LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Mubucho
(dasatinib)

SE/H/2099/01-06/DC

This module reflects the scientific discussion for the approval of Mubucho. The procedure was finalised on 2022-09-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Mubucho, 16 mg, 40 mg, 55 mg, 63 mg, 79 mg, 111 mg, Film-coated tablet.

The active substance is dasatinib (anhydrous). A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Mubucho, 15,8 mg, 39,5 mg, 55,3 mg, 63,2 mg, 79 mg, 110,6 mg, film-coated tablet is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Zentiva k.s., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, FR, IE and PT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Sprycel, (20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg) authorised in UNION since 2006-11-20, with Bristol-Myers Squibb Pharma EEIG as marketing authorisation holder.

The reference product used in the pharmacokinetic studies is Sprycel, 140 mg, film-coated tablet from Ireland with Bristol-Myers Squibb Pharma EEIG, Ireland as marketing authorisation holder.

Potential similarity with orphan medicinal products

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Mubucho is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Iclusig, Xaluprine, Blincyto, Besponsa, Kymriah and Scemblix.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Iclusig, Xaluprine, Blincyto, Besponsa and Kymriah in the treatment of *Acute Lymphoblastic Leukaemia* does not prevent the granting of the marketing authorisation of Mubucho. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Iclusig and Scemblix in the treatment of *Chronic Myeloid Leukaemia*, does not prevent the granting of the marketing authorisation of Mubucho. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

No consensus was reached at day 210, the application was therefore discussed at the CMDh. After the CMDh-meeting the procedure was referred to CHMP, please see section VI for further information.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of dasatinib are well known. As dasatinib is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Mubucho is intended for a generic substitution, it is not expected to lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Mubucho from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted 1 pilot study and 5 pharmacokinetic studies.

Pharmacokinetic properties of the active substance according to the reference product
Absorption: Following an oral dose of dasatinib maximal plasma concentrations occur at approximately 0.5-3 hours.

Data from healthy subjects administered a single 100 mg dose of dasatinib 30 minutes following a high-fat meal indicated a 14 % increase in the mean AUC of dasatinib. A low-fat meal 30 minutes prior to dasatinib resulted in a 21 % increase in the mean AUC of dasatinib. The observed food effects do not represent clinically relevant changes in exposure. Dasatinib exposure variability is higher under fasted conditions (47 % CV) compared to light-fat meal (39 % CV) and high-fat meal (32 % CV) conditions.
Dasatinib can be taken with or without a meal and should be taken consistently either in the morning or in the evening.

Linearity: Following oral administration, the increase in the mean exposure (AUCτ) is approximately proportional to the dose increment across doses ranging from 25 mg to 120 mg twice daily.

Elimination: The mean terminal half-life of dasatinib is 3 hours to 5 hours.

Pharmacokinetic studies

A pilot study (611/16) was performed with three different prototype formulations compared to the reference product Sprycel, 140 mg in order to select one of the prototypes for further development. Test 1 was further developed and included in study 699/18.

Study 699/18 was a dose-finding study performed in two stage design. In the first stage, 140 mg dasatinib was compared to 140 mg Sprycel in presence of omeprazole. Bioequivalence was not shown. The applicant proceeded with stage 2 where the test and the reference product were compared without omeprazole. Based on the result from stage 2, the applicant concluded that the dose could be reduced with 20 %. However, dose reduction of 21 % has been selected in order to prevent medication errors.

Table 1. Stage 2 ('Dose-finding study') with 140 mg dasatinib and 140 mg Sprycel. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for dasatinib, n=23 (normochlorhydric subcohort).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**623.67 ± 204.01**	**194.19 ± 105.77**	**1.02 (0.50-2.50)**
Reference	**489.20 ± 206.41**	**153.56 ± 67.49**	**0.67 (0.50 -2.00)**
***Ratio (90% CI)**	**133.79 (121.55-147.25)**	**119.69 (104.27-137.40)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Study 744/19 was a confirmation study where 110.6 mg of the test product was compared with 140 mg Sprycel under fasting conditions. Bioequivalence was shown.

Table 2. Pivotal bioequivalence study with 110.6 mg dasatinib and 140 mg Sprycel. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD (CV), t_{max} median, range) for dasatinib, n=80.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**444.66±153.01 (34.41)**	**132.29±61.65 (46.60)**	**1.00 h (0.50 – 4.00 h)**
Reference	**482.41±221.40 (45.89)**	**139.65±66.64 (47.72)**	**0.83 h (0.33 – 24.00 h)**
***Ratio (90% CI)**	**99.36 (89.39- 110.43)**	**100.39 (86.83- 116.06)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Study 753/19 was a food effect study where 110.6 mg of the test product was administered under both fasted and fed conditions and 140 mg Sprycel was administered under fed conditions. When test (fed) and reference (fed) was compared, both AUC_{0-t} and C_{max} fell outside the conventional acceptance

range.

Table 3. Food effect study with 110.6 mg dasatinib and 140 mg Sprycel. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, (CV%), t_{max} median, range) for dasatinib, test and reference with food, n=35.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (fed) (CV%)	**467.54 ± 111.37 (23.82)**	**137.91 ± 52.95 (38.39)**	**1.25 (0.75-4.00)**
Reference (fed) (CV%)	**556.26 ± 191.77 (34.48)**	**152.31 ± 65.36 (42.91)**	**1.25 (0.50-3.00)**
***Ratio (90% CI)**	**87.77 (78.10-98.65)**	**93.46 (78.35-111.48)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration
CV% coefficient of variation (%); %CV=100*(SD/MEAN)

**calculated based on ln-transformed data*

Study 754/19 was a drug interaction study with omeprazole where 110.6 mg of the test product was administered with and without omeprazole under fasting conditions. Omeprazole was administered 22 hours before dasatinib. AUC_{0-t} and C_{max} was reduced by 20 % and 38 % respectively when the test product was administered 22 hours following the last dose of omeprazole.

Table 4. Drug interaction study with 110.6 mg dasatinib. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for dasatinib, n=35.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (with omeprazole)	316.84 ± 117.47	81.87 ± 41.20	1.25 (0.50-5.00)
Test	398.95 ± 137.36	132.05 ± 60.49	0.83 (0.33-4.00)
***Ratio (90% CI)**	79.70 (72.56-87.54)	62.34 (51.25-75.82)	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Study 765/19 was a dose-proportionality study performed with 15.8 mg, 55.3 mg and 110.6 mg of the test product under fasting conditions. Dose proportionality was established between 15.8 mg and 110.6 mg for the applied product. A biowaiver was sought for the additional strengths of 15.8 mg, 39.5 mg, 55.3 mg, 63.2 mg and 79 mg.

Table 5. Estimation of slope (β) of the regression line and corresponding 90% confidence intervals for dasatinib 110.6 mg, 55.3 mg and 15.8 mg, film-coated tablets.

Parameter	Slope Estimate	90% confidence limits	
		Lower	Upper
$AUC_{(0-t)}$ (ng·h/mL)	1.1105	1.0551	1.1658
C_{max} (ng/mL)	0.9704	0.8885	1.0524

Discussion and overall conclusion

The applicant submitted several studies in order to support the approval of dasatinib 15.8 mg, 39.5 mg, 55.3 mg, 63.2 mg, 79 mg, 110.6 mg film-coated tablets. The applicant states that the applied product is suprabioavailable compared to the reference product and that it has improved formulation performance, especially reduced pH dependency of absorption.

Study 699/18 showed that the applied product had higher bioavailability than the reference product. Thus, the dasatinib dose was reduced by about 21 % to compensate for higher bioavailability. The new formulation, however, had a somewhat lower food effect and thus AUC_{0-t} and C_{max} fell outside the conventional acceptance criteria of 80.00-125.00 % in the fed state (study 753/19) while the results in the fasted state were within the conventional acceptance criteria of 80.00-125.00 % (study 744/19) when comparing the test product 110.6 mg strength to the reference product 140 mg strength. According to 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*), bioequivalence must be shown in both fasted and fed state for generic applications.

Subject 21 was not included in the statistical analysis for study 753/19 (food effect study) even though the subject had evaluable result for two periods (T_{fed} and R_{fed}). The applicant was asked to re-calcualte the statistical analysis with this subject included. The ratio for C_{max} was 94.05 (79.25-111.62) and for AUC_{0-t} 87.84 (78.44-98.37), which did not change the conclusion of study 753/19.

Given that the applied product is a hybrid, based on the suprabioavialability shown compared to the reference product, differences from the reference product can be accepted if they are clinically justified. The applicant regarded that AUC_{0-t} and C_{max} falling slightly outside the lower bioequivalence acceptance limit in the fed state did not raise any clinical concerns and submitted further justification. Based on the fact that similar bioavailability was shown in fasting conditions, that the reference product can be taken with or without food and that the exposure of applied product when given with a meal is well within the exposure window defined by the concentrations of dasatinib achieved for the reference product, the AUC_{0-t} and C_{max} falling slightly outside the lower bioequivalence acceptance limit in the fed state is regarded justified.

In the submitted SmPC, the applicant suggests the same food recommendation as the reference product, i.e. dasatinib can be taken with or without a meal. It has however another recommendation regarding interaction with PPI. While the reference product does not recommend concomitant use of H_2 antagonists and PPIs with dasatinib, following is suggested for the applied product:
"...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]." This wording is acceptable. However, these experiments cannot claim formal significant difference between the formulations as the estimates of PPI effect come from different studies.

Absence of studies with the additional strengths of 15.8 mg, 39.5 mg, 55.3 mg, 63.2 mg and 79 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the

investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of dasatinib is linear between 15.8 mg and 110.6 mg.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.

The changes in relation to the reference product related to decreased gastric acidity and concomitant PPI administration in the SmPC have been sufficiently justified based on the pharmacokinetic data presented. The risk for dosing errors have been adequately addressed in the SmPC. It has been clearly highlighted that Mubucho is not interchangeable with other dasatinib formulations, and that the dosing recommendation of the intended product must be followed. In addition, only the recommended doses for Mubucho are presented in 4.2.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Mubucho.

Safety specification
Summary table of proposed safety concerns (RMP Part II: Module SVIII):

Summary of safety concerns	
Important identified risks	• Myelosuppression • Fluid retention • Bleeding related events • QT Prolongation • Pulmonary Arterial Hypertension (PAH) • Pregnancy related malformative or foeto/neonatal toxicity
Important potential risks	• Severe hepatotoxicities • Direct cardiotoxic effects (e.g. cardiomyopathy) • Growth and development disorders and bone mineral metabolism disorders in the pediatric population • Toxic skin reactions • CYP3A4 drug interactions • Hepatitis B Virus (HBV) reactivation • Nephrotic syndrome • Medication error
Missing information	• Carcinogenicity • Pediatric data: children under 1 year of age • Reproductive and lactation data

In addition to the safety concerns aligned to the safety concerns in the RMP for the reference product, an additional important potential risk “Medication error” is proposed for Mubucho. This risk may occur in the case of switching from standard dasatinib formulation since the dose of Mubucho is 21% lower than the dose of the standard dasatinib formulation, rounded to the nearest whole tablet.

Pharmacovigilance Plan
No additional pharmacovigilance activities are proposed by the applicant.

Risk minimisation measures
According to the Applicant the Mubucho risk minimisation measures for the safety concerns identical with Sprycel are aligned to reference product risk minimisation measures. In addition, specific routine risk minimisation measures are proposed to mitigate the risk for Medication errors.

The MAH will review available information on medication errors with dasatinib in the Periodic Benefit Risk Evaluation Report to evaluate effectiveness of risk minimisation measures.
Only the risk minimisation measures proposed for the important potential risk "Medication error" specific for the Mubucho is described in detail below as other concerns are identical with Sprycel (Bristol-Myers Squibb Pharma EEIG).

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Medication error	Routine risk communication: SmPC sections 4.2, 4.4, 4.5 and 5.2 PL sections 2 and 3 Information on the outer package of the product. (Verify product name and dosage before taking this medicine. [Product name] is not equivalent to other dasatinib-containing products.) Routine risk minimisation activities recommending specific clinical measures to address the risk: 4.2 Special warnings and precautions for use – Product name] cannot be used interchangeably with other dasatinib formulations. The dose of [Product name] have been reduced by 21% compared to other dasatinib products to achieve similar exposure. In case of switch between dasatinib-containing products, the dosing recommendations of the intended product must be followed. 4.4 Special warnings and precautions for use – [Product name] has a higher bioavailability than other dasatinib-containing products and cannot be used interchangeably with other dasatinib formulations. In case of switch between dasatinib-containing products, the dosing recommendations of the intended product must be followed (see section Posology). Decreased gastric acidity (the pH dependency should be taken into account when changing dasatinib formulation.) 4.5 Interactions – H2 antagonists and proton pump inhibitors PIL (3) How to take: Do not switch between taking [Product name] tablets and other dasatinib-tablets without talking to your doctor. The strength of [Product name] tablets is different from other dasatinib-containing medicines. Other routine risk minimisation measures beyond the Product Information Legal status – categorisation at member state level

Routine risk minimisation measures deemed sufficient to manage the safety concerns of Mubucho.

Additional Risk Minimisation Measures
There are no additional risk minimisation measures in the RMP for the reference producty Sprycel. For the hybrid product Mubucho additional risk minimisation measures such as educational materials are proposed in order to mitigate the risk of medication errors. This is endorsed.

Educational materials for physicians and patients on the risk of medication error
Educational materials to be circulated to pharmacists and physicians who may be involved in treating patients with dasatinib in order to inform them on the risk of medication error. Pharmacists shall

reduce the risk of medication error at the point of dispensing. Physicians/Pharmacists shall further distribute the patient material to the patients (precise distribution plan will be agreed on national level.)
Precise list of HCPs should be agreed on national level.

Objectives:
The applicant/MAH shall ensure that all the physicians, which may prescribe [Product name], have at their disposal educational materials that include Prescriber Guide conveying the key messages regarding correct posology of [Product name] with respect to the risk of medication error. The applicant/MAH shall ensure that all the pharmacists, who may dispense [Product name], have at their disposal educational materials conveying the key messages regarding correct posology of [Product name] with respect to the risk of medication error.
The risk should be managed primarily at the point of prescribing and dispensing.

Rationale for the additional risk minimisation activity:
The educational materials shall be delivered to prescribers and dispensing pharmacists. The national specialities must be adapted at national level with the national competent authorities as well as implementation plan.

Target audience and planned distribution path:
All healthcare professionals who are expected to prescribe/dispense [Product name] are provided with the following educational package for all indications:
- HCP (Healthcare professional) Guide

The distribution plan needs to be tailored nationally and agreed with relevant member state authority.

Key messages of the additional risk minimisation measures provided in Annex 6 of the RMP are otlined below:

The HCP Guide shall contain the following key elements:
- Description of [Product name] formulation and differences from standard dasatinib formulation
  - The information that [Product name] cannot be used interchangeably with other dasatinib formulations
  - The recommended posology of the product. Information about reduction of the dose by 21 % compared to other dasatinib products to achieve similar exposure.
  - Impact of pH
  - Information that dose adjustments might be necessary in patients with achlorhydria/hypochlorhydria/decreased gastric acidity;
  - Information on drug interactions (histamine-2 antagonists, proton pump inhibitors, antacids)
  - Information on timely administration of histamine-2-antagonists, proton pump inhibitors and Aluminium hydroxide/Magnesium hydroxide

Additionally, the outer packaging was changed to carry a following warning: Verify product name and dosage before taking this medicine. [Product name] is not equivalent to other dasatinib-containing products.

The RMP v0.4 updated in the relevant sections with the suggested amendments has been provided.

The proposed plan to periodically review in PSURs/PBERs the reports of medical errors as method to measure the effectiveness of HCP educational materials as RMM is considered appropriate.

Conclusion on RMP
The Risk Management Plan is endorsed.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PlL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

At day 210 the procedure was referred in accordance with Art. 29(1) to the CMDh since the Benefit/Risk ratio was considered negative by some concerned member states.

The referral was triggered as the application was considered by the objecting CMSs as a “failed” generic and changing the posology in comparison to the RefMP due to the suprabioavailability constitutes a safety risk. New clinical data would need to be provided to prove safety and efficacy of the new strengths for the applied product. There were also concerns about the bioequivalence data in fed state and the concomitant use of the product with PPI or H2 antagonists.

During the CMDh referral, the RMS clarified their position. The RMS considered that Art. 10(3) can be used as legal basis for suprabioavailable products, and that the product has been developed in accordance with the available guidance. The RMS considered that the proposed risk minimisation measures adequately address the potential risk for medication errors and that the applicant had addressed the other outstanding issues.

During the CMDh meeting, there was an oral explanation with the applicant who presented their responses to the questions raised, followed by a trend vote in the CMDh with a majority in agreement with the position of the RMS to conclude the procedure positively.

Since no consensus was reached at the level of CMDh, the procedure was then referred to CHMP in accordance with Art. 29(4).

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 Mubucho:

- 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 Mubucho 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 19 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 Mubucho 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 Mubucho to the reference product is established.

On the second point, since Mubucho 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 Mubucho 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 Mubucho 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 Mubucho, as well as the routine and additional proposed risk minimisation measures. Additionally, the CHMP took into consideration the potential advantageous pharmacokinetics characteristics of Mubucho 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. Following the positive CHMP opinion, the European Commission has adopted the Commission Implementing decision for granting of the marketing authorisation on Mubucho on 2022-07-19.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  For the hybrid product Mubucho additional risk minimisation measures such as educational materials for Health Care Professionals (HCP Guide) are proposed to mitigate the risk of medication errors.
  The educational materials shall be delivered to prescribers and dispensing pharmacists. The distribution plan and the key messages in the HCP Guide should be tailored nationally and agreed with the national competent authorities.

VII. APPROVAL

The decentralised procedure for Mubucho, 16 mg, 40 mg, 55 mg, 63 mg, 79 mg, 111 mg, Film-coated tablet was positively finalised on 2022-09-15.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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