LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dogrivio
(dolutegravir sodium)

SE/H/2740/001-002/DC

This module reflects the scientific discussion for the approval of Dogrivio. The procedure was finalised at 2026-02-10. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Dogrivio, 25 mg, 50 mg, Film-coated tablet.

The active substance is dolutegravir, dolutegravir sodium. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Dogrivio is used in combination with other anti-retroviral medicinal products
for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children of at least 6 years of age or older and weighing at least 20 kg.

II.2 General comments on the submitted dossier

The application for Dogrivio, 25 mg, 50 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following concerned member states (CMS): SE/H/2740 *CY*.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Tivicay, 50 mg, film-coated tablet, authorised in EU since 2014, with ViiV Healthcare BV as marketing authorisation holder.

The reference product used in the bioequivalence study is Tivicay, 50 mg, film-coated tablet, from Germany with ViiV Healthcare BV as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided. No issues regarding GCP have been identified. The clinical and the bioanalytical facilities have been regularly inspected by competent authorities. The most recent inspection is by ES/NL in 2024 and was without critical findings. No inspection of the submitted study is necessary.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
The pharmacodynamic, pharmacokinetic and toxicological properties of dolutegravir are well known. As dolutegravir is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Shortly, dolutegravir is a pyridine carboxylic acid compound that is considered to be a second-generation HIV1 integrase inhibitor. Dolutegravir binds to the HIV integrase active site blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. It was first approved for treatment HIV1 infection in the European Union in 2014 (Reference product: Tivicay). The provided non-clinical overview is mainly based on information derived from the Tivicay EPAR with some additional public literature studies on developmental & reproductive toxicity (which do not change the overall conclusions that there are no clear indications that dolutegravir is developmentally or reproductive toxic). It is noted in the Tivicay SmPC (4.6.) that a large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity and the same information is provided in the Dogrivio SmPC.

Environmental Risk Assessment (ERA)
The original dolutegravir ERAs were approved under the 2006 CHMP ERA GL framework but the present dolutegravir ERA is subject to the 2024 CHMP ERA GL. An ERA-document has been submitted that identifies the Tivicay ERA as a reference ERA under the ‘Art 10-ERA’ approach. The reference ERA concludes that dolutegravir is not an environmental risk based on risk quotients (RQ).

While dolutegravir can be considered very persistent in the environment, it is not an PBT or vPvB.

The owner of the reference ERA (ViiV Healthcare BV) has not agreed to data sharing and the ERA-document states that the conclusions of the reference ERA are relevant for the present product as well. Nominally, the reference ERA does not fully fulfil all the 2024 CHMP ERA GL technical criteria (containing an acute toxicity earthworm study instead of the presently required chronic/reproductive toxicity earthworm test (OECD TG220 or TG222). That being said, the absence of the latter in the reference ERA in an Art 10-ERA approach is considered provisionally acceptable in this case as the NOEC for the reference ERA acute toxicity test was at the maximum concentration of 1000 mg/kg dw and the lowest terrestrial NOEC in the soil assessment was 12 mg/kg dw – giving a soil RQ < 0.01. As such, an earthworm reproductive toxicity sensitivity several orders of magnitude beyond the acute toxicity NOEC would be required to shift the environmental risk conclusions (i.e., towards soil RQ > 1), which is considered very unlikely. Invoking the reference ERA conclusions is therefore considered acceptable although the absence of actual earthworm toxicity data leaves some uncertainty. A commitment has therefore been provided that if information about earthworm chronic toxicity becomes available, an updated ERA document will be submitted.

Summary of main study results (derived from Dovato EPAR)

Substance (INN/Invented Name): Dolutegravir			
CAS-number (if available): #1051375-19-9 (sodium salt) & #1051375-16-6 (free acid)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG107	Log D (pH 5)= -2.28 Log D (pH 7)= -2.45 Log D (pH 9)= -3.21	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-2.45	not B
	BCF	NA	not B
Persistence	DT50 / ready biodegradability	DT50 > 1000d Not readily biodegradable	vP in sediment-water and soil
Toxicity	NOEC or CMR	NA	T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.50	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OPPTs 835.1110	<u>*Sludge*</u> Kdoc =10609-15367 L/kg Kf = 14407 L/kg (Koc=4.16)	Adsorption to sludge
Ready Biodegradability Test	OECD TG301	Not readily biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50,\ whole\ system}$ > 1000 d % shifting-to-sediment: 82.1-88			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*P. subcapitata*	OECD TG201	*Biomass* NOEC EC50 *Yield* NOEC EC50 *Growth* NOEC EC50	 0.0954 0.233 0.0954 0.226 0.305 1.032	mg/ L	Biomass and yield the most sensitive endpoints.
Daphnia sp. Reproduction Test	OECD TG211	*Reprod.* NOEC LOEC *Length* NOEC LOEC *Mortality* NOEC LOEC EC50	 0.834 2.69 0.834 2.69 0.239 0.834 >0.834	mg/ L	Survival most sensitive.
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD TG210	*Hatching* NOEC LOEC *Length-weight* NOEC LOEC *Larval-survival* NOEC LOEC	 3.57 11.0 0.753 3.57 0.22 0.753	mg/ L	No surviving fry at 11 mg/L.
Activated Sludge, Respiration Inhibition Test	OECD TG209	EC10 EC50 NOEC	108 684 24	mg/ L	No inhibitory effect
Sediment dwelling organism / *Chironomus riparius*	OECD TG218	NOEC LOEC	858 >858	mg/ kg	
Phase IIb Studies					
Bioaccumulation	OECD TG305	BCF	NA	L/kg	Not conducted.

Aerobic and anaerobic transformation in soil	OECD TG307	DT50	>1000	d	for 3 soils (in South Witham soil not possible to determine).
Soil Micro organisms: Nitrogen Transformation Test	OECD TG216	NOEC	985	mg/ kg	EC50 could not be calculated
Terrestrial Plants, Growth Test *Wheat, Onion, Dwarf bean, Tomato, Turnip, Pea*	OECD TG208	NOEC LOEC EC50	12 37 79.9 (pea) to >1000 (wheat, onion)	mg/ kg	Pea was most sensitive
Earthworm, Acute Toxicity Tests/ *Eisenia fetida*	OECD TG207	NOEC LOEC	1000 >1000	mg/ kg dw	OBS, the 2024 CHMP ERA GL requires chronic toxicity tests in earthworm.
Collembola, Reproduction Test/ *Folsomia candida*	OECD TG232	NOEC LOEC	29 52	mg/ kg	

NB: In case Phase I or Phase II studies or results of specific parameters have not been submitted these tables/parameters should be deleted

Conclusions on ERA studies:
The use of Tivicay ERA as a reference ERA (for Art 10-ERA document purposes under the 2024 ERA-GL) is considered acceptable.

Overall conclusions
There are no objections to approval of Dogrivio from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one pivotal bioequivalence study comparing Dolutegravir, 50 mg, film-coated tablets with the reference product Tivicay, 50 mg, film-coated tablets. In addition, a pilot study was performed during formulation development (this study is not further discussed in this report).

Pharmacokinetic properties of the active substance
The absolute oral bioavailability of dolutegravir has not been established. Following an oral dose of dolutegravir maximal plasma concentrations occur at approximately 1-3 hours.
The general recommendation in the SmPC of the originator is that the product can be taken with or without food. Food increases the extent and slows the rate of absorption of dolutegravir. These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, dolutegravir is recommended to be taken with food by patients infected with HIV with integrase class resistance.

The pharmacokinetics of dolutegravir is linear within the dose range 25-50 mg following oral administration of the tablet formulation. Non-linear pharmacokinetics (less than proportional increase in exposure with increasing dose) is observed in the range 2 to 100 mg.

The terminal half-life is approximately 14 hours.

Study 0108-24

Methods

This was a single-dose, two-way crossover study conducted in 46 healthy volunteers, comparing Dolutegravir, 50 mg, film-coated tablets with Tivicay, 50 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of dolutegravir were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 17th June and 30th June 2024.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for dolutegravir, n=42.

Treatment	**AUC_{0-t}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	**47766 ± 17699**	**2499 ± 928**	**2.125 (0.667 - 5.000)**
Reference	**47516 ± 16942**	**2510 ± 867**	**2.500 (0.667 - 4.500)**
***Ratio (90% CI)**	**101.5 (94.58 – 109.00)**	**99.9 (93.05 – 107.21)**	**-**
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*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 25 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and ICH M13A and also in line with the product-specific bioequivalence guideline for dolutegravir tablets. The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Dolutegravir, 50 mg, film-coated tablets are considered bioequivalent with Tivicay, 50 mg, film-coated tablets.

Absence of studies with the additional strength of 25 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 dolutegravir is linear between 25 mg and 50 mg.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
SE/H/2740: Proposed MAH in RMS, CMS CY, EL: Elpen Pharmaceutical Co. Inc.;
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Dogrivio.

Part II Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Neural tube defects
Missing information	• Use in pregnancy/breastfeeding

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plans, version 0.4 signed 2026-01-27 for Dogrivio is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Dogrivio is found adequate. There are no objections to approval of Dogrivio, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments

Description	Due date
Non-clinical/ERA commitment: Submission of a variation type IB C.I.z. in line with the current ERA guideline requirements, if new data emerges that require an update to the ERA, i.e. that alters the conclusions of the current assessment (i.e., access to earthworm chronic toxicity data which is presently missing in the Tivicay reference ERA).	Not specified, depends on if new data becomes available.

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**
  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**
  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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 PL 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. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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