IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Xonvea MR 20 mg/20 mg modified-release tablets
Doxylamine hydrogen succinate
Pyridoxine hydrochloride
PA22998/003/001

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 Xonvea MR 20mg/ 20mg modified-release tablets, from Exeltis healthcare S.L., on 18th January 2024 for the symptomatic treatment of nausea and vomiting of pregnancy (NVP) in pregnant women ≥18 years who do not respond to conservative management (i.e., lifestyle and diet change).
Limitations of use: The combination doxylamine/pyridoxine has not been studied in case of hyperemesis gravidarum (see section 4.4).

This application is submitted via a Decentralised Procedure (DCP) as a mixed application under Article 8(3) of Directive 2001/83/EC with the Reference Member State (RMS) being Ireland and the following concerned member states (CMS) DE under IE/H/1174/001/DC; (CMS) DK, FI, NO, SE under IE/H/1175/001/DC and (CMS) CZ, EE, ES, FR, IT, LT, LV, PT, SK, AT, HU, LU, NL under IE/H/1167/001/DC
There is significant published information on the mono-components as well as the combination. Relevant published data has been used to support this application. This combination has a well-established efficacy and safety experience with over an estimated 38 million pregnancies worldwide.

Legal status: Product 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

Name of the product	Xonvea MR 20mg/ 20mg modified-release tablets
Name(s) of the active substance(s) (INN)	Doxylamine hydrogen succinate and pyridoxine hydrochloride
Pharmacotherapeutic classification (ATC code)	R06AA59
Pharmaceutical form and strength(s)	20 mg/ 20 mg modified-release tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA22998/003/001
Marketing Authorisation Holder	Exeltis Healthcare S.L.
MRP/DCP No.	IE/H/1167/001/E/001
ConcernedMember State	BE, PL

II. QUALITY ASPECTS

II.1. Introduction

This application is for Xonvea MR 20mg /20mg modified-release tablets.

II.2 Drug substance

The active substances are doxylamine hydrogen succinate and pyridoxine hydrochloride, both established active substances and both described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP). All aspects of the manufacture and control of both active substances are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

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

Each modified-release tablet contains 20 mg doxylamine hydrogen succinate and 20 mg pyridoxine hydrochloride. Xonvea MR is comprised of an enteric-coated core containing 10 mg doxylamine hydrogen succinate and 10 mg pyridoxine hydrochloride and an immediate-release multilayer coating containing 10 mg doxylamine hydrogen succinate and 10 mg pyridoxine hydrochlorideThe excipients in the medicinal product are listed in section 6.1 of the SmPC. Appropriate justification for the inclusion of each excipient has been provided.

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/*Ancillary Substances*)

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 the modified-release 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. requirements and EU legislation for use with foodstuffs.

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 Xonvea MR 20mg /20mg modified-release tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Xonvea MR 20 mg/ 20 mg modified-release tablets are comprised of an enteric-coated core containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride and an immediate-release multilayer coating 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-nauseant 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 antagonise 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 non-clinical 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, nonconjugated 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 B6, less than 3% of the oral dose was detected in foetal/uterine tissue of the pregnant rats.

Maternal pharmacokinetics have been described in three species of monkey administered Bendectin (doxylamine 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.

Neither doxylamine nor pyridoxine are associated with a genotoxic or carcinogenic risk. 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 Xoneva 20 mg/ 20 mg modified-release 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 any of the 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 the combination product (Bendectin) 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 extracardiac 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 extracardiac changes were observed in any other term infants.

Given the proposed indication, caution in the use of this product is warranted but clinical exposure data and epidemiological review provide a better evidence base given the extensive use of this combination product to date in women suffering from nausea and vomiting of pregnancy.

III.5 Ecotoxicity/environmental risk assessment

Doxylamine succinate is not a PBT substance as 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, Xonvea MR 20 mg/ 20 mg modified-release tablets are 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 HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

The pharmacokinetics of Xonvea MR 20 mg/ 20 mg modified-release tablets has been characterised in healthy non-pregnant adult women in a single-dose study (one tablet) and a multiple-dose study (two tablets daily from Day 1 to 11).

Absorption
Doxylamine and pyridoxine are absorbed in the gastrointestinal tract, mainly in the jejunum. When formulated as a modified-release tablet, after single dose administration, the median peak plasma concentration of doxylamine and pyridoxine was achieved within 4.5 and 0.5 hours, respectively.
Multiple-dose administration resulted in:
• Increased concentrations of doxylamine as well as increased Cmax by 1.8 and AUC of absorption by 2.0. The time to reach the maximum concentration was reduced by multiple doses, from a mean of 20.0 hours (range of 2.00-23.0) to 3.50 hours (range of 1.00-20.0). The mean accumulation index was 1.99 suggesting that doxylamine accumulates following multiple dosing.
• Although no accumulation was observed for pyridoxine, the mean accumulation index for the main active metabolite pyridoxal 5'-phosphate was 2.61 following multiple-dose administration. The time to reach the maximum concentration was slightly affected by multiple doses, from a mean of 21.0 hours (range of 15.0-23.9) to 15.0 hours (range of 2.00-24.0).

In a food-effect, single-dose, crossover clinical trial conducted in 23 healthy, premenopausal women:

• The administration of a high fat, high calorie meal delayed the absorption of doxylamine, pyridoxine, and pyridoxine metabolites. This delay was associated with lower peak concentrations of doxylamine, pyridoxine, and pyridoxal.
• The extent of absorption for pyridoxine was decreased. The effect of food on the peak concentration and the extent of absorption of the pyridoxine component is more complex because pyridoxine metabolites such as pyridoxal, pyridoxamine, pyridoxal 5′-phosphate, and pyridoxamine 5′-phosphate also contribute to biological activity.
• Food significantly reduced the bioavailability of pyridoxine, lowering its Cmax and AUC by approximately 67% and 37%, respectively, compared to fasting conditions. In contrast, food did not affect the Cmax and AUC of the main active metabolite pyridoxal 5′-phosphate.

Distribution
Doxylamine is low protein binding (unbound fraction of 28.7% in rat), highly permeable, and is not a substrate of P-glycoprotein, leading to a wide distribution into tissues. Doxylamine crosses the blood-brain barrier and has a high affinity for H1 receptors.
Pyridoxine is highly protein bound, primarily to albumin. Its metabolites, pyridoxal and pyridoxal 5'-phosphate are partially and almost completely bound to albumin in plasma, respectively. Its main active metabolite pyridoxal 5'-phosphate (PLP) accounts for at least 60% of circulating vitamin B6 concentrations.

Biotransformation
Doxylamine is biotransformed in the liver primarily by the cytochrome P450 enzymes CYP2D6, CYP1A2, and CYP2C9, to its principle metabolites N-desmethyl-doxylamine and N,N-didesmethyldoxylamine. Pyridoxine is a prodrug primarily metabolised 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 biologic activity.

Elimination
The principle metabolites of doxylamine, N-desmethyl-doxylamine and N,N-didesmethyldoxylamine, are excreted by the kidney.
Renal elimination is also the main pathway of excretion for the derivatives of pyridoxine metabolism (reported to be 74% of a 100 mg intravenous dose of pyridoxine), mainly as the inactive form 4-pyridoxic acid.
When formulated as a modified-release tablet, after single dose administration, the terminal elimination half-life of doxylamine and pyridoxine are 12.43 and 0.27 hours, respectively.

Hepatic Impairment: No pharmacokinetic studies have been conducted in hepatic impaired patients.

Renal Impairment: No pharmacokinetic studies have been conducted in renal impaired patients.

IV.3 Pharmacodynamics

Doxylamine hydrogen succinate is an ethanolamine derivative, a first generation antihistamine that is competitively, reversibly and non-specifically blocking H1-receptors. It is also a non-specific antagonist that blocks other receptors, such as central or peripheral muscarinic receptors. The antiemetic effect of doxylamine is also associated with the blocking of the central cholinergic and H1 receptors, although the mechanism of action is unknown.

Pyridoxine hydrochloride, a water-soluble vitamin, is converted to pyridoxal, pyridoxamine, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate. Although pyridoxal 5'-phosphate is the main active antiemetic metabolite, the other metabolites also contribute to the biological activity. The mechanism of action of the combination of doxylamine hydrogen succinate and pyridoxine hydrochloride to treat nausea and vomiting of pregnancy has not been established.

IV.4 Clinical Efficacy

No new clinical efficacy study was conducted to further support Xonvea MR 20 mg/ 20 mg modified-release tablets formulation efficacy. Clinical efficacy data from Diclectin 10mg/10mg gastro-resistant tablet clinical development program were presented and discussed to support the MAA for Bonjesta. A multiple dose bioequivalence study (study 150033) and a single dose bioequivalence study (study 150336) have been conducted between to establish the bioequivalence between both formulations and to provide for waiving of efficacy studies as detailed in Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 Rev1. While the release pattern of the 20mg/ 20 mg modified-release (with an immediate release and a gastro-resistant component) tablet formulation (Xonvea MR 20 mg/ 20 mg modified-release tablets) is different from the release pattern of the 10mg/ 10mg gastro-resistant tablet formulation of doxylamine and pyridoxine, comparable exposures (90% CI within 80-125%) for AUC, Cmax and Cmin were shown for

doxylamine and pyridoxal 5'- phosphate following administration of the same daily dose and therefore the results of the efficacy study with the 10mg/ 10mg gastro-resistant tablet formulation are also supportive for the 20mg/ 20mg tablet formulation (Xonvea MR 20 mg/ 20 mg modified-release tablets).

The pivotal efficacy study has been conducted with a 10mg/ 10mg gastro-resistant tablet formulation of doxylamine and pyridoxine. This study, DIC-301, was a double-blind, multicentre, randomised, placebo-controlled trial of the efficacy of Diclectin for nausea and vomiting of pregnancy.
Two 10mg/ 10mg gastro-resistant tablet were administered at bedtime on Day 1. If symptoms of nausea and vomiting persisted into the afternoon hours of Day 2, the woman was directed to her usual dose of two tablets at bedtime that night and, beginning on Day 3, to take one tablet in the morning and two tablets at bedtime. Based upon assessment of remaining symptoms at her clinic visit on Day 4 (± 1 day), the woman may have been directed to take an additional tablet mid-afternoon. A maximum of four tablets (one in the morning, one in the mid-afternoon and two at bedtime) were taken daily for a maximum daily dose of 40mg of doxylamine and 40mg of pyridoxine.
Over the treatment period, 60% of product-treated patients received the maximum daily dose of 40mg of doxylamine and 40mg of pyridoxine.

The primary efficacy endpoint was the change from baseline at Day 15 in the Pregnancy Unique-Quantification of Emesis (PUQE) score. The PUQE score incorporates the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe). At baseline, the mean PUQE score was 9.0 in the product arm and 8.8 in the placebo arm. There was a 0.9 (95% confidence interval 0.2 to 1.2 with p-value 0.006) mean decrease (improvement in nausea and vomiting symptoms) from baseline in PUQE score at Day 15 with the product compared to placebo (see Table 1).

Table 1 - Change from Baseline in the Primary Endpoint, Pregnancy Unique-Quantification of Emesis (PUQE) Score at Day 15*

PUQE Score**	**Doxylamine Hydrogen Succinate +Pyridoxine Hydrochloride**	**Placebo**	**Treatment Difference [95% Confidence Interval]**
Baseline Change from baseline at Day 15	9.0 ± 2.1 -4.8 ± 2.7	8.8 ± 2.1 -3.9 ± 2.6	-0.9 [-1.2, -0.2] §

* Intent-to-Treat Population with Last-Observation Carried Forward
** The Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score incorporated the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms rated form 3 (no symptoms) to 15 (most severe). Baseline was defined as the PUQE score completed at the enrolment visit.
§ Calculated Cohen's d coefficient = 0.34. The difference in mean PUQE score reduction is considered a "medium-size effect" as per Cohen's d coefficient (of 0.34) where >0.20 = medium effect.

In the literature, the safety and effectiveness of the combination of doxylamine hydrogen succinate and pyridoxine hydrochloride has been demonstrated in the treatment of NVP in pregnant women.

IV.5 Clinical Safety

The application for Xonvea MR 20 mg/ 20 mg modified-release tablets concerns a fixed-dose combination product containing two well-known active substances, doxylamine and pyridoxine. The safety profile of doxylamine 10 mg/pyridoxine 10 mg fixed dose combination is well-established in the target population (pregnant women) and has been authorised in the UK since July 2018 and the Netherlands and Ireland since 2019. Doxylamine 10 mg/pyridoxine 10 mg fixed dose combination has been marketed in Canada by Duchesnay since 1983, and in the US under the trade name Diclegis, since 2013. Bonjesta doxylamine 20 mg/pyridoxine 20 mg was approved by FDA in 2016. No new or unexpected safety concerns arose during review of information provided for this application for doxylamine 20mg/ pyridoxine 20mg modified-release tablets which has the same max daily dose of 40 mg-40 mg as the established 10mg/10mg formulation.

The evidence of the safety is supported by the clinical pharmacokinetic and clinical efficacy studies discussed above, published data, as well as post marketing data and published. The applicant presented safety data from 13 studies:

<u>Doxylamine 10 mg/pyridoxine 10 mg fixed dose combination</u>
• A relative bioavailability study has been conducted comparing Diclectin formulation to an oral solution combining both actives (study 02163).

• Another relative bioavailability has been conducted to compare Diclectin to a 20 mg delayed-release tablet of doxylamine succinate and to a 20 mg delayed-release tablet of pyridoxine hydrochloride (study 160286).
• Two bioequivalence studies, fasted and fed, have been conducted to support the addition of a manufacturing site, located in Blainville, Quebec, Canada (respectively studies 110567 and 120144).
• Two bioequivalence studies, fasted and fed, have been conducted to support an alternate enteric coating agent, the Acryl-Eze Clear coating (respectively studies 120292 and 120358).
• Two food effect bioavailability studies have been conducted (studies 02191 and 70294). Study 70294 was conducted with methods available to analyze all active vitamin B6 metabolites.
• A repeat dose study (study 70381) and an efficacy study (study DIC-301) were also conducted. Pharmacokinetic data from both studies are presented.

Doxylamine 20 mg/pyridoxine 20mg modified-release tablets
• A comparative food effect bioavailability study was conducted under fed and fasting conditions using methods available to analyze doxylamine, pyridoxine as well as active B6 metabolites (study 140115).
• A single dose bioequivalence study was conducted under fasting conditions comparing one tablet of Bonjesta (test product; 20mg-20mg prolonged release tablet) and two tablets of Diclectin (reference product; 10mg-10mg delayed release tablet), using methods available to analyze doxylamine, pyridoxine as well as active B6 metabolites (study 150336).
• A multiple dose bioequivalence study was conducted under fasting conditions during eleven consecutive days to establish the pharmacokinetic profiles of Bonjesta (test product) and Diclectin (reference product) in order to evaluate bioequivalence on the basis of rate and extent of absorption, using methods available to analyze doxylamine, pyridoxine as well as active B6 metabolites (study 150033).

In the pivotal efficacy study (DIC-301), for the 10mg/ 10mg gastro-resistant tablet formulation of doxylamine and pyridoxine, conducted in the target population including 261 women with nausea and vomiting of pregnancy (128 treated with placebo and 133 with Diclectin -doxylamine hydrogen succinate/pyridoxine hydrochloride), the most frequently reported adverse reaction (≥5% and exceeding the rate in placebo) was somnolence in a double-blind, randomised, placebo-controlled trial of 15 days duration.
A total of 9 serious adverse events were reported by 9 subjects for this study with 3.0% (4/133) in the treatment group, and 3.9% (5/128) in the placebo treatment group. Reported SAEs were: bile duct stone (1), missed abortion (2), spontaneous abortion (3), fetal disorder (1), intrauterine death (1), and premature rupture of membranes (1). There were 4 subjects (2 Diclectin, 2 placebo) that discontinued study drug due to their SAEs: missed abortion (1 subject, Diclectin), spontaneous abortion (1 subject, Diclectin; 1 subject, placebo), and bile duct stone (1 subject, placebo). None of the 9 reported SAEs required unblinding of the study drug. Eight of the SAEs were considered not related to the study drug and 1 SAE was considered unlikely related. No SAEs were considered possibly, likely or definitely related to the study drug.

Table 14 Study DIC-301 Serious Treatment Emergent Adverse Events in the Safety Population

System Organ Class (SOC) Preferred Term	Diclectin (N = 133)	Placebo (N = 128)	*P* value[a]
Number of Subjects with at least one Serious TEAE	**4 (3.0%)**	**5 (3.9%)**	0.745
Hepatobiliary disorders	0	**1 (0.8%)**	0.490
Bile duct stone	0	1 (0.8%)	0.490
Pregnancy, peurperium and perinatal conditions	**4 (3.0%)**	**4 (3.1%)**	1.000
Abortion missed	1 (0.8%)	1 (0.8%)	1.000
Abortion spontaneous	2 (1.5%)	1 (0.8%)	1.000
Fetal disorder	0	1 (0.8%)	0.490
Intra-uterine death	1 (0.8%)	0	1.000
Premature rupture of membranes	0	1 (0.8%)	0.490

[a] The *P value* was calculated using Fisher's exact test method
Intent-to-Treat (ITT) safety population: Any subject who took at least one dose of study medication during the study.
[5.3.5.1 Study DIC-301 p. 57]

Rates of foetal death were the same in both arms an in all cases the event was considered unrelated to study drug. No concerns are raised in relation to the TEAE, pregnancy related AEs which were reported as part the study.

No serious adverse events were reported for all the studies conducted with healthy non-pregnant women and no concerns are raised in relation to the TEAEs which were reported as part of the clinical development program (Studies 02163, 02191, 70294, 70381, 110567, 120144, 120292, 120358, 160286, 140115, 150033 and 150336).

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 Doxylamine, Pyridoxine hydrochloride.

Safety specification

The applicant proposed the following list of safety concerns in the revised RMP (v4.0; date of final sign-off 11/01/2023)

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

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

Periodic Safety Update Report (PSUR)
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.

IV.6 Discussion on the clinical aspects

The benefit/risk assessment Xonvea MR 20 mg/ 20 mg modified-release tablets is considered positive for the symptomatic treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management (i.e., lifestyle and diet change).
Limitations of use: The combination doxylamine/pyridoxine has not been studied in case of hyperemesis gravidarum.

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 Xonvea MR 20 mg/ 20 mg modified-release tablets.

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.

The benefit/risk assessment of Xonvea MR 20 mg/ 20 mg modified-release tablets is considered positive for the symptomatic treatmentof nausea and vomiting of pregnancy (NVP) in women ≥18years who do not respond to conservative management (i.e., lifestyle anddiet change).

Limitations of use: The combination doxylamine/pyridoxine has not been studied in case of hyperemesis gravidarum.

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

The HPRA, on the basis of the data submitted, considered that Xonvea MR 20 mg/ 20 mg modified-release tablets demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation..

VI. REVISION DATE

18.01.2029