IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Doxylamine/Pyridoxine Exeltis 10 mg/10 mg gastro-resistant tablets
Pyridoxine hydrochloride
Doxylamine
PA22998/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Doxylamine/Pyridoxine 10/10 mg Gastro-resistant tablet, from Exeltis healthcare S.L on 17th December 2021 for the symptomatic treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management. Limitations of use: The combination doxylamine/pyridoxine has not been studied in case of hyperemesis gravidarum. Doxylamine/Pyridoxine Exeltis 10/10 mg Gastro-resistant tablet is a fixed dose combination product containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride also referred to by the applicant as Diclectin.

The original application was submitted via a Decentralised Procedure (DCP) as a full mixed application under Article 8(3) of Directive 2001/83/EC, supported by genotoxicity and clinical studies submitted by the applicant, as well as bibliographic data, with the Reference Member State (RMS) being Ireland and Germany, Spain, France, Italy and Poland as Concerned Member States.

During the mutual recognition procedure IE/H/1111/001/E/001 CMSs Austria, Belgium, Czech republic, Estonia, Lithuania, Latvia, Hungary and Slovakia were added.

This product is subject to prescription which may be renewed. The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

II. QUALITY ASPECTS

This application is for Doxylamine/Pyridoxine Exeltis 10/10 mg Gastro-resistant Tablet.

II.2 Drug substance

The active substances are doxylamine hydrogen succinate and pyridoxine hydrochloride, established active substances described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Composition of the medicinal product

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur.EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Doxylamine/Pyridoxine Exeltis 10/10 mg gastro-resistant tablet.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Doxylamine/Pyridoxine 10/10 mg gastro-resistant tablets is a fixed dose combination product containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. The applicant has provided a mixed dossier for these known active substances, with mostly bibliographic non-clinical data and sponsor-conducted genotoxicity studies.

The HPRA has been assured that GLP standards were followed in an appropriate manner in the genotoxicity studies conducted by the sponsor. The GLP compliance status of the non-clinical data from the published literature cannot be determined.

III.2 Pharmacology

A limited bibliographic overview was provided of the pharmacology of these two unrelated compounds, doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B6), which provide anti-nausea and anti-emetic activity in combination. Doxylamine succinate is a histamine 1 (H1) antagonist which selectively binds to and inhibits the action of endogenous histamine. H1 antagonists can also antagonize the muscarinic acetylcholine receptor M1. Pyridoxine hydrochloride, also known as vitamin B6, in coenzyme form performs a wide variety of functions in the body with involvement in more than 100 enzyme reactions, including the breakdown of proteins, fats and carbohydrates from food into products needed by the body. Vitamin B6 plays a role in cognitive development through the biosynthesis of neurotransmitters and in maintaining normal levels of homocysteine, an amino acid in the blood. Vitamin B6 is involved in gluconeogenesis and glycogenolysis, immune function (it promotes lymphocyte and interleukin-2 production), and haemoglobin formation.

No new nonclinical pharmacology studies were completed and sections on secondary pharmacology and safety pharmacology have been omitted from the non-clinical overview. On the basis that there is sufficient clinical experience with these active substances, the submission of further non-clinical pharmacology data was not requested.

III.3 Pharmacokinetics

A limited bibliographic overview was provided of the available non-clinical pharmacokinetics data in the scientific literature. Much of the available data for both monocomponents is derived from rodents, although some data from combination studies of both components in non-human primates was included. For doxylamine, oral bioavailability was limited (24.7%), absorption was more rapid following intranasal delivery, although Tmax was 0.5h for intranasal delivery and 1.5 h following oral administration. Distribution has been demonstrated in murine post-implantation embryos to highlight any potential risk to newborns following oral administration. There is evidence that there is distribution of doxylamine to the early post-implantation rodent embryo. This transfer is likely independent of any pH gradient between maternal plasma and embryo compartments. Metabolism was determined in rats, non-conjugated doxylamine metabolites were identified as doxylamine N-oxide, desmethyldoxylamine, didesmethyldoxylamine and ring-hydroxylated products of doxylamine and desmethyldoxylamine. Conjugated glucuronide doxylamine metabolites were also identified as doxylamine O-glucuronide, N-desmethyl-doxylamine O-glucuronide, and N,N-didesmethyldoxylamine O-glucuronide. Doxylamine succinate is a phenobarbital-type inducer of liver microsomal enzymes and produces changes in thyroid hormone balance in mice, however these changes have not been detected in the clinic where there are no indications of enzyme induction and no effects on thyroid hormone function. Elimination is more predominant via urine, although the extent of urinary or faecal elimination could be dependent on dose administered – a higher level of faecal elimination was shown with low doses of doxylamine administration.

For pyridoxine, limited pharmacokinetic data was presented in pregnant and non-pregnant rats. Levels of plasma pyridoxal-5-phosphate (PLP) are lower in pregnant rats than compared to control animals, this is likely not to be due to foetal sequestration of vitamin B-6, less than 3% of the oral dose was detected in foetal/uterine tissue of the pregnant rats.

Maternal pharmacokinetics has been described in three species of monkey administered a drug product containing equal concentrations of doxylamine hydrogen succinate and pyridoxine hydrochloride: cynomolgus, rhesus and baboon. No morphologic abnormalities were observed in either non-human primate species, and pharmacokinetic parameters did not alter between pregnant or non-pregnant animals, suggesting no significant exposure to foetal tissue as a result of treatment with the combination product.

No information on pharmacokinetic drug interactions was provided. Given the extent of clinical data available for these active substance, no further non-clinical pharmacokinetics data were requested.

III.4 Toxicology

The toxicology data presented is bibliographic, with the exception of GLP-compliant in vitro and in vivo genotoxicity studies. Both doxylamine and pyridoxine are not genotoxic or carcinogenic. The target organs for toxicity are, for doxylamine, the liver with associated organ weight changes, and for pyridoxine, at high doses neuronal degeneration, ataxia and weight loss. High margins of safety exist however between these observed changes and the anticipated maximum clinical dose for Doxylamine/ Pyridoxine Exeltis 10/10 mg gastro resistant tablets. Doxylamine has been shown to be transferred via the placenta to a limited extent, although there is no clear data for pyridoxine. Animal studies on reproductive and developmental toxicity have been completed with the combination of doxylamine and pyridoxine in rats, rabbits and non-human primates. Skeletal changes and reduced foetal viability have been detected; but there was no evidence of teratogenicity in either tested species using the combination product and the changes detected in rats and rabbits were at doses determined to be toxic to the mother.

Two studies are reported by Hendrickx et al (1985), based in the California Primate Research Center, utilised exposure to a combination product containing equal concentrations of doxylamine hydrogen succinate and pyridoxine hydrochloride to cynomolgus monkeys, rhesus monkeys and baboons. The most significant change detected was the high incidence of ventricular septal defects, although this appears to be a delay in closure of the ventricular septum which closes at term. There was no evidence of a dose effect, and no further cardiac or extra-cardiac changes were observed in any other term infants. Of the total number of pregnant non-human primates treated with the combination (45+91=136 cynomolgus monkeys, 19 rhesus monkeys, 25 baboons), only one infant showed evidence of a heart defect. No further cardiac or extra-cardiac changes were observed in any other term infants.

Clinical exposure data and epidemiological review provide a better evidence base given the extensive use of this combination product to date in pregnant women suffering from morning sickness.

III.5 Ecotoxicity/environmental risk assessment

Doxylamine succinate is not a PBT substance as the log Kow does not exceed 4.5. Pyridoxine hydrochloride is a vitamin, the use of which is unlikely to result in significant risk to the environment. Considering the above data, Doxylamine/Pyridoxine Exeltis 10/10 mg Gastro-resistant Tablet is not expected to pose a risk to the environment

III.6 Discussion on the non-clinical aspects

An adequate mixed non-clinical dossier for these known active substances, with mostly bibliographic non-clinical data and sponsor-conducted genotoxicity studies, has been provided in support of this product.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of the combination of doxylamine and pyridoxine is well known. The fixed dose combination of doxylamine and pyridoxine has been authorised in the UK since July 2018 and the Netherlands and Ireland since 2019.

The clinical data supporting this application is largely derived from the Diclectin clinical program. Diclectin (fixed dose combination 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) has been marketed in Canada by Duchesnay since 1983, and in the US under the trade name Diclegis, since 2013. The applicant for this procedure, Exeltis healthcare S.L, is a licensee of Duchesnay.
A statement on the application of appropriate GCP standards in the submitted studies has been provided.

IV.2 Pharmacokinetics

An overview of the pharmacokinetics characteristics of the monocomponents using literature data was provided by the applicant. The main pharmacokinetic characteristics obtained with the mono-components are summarised below.

Doxylamine

Absorption
Doxylamineis absorbed well when administered orally. Peak plasma concentration is achieved within 2-3 hours post dose when administered as a solution or immediate release tablet.

Distribution
Doxylamine has a low protein binding and permeability, and is not a substrate of P-glycoprotein and is widely distributed into tissues. Doxylamine crosses the blood-brain barrier and has a high affinity for H1 receptors in the brain.

Metabolism
Doxylamine is biotransformed in the liver by N-dealkylation to its principle metabolites, N desmethyldoxylamine and N, N-didesmethyldoxylamine, which are excreted by the kidney

Excretion
A biotransformation study in human reported 60% of the dose excreted as unchanged doxylamine in urine together with five minor metabolites accounting for another 10% of the dose. The principle metabolites of doxylamine, N-desmethyl-doxylamine and N,N-didesmethyldoxylamine, are excreted by the kidney.

Pyridoxine

Absorption
Pyridoxine is readily absorbed in the GI tract, mainly in the jejunum. The extent and rate of absorption of pyridoxine is strongly dependent upon formulation with decreasing bioavailability corresponding to a decrease in-vitro solubility of tablets. The absolute bioavailability has been reported to be close to 100%.

Distribution
Pyridoxine is highly protein bound, primarily to albumin. Its metabolites pyridoxal and pyridoxal 5'-phosphate are, respectively, partially and almost completely bound to albumin in plasma. Its main active metabolite pyridoxal 5'-phosphate (PLP) accounts for at least 60% of circulating vitamin B6 concentrations.

Metabolism
Pyridoxine is primarily metabolized in the liver with a high first pass effect. The metabolic scheme for pyridoxine is complex, with formation of primary and secondary metabolites along with interconversion back to pyridoxine. Pyridoxine and its metabolites, pyridoxal, pyridoxamine, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate contribute to the biologic activity. In contrast, the major metabolite 4-pyridoxic acid is inactive and is excreted in urine. Following phosphorylation, the main active metabolite, pyridoxal 5'-phosphate, is released into the circulation and is highly protein bound, accounting for at least 60% of circulating vitamin B6.

Excretion
Renal elimination is also the main pathway of excretion of derivatives of pyridoxine metabolism (reported to be 74% of a 100 mg intravenous dose of pyridoxine), mainly as the inactive form 4-pyridoxic acid.

Pharmacokinetic studies

In accordance with current CHMP guidelines, a pivotal pharmacokinetic study, was submitted to support the application.

Supportive studies (including supplementary, relative bioavailability and a food effect) were also presented.

Pivotal study -
A randomised, open-label, 3-way crossover comparative bioavailability study comparing Diclectin 10 mg/10 mg Delayed-Release Tablets (A) with Doxylamine 20 mg Delayed-Release Tablet (B) and Pyridoxine 20 mg Delayed-Release Tablet (C), following a single dose of 20 mg Doxylamine and/or 20 mg Pyridoxine in healthy subjects under fasting conditions
The results of this study demonstrate that the pharmacokinetics of the monocomponents with the same pharmaceutical form are essentially similar when administered separately and in combination.

Supplementary Bioequivalence Study-
This was a single centre, randomised, single dose, open-label, 2-way, cross-over relative bioavailability study to compare the rate and extent of absorption of Diclectin (Test) versus a combination of doxylamine succinate 10 mg/10 mL and pyridoxine hydrochloride 10 mg/10mL oral solutions (Reference) administered as 2 x 10mg/10 mg delayed-release tablets or 1 x 20 mL + 1 x 20 mL oral solutions under fasting conditions. Treatment periods were separated by a washout of at least 28 days.
This study provided additional data on PK profile. Tmax occurred approximately 4.5 hours earlier for doxylamine and 3.5 hours earlier for pyridoxine with the oral solution as compared to fixed dose tablet. Some difference in Cmax tmax and tlag were observed but are expected given the actives in the fixed dose combination (FDC) were in tablet formulation while the mono-components actives were in oral solution. Although this study does not demonstrate bioequivalence of Diclectin versus the mono-components administered separately, it shows evidence of bioequivalence of fixed dose combination versus mono-components taken simultaneously in solution.

Relative bioavailability –
This was a single and multiple-dose, single-centre, open-label study to assess the pharmacokinetic profile and safety of Diclectin in healthy non-pregnant female subjects, administered under empty stomach conditions (defined as at least 2 hours after eating).

Pharmacokinetics of Diclectin after single and repeat dose in healthy non-pregnant women was evaluated in this study under fasted conditions. Multiple dose administration of Diclectin resulted in an increase in plasma exposure to doxylamine (approximately two-fold increase in Cmax) compared to single dose administration.
The proposed wording for section 5.2 of the SmPC derived from this study is considered acceptable.

Pharmacokinetics in target population –

PK data from the efficacy study (discussed further in clinical efficacy section) in pregnant population demonstrated exposures broadly within the range of those observed in the relative bioavailability done study discussed above conducted in healthy females.

Food effect study

A randomised, open-label, 2-way crossover, relative bioavailability study of Doxylamine/Pyridoxine 10 mg/10 mg (Diclectin) Delayed-Release Tablets following a 2 x 10 mg/10 mg dose in healthy adult females under fasting and fed conditions.

The objective of this study was to assess the effect of food on the bioavailability of Diclectin, (doxylamine-pyridoxine) administered as 2 x 10 mg/10 mg delayed-release tablets (for a total dose of 20 mg/20 mg), in healthy adult females under fasting and fed conditions.
The study demonstrated that there is a significant delay to absorption in the fed state.

IV.3 Pharmacodynamics

The clinical pharmacodynamics properties of doxylamine and pyridoxine are well-known. No new pharmacodynamic data were submitted and none are required for this type of application. The applicant has provided an adequate overview of the pharmacodynamic properties of the combination, taking into account the fixed dose combination requirements (CHMP/EWP/240/95 Rev. 1).

IV.4 Clinical Efficacy

A pivotal phase III clinical efficacy trial at 6 US sites was conducted. The efficacy results from this trial, Study DIC-301, A Double-Blind, Multicenter, Randomized, Placebo Controlled Trial of the Efficacy of Diclectin for Nausea and Vomiting of Pregnancy, in addition to published data, in particular from the Drug Efficacy Study Implementation (DESI) study which was carried out in the USA in 1975 and a summary of the literature evidence for varying combinations of the active substances.
Study DIC-301
A double-blind, multicentre, randomised, placebo-controlled trial of the efficacy of Diclectin for nausea and vomiting of pregnancy.

Primary endpoints
The primary objective was to compare the efficacy of Diclectin to placebo in the treatment of nausea and vomiting of pregnancy (NVP) using the Pregnancy Unique-Quantification of Emesis (PUQE) assessment tool to assess efficacy.

The primary endpoint was met with a statistically significant improvement in PUQE score. The effect size was small (a difference of 0.9 greater decrease in PUQE score). The applicant has also provided detailed explanations of the study outcome in terms of clinical meaningfulness of the result and positive impact upon patients.

Given the small treatment effect, and in the absence of data supporting the routine use of doxylamine/pyridoxine as treatment hyperemesis gravidarum wording is included in sections 4.1 and 4.4 of the SmPC outlining the limitations of use for hyperemesis gavidarum.

While the results of DIC-301 to demonstrate modest clinical improvements, these effects can be viewed in the context of the submitted additional data, current clinical practice and published literature to support the efficacy data from the pivotal study.

Bibliographic Data
The applicant has provided a comprehensive and up-to-date bibliographic review to include all relevant data to address the FDC requirements and further support the Diclectin application. This includes recent publications as well as older references are still considered pertinent, given the age of the innovator product.

The publications include specific data on the single active substances with and without a comparison to the fixed dose combination.

Included are publications that show that the fixed dose combination is effective both statistically and clinically.

Conclusion on clinical efficacy

Overall, the evidence from the clinical studies, literature and evidence of its current clinical use taken together is considered sufficient to support the efficacy of Diclectin for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management

IV.5 Clinical Safety

In a double-blind, randomised, placebo-controlled trial of 15 days duration, 261 women with nausea and vomiting of pregnancy were included of which 128 were treated with placebo and 133 with doxylamine succinate/pyridoxine hydrochloride. The mean gestational age at enrolment was 9.3 weeks; gestation range was from 7 to 14 weeks. The incidence of treatment-emergent adverse events was similar for both treatment and placebo groups. The most frequently reported adverse reaction (≥5% and exceeding the rate in placebo) was somnolence.

Post marketing experience

Extensive post-marketing clinical data exist for Diclectin. The components of Diclectin have been used for the treatment of NVP for over 60 years with over 35 million pregnancies. Diclectin tablets have been marketed in Canada since 1975 and specifically by Duchesnay since 1983. In addition, in the US the product has been marketed by Duchesnay since 2013; marketed in Israel since 2015 (approved in 2014) and subsequently approved in South Korea in 2015, Singapore in 2017, UK in 2018, Ireland and Netherlands in 2019.

Birth outcomes
Data analysis was completed using data collected from the Motherisk NVP Disease Management and Surveillance Helpline to determine the use of Diclectin in a population-based setting and to assess pregnancy outcomes. The proportion of major and minor birth defects was similar between the total cohort and the Diclectin Monotherapy Group, and is consistent with the expected 2-3% in the general population for major birth defects. The mean gestational age at delivery and birth weight for the two groups are also consistent with the expected values in the general public. These data indicate that the use of Diclectin does not increase the risk for major or minor birth defects, and other adverse pregnancy outcomes.

Conclusion on clinical safety

Since the approval and worldwide marketing of Diclectin, an estimated number of over 9 million pregnant women have been exposed to the product.
The adverse reaction profile identified in throughout the clinical development programme, including DIC-301, conducted with the target population of pregnant women, can be primarily attributed to the expected anti-histaminergic and anticholinergic activity of doxylamine. It can be adequately managed with appropriate warnings in Section 4.4 of the SmPC and the description of selected adverse events in Section 4.8 of the SmPC.
Post-marketing experience with Diclectin supports a positive benefit-risk assessment with the majority of reported events consistent with the known safety profile of the product.

Risk Management Plan

A Risk Management Plan, version 2.3, dated 03 February 2022, has been submitted, 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 Doxylamine/Pyridoxine Exeltis 10/10mg Gastro-resistant Tablet. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

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. The Marketing Authorisation Holder shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

IV.6 Discussion on the clinical aspects

The benefit/risk assessment for Doxylamine/Pyridoxine Exeltis 10/10 mg Gastro-resistant tablet is considered positive for the symptomatic treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management

Method of Sale and Supply

This product subject to prescription which may be renewed.

V. OVERALL CONCLUSIONS

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Doxylamine/Pyridoxine Exeltis 10/10 mg gastro-resistant tablet.

An adequate mixed non-clinical dossier for these known active substances, with mostly bibliographic non-clinical data and sponsor-conducted genotoxicity studies, has been provided in support of this product.

Overall, the evidence from the clinical studies, literature and evidence of its current clinical use taken together is considered sufficient to support the efficacy of Diclectin for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management

Since the approval and worldwide marketing of Diclectin, an estimated number of over 9 million pregnant women have been exposed to the product.
The adverse reaction profile identified in throughout the clinical development programme, including DIC-301, conducted with the target population of pregnant women, can be primarily attributed to the expected anti-histaminergic and anticholinergic activity of doxylamine. It can be adequately managed with appropriate warnings in Section 4.4 of the SmPC and the description of selected adverse events in Section 4.8 of the SmPC.
Post-marketing experience with Diclectin supports a positive benefit-risk assessment with the majority of reported events consistent with the known safety profile of the product

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

VI. REVISION DATE

16.12.2026