19 May 2022
EMA/594862/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Daruph / Anafezyn and associated names

INN/active substance: dasatinib (anhydrous)

Applicant: Zentiva k.s.

Procedure number: EMEA/H/A-29(4)/1516

Note:

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

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1. Information on the procedure

An application was submitted under the decentralised procedure for 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) Sprycel (dasatinib monohydrate) is 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[1]. 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.

2. Scientific discussion

2.1. Introduction

This application concerns a hybrid application of Daruph (dasatinib anhydrous) 16 mg, 40 mg, 55 mg, 63 mg, 79 mg, 111 mg, film-coated tablet according to article 10(3) of Directive 2001/83/EC. A duplicate application was submitted for the product Anafezyn.

The development programme has been consulted in a scientific advice procedure at the Dutch Medicines Evaluation Board (MEB) on 8 May 2019.

The indications sought are in full agreement with the indications of the reference product:

Adult patients with:

- Newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase (CML-CP).
- Chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.

[1] The notification was subsequently revised on 14 January 2022.

- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

Paediatric patients with:

- Newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- Newly diagnosed Ph+ ALL in combination with chemotherapy.

Daruph/Anafezyn uses dasatinib anhydrous as compared to dasatinib monohydrate contained in the reference product, Sprycel. There are other dasatinib anhydrous products approved as generic products. Daruph/Anafezyn does not contain any excipients retarding the drug release of dasatinib anhydrous to mimic the drug release of less soluble dasatinib monohydrate used in Sprycel.

Clinical data

To support the marketing authorisation applications the applicant has conducted 1 pilot study and 5 pharmacokinetic studies:

- 611/16 – Pilot study
- 699/18 – Proof-of-concept, dose finding bioavailability study
- 744/19 – Pivotal bioequivalence study under fasting conditions
- 753/19 – Food effect study
- 754/19 – Drug interaction study with omeprazole
- 765/19 – Dose-proportionality study

Suprabioavailability was shown in the proof-of-concept, dose finding bioavailability **study 699/18**, thus the dose was reduced with 21% compared to the reference product.

Bioequivalence was subsequently shown in the pivotal comparative bioavailability study under fasting conditions **study 744/19** when 110,6 mg of the test product was compared with 140 mg of the reference product under fasting conditions. **Study 744/19** was performed with normochlorhydric subjects only.

Bioequivalence was not shown in the food effect **study 753/19** when 110,6 mg of the test product was compared with 140 mg of the reference product under fed conditions. The 90% confidence interval for the ratio of the test and reference product was 87.77 (range 78.10-98.65) for AUC_{0-t} and 93.46 (range 78.35-111.48) for C_{max}.

The drug interaction study with omeprazole (**study 754/19**) showed that the AUC_{0-t} and C_{max} was reduced by 20% and 38% respectively when the 110.6 mg of the test product was administered 22 hours following the last dose of omeprazole. Under similar conditions, the AUC and C_{max} was reduced by 43% and 42% respectively for the reference product according to Sprycel's SmPC.

2.2. Assessment of the issues raised as a potential serious risk to public health

2.1.1. Bridging of Daruph/Anafezyn to the reference medicinal product Sprycel

In this hybrid application, the bridge of Daruph/Anafezyn to the reference medicinal product Sprycel was requested to be further justified, since:

a. bioequivalence demonstrated in **study 744/19** in fasted conditions was conducted in a pre-selected population of normochlorhydric patients. Objecting Member States

considered that these results were not representative of the entire population (i.e. pH with higher gastric pH).

b. bioequivalence was not demonstrated in **study 753/19** that was conducted in fed conditions. Considering that the criteria in Dasatinib film-coated tablets 20, 50, 70, 80, 100 & 140 mg and suspension 10 mg/ml product-specific bioequivalence guidance (EMA/CHMP/675838/2014/Rev.1*) are not fulfilled, objecting Member States considered that additional clinical studies were required.

The applicant clarified that Daruph/Anafezyn was developed as a suprabioavailable formulation that would display lower sensitivity to reduced gastric acidity (increased stomach pH) by utilizing the solubility-linked properties of dasatinib anhydrate.

Given the changes introduced by Zentiva vis-à-vis the reference medicinal product, namely, reduction of dose strength of 21% and the SmPC claims related to co-administration of acid reducing agents, a clinical programme consisting of a pivotal comparative bioequivalence study under fasted conditions (**study 744/19**), a food-effect study (**study 753/19**), confirmation of dose-proportionality and a PPI drug-drug interaction study (**study 754/19**)) was performed. The applicant considered the clinical programme of this suprabioavailable product adequate to support an application under Article 10(3) of Directive 2001/83/EC since it follows: 1) the principles of Annex II of the Notice to Applicants (NtA), Volume 2A, Chapter 1 (2019) stating that for *suprabioavailable products, bioavailability studies using the same dosage intervals but reduced doses (intended to achieve same plasma/blood concentrations as a function of time) are the additional studies usually required under Article 10(3)* and; 2) the recommendations for development of suprabioavailable products (EMA Website, Clinical pharmacology and pharmacokinetics: Questions and Answers [Q&A], Section 1.2, January 2011) '*If suprabioavailability is found, the development of a lower dosage strength should be considered. In this case, the biopharmaceutical development should be reported and a final comparative bioavailability study comparing the reformulated new product with the approved reference medicinal product should be submitted.'*

Suprabioavailability of the Zentiva formulation was consistently demonstrated *in-vivo* (**studies 611/16** and **699/18**) and considerably higher bioavailability remained even after exclusion of low-lier profiles from the reference product. Therefore, the EMA recommendations for development of suprabioavailable products was followed by the applicant, with the proof-of-concept **study 699/18** used to evaluate the potential of dose reduction and **study 744/19** being the final and pivotal comparative bioavailability study. The design of the pivotal study is further detailed below.

a) Bridging to the reference product – fasted conditions

Normochlorhydric study population

Study 744/19 was designed to enroll healthy subjects in a 2-stage screening procedure where subjects who passed the first stage (standard battery of screening tests and checks of inclusion and exclusion criteria) proceeded to a second stage in which gastric pH-metry using a nasogastric probe was performed under fasting conditions. Only subjects with normal gastric pH (< 4) were permitted to participate in the bioequivalence assessment.

The selection of the normochlorhydric population for the pivotal **study 744/19** was discussed at a scientific advice meeting at the MEB. This pre-selected population was decided by the applicant to standardize the study conditions and eliminate the effect of low absorbers of the reference drug product but also to decrease the intra-subject variability in order to allow relevant comparisons between the test and reference products and the conduct of smaller bioequivalence studies.

Phenotyping (and/or genotyping) of subjects was chosen in accordance with the EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) for pharmacokinetic reasons. Overall, the applicant considered this approach as an alternative to the standardization approach introduced in the latest revision of the EMA PSBGL for dasatinib (EMA/CHMP/675838/2014/Rev. 1) where low-lier exclusion is possible from the statistical analysis of the fasting study.

In **study 744/19**, bioequivalence was demonstrated between test (developed product at a reduced dose (21%)) and reference formulations with point estimates for C_{max} and AUC_{0-t} falling within the acceptance criteria (80.00 – 125.00%) (**Table**).

Table 1 Results from bioequivalence study 744/19 comparing test product (dasatinib 110.6mg) at reduced dose versus reference product (Sprycel 140mg)

PK metric	PE (%)	90% CI	
		Lower (%)	Upper (%)
C_{max}	100.39	86.83	116.06
$AUC_{(0-t)}$	99.36	89.39	110.43

The study was designed as single-dose, four-period, cross-over fully replicateds tudy in normochlorhydric healthy volunteers (N=40). The test-to-reference point estimate and the 90% confidence intervals are presented; data were analyzed by PROC GLM procedure in SAS (version 9.4, SAS Institute Inc., USA). Abbreviations: CI – confidence interval, PE – point estimate.

Extrapolation to subjects with higher pH

Data from the proof of concept **study 699/18** at full dose (no reduction of the test product by 21%) stage 1 showed that in subjects with suppressed gastric acid production following multiple doses of PPI, dasatinib exposure from Daruph/Anafezyn was higher than for the reference product Sprycel. Furthermore, data from study stage 2 (where gastric pH was monitored by nasogastric tube) showed that exposure for the test product is lower in subjects with high gastric pH (> 4) than in subjects with low pH (< 4), but higher than dasatinib exposure for reference product in subjects with high pH (**Table**). This constitutes the main data of Daruph/Anafezyn in patients with high gastric pH.

Table 2 Comparison of dasatinib exposure in subjects with different stomach pH in study 699/18.

Product	Geomean $AUC_{(0-t)}$ [ng/mL]	
	low pH (<4)	high pH (>4)
Test	555.15	408.37
Reference	468.63	115.10

Presented for subjects with median pH within 0 – 4 hours < 4 (low pH, N=27(26) for T(R)) and > 4 (high pH, N=5); analyzed by R-software, version 4.1.2 (R Core team, 2021).

The applicant acknowledged that test and reference products were compared at full dose. However, they considered that this outcome remains true after reduction of the test exposure by 21% (as employed in the final product).

The applicant considered that these results illustrate the low absorption of the reference product linked to low or diminished gastric acid secretion as previously reported in published studies (Yago et al., 2014) and in line with the SmPC for Sprycel indicating that that the solubility of dasatinib is pH dependent.

The applicant considered that the conclusions from the indirect comparisons on the interaction studies with PPI (lower exposure reduction for Daruph/Anafezyn (20%, **study 754/19**) compared to Sprycel

(43%)) could be extrapolated to the clinical situation of subjects with increased gastric pH and concluded that the exposure of Daruph/Anafezyn in patients with higher stomach pH would be higher than the exposure of the reference product but remain below the exposure in normochlorhydric subjects.

Finally, the applicant noted the results of the interaction **study 754/19** with omeprazole where the concentration for Daruph/Anafezyn + PPI (simulating the achlorhydric condition) were higher than the reference product + PPI but lower than normochlorhydric subjects. Daruph/Anafezyn is less sensitive to the risk of decreased uptake with high gastric pH than the approved reference product.

Considering that no phenotyping is performed in patients before the initiation of standard dasatinib treatment, the CHMP agreed that there is no specific concern for the administration of Daruph/Anafezyn to achlorhydric subjects. Further, the dosing of dasatinib is individual and adjusted based on individual patient response and tolerability.

Additionally, information regarding possible decreased exposure in achlorhydric patients are included in the SmPC section 4.2 of Daruph/Anafezyn, unlike the SmPC of the reference product that does not have information on the risk for decreased exposure in patients with achlorhydria/hypochlorhydria: "*Achlorhydria/hypochlorhydria: Dasatinib plasma concentration may be reduced in patients with decreased gastric acidity (see section 4.5). Dose adjustments may be necessary in such situations.*" This clearly informs the prescribers about the possible reduced exposure in achlorhydric patients. Thus, the CHMP considered that the issues that may arise from only using normochlorhydric subjects in the pivotal study have been sufficiently addressed in the SmPC.

For these reasons, the CHMP found it acceptable that the fasting BE study is performed in subjects with normal stomach pH only to obtain standardised conditions. Overall, the CHMP agreed that data from the PPI-study **754/19** shows that the test formulation is less likely to have erratic or lowered absorption in subjects with abnormally high stomach pH (achlorhydria/hypochlorhydria) than the reference product. The difference in pH dependency of the two formulations is sufficiently addressed in the SmPC, as are the risks associated with a switch (which is not recommended) between the formulations in patients with high gastric pH. A lower impact of increased gastric pH is acceptable for a product approved as a hybrid. Given that the effect of increased gastric pH is less for the test product than for the reference product, this is not considered a concern neither for efficacy nor for safety.

b) Bridging to the reference product – food effect

A food effect study **(study 753/19)** was conducted to compare the bioavailability of the test product in healthy volunteers under fed and fasting conditions.

The test and reference products were administered under fed conditions in order to permit a comparison of food effects; in the context of an hybrid application (e.g., due to an improvement in API solubility) :(EMA Website, Clinical pharmacology and pharmacokinetics: Questions and Answers [Q&A], Section 1.2, January 2011) '*The potential for a difference in food effect on the rate and/or extent of absorption or a difference in absorption interactions between the reformulated new product and the approved reference product should be discussed and when relevant evaluated in vivo'* .

A lower impact on the bioavailability of the test product when compared to the reference product was observed when both are administered under fed conditions with exposures to dasatinib following a high-fat, high-calorie meal increased by 11% and 27% for test and reference products, respectively (**Table 3**).

Table 3 Results from food effect study 753/19 comparing test product (Dasatinib 110.6 mg) in fed and fasting conditions and reference (Sprycel 140 mg) in fed state.

PK metric	PE (%)	90% CI	
		Lower (%)	Upper (%)
Test fed vs. Test fasting			
C_{max}	106.19	89.09	126.57
$AUC_{(0-t)}$	111.49	101.88	122.00
Test fed vs. Reference fed			
C_{max}	93.46	78.35	111.48
$AUC_{(0-t)}$	87.77	78.10	98.65

The study was designed as single-dose, three-period, cross-over study in healthy volunteers (N=35). The test-to-reference point estimate and the 90% confidence intervals are presented; data were analyzed by PROC GLM procedure in SAS (version 9.4, SAS Institute Inc., USA). Abbreviations: CI – confidence interval, PE – point estimate.

The CHMP agreed with the applicant's argumentation that bioequivalence not met in the fed conditions is not of concern for efficacy nor safety as the absorption from the test product in the fed state is well between the extent of absorption achieved from the reference product under fed and fasted conditions, and as the reference product can be taken with or without food.

Finally, the exposure variability reflected by the inter-subject coefficient of variation for the area under the curve, AUC(0-t), as observed in the **study 753/19** is lower for Daruph/Anafezyn (23.82%) than for the reference product (34.48%), suggesting that a more consistent exposure may be expected from Daruph/Anafezyn under fed conditions.

c) Conclusion on the bridging:

The CHMP sought advice from the PKWP during the procedure on whether the PK bridge is established in this hybrid application (see Section 3. Expert consultation). The PKWP concluded that the systemic exposure of the applied product 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 results of the comparative bioavailability studies in fasted and fed conditions are sufficient to establish the bridge to the reference medicinal product.

2.1.2. Potential risk of medication errors

A potential risk of medication error was raised for Daruph/Anafezyn that has a different dosage from the other approved dasatinib products. Therefore, the healthcare professionals (HCPs) need to understand the correspondence with the already authorised ones in case of switch between products, even though such switch is not recommended according to the SmPC. The risk minimisation measures proposed by the applicant in their marketing authorisation application were not considered sufficient by the objecting Member States to adequately mitigate this risk and the applicant was therefore asked to provide further proposals and justification for risk minimisation measures to ensure the safe use of Daruph/Anafezyn and monitor their effectiveness.

In their response, the applicant indicated that, comparing with other dasatinib products, tablets with different strengths have been proposed for Daruph/Anafezyn. The strength for each tablet was adjusted by 21% to compensate for the supra-bioavailability shown in **study 699/18**.

Daruph/Anafezyn has been shown to be less affected by decreased gastric acidity (higher gastric pH) than the reference product Sprycel. The applicant therefore considers that the pharmacokinetic profile of Daruph/Anafezyn results in benefits to specific patient groups (e.g. patients with higher gastric pH such as the elderly, patients with achlorhydria or patients with concomitant gastric acid suppressing medication).

- Based on the results from the interaction **study 754/19**, the product information of Daruph/Anafezyn implements the possibility to be administered with PPI and/or H2-antagonists in a staggered manner. In contrast, the SmPC for the reference product states that concomitant use of H2-antagonists and PPI is not recommended, due to the associated reduction in the exposure to dasatinib. Given the existing patient pool who currently receives concomitant tyrosine-kinase inhibitors (TKI) and acid-reducing agents (Sharma et al., 2019), the possibility to achieve adequate exposure with Daruph/Anafezyn is considered by the applicant as an important advantage and benefit for the patients.
- In addition, the applicant pointed out that a more consistent dosing would be expected since a lesser food effect is suggested in the fed study (**study 753/19**) even though this is of limited clinical relevance since the reference product Sprycel can also be taken with or without a meal.

The CHMP acknowledged dasatinib gastric pH dependency leading to variation in drug exposure and drug-drug interaction with PPI and H2 antagonists with potential risk of clinical consequences. Based on the available data, the CHMP agreed that with Daruph/Anafezyn there is a lower impact on dasatinib PK parameters in cases of gastric pH changes induced by intrinsic or extrinsic factors. This difference in gastric pH sensitivity of dasatinib, with a more stable exposure for the test product than the reference product, might be advantageous in the clinical context of CML/AML, for patients requiring treatment with PPI/H2 blockers concomitantly with dasatinib.

Based on the current ESMO guideline on the treatment of CML, choice of treatment and changes to treatment are based on the response to treatment i.e. on the degree of cytogenetic and molecular response and on the detection of BCR-ABL1 kinase domain mutations (Hochhaus et al., 2017). Dose escalation is considered in patients who did not achieve an adequate response while tolerating the treatment. Dose de-escalation is considered in patients who achieve sustained remission. In terms of safety, TKIs grade 3-4 adverse effects require dose discontinuation or dose reduction. In all situations, patients are closely and constantly monitored by physicians and the treatment choice is expected to be in line with clinical guidelines and current evidence. The applicant acknowledged that medication errors resulting from wrong prescribing of chemotherapeutic agents are reported in the scientific literature (Weingart et al., 2018), and that the risk of potential prescription medication errors with Daruph/Anafezyn cannot be fully excluded.

In the clinical scenario where Sprycel and Daruph/Anafezyn products are marketed concomitantly, the hypothetical risk of medication error, according to the applicant, would result from the fact that different strengths of Sprycel and Daruph/Anafezyn are bioequivalent, therefore overdose or underdose in a patient might occur. These types of error would be classified as *"Prescribing", "Wrong dose prescription/wrong dose preparation", "Improper dose"* and *"Administration errors"* in case a patient/caregiver would use the medicine incorrectly (e.g. due to misunderstanding) (Tariq et al., 2021). When considering a specific scenario, when e.g. a physician would like to prescribe a drug level equivalent to 100 mg of Sprycel and he/she unintentionally prescribes 111 mg of Daruph/Anafezyn, these would result in a patient overdose with potential of dose dependent adverse events (e.g. myelosuppression and bleeding). In 2006, dose-escalation study of dasatinib was conducted in 84 patients with CML (in any phase) and ALL (Ph-positive) who were intolerant or resistant to imatinib. Patients were prescribed a total of 15 mg to 240 mg dasatinib as one daily dose or split in two. The primary objective was to evaluate the tolerability and safety of dasatinib treatment. The highest

toxicity observed was reversible myelosuppression; non-malignant pleural effusion was also observed but at a lower rate (Conchon et al., 2011). Also, the opposite scenario resulting in patient underdose could not be excluded. Based on the treatment recommendations for CML, it is critically important to carefully follow patient's disease status on a regular basis (Schiffer et al., 2020). Therefore, the applicant considered that medication errors are expected to be spotted and managed appropriately.

The CHMP asked the applicant to comment on the specific clinical scenario where *"A risk of therapeutic error is also raised when dose reduction is needed due to patient's scarce tolerability (e.g. from 80 mg of Sprycel), where the physician may actually prescribe a dose even higher using Daruph (79 mg that corresponds to 100 mg of the reference) and lead to even more serious safety consequences*". The applicant highlighted that dasatinib dose reductions are made in case of serious adverse events (e.g. myelosupression) or if there is a risk of drug-drug interactions. In such cases, patients are expected to be monitored even more closely. Therefore, it is assumed that the prescribing physician would ensure that the appropriate dose is prescribed and provide treatment details and necessary instructions to their patients.

In addition, the applicant stressed out that physicians treating leukaemia patients are already experienced in using non-bioequivalent dasatinib-containing products in clinical practice since Sprycel (powder for) oral suspension was shown to be 19% less than Sprycel film-coated tablets, and these two formulations that are not freely interchangeable are authorised in the EU since November 2006. Although it is acknowledged that different dosage forms may partly prevent the risk of medication error, clinicians are nevertheless used to follow different dosing recommendations for particular dasatinib products.

The CHMP acknowledged the particularity of dasatinib-containing products including the reference product Sprycel that are available in many different strengths, to allow tailoring the treatment for each patient individually in accordance to the clinical practice guidelines for ALL and CML. Dose adjustments recommended for dasatinib are either dose-escalation to achieve a haematologic, cytogenetic and molecular response monitored at specific time points per current treatment guidelines, or dose reduction in case of adverse reactions.

The CHMP recognised also that these differences in strength and pH- sensitivity between the intended hybrid product and the other dasatinib products might have clinical consequences in case of a non-recommended switch between dasatinib products.

The applicant reflected medication error as an important potential risk in the RMP and proposed the following minimisation measures:

Risk minimisation measures

The proposed dose reduction of 21% takes consideration of the potential for medication errors since the applicant has chosen to have Daruph/Anafezyn strengths different from the other dasatinib products.

1. Routine risk minimisation measures:

SmPC sections 4.2 and 4.4 (as warning) contain information about the strength reduction by 21% per tablet compared to other dasatinib products due to supra-biovailability and, importantly, that in case of switching between dasatinib-containing products, the dosing recommendations of the intended product must be followed. Sections 4.4 and 4.5 have been amended with information about handling of concomitant administration of PPI or H2 antagonists and on the risk for reduced exposure of dasatinib. The CHMP considered that the differences between the applied product and other dasatinib products are outlined appropriately throughout the SmPC.

Moreover, the applicant proposed a special warning on the outer package to mitigate the risk of medication error at the level of dispensing pharmacists and patients. The applicant also proposed branded product names instead of INN-based, to enable a clear identification of the product. The CHMP considered the naming and proposed warning on the outer package adequate.

2. Additional risk minimisation measures:

To further manage the risk of medication errors and to emphasise correct posology, an HCP guide targeting prescribing physicians and dispensing pharmacists was proposed by the applicant and endorsed by CHMP. The proposed educational materials provide a summary of the clinically significant information from the SmPC highlighting the differences between products and the management of coadministration with PPI/H2 antagonists. In addition, a table with the recommended doses of Daruph/Anafezyn in case of switching from a standard dasatinib formulation was agreed to be introduced. The guide also prompts HCPs to inform their patients adequately.

Overall conclusions on routine and additional risk minimisation measures:

The CHMP concluded that the information in SmPC/PiL and the proposed key messages in the educational materials are appropriate as routine- and additional risk minimisation measures. These measures are of clinical relevance for the following reasons:

- HCP educational materials highlighting the above-mentioned differences including the management of coadministration of PPI/H2 antagonists will help prescribers to select the relevant dasatinib product amongst the different available dasatinib products based on patient's comorbidities and susceptibility for specific adverse reactions (TKI/dasatinib GI toxicity: e. g. GI bleeding, gastritis, dyspepsia).
- Periodical monitoring of treatment response and tolerability in clinical practice warrants prompt identification of medication errors. Specialists' adherence to national and international (ESMO) guidelines for chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) and experience with these diagnostic entities will allow early identification of possible medication errors. Individual dose adjustments based on patients' response and tolerance are common in onco-haematology clinical practice.

The CHMP was of the view that the proposed risk minimisation measures are in accordance with the general pharmacovigilance guidelines concerning the prevention medication errors (Good practice guide on risk minimisation and prevention of medication errors. Rev 2015). Moreover, medication errors caused by confusion with a newly introduced medicinal product containing the same active substance as an authorised/established one, but different in some aspect, have been recognized and addressed generally by the CHMP's Position paper on potential medication errors in the context of benefit-risk balance and risk minimisation measures-2013. The measures for risk minimisation and monitoring of the effectiveness of these measures proposed for Daruph/Anafezyn are in accordance with the recommendation included in this position paper.

In line with pharmacovigilance GVP XVI, the additional risk minimisation measures (key messages, additional measures, follow-up of effectiveness) will be tailored at national level in accordance with the national legal requirements and local healthcare systems.

Overall, the CHMP concluded that the risk for medication errors has been duly recognised and that the proposed risk minimisation measures are appropriate to mitigate it.

3. Evaluation of effectiveness of risk minimisation measures:

The applicant proposed to monitor the effectiveness of risk minimisation measures through reporting of medication errors and to provide details on the dissemination of educational material in future Periodic

Safety Updated Reports (PSURs) for Daruph/Anafezyn. This was agreed and considered sufficient by the CHMP.

2.1.3. Concomitant administration with PPI and H2 antagonists

In this marketing authorisation application, the applicant proposed a warning allowing the concomitant use with PPI and H2 antagonists, although such concomitant use is not recommended with the reference product. The objecting Member States did not consider that the provided clinical data from the interaction **study 754/19** with omeprazole were considered sufficient to support the change. The applicant was therefore requested to substantiate the impact of co-administration with PPI and H2 antagonist in terms of efficacy and safety, since the anti-acid therapies are often administered in cycles, potentially leading to non-predictable changes of exposure to dasatinib.

In their response, the applicant indicated that chronic acid suppression with the use of PPIs, or other medicines capable of decreasing gastric acid production, such as H2-antagonists, could reduce the exposure and thereby the effectiveness of medicines that require an acidic environment for absorption. The concomitant use of TKIs and PPIs leads to a pharmacokinetic-based drug-drug interaction by reducing the TKI absorption because of increased gastric pH (decreased gastric acidity). Even though not recommended, co-administration of dasatinib products and PPIs occurs quite frequently in clinical practice as illustrated by the applicant's analysis of co-prescription data from Germany between 2017 and 2019, which showed that 21% to 24% of patients received dasatinib are co-prescribed with PPI drugs.

Following the review of data generated in the proof-of-concept study (**study 699/18**) as well as data for the reference product (Sprycel SmPC, EMEA/H/C/000709), the applicant concluded that the absorption of the reference product Sprycel may be reduced by 43% up to 86% when given with omeprazole. Since patients taking PPIs with the reference product are not following any specific posology recommendations, their plasma concentrations fluctuate in a non-predictable manner within the above-mentioned range or even outside when the anti-acid therapy is administered in cycles.

Following staggered administration of Daruph/Anafezyn with omeprazole 40 mg given once-daily in 4-days prior to dasatinib administration, the exposure of dasatinib was reduced by 20% (PPI-interaction **study 754/19**).

This reduction of exposure was of a similar extent as other known interactions for dasatinib that do not warrant dose adjustment or considered not likely relevant:

- In severely hepatic-impaired subjects, the mean C_{max} and AUC of dasatinib were decreased by 43% and 28%, respectively, compared to subjects with normal hepatic function (Sprycel SmPC, EMEA/H/C/000709). Although caution is recommended when administering dasatinib to patients with hepatic impairment, no dose adjustment is warranted in these patients and they may receive the normally recommended starting dose of dasatinib.
- The concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed based on a prediction of AUC decrease for dasatinib of approximately 25%. According to the Sprycel SmPC, this reduction is deemed not likely to be clinically meaningful.

In addition, using staggered administration, the applicant concluded that the level of reduction of dasatinib absorption observed for the test product was minimised compared to the reference product. The 20% reduction is consistent with other interactions for dasatinib which are associated with exposure reductions of a similar extent. Following the proposed recommendations for administration of PPI/H2-antagonists with Daruph/Anafezyn, the applicant considered that the changes in exposure are

consistent and predictable. Overall, the applicant concluded that Daruph/Anafezyn formulation offers an advantage for patients requiring acid-suppression therapy on top of their oncology treatment.

The CHMP noted that that the exposure reduction of 20% observed in the **study 754/19** between Daruph/Anafezyn and PPIs with staggered administration is in the same range as dexamethasone (predicted 25% reduction). This interaction has previously been assessed as "likely not clinically relevant".

The **study 754/19** did not include the reference product. Hence, no direct comparison could be made between the reference product and Daruph/Anafezyn and no significant difference could be claimed.

It is expected that H2 antagonists will have a similar or possibly less impact on gastric pH compared to PPIs. In addition, the duration of the pH effect of H2 antagonists is anticipated to be shorter compared to PPIs. The CHMP agreed to extrapolate the results of PPI to the H2 antagonists, as was done for the reference product.

In this study, maximum effect of acid suppression was achieved within 4 days of omeprazole treatment, meaning that a "worse-case" was achieved with maximal inhibition of gastric acid secretion and thereby maximal reduction of dasatinib exposure when applying the clearly stated warning of staggered administration. Hence, the CHMP considered that other administration schemes, including cyclic exposure, are not expected to result in greater reduction of exposure to dasatinib when the provided guidance is followed.

Specialists treating these patients titrate the dose based on close monitoring for drug effect and the dose can be increased in the case the patient does not respond to treatment.

Based on the above, the following warnings on PPI/H2 in the SmPC of Daruph/Anafezyn, as proposed by the applicant, was considered by CHMP to adequately inform on the impact PPI/H2 and Anafezyn/Daruph is expected to have on the patient's exposure to dasatinib:

- Section 4.4

Decreased gastric acidity

[…] In order to minimize the impact of reduction of exposure to dasatinib, H_2 antagonists and proton pump inhibitors are recommended to be taken 2 hours following the administration of [Product name] (see section 4.5). […]

- Section 4.5

Histamine-2 antagonists and proton pump inhibitors
In a study administration of a single dose 111 mg [product name] 22 hours following a 4-day, 40 mg omeprazole dose at steady state the AUC of dasatinib was reduced by 20% and Cmax by 38%. In order to minimize the impact of reduction of exposure to dasatinib, H2 antagonists and proton pump inhibitors are recommended to be taken 2 hours following the administration of [Product name] (see section 4.4). […]

3. Expert consultation

The Pharmacokinetics Working Party (PKWP) was consulted on the following question: *is the pharmacokinetic bridge to the reference product acceptable in this hybrid application?*

PKWP Response

This dasatinib immediate release product (Daruph; containing the anhydrous form of dasatinib) is submitted according to article 10.3 (hybrid) due to its supra-bioavailability and different strengths compared to the reference product Sprycel (containing the monohydrated form of dasatinib). As indicated in EMA's Q&A 1.2 of the clinical pharmacology and pharmacokinetics[2], in those cases where the applied products claims to be supra-bioavailable, the development of a lower dosage strength has to be considered and a comparative bioavailability study comparing the lower dosage strength of the supra-bioavailable product with the approved reference medicinal product should be submitted to bridge to the reference dossier. Further, the potential for a difference in food effect on the rate and/or extent of absorption or a difference in absorption interactions between the reformulated new product and the approved reference product should be discussed and when relevant evaluated in vivo.

The early pilot studies of Dasatinib Daruph indicated a higher absorption for the applied product compared to Sprycel and a final comparative bioavailability study comparing the reformulated new product with the approved reference medicinal product has been submitted. Product-specific guidance helps applicants meet the expectations of regulators in the European Union, particularly for generic applications. Demonstration of bioequivalence in fasted state and fed state in accordance with the requirements of the dasatinib PSBGL[3] would therefore be desirable, but needs to be considered here in the context of an article 10.3 (hybrid) application. For a hybrid application, pharmacokinetic differences may be considered for clinical relevance.

Demonstration of bioequivalence in the presence of PPI would also be desirable, but the pharmacokinetic differences may be acceptable if any potentially relevant differences, e.g. reduced interaction with PPI, are addressed in the SmPC dosing recommendations.

The applicant has conducted pharmacokinetic studies for a pharmacokinetic bridge between the applied product and the EU reference medicinal product by investigating bioequivalence / relative bioavailability in fasted state, the food effect of the applied formulation and relative bioavailability in fed state with respect to the reference medicinal product, as well as the impact of high stomach pH caused by the administration of a PPI on the absorption of the applied product and the reference medicinal product. In addition, the dose proportionality of the systemic exposure of the applied strengths has been investigated.

These studies are considered sufficient to characterise the systemic exposure of the applied product and the impact of the relevant factors that affect the bioavailability of the applied product and the reference medicinal product (food intake and stomach pH, since the monohydrated and anhydrous forms of dasatinib have different pH solubility profiles).

Equivalence between Dasatinib Daruph and Sprycel under fasting conditions was demonstrated in subjects with normal gastric pH (pH<4). The potential difference in the food effect on the rate and/or extent of absorption has been characterised:

- Dasatinib exposure under fed conditions for Dasatinib Daruph was higher compared to fasted conditions.
- Equivalence under fed conditions between Dasatinib Daruph and Sprycel could not be demonstrated; however, a lower food effect has been found for Dasatinib Daruph compared to reported values of Sprycel.

Since Sprycel can be administered under fasted and fed conditions and:

[2] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers

[3] https://www.ema.europa.eu/documents/scientific-guideline/dasatinib-film-coated-tablets-20-50-70-80-100-140-mg-suspension-10-mg/ml-product-specific-bioequivalence-guidance-revision-1_en.pdf

- Dasatinib exposure for Dasatinib Daruph is bioequivalent under fasted conditions, and
- Dasatinib exposures for Dasatinib Daruph under fed conditions are falling in between those of Sprycel under fasting and fed conditions,

this is considered acceptable from a pharmacokinetic point of view for a hybrid application.

A potential difference in absorption interactions with PPI that increase the pH of the stomach and decrease differently the in vivo dissolution and absorption of the anhydrous form and the monohydrate form of dasatinib in the reformulated new product and the reference product has been described. In the case of high gastric pH due to the concomitant intake of a PPI, the absorption / exposure after administration of the applied product is more consistent than the exposure observed in the reference medicinal product. Therefore, this difference is considered acceptable from a pharmacokinetic point of view for a hybrid application.

The selection of subjects with acidic gastric pH (pH<4) for inclusion in the fasted study has reduced the incidence of low-liers, which could question if safe and efficacious dasatinib plasma levels are ensured in the entire population treated with Dasatinib Daruph under fasted conditions. This study confirms that the high gastric pH is a necessary factor that causes the occurrence of low-liers. The impact of a high gastric pH has been quantified in studies with a PPI, which showed that dasatinib exposure was decreased when PPIs were co-administered, but the decrease in dasatinib plasma levels were much less for Dasatinib Daruph compared to Sprycel. In addition, in the dose finding study, subjects with and without gastric pH<4 were included and the average exposure was lower in subjects with a gastric pH>4 compared to subjects with a gastric pH<4, however less pronounced for Dasatinib Daruph. Moreover, between-subject variability increased more for Sprycel than for Dasatinib Daruph under this condition.

In conclusion, the systemic exposure of the applied product Dasatinib Daruph has been sufficiently characterised and compared with that of the reference product Sprycel, to conclude that the applied product exhibits more consistent systemic exposure in the absence and the presence of PPI.

Overall conclusion: these studies have addressed the scientific issues that need to be considered:

1) Bioequivalence has been demonstrated in fasted state in subjects with a sufficiently low gastric pH (pH<4)
2) Food effect
3) Absorption interaction when gastric pH is >4
4) Strength proportionality

PKWP focussed only on the question whether the pharmacokinetic bridge to the reference product is acceptable in this hybrid application. PKWP neither addressed how the benefit-risk assessment might be impacted nor how the risk of medication errors and co-administration of omeprazole at other time intervals with dasatinib treatment could be adequately addressed.

4. Benefit-risk balance

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.

5. Grounds for 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.

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Appendix 1 – Divergent positions

Article 29(4) of Directive 2001/83/EC

Procedure No: EMEA/H/A-29(4)/1516

Daruph and Anafezyn and associated names (INN: dasatinib (anhydrous))

Divergent statement

The following CHMP Members consider that the benefit/risk of Daruph and Anafezyn and associated names is not favourable based on the following grounds:

- The products applied for introduce an important risk of medication error that may lead to serious adverse events or lack of efficacy in a situation where the reference product (containing dasatinib monohydrate) and several generic products, including products that contain the same stable form of dasatinib anhydrous as present in Daruph, with the same pharmaceutical form (tablets) are on the market, none of them requiring dose adjustments versus the reference product.
- This risk is not outweighed by an approximately 20% absolute improvement in bioavailability of dasatinib in the products applied for compared to the reference product when taken concomitantly with a proton pump inhibitor, as estimated from a cross-study comparison, the clinical relevance of which has not been demonstrated.
- The proposed additional risk minimisation measures are not considered to sufficiently mitigate the risk of medication errors, especially in the outpatient setting.

CHMP Members expressing a divergent opinion:

- Frantisek Drafi (SK)
- Martina Weise (DE)