfilled. The selection of normochlorhydric subjects was to standardize the study conditions, given a lower impact of gastric pH on the bioavailability of the test product. This is acceptable to the CHMP since the impact of hypochlorhydria has been appropriately characterized and since the test product is less likely to have lowered absorption compared to the reference product.
- A lower food effect compared to the reference product was observed in the comparative **study 753/19** in fed conditions. The absorption of Daruph/Anafezyn remained between the extent of absorption from the reference product under fed and fasted conditions. As this is a hybrid product, strict bioequivalence criteria for the fed study are not required; it suffices that

exposure in the fed state is within the ranges seen with the reference product when administered with or without food.

The PKWP was consulted and concluded that the systemic exposure of Daruph/Anafezyn has been sufficiently characterised and compared with that of the reference product Sprycel (dose proportionality, food effect and PPI interaction liability), to conclude that the applied products exhibit more consistent systemic exposure in the absence and the presence of PPI.

Overall, the CHMP concluded that the bridge of Daruph/Anafezyn to the reference product is established.

On the second point, since Daruph/Anafezyn uses different dosages compared to the other approved dasatinib products, a potential risk for medication errors was acknowledged by the CHMP. Indeed, in case of switch (although not recommended), the correspondence of dosages between Daruph/Anafezyn and other approved dasatinib products needs to be understood by healthcare professionals (HCPs). To address this concern and potential clinical consequences, the applicant proposed routine risk minimisation measures (unique product name, warnings in sections 4.2 and 4.4 of the SmPC, warning on outer package) and additional risk minimisation measures (educational materials for HCPs). The minimisation measures aim at addressing the potential risk of medication error at all levels: prescribing (unique product name, SmPC, HCP guide for prescribing physicians), dispensing (unique product name, outer package, SmPC, HCP Guide for pharmacists) and administration (unique product name, outer package, package leaflet). The proposed risk minimisation measures and the post marketing follow-up of the effectiveness of these measures through periodic reporting in PSURs are considered acceptable by the CHMP.

On the last point, concomitant use of PPI/H2 antagonists is not recommended with the reference product because of a risk of decreased exposure of dasatinib. However, the interaction **study 754/19** of Daruph/Anafezyn with omeprazole indicates a decreased mean exposure change of maximum 20% of dasatinib. The magnitude of the decrease is in the same range as the interaction with dexamethasone, which was deemed 'likely not clinically relevant' for the reference product. Therefore, the CHMP agreed with the applicant that the results of **study 754/19** together with the justification based on extrapolation support a change of warnings compared to the reference product on concomitant use with PPI/H2 related to the risk of reduced exposure of dasatinib through the inclusion of results of the **study 754/19** in SmPC section 4.5 and the possibility of concomitant administration in SmPC section 4.4.

In conclusion, the CHMP acknowledged the potential risk of medication errors of Daruph/Anafezyn, as well as the routine and additional proposed risk minimisation measures. Additionally, the CHMP took into consideration the potential advantageous pharmacokinetics characteristics of Daruph/Anafezyn in the clinical context of CML/AML, for patients requiring concomitant treatment with PPI/H2 blockers. The CHMP considered overall that the benefit/risk balance is positive.

Grounds for the CHMP opinion

Whereas,

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC.
- The Committee considered the totality of the data submitted and presented in an oral explanation by the applicant in relation to the objections raised as potential serious risks to public health.
- The Committee considered that the results of the comparative bioavailability studies in fasted and fed conditions are sufficient to establish the bridge to the reference medicinal product.

- The Committee was of the view that the potential risk of medication error is sufficiently addressed through risk minimisation measures, consisting in the unique product name, warnings on the outer packaging, SmPC and package leaflet in addition to the health care professional guide.
- The Committee considered that the results of the drug interaction study with omeprazole and their extrapolation to other PPI and H2 antagonists are sufficient evidence to support differences in warnings compared to the reference product regarding the concomitant use of PPI and H2 antagonists

The Committee, as a consequence, considers that the benefit-risk balance of Daruph and Anafezyn and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion. The product information remains as per the final version achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.