Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Xonvea 10 mg/10 mg gastro-resistant tablets

(doxylamine succinate and pyridoxine hydrochloride)

UK Licence No: PL 16853/0147

Alliance Pharmaceuticals Limited

LAY SUMMARY

Xonvea 10 mg/10 mg gastro-resistant tablets

(doxylamine succinate and pyridoxine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Xonvea 10 mg/10 mg gastro-resistant tablets (PL 16853/0147). For ease of reading, the product will be referred to as 'Xonvea' in this lay summary. The summary explains how the application for Xonvea was assessed and the authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Xonvea.

For practical information about using Xonvea, patients should read the package leaflet or contact their doctor or pharmacist.

What is Xonvea and what is it used for?
Xonvea is used in pregnant women, to help stop them from feeling sick (nausea) and being sick (vomiting). It is used when changes in diet, or other non-medicinal treatments have not worked.

How does Xonvea work?
Xonvea contains two substances called doxylamine succinate and pyridoxine hydrochloride. Doxylamine succinate belongs to a group of medicines called 'antihistamines'. Pyridoxine hydrochloride is another name for vitamin B6.

How is Xonvea used?
Xonvea is available as gastro-resistant tablets and the tablets are taken by mouth (orally).

Xonvea can only be obtained with a prescription. The tablets should always be taken exactly as advised by the patient's doctor, pharmacist or nurse. The patient should check with the doctor, pharmacist or nurse if not sure.

The doctor will start treatment with a low dose and may increase the dose – this will depend on how well the medicine works for the patient.

Taking this medicine

- Xonvea should be taken on an empty stomach
- The tablet(s) should be swallowed whole with a glass of water
- The patient should not crush, chew, or split the tablets before swallowing
- If the patient cannot swallow Xonvea tablets whole, she should tell her doctor, pharmacist or nurse.

How to start taking Xonvea and increase the dose, if needed:

- **Day 1**
  - Two tablets, should be taken by mouth at bedtime.
- **Day 2**
  - Two tablets, should be taken by mouth at bedtime.
  - If nausea and vomiting is better or controlled on Day 2, the patient should continue to take 2 tablets every night at bedtime. This will be the patient's usual dose unless the patient's doctor, pharmacist or nurse advises otherwise.

- **Day 3**
  - If the patient still had nausea and vomiting on Day 2, she should take 3 tablets, by mouth on Day 3 (1 tablet in the morning and 2 tablets at bedtime).

- **Day 4**
  - If the patient's nausea and vomiting was better or controlled on Day 3, the patient should continue to take 3 tablets each day (1 tablet in the morning and 2 tablets at bedtime). This will be the patient's usual dose unless the patient's doctor, pharmacist or nurse advises otherwise.
  - If the patient still had nausea and vomiting on Day 3, she should take 4 tablets, by mouth each day (1 tablet in the morning, 1 tablet in the mid-afternoon, and 2 tablets at bedtime).

The patient should not take more than 4 tablets each day (1 in the morning, 1 in the mid-afternoon, and 2 at bedtime).

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

What benefits of Xonvea have been shown in studies?
Studies have been submitted to support this application for Xonvea indicated in pregnant women, to help stop them from feeling sick (nausea) and being sick (vomiting), when changes in diet, or other non-medicinal treatments have not worked.

These studies have shown that Xonvea is effective in the proposed indication.

What are the possible side effects of Xonvea?
Like all medicines, Xonvea can cause side effects although not everybody gets them.
The following side effects may happen with this medicine:

Very common (may affect more than 1 in 10 people)
- feeling sleepy

Common (may affect up to 1 in 10 people)
- feeling dizzy
- feeling tired
- dry mouth

For the full list of all side effects reported with Xonvea, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Xonvea approved?
It was concluded that, in accordance with EU requirements that, for Xonvea, the benefits are greater than its risks and it was recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Xonvea?
A Risk Management Plan has been developed to ensure that Xonvea is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Xonvea, including the appropriate precautions to be followed by healthcare professionals and patients

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Xonvea

A Marketing Authorisation was granted in the UK to Alliance Pharmaceuticals Limited on 03 July 2018.

The full PAR for Xonvea follows this summary.

For more information about treatment with Xonvea, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2018

SCIENTIFIC DISCUSSION

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Scientific Discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Alliance Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Xonvea 10 mg/10 mg gastro-resistant tablets (PL 16853/0147) on 03 July 2018. For ease of reading, the product may be referred to as 'Xonvea' in this scientific summary. In addition, the product may be referred to as 'Diclectin', the proposed name used during the assessment of the application.

Xonvea is a Prescription Only Medicine (POM) indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

The application for Xonvea was submitted as a full mixed application under Article 8(3) of Directive 2001/83/EC, as amended, supported by non-clinical and clinical studies submitted by the applicant, as well as bibliographic data.

The product is a gastro-resistant tablet containing a fixed dose combination (FDC) of 10 mg doxylamine succinate (an antihistamine) and 10 mg pyridoxine hydrochloride (Vitamin B6), as the active substances. Doxylamine succinate and pyridoxine hydrochloride provide anti-nauseant and antiemetic activity. The mechanism of action of Xonvea is unknown. The delayed action of Xonvea permits the night-time dose to be effective in the following morning hours, when the patient needs it most.

Despite the proven efficacy of the fixed dose combination of doxylamine and pyridoxine in the treatment of nausea and vomiting of pregnancy (NVP), its mechanism of action is not well established since the etiology of NVP is not well-known.

The delayed-release, fixed dose combination of doxylamine succinate and pyridoxine hydrochloride, as a treatment for nausea and vomiting of pregnancy, has a long history, being first introduced to the United Kingdom (UK) in a product marketed by Merrell Dow in 1958 as Debendox, a triple active delayed-release combination containing 10 mg of each of doxylamine succinate, pyridoxine hydrochloride and dicyclomine hydrochloride. The product was reformulated in 1976 and dicyclomine hydrochloride was removed as it was found not to contribute to the anti-emetic properties of the drug combination. The reformulated product was available as Debendox in the UK and Australia, Lenotan in Germany, Merbental in Spain and Bendectin in North America. In 1983, Merrell Dow voluntarily withdrew the product from the market, for non-medical reasons, citing litigation burdens and adverse publicity affecting the product. Debendox has not been on the UK market since the 1980s.

The current delayed-release formulation of Diclectin (Xonvea) has been on the Canadian market since 1979 under the trade name Diclectin, and on the US market since 2013 under the trade name Diclegis. The proposed product, Xonvea, contains the same active ingredients, route of administration, dosage form, strength and conditions of use as Debendox/Bendectin, as reformulated in 1976.

During assessment of the application major objections were raised with respect to the pharmacokinetic and efficacy data submitted. The application was considered by the Commission on Human Medicines (CHM) at their meetings in July 2017 and May 2018. In response to the CHM advice, the applicant provided additional data and detailed clarification of the points that had been raised. The information provided was adequate and the issues were resolved.

The non-clinical dossier is largely based on available data in the published literature, with genotoxicity (both *in vitro* and *in* vivo studies) studies being conducted by the applicant.

The clinical dossier supporting this application consisted of clinical studies, evidence from published literature and postmarketing data from other countries. The clinical studies are stated to have been conducted in accordance with the current ICH – GCP guidelines. It is presumed that the literature-based studies, which cover a long period of time, were generally conducted in line with the prevailing standards at that time.

The application was granted a Paediatric Investigation Plan (PIP) waiver.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder.

It was judged that the benefits of taking Xonvea outweigh the risks.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Xonvea 10 mg/10 mg gastro-resistant tablets are white, round, film-coated tablets with a pink image of a pregnant woman on one side.

Each gastro-resistant tablet contains 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, as the active substances. The product also contain pharmaceutical excipients in the tablet core, coating, waxing and printing ink, namely, microcrystalline cellulose, magnesium trisilicate, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, hypromellose (E464), macrogol 400 (E1521), macrogol 8000 (E1521), methacrylic acid-ethyl acrylate copolymer (1:1), talc (E553b), sodium bicarbonate (E500), sodium lauryl sulfate (E487), triethyl citrate, simeticone emulsion, titanium dioxide (E171), polysorbate 80 (E433), carnauba wax, shellac, Allura Red AC aluminum lake (E129), propylene glycol (E1520) and indigo carmine aluminum lake (E132). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is packaged in polyvinylchloride/aluminium unit dose blisters, in pack sizes of 20, 30 and 40 gastro-resistant tablets. Not all pack sizes may be marketed.

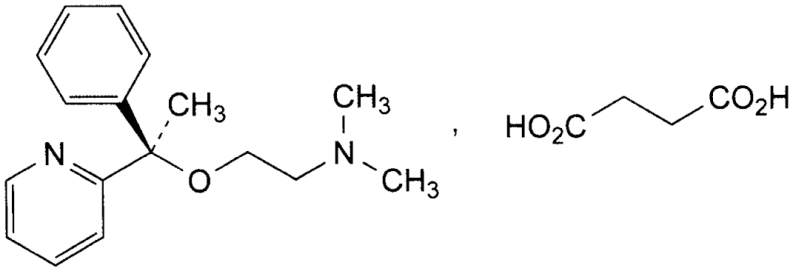
Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Doxylamine succinate

INN:	Doxylamine
BP/Ph Eur:	Doxylamine succinate (BP); doxylamine hydrogen succinate (Ph Eur)
Chemical name:	N,N-Dimethyl-2-[(1*RS*)-1-phenyl-1-(pyridin-2-yl)ethoxy]ethanamine hydrogen butanedioate.

Structure:



and enantiomer

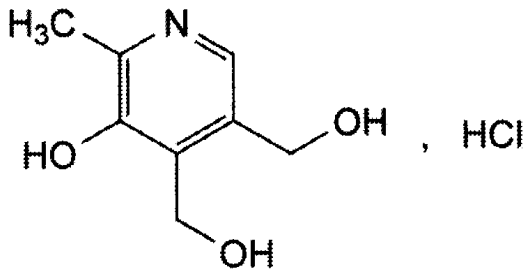
Molecular formula: $C_{17}H_{22}N_2O,C_4H_6O_4$
M_r: 388.5
Appearance: White or almost white powder.
Solubility: It is very soluble in water and freely soluble in ethanol (96%)

Chirality Doxylamine succinate is a chiral compound with one asymmetric carbon atom. The active substance is a racemic mixture.

Doxylamine succinate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, doxylamine succinate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Pyridoxine hydrochloride
INN: Pyridoxine hydrochloride
Chemical name: (5-Hydroxy-6-methylpyridine-3,4-diyl)dimethanol hydrochloride.
Structural formula:



Molecular formula: $C_8H_{11}NO_3,HCl$
Molecular mass: 205.6 g/mol
Appearance: White or almost white, crystalline powder
Solubility: Freely soluble in water and slightly soluble in ethanol (96%)

Pyridoxine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, pyridoxine hydrochloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable, gastro-resistant tablets, containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. Suitable pharmaceutical development data have been provided for this application.

With the exception of simeticone emulsion, all excipients comply with their respective European Pharmacopoeia monographs. Simeticone emulsion is controlled to its United States Pharmacopoeia (USP) monograph.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 42 months with no special storage instructions has been accepted.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Batch analyses have been provided for the test and reference batches used in the bioequivalence/bioavailability studies. The bioequivalence/bioavailability studies is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for this application, from a quality point of view.

NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of doxylamine succinate and pyridoxine hydrochloride are well-known. As the active substances are widely-used, the applicant has provided an overview largely based upon literature, with new non-clinical data in the form of *in vitro* and *in vivo* genotoxicity studies for both substances. The applicant's approach to an overview, based on the legal basis and available literature is, thus, appropriate.

The non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology is adequate and is a detailed assessment of the non-clinical properties of both doxylamine succinate and pyridoxine hydrochloride.

III.2 Pharmacology
The pharmacology of doxylamine succinate and pyridoxine hydrochloride is well known and is extensively described in the literature. The applicant has not provided a detailed summary of the pharmacology of both active substances; sections such as secondary pharmacology and safety pharmacology have not been submitted. It is however accepted that there is sufficient clinical experience with these compounds and with oral administration and so the submission of further non-clinical data is not required.

III.3 Pharmacokinetics

The non-clinical pharmacokinetics of doxylamine succinate and pyridoxine hydrochloride have been briefly reported in published literature and these have been discussed in the non-clinical overview. Much of the data for doxylamine succinate and pyridoxine hydrochloride is derived from rodents, although some data are supplied in combination studies of both components in non-human primates.

For doxylamine succinate, oral bioavailability was limited (24.7%), absorption was more rapid following intranasal delivery, although T_{max} 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 succinate administration.

For pyridoxine hydrochloride, limited pharmacokinetic data were 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 fetal sequestration of vitamin B-6, less than 3% of the oral dose was detected in fetal/uterine tissue of the pregnant rats.

Maternal pharmacokinetics has been described in three species of monkey (cynomolgus, rhesus and baboon) using Bendectin (doxylamine succinate and pyridoxine hydrochloride). 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 fetal tissue as a result of treatment with the combination product.

Given the extent of clinical data obtained for this fixed drug combination and the discussions and summaries provided, the shortcomings of the non-clinical overview in this section are acceptable.

III.4 Toxicology

The applicant's non-clinical overview has discussed the toxicity of doxylamine and pyridoxine in some detail. An adequate review of general toxicity, potential genotoxicity and carcinogenicity has been provided. Much of the data presented are derived from the literature. In addition, the applicant has provided unique new genotoxicity data for both components in Diclectin.

Neither doxylamine or pyridoxine are 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 Diclectin.

Doxylamine has been shown to be transferred via the placenta to a limited extent, although there are 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 fetal viability have been detected; however there was no evidence of

teratogenicity in either tested species using the combination product. The changes detected in rats and rabbits were at doses determined to be toxic to the mother.

Two studies (1985) report exposure to the combination product (Bendectin) in 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. The applicant's rationale for not pursuing additional monitoring beyond the standard in the Risk Management Risk (RMP) is acceptable.

Regarding the drug substances and final drug product, the residual solvents and excipients in the formulation are discussed and raise no toxicological concerns.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

The applicant has provided an ERA, providing a discussion to assess a Phase I ERA for pyridoxine hydrochloride and doxylamine succinate. The potential environmental exposure in surface water (PEC_{sw}) estimation is calculated as 0.0062 µg/L, below the action limit of 0.01 µg/L. The applicant concludes that as the PEC_{sw} is below 0.01 µg/l, the possibility of environmental risks can be excluded, below the action limit of 0.01 µg/L. The calculation for PEC_{sw} is reliant on prevalence data in the UK of conceptions and estimations of the total number of females of child bearing age (ages 15-44).

It is agreed that pyridoxine hydrochloride is a vitamin B6 analog and is unlikely to result in a significant risk to the environment.

Doxylamine succinate is not considered to present a potential risk to surface water, microorganisms and ground water or to sediment-dwelling invertebrates. The applicant has completed an Organisation for Economic Cooperation and Development (OECD) 107 study, using the shake-flask method, to determine the octanol-water partition coefficient for doxylamine succinate.

The results are summarised below:

Phase I: Estimation of exposure- screening for persistence, bioaccumulation and toxicity

pH	Temperature (°C)	Partition Coefficient (K_{ow})	$Log_{10}K_{ow}$
5	21.5 ± 0.5	0.913	-0.055
7	22.6 ± 0.5	1.79	0.235
9	22.2 ± 0.5	64.6	1.80

Since the $log_{10}Kow$ is < 4.5 for doxylamine succinate, it is not considered to present a potential risk to surface water, microorganisms and ground water or to sediment-dwelling invertebrates. In accordance with "*Guideline on the environmental risk assessment of medicinal products for human use*" (EMEA /CHMP/SWP/4447/00), no persistence, bioaccumulation and toxicity screening is required for this substance.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted, from a non-clinical point of view.

CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of doxylamine succinate and pyridoxine hydrochloride, is well-known. Diclectin has a history of well-established use due to the previously licensed originator product Debendox/Bendectin.

A comprehensive review of the published literature has been provided by the applicant for the combination product and its active substances.

Diclectin was originally developed over 30 years ago as a combination product and not developed with the aim of combining actives already approved to treat NVP to obtain a greater efficacy and/or safety. Its development pre-dates the current recommendations for development of a Fixed Dose Combination (FDC) medicine.

In light of the product's development history, the majority of the published clinical data exists for the combination product, and not the individual active substances, neither of which has been approved on its own for the treatment of NVP. Despite this, the information available from the literature demonstrates the respective relevant contributions of the active substances (pyridoxine hydrochloride and doxylamine succinate) to Diclectin, and the improved efficacy of Diclectin compared to each monotherapy component.

However, in accordance with the criteria set out in the guideline on clinical development of fixed dose combination medicinal products (EMA/CHMP/158268/2017), a Randomised Controlled Trial (RCT) is required to prove superiority in single (or multiple) active components of a FDC to demonstrate that the FDC has greater efficacy in comparison with the respective mono-components.

In support of this application, the applicant has submitted newly generated and bibliographic data to support the application. The newly generated data include a pharmacokinetic and efficacy study, which are detailed in below.

IV.2 Pharmacokinetics

The pharmacokinetic profiles of doxylamine succinate and pyridoxine hydrochloride are well known. The pharmacokinetic data presented, both newly generated and bibliographic, are considered adequate to support this application.

In accordance with current CHMP guidelines, a pivotal pharmacokinetic study, 160286, was submitted to support the application.

Supportive studies submitted: a supplementary study (Study 02163), in addition to a relative bioavailability (Study 70381) and a food effect study (Study 70294).

Pivotal study - 160286

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

A single oral dose of either Diclectin 10 mg/10 mg (doxylamine succinate/pyridoxine hydrochloride 10 mg/10 mg) delayed-release tablet as 2 x 10 mg/10 mg delayed-release tablets, or doxylamine succinate 20 mg as 1 x 20 mg delayed-release tablet, or pyridoxine hydrochloride 20 mg as 1 x 20 mg

delayed-release tablet was administered, in each study period. The treatment phases were separated by a washout period of 21 days.

Blood samples were collected for plasma levels as follows:

For doxylamine (Treatments A and B): before dosing and up to and including 60 hours after each administration**.**

For pyridoxine (Treatments A and C): before dosing and up to and including 8 hours after each administration**.**

For pyridoxal-5'-phosphate (Treatments A and C): before dosing and up to and including 72 hours after each administration.

For pyridoxine and pyridoxal 5'-phosphate, baseline-uncorrected and baseline-corrected data were presented. However, since no pre-dose concentrations were measured for pyridoxine, no baseline adjustment was performed for this analyte. Pharmacokinetics results are presented in Table 1, with the ratios and confidence intervals presented in Table 2.

Table 1 Pharmacokinetic Results of Study 160286

Mean ± SD	Plasma Doxylamine		Plasma Pyridoxine		Plasma Baseline Corrected Pyridoxal 5'-Phosphate		Plasma Baseline Uncorrected Pyridoxal 5'-Phosphate	
	Diclectin	Doxylamine succinate	Diclectin	Pyridoxine hydrochloride	Diclectin	Pyridoxine hydrochloride	Diclectin	Pyridoxine hydrochloride
AUC_{last} (ng•h/mL)	1385.57± 392.53	1402.68 ± 427.73	44.37 ± 12.88	57.88 ± 16.47	N/A	N/A	N/A	N/A
AUC_{0-72h} (ng•h/mL)	N/A	N/A	N/A	N/A	864.9 ± 304.61	915.09 ± 305.57	1439.71 ± 433.04	1540.42 ± 491.64
AUC_{inf} (ng•h/mL)	1446.31 ± 443.76	1468.94 ± 499.90	44.67 ± 12.94	58.05± 16.46	N/A	N/A	N/A	N/A
C_{max} (ng/mL)	95.77 ± 15.46	97.45 ± 17.62	50.33 ± 24.13	111.97 ± 59.92	24.76 ± 8.56	23.80 ± 7.54	32.72 ± 10.19	32.46 ± 9.99
t_{max} (h)[a]	5.000 (3.000-5.500)	4.500 (3.000-4.500)	2.500 (1.000-4.670)	1.750 (0.500-3.000)	7.50 (3.000-16.033)	5.000 (2.000-16.000)	7.500 (3.000-16.033)	5.000 (2.000-16.000)
K_{el} (h^{-1})	0.0590 ± 0.0104	0.0584 ± 0.0105	2.5817 ± 1.1356	2.6437 ± 0.8182	N/A	N/A	N/A	N/A
$t_{½\ el}$ (h)	12.13 ± 2.32	12.30 ± 2.59	0.60 ± 1.00	0.29± 0.09	N/A	N/A	N/A	N/A

N/A: Not Applicable
[a] Median (range)

Table 2 Ratios and Confidence Intervals for Study 160286

Analytes	Parameter	Ratio[a] (%)	90% Confidence Intervals[b] (%)	CV[c] (%)
Doxylamine	AUC_{last}	99.19	94.03 – 104.62	10.77
	AUC_{inf}	99.09	93.72 – 104.76	11.24
	C_{max}	98.43	93.76 - 03.32	9.79
Pyridoxine	AUC_{last}	77.01	69.81 - 84.95	19.44
	AUC_{inf}	77.36	70.19 - 85.25	19.25
	C_{max}	46.84	40.28 - 54.47	30.27
Baseline Corrected Pyridoxal 5'-Phosphate	AUC_{0-72}	93.79	86.89 – 101.25	14.65
	C_{max}	102.24	95.25 – 109.73	13.95
Baseline Uncorrected Pyridoxal 5'-Phosphate	AUC_{0-72}	94.12	87.95 - 00.73	12.99
	C_{max}	100.21	93.59 - 107.31	13.48

[a] Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)}$ X 100
[b] 90% Geometric Confidence Interval using ln-transformed data
[c] Within-subject Coefficient of Variation (CV)

Comparing Diclectin to doxylamine delayed-release tablets and pyridoxine delayed-release tablets for the ln-transformed AUC_{last}, AUC_{inf}, and C_{max}, no statistically significant difference between Diclectin and doxylamine tablets was detected.

However, a statistically significant difference between Diclectin and pyridoxine tablet was detected for the ln-transformed AUC_{last}, AUC_{inf}, and C_{max}, respectively for pyridoxine.

All study formulations were well tolerated, with no major side effects. No relevant differences in safety profiles were observed between the preparations, particularly with respect to the pattern of adverse events.

Conclusion of Study 160286
This study complies with the current CHMP guidelines. The results of this study show that the pharmacokinetics of the monocomponents with the same pharmaceutical form are essentially similar when administered separately and in combination.

Supplementary Bioequivalence Study 02163
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 aimed to compare the Diclectin formulation to an oral solution combining both active substances. This study was originally included in the dossier only to support Diclectin's safety.

Table 3 Geometric means Ratios, 90% Geometric Confidence Intervals, the within-subject CV for the reference formulation (CV_{WR}) and Relative Bioavailability (Frel) -Study 02163 (Fasted)

Analyte	Parameter	Ratio of LS Means (%)	90% Confidence Intervals (%)	CV_{WR} (%)	*P*[a]	Frel (%)
Doxylamine	AUC_{last}	103.27	97.60-109.23	9.67	0.3320	
	AUC_{inf}	103.53	97.96-109.42	9.53	0.2894	104.51 ± 14.69
Pyridoxine	AUC_{last}	78.28	66.94-91.55	26.43	0.0151	
	AUC_{inf}	89.93	79.33-101.96	17.91	0.1573	92.49 ± 21.71
Pyridoxal	AUC_{last}	80.57	73.31-88.56	15.79	0.0011	
	AUC_{inf}	91.53	79.39-105.52	20.34	0.2877	96.11 ± 30.74
Pyridoxal 5'-phosphate	AUC_{last}	105.15	88.73-124.61	29.80	0.6125	
	AUC_{inf}	102.45	81.90-128.14	30.50	0.8488	109.58 ± 43.25
Total Pyridoxine[b]	AUC_{last}	103.67	90.55-118.68	23.56	0.6485	
	AUC_{inf}	92.62	76.38-112.32	28.90	0.4922	99.77 ± 38.77

LS: Least square; CV: Coefficient of Variation
[a] Treatment difference is significant if $P<0.0500$
[b] Total pyridoxine includes pyridoxine, pyridoxal, pyridoxal 5'-phosphate

In study 02163, comparing Diclectin to an oral solution of doxylamine and pyridoxine, no significant difference in the overall exposure (AUC_{inf}; $P>0.0500$) was observed for all moieties when doxylamine and pyridoxine were given as an oral solution and as Diclectin (Table 3). The bioequivalence criteria (80.00 % - 125.00%) were not strictly met for pyridoxine and metabolites; however, the reported confidence intervals contain 100% and are close to these criteria. Although, bioequivalence criteria are generally based on both AUC_{inf} and C_{max}, the use of a modified release formulation was expected to fail the 80.00% - 125.00% criteria for C_{max}; later t_{max} and longer t_{lag} were also expected with this formulation. This indicates that exposure between the oral solution and Diclectin can be considered similar, even though there was a high estimated intra-subject variability.

Table 4 reports the summary statistics for the parameters that were expected to change with a change in formulation, namely C_{max}, t_{max} and t_{lag}. There is a clear delay in the absorption process, with an increase in both t_{max} and t_{lag}, when the combination is administered as the delayed release formulation. C_{max} was not greatly affected by the difference in formulation for doxylamine and pyridoxal 5'-phosphate, while it was lower for pyridoxine and pyridoxal when the combination was administered as Diclectin. The apparent no or minimal change in C_{max} for doxylamine suggests that the effect of the Diclectin formulation delays the start of the absorption process rather than reducing the rate of absorption. A more complex effect is observed for pyridoxine and its metabolites.

Table 4 Summary statistics (mean±SD) for C_{max}, t_{max} and t_{lag} – Study 02163 (fasted)

Mean ± SD (Plasma)	Doxylamine		Pyridoxine		Pyridoxal		Pyridoxal 5'-Phosphate	
	Diclectin	Solution	Diclectin	Solution	Diclectin	Solution	Diclectin	Solution
C_{max} (ng/mL)	90.4 ± 13.l	98.7 ± 18.l	50.7 ± 31.0	96.5 ± 46.7	62.3 ± 19.1	82.8 ± 21.2	42.9 ± 17.5	41.6 ± 14.5
t_{max} (h)[a]	6.00 (3.00 – 10.00)	1.50 (1.00 – 3.67)	4.00 (1.50 – 5.50)	0.50 (0.25 – 1.00)	5.00 (2.33 – 8.00)	1.00 (0.75 – 1.50)	8.00 (3.00 – 12.00)	8.00 (2.67 – 12.2)
t_{lag} (h)[a]	3.33 (1.00 – 6.00)	0.250 (0.000 – 0.250)	3.00 (0.750 – 6.00)	0.000 (0.000 – 0.250)	N/A	N/A	3.84 (0.000 – 6.00)	0.250 (0.000 – 1.00)

[a] Median (range)

The results from study 02163 provided evidence that the pharmacokinetics of the monocomponents administered together as an oral solution were consistent with the pharmacokinetics of Diclectin. Although study 02163 does not demonstrate bioequivalence of Diclectin versus the mono-components administered separately, it shows evidence of bioequivalence of the fixed dose combination versus mono-components taken simultaneously in solution.

Study 70381: 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).

The primary objective of this study was to assess the pharmacokinetic profile of the active ingredients of Diclectin delayed-release tablets after single doses and at steady state after multiple doses in healthy non-pregnant female volunteers. The secondary objective of this study was to assess the safety and tolerability of Diclectin in healthy non-pregnant female volunteers.

Subjects were administered a single oral dose of Diclectin, as 2 x 10 mg/10 mg delayed release tablets at 22:00 h on Days 1 and 2, and were administered multiple oral doses from Days 3 through 18, according to the following regimen: 1 x 10 mg/10 mg delayed release tablet at 09:00 and 16:00, and 2 x 10 mg/10 mg delayed-release tablets at 22:00, under empty-stomach conditions (defined as at least 2 hours after eating).

Doxylamine, pyridoxine, pyridoxal and pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate were measured.

Results:
The main pharmacokinetic results of the study are presented in the Table 5 and Table 6 below:

Table 5 Pharmacokinetics parameters of Diclectin following single and multiple dose administration

Value	Doxylamine Mean ± SD N = 18		Pyridoxine Mean ± SD N = 18		Pyridoxal Mean ± SD N = 18	
	Single Dose	Multiple Dose	Single Dose	Multiple Dose	Single Dose	Multiple Dose
AUC_{last} (ng•h/mL)	911.40 ± 205.62	3661.27 ± 1279.16	39.34 ± 16.53	59.30 ± 33.90	187.46 ± 44.69	1296.71 ± 363.05
AUC_{inf} (ng•h/mL)	1280.90 ± 369.32	3721.46 ± 1318.50	43.39 ± 16.46	64.45 ± 36.36	211.60 ± 46.09	1587.22 ± 550.04
AUC_{0-24} (ng•h/mL)	911.40 ± 205.62	2531.40 ± 719. 47	40.70 ± 16.45	62.74 ± 33.68[a]	195.13 ± 46.18	1147.19 ± 241.34
C_{max} (ng/mL)	83.26 ± 20.62	168.58 ± 38.49	32.57 ± 15.03	46.05 ± 28.30	74.29 ± 21.80	210.02 ± 54.36
t_{max}* (h)	7.50 (3.33-11.00)	8.00 (4.67-11.00)	5.50 (2.67-9.02)	5.25 (4.00-8.00)	6.00 (3.33-9.00)	6.75 (5.00-9.00)
K_{el} (h^{-1})	0.0719 ± 0.0152	0.0615 ± 0.0133	1.7604 ± 0.8190	1.6590 ± 0.4872	0.6004 ± 0.1739	0.0538 ± 0.0304
$t_{1/2el}$ (h)	10.05 ± 2.09	11.91 ± 3.33	0.49 ± 0.23	0.45 ± 0.14	1.29 ± 0.50	19.44 ± 14.46
AI**	-	2.76 ± 0.30	-	1.59 ± 0.51[a]	-	6.09 ± 1.55

(-) Calculation not applicable

[#] Baseline corrected pharmacokinetic parameters

[a] N=17

[b] N=15

[c] N=14

[d] N=4

* Medians and ranges are presented ** Calculated as AUC_{0-24} Day 18 / AUC_{0-24} Day 1

Abbreviations for tables 5, 6 and 7:

AUC_{last} Area under the concentration time curve from time 0 to the last detectable concentration using the linear trapezoidal rule

AUC_{inf} Area under the concentration time curve (0-hour to infinity). Calculated as AUC_{0-last} + (C_t/K_{el}), were C_t = the last observed non-zero concentration for that treatment, AUC_{0-last} =the AUC from time zero to the time of the last non-zero concentration for that treatment and K_{el}.

AUC_{0-24} Area under the concentration time curve (0 to 24 hours) calculated by use of the linear trapezoidal rule (equivalent to AUC_X)

C_{max} Observed maximum concentration after single dose and multiple dose administration

T_{max} Time to reach the C_{max}

Kel Elimination rate constant, calculated from the long-linear terminal portion of the concentration-time curve. Calculations were made between a time point where log-linear elimination phase begins (TLIN) and the time at which the last concentration above the limit of quantitation (LQCT) occurred. Whenever possible, at least 4 non-zero observations during the terminal elimination phase were used to calculate the Kel. A minimum of 3 observations was used if fewer than 4 observations were available. The Kel was taken as the slope multiplied by (-1).

T ½ el Apparent elimination half-life, calculated as In2/Kel

AI The accumulation index was calculated as the ration of AUC_{0-24} on day 18 and AUC_{0-24} on day 1. When possible, the accumulation index was also calculated as AI = 1/[1-e-kel*tau]. Tau is the (assumed equal) dosing interval (24 hrs will be used for this calculation) for steady-state data

Table 6 Pharmacokinetics parameters of Diclectin following single and multiple dose administration (cont'd)

Value	Pyridoxal 5'-phosphate[#] Mean ± SD N = 18		Pyridoxamine Mean ± SD N = 18		Pyridoxamine 5'-phosphate[#] Mean ± SD N = 18	
	Single Dose	Multiple Dose	Single Dose	Multiple Dose	Single Dose	Multiple Dose
AUC_{last} (ng•h/mL)	442.01 ± 155.63	4766.31 ± 1137.10	467.28 ± 514.41	1607.17 ± 696.39	3457.82 ± 2393.20	58859.26 ± 58292.60
AUC_{inf} (ng•h/mL)	1536.39 ± 721.51	6099.69 ± 1383.66	4121.04 ± 2712.73	2607.78 ± 824.65	5231.93 ± 3839.39	94459.22 ±58010.53
AUC_{0-24} (ng•h/mL)	442.01 ± 155.63[a]	1725.01 ± 358.01[a]	565.61 ± 527.50[b]	1786.34 ± 683.05[a]	3503.62 ± 2385.10	17085.23 ± 14937.64
C_{max} (ng/mL)	30.01 ± 10.03	84.91 ± 16.85	532.21 ± 736.88	535.57 ± 157.72	739.29 ± 450.99	2290.90 ± 1703.36
t_{max}* (h)	11.5 (4.33-24.00)	4.92 (0-24.00)	6.00 (1.33-9.02)	7.00 (4.33-9.00)	14.0 (2.33-24.00)	11.0 (0-36.00)
K_{el} (h^{-1})	0.0204 ± 0.0078	0.0139 ± 0.0035	0.0932 ± 0.0749[b]	0.2913 ± 0.1182	0.1584 ± 0.0985	0.0189 ± 0.0097
$t_{1/2el}$ (h)	36.99 ± 12.01	53.46 ± 15.30	10.98 ± 8.82	2.90 ± 1.52	5.42 ± 3.37	44.33 ± 21.70
AI**	-	3.98 ± 0.67[a]	-	6.17 ± 6.87[c]	-	6.67 ± 6.18[d]

(-) Calculation not applicable
[#] Baseline corrected pharmacokinetic parameters
[a] N=17
[b] N=15
[c] N=14
[d] N=4
* Medians and ranges are presented
** Calculated as AUC_{0-24} Day 18 / AUC_{0-24} Day 1

Doxylamine accumulates following multiple dosing with steady state attained after Day 9. The concentrations of pyridoxine and metabolite, pyridoxamine, were not significantly different after single or multiple dose administrations of Diclectin. The concentrations of the pyridoxine metabolites (pyridoxal, pyridoxal 5'-phosphate, and pyridoxamine 5'-phosphate) increased following multiple dose administrations of Diclectin. Multiple dose administrations of Diclectin seem to increase the extent of absorption (AUC_{0-24}) of pyridoxine and all pyridoxine metabolites as well as the rate of absorption (C_{max}) of pyridoxal, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate. The time to reach the maximum concentration (T_{max}) does not seem to be affected by multiple doses.

Given there is no comparison to the individual active substances or licensed single active substances it is not possible to use this approach to extrapolate to the bibliographic data used in support of this application.

Study 70294-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**.**

All subjects fasted for at least 10 hours prior to drug administration and those in the fed group received a standard high-fat, high-caloric meal within 30 minutes before drug administration. After dosing, subjects were subsequently fasted for a period of at least 4 hours. The treatment phases (fasting and fed conditions) were separated by a washout period of 27 days.

Doxylamine, pyridoxine, pyridoxal and pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate were measured.

Results

Table 7 Pharmacokinetic parameters of Diclectin under fed and fasted conditions in healthy female volunteers

Mean ± SD	Plasma Doxylamine		Plasma Pyridoxine		Plasma Pyridoxal		Baseline Corrected Plasma Pyridoxal 5'-Phosphate		Plasma Pyridoxamine		Baseline Corrected Plasma Pyridoxamine 5'-Phosphate	
	Diclectin Fed	Diclectin Fasted	Diclectin Fed	Diclectin Fasted	Diclectin Fed	Diclectin Fasted	Diclectin Fed	Diclectin Fasted	Diclectin Fed	Diclectin Fasted	Diclectin Fed	Diclectin Fasted
AUC_{last} (ng•h/mL)	1488.03 ± 463.21	1407.20 ± 336.94	18.32 ± 14.52	33.75 ± 13.71	138.40 ± 70.85	193.66 ± 53.95	2096.63 ± 916.50	1975.12 ± 881.98	342.15 ± 399.55	5646.73 ± 19038.59	52045.43 ± 47013.65	51967.10 ± 41092.51
AUC_{inf} (ng•h/mL)	1579.01 ± 422.72	1447.89 ± 332.18	24.18 ± 13.99	39.48 ± 12.85	197.11 ± 76.34	231.20 ± 71.75	2838.60 ± 1469.78	2415.23 ± 1087.78	3239.49	1530.63 ± 822.85	184751.02 ± 259063.79	47527.96 ± 28290.13
C_{max} (ng/mL)	75.74 ± 16.59	94.90 ± 18.40	13.71 ± 10.77	35.54 ± 21.40	45.63 ± 25.00	85.39 ± 21.53	34.16 ± 11.88	29.75 ± 10.93	367.37 ± 381.33	487.32 ± 651.49	994.09 ± 652.73	1325.08 ± 745.22
t_{max} (h)[a]	11.8 (4.00 - 24.1)	4.50 (1.50 - 24.0)	9.00 (4.00 - 24.0)	2.50 (1.00 - 4.52)	10.0 (4.00 - 24.1)	3.03 (1.02 - 5.00)	16.0 (6.53 - 24.1)	13.0 (3.50 - 48.0)	8.75 (4.00 - 24.0)	3.00 (1.00 - 96.0)	20.0 (2.00 - 2.16)	4.00 (2.00 - 2.16)
K_{el} (h^{-1})	0.0581 ± 0.0118	0.0586 ± 0.0147	1.6606 ± 0.5901	2.1215 ± 0.7242	0.4662 ± 0.2323	0.5337 ± 0.2804	0.0126 ± 0.0161	0.0115 ± 0.0084	0.0936	0.3213 ± 0.1569	0.0294 ± 0.0395	0.0534 ± 0.1136
$t_{½\ el}$ (h)	12.48 ± 2.88	12.64 ± 3.43	0.48 ± 0.21	0.37 ± 0.16	2.01 ± 1.25	2.14 ± 2.18	94.61 ± 56.93	81.60 ± 42.17	7.40	3.08 ± 2.54	105.49 ± 147.79	66.47 ± 51.29

[a] Median (range)

The administration of Diclectin delayed-release tablets with a standard high-fat, high caloric meal delayed the absorption of both doxylamine and pyridoxine by approximately 7 hours when compared to administration under fasting conditions (based on median t_{max} results).

Although the delay in absorption of doxylamine under fed conditions was associated with a lower peak concentration, the extent of absorption was not affected. However, the rate and extent of absorption of pyridoxine was significantly reduced when administered with food. The effect of food on the pyridoxine component is more complex, in that pyridoxine and its B6 vitamin metabolites, pyridoxal, pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate also contribute to the biological activity.

The study demonstrated that there is a significant delay to absorption in the fed state.

Conclusion of pharmacokinetic data

The submitted data comply with the current CHMP guidelines, because the studies provide adequate data comparing the individual active substances and combination product (in the same pharmaceutical form) and demonstrate similar pharmacokinetics and no interaction as per EMA/CHMP/158268/2017.

The bridge between existing clinical data on the FDC product and the literature data on the single active substances has been demonstrated with pharmacokinetic and bioequivalent data from Study 160286 and Study 02163. This is further supported by an integrated analysis evaluating published data on each mono-component, with a dose adjustment, against Diclectin, the oral solution of doxylamine and pyridoxine and separate doxylamine and pyridoxine delayed-release tablets.

Therefore, no further study data need to be provided comparing the bioavailability of the actives when administered individually or in combination.

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

In accordance with the requirements for fixed dose combinations (CHMP/EWP/240/95/Rev 1), the applicant submitted the following to support the application:

1. A pivotal Phase III efficacy study (Study DIC-301)
2. Published data from the Drug Efficacy Study Implementation (DESI) study which was carried out in the USA in 1975
3. A summary of the literature evidence for varying combinations of the active substances.

A summary of the data is provided below.

Study DIC-301
A double-blind, multicentre, randomised, placebo-controlled trial of the efficacy of Diclectin for nausea and vomiting of pregnancy.

Primary Objective: The primary objective of this study was to compare the efficacy of Diclectin to placebo in the treatment of nausea and vomiting of pregnancy (NVP).

Secondary Objectives: The secondary efficacy endpoints included: (a) Three components constituting the Pregnancy Unique-Quantification of Emesis (PUQE) (b) Global Assessment of Well-Being (c) Number of tablets taken (d) Time loss from household tasks and/or employment (e) Total number of visits and phone calls to health care providers (f) Rates of hyperemesis gravidarum (g) Compliance with study medication.

Study Population
The intent-to-treat efficacy population (ITT-E) contained 256 subjects. Subjects were pregnant women, at least 18 years of age, with a gestational age of 7-14 weeks, suffering from nausea and vomiting of pregnancy (NVP), with a PUQE score ≥ 6, and not responding to conservative management consisting of dietary/lifestyle advice according to the 2004 American College of Obstetrics and Gynecology (ACOG) Practice Bulletin.

The Intent-to-Treat efficacy (ITT-E) population consisted of any subject who took at least one dose of study medication and had at least one post-baseline PUQE measurement.

Study Treatments
Diclectin delayed-release tablets containing doxylamine succinate USP 10 mg and pyridoxine hydrochloride 10 mg were administered orally at bedtime. The minimum assigned study medication was 2 tablets daily at bedtime, increasing when indicated to the maximal dosage of 4 tablets per day according to the subject's symptomatology.

The study had a 15-day period consisting of 14 dosing days.

Blood sampling for determination of pharmacokinetic (PK) measurements of pyridoxine, pyridoxal, pyridoxal 5-phosphate and doxylamine concentrations on Day 1, Day 4 (± 1 day), Day 8 (± 1 day), and Day 15 (± 1 day) was conducted. A summary of the PK results and statistical analyses are presented below.

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.

Secondary Endpoints
The secondary efficacy endpoints included evaluation of the (a) three components constituting the PUQE score (b) Global Assessment of Well-Being (c) Number of tablets taken (d) Time loss from household tasks and/or employment (e) Total number of visits and phone calls to health care providers (f) Rates of hyperemesis gravidarum (g) Compliance with study medication.

RESULTS
Primary efficacy analysis
The mean PUQE scores were comparable at baseline in the two treatment groups. Both treatment groups showed negative mean changes from baseline in PUQE score, indicating improvement in NVP symptoms. The mean (SD) change in the Diclectin group was -4.8 (2.7) and the mean change in the placebo group was -3.9 (2.6). The difference between these two mean changes was statistically significant (*P*=0.006), indicating statistically significantly greater improvement in the Diclectin group than in the placebo group.

Table 8 Primary efficacy analysis: Change from baseline to Day 15 (± 1day) in PUQE score for ITT-E population

Data/Category	Statistics	Treatment Group		*P* value for comparison
		Diclectin (N=131)	Placebo (N=125)	
Baseline	N Mean ± SD Median Min, Max	131 9.0 ± 2.1 9.0 6, 15	125 8.8 ± 2.1 8.0 6, 15	
Day 15 (± 1 day)	N Mean ± SD Median Min, Max	131 4.2 ± 1.9 3.0 3, 11	125 4.9 ± 2.3 4.0 3, 12	
Change from Baseline	N Mean ± SD Median Min, Max %	131 -4.8 ± 2.7 -5.0 -11, 3 53.0	125 -3.9 ± 2.6 -4.0 -11, 2 44.0	0.006[1]

Change from Baseline (Screening) is defined as post-baseline minus Baseline. Subjects who discontinued the study prematurely had subsequent missing PUQE scores estimated using a LOCF approach.
[1] *P values* for treatment comparison (Diclectin vs. Placebo) from rank-based analysis of variance stratified by centre

The mean change from baseline to Day 15 in PUQE score was numerically larger for the Diclectin treatment group than the placebo treatment group in subjects with complete data via Last Observation Carried Forward (LOCF) analyses and for per protocol subjects. For subjects with complete data (using LOCF), the mean change in PUQE score (SD) was -5.1 ± 2.5 for the Diclectin treatment group and -4.5 ± 2.5 for the placebo treatment group (*P*=0.184). For per protocol subjects, the mean change in

PUQE score was -5.3 ± 2.4 for Diclectin treatment group and -4.6 ± 2.4 for the placebo treatment group (*P*=0.069). Neither of these differences between treatment groups were statistically significant.

Re-analysis of primary end-points

The study DIC-301 primary endpoint results were re-analysed, on request, using the all-randomised population carrying baseline observations forward for those with no post-baseline measurements. The re-analysis of the data revealed a statistically significant result in the all randomised population, consistent with the primary analysis. The results are presented in Table 9 and Table 10 below.

Table 9 Change from baseline to Day 15 (±1 day) in PUQE score for all patients

Data/Category	Statistics	Treatment Group		*P* value for comparison
		Diclectin (N=140)	Placebo (N=140)	
Baseline	N Mean ± SD Median Min, Max	140 9.0 ± 2.1 9.0 6, 15	140 8.9 ± 2.1 8.0 5, 15	
Day 15 (± 1 day)	N Mean ± SD Median Min, Max	140 4.5 ± 2.3 3.0 3, 15	140 5.4 ± 2.7 4.0 3, 13	
Change from Baseline	N Mean ± SD Median Min, Max	140 -4.5 ± 2.9 -4.5 -11, 3	140 -3.5 ± 2.8 -3.0 -11, 2	0.0018[1]

Baseline observations carried forward for those with no post-baseline measurements
[1]*P* value for treatment comparison (Diclectin vs. Placebo) from rank-based analysis of variance stratified by centre.

Table 10 Least Square Mean difference and 95% Confidence Intervals

Least Square Mean Difference	95 % Confidence Interval
-0.927	-1.494, -0.360

Secondary efficacy analyses

Components of the PUQE score

Mean changes from baseline to Day 15 (± 1 day) hours of nausea, number of times vomiting, and number of times retching for the ITT-E Population decreased similarly (consistently higher decrease) in both treatment groups. The mean (± SD) hours of nausea decreased from 4.0 ± 1.0 to 1.5 ± 1.0 (change from baseline -2.6 ± 1.2) with Diclectin treatment and from 4.1 ± 0.9 to 1.6 ± 0.9 (change from baseline -2.5 ± 1.1) for placebo (*P*=0.649). The mean (± SD) number of times vomited decreased from 2.2 ± 1.2 to 1.1 ± 0.3 (change from baseline -1.1 ± 1.2) with Diclectin treatment, and from 2.1 ± 1.2 to 1.2 ± 0.5 (change from baseline -0.8 ± 1.2) with placebo (*P*=0.084). The mean (± SD) number of times retching decreased from 2.7 ± 1.1 to 1.2 ± 0.5 (change from baseline -1.5 ± 1.2) for Diclectin treatment, and from 2.6 ± 1.2 to 1.4 ± 0.7 (change from baseline-1.3 ± 1.1) with placebo treatment (*P*=0.082).

In summary, the mean PUQE component scores were comparable at baseline for the two treatment groups. Mean changes in these scores were all negative for both treatment groups, indicating improvement. Mean changes from baseline were similar for the two treatment groups for all 3 component scores; no statistically significant differences were seen.

Global assessment of well-being (Quality of Life (QOL))
The mean change from baseline to Day 15 (± 1 day) in Global Assessment of Well-Being scores for the ITT-E Population was statistically significantly higher for subjects treated with Diclectin than for those treated with placebo (*P*=0.005). The mean (± SD) Global Assessment of Well-Being score increased (indicating improvement in well-being) from 5.0 ± 2.3 to 7.8 ± 2.2 (change from baseline 2.8 ± 2.8) with Diclectin treatment and increased from 5.4 ± 2.2 to 7.2 ± 2.0 (change from baseline 1.8 ± 2.2) with placebo treatment.

Number of tablets taken
The mean number of tablets (SD) taken was similar for both treatment groups, with 36.6 ± 13.3 tablets taken for Diclectin-treated subjects and 34.0 ± 15.1 tablets taken for placebo-treated subjects (*P*=0.139).

The proportion of subjects who took the required 28 tablets was greater for Diclectin-treated subjects (11/131 subjects; 8.4%) than for placebo-treated subjects (6/125 subjects; 4.8%). The proportion of subjects taking fewer than 28 tablets was lower in the Diclectin-treated subjects (31/131 subjects; 23.7%) than for placebo-treated subjects (38/125 subjects; 30.4%). The remaining subjects in each treatment group took more than 28 tablets (89/131 [67.9%] Diclectin-treated subjects and 81/125 [64.8%] placebo treated subjects). The difference in the distributions of subjects in these categories for the two treatment groups was not statistically significant (*P*=0.283).

Time loss from household tasks and/or employment
The mean (± SD) time loss from household tasks was similar for both treatment groups, with 6.09 ± 15.54 hours for Diclectin treatment and 5.51 ± 12.83 hours for placebo (*P*=0.734). The mean (SD) time loss from employment was numerically less for the Diclectin treatment group, with 0.92 ± 3.86 hours versus 2.37 ± 10.23 hours for the placebo treatment group; however, this difference was not statistically significant (*P*=0.064).

Visits and telephone calls to health care providers
The mean (SD) number of visits to health care providers was similar for both treatment groups with 0.1 ± 0.5 visits with Diclectin treatment and 0.1 ± 0.4 visits for placebo treatment (*P*=0.885). The mean (SD) number of phone calls to health care providers was also similar for both treatment groups with 0.1 ± 0.4 phone calls for Diclectin treatment, and 0.1 ± 0.3 phone calls for placebo treatment (*P*=0.581).

Rates of hyperemesis gravidarum
There were no subjects with reported hyperemesis gravidarum in either treatment group.

Compliance with study medication
The difference in the study drug compliance between groups was not statistically significant (*P*=0.283). The compliance with study medication did not differ between treatment groups with 67.9% (89/131) of Diclectin-treated subjects and 64.8% (81/125) of placebo-treated subjects taking more than 28 tablets. Study drug compliance was also similar for Diclectin-treated and placebo-treated subjects taking 28 tablets (8.4% and 4.8%) and fewer than 28 tablets (23.7% and 30.4%), respectively. Overall, there were 29 (20.7%) Diclectin-treated subjects and 48 (34.3%) placebo-treated subjects that were outside 80 to 120% dosing compliance.

Post ad hoc analysis
In order to supplement the previously presented clinical data, a post hoc analysis was conducted to evaluate the change from baseline in PUQE score to Days 3, 4 and 5. The objective of this additional analysis was to assess the efficacy compared to placebo at an earlier stage in the trial and minimise the impact of any natural course of NVP improvement. Results at day 3 demonstrated a difference in PUQE score from baseline between Diclectin-treated and placebo-treated women significantly lower by 1.0 PUQE units (*P*=0.002). At Day 4, the difference was 1.1 PUQE units (*P*<0.001); and at day 5, 1.0 PUQE units (*P*=0.006) [2016].

Following MHRA recommendation, a subsequent post ad hoc analysis was conducted to assess the change in PUQE score from baseline to Day 10. The objective of this additional analysis was to obtain a middle analysis point between Days 5 and 15 and evaluate the evolution of the PUQE score change from baseline throughout the whole trial duration of 15 days. Moreover, the analysis in the morning of Day 10 provides data several days after the maximum dose has been reached by the patient, since the maximum possible dosage of 4 tablets per day is reached on Day 4, as per study protocol.

Results at Day 10 demonstrated a difference in PUQE score from baseline between Diclectin-treated and placebo-treated women significantly lower by 0.8 PUQE units (P=0.032).

Study DIC-301 demonstrated a greater improvement of 0.8 to 1.1 PUQE units for Diclectin, compared to placebo, for Days 3, 4, 5, 10 and 15. These statistically significant differences, based on the PUQE scale, represent improvements that are clinically meaningful for pregnant women suffering from NVP.

It could represent a difference from three hours of nausea per day to only one hour or less. Severity of nausea in NVP being similar in character and intensity to nausea associated with chemotherapy [2000] and persistent nausea being the symptom that most adversely affects quality of life [2016], this difference is highly clinically meaningful for the pregnant women suffering from NVP and positively influences the Quality of Life (QOL).

Conclusion
The primary end point was met from a statistical perspective, giving a statistically significant improvement in the PUQE score from baseline at day 15. However, the clinical change was small, only (-4.8 vs -3.9) and was equal to the difference in the baseline measurement. This change was carried through in the secondary end points, some of which showed statistical superiority but in which the changes were small. The applicant has provided a detailed explanation of this study outcome, including the clinical meaningfulness of the results and positive impact upon patients. The applicant's argument put forward to support the clinical relevance of the study outcome include reference to recent expert clinical opinion, current clinical practice and published literature; this is acceptable.

To further support the application the applicant submitted published data from the Drug Efficacy Study Implementation (DESI) study which was carried out in the USA 1975. Details of the DESI study are provided below.

DESI study
An 8-way, randomized, double-blind, placebo-controlled, multi-centre trial, involving patients who had nausea and/or vomiting of pregnancy, was submitted in the Bendectin New Drug Application following the FDA Drug Efficacy Study Implementation ("DESI") program.

The DESI study compared doxylamine, pyridoxine, and dicyclomine hydrochloride, alone or in various combinations, with placebo in an 8-way study design in a total of 2,308 patients. This included the comparison of the proposed combination product (doxylamine and pyridoxine) to doxylamine alone and pyridoxine alone. The applicant has stated that although performed over 40 years ago, the study was conducted in accordance to standards comparable to the current clinical practice.
In this study, pregnant women experiencing nausea and vomiting were randomised to receive 2 tablets of:
i. doxylamine succinate 10 mg / dicyclomine hydrochloride 10 mg / pyridoxine hydrochloride 10 mg - or
ii. doxylamine succinate 10 mg / pyridoxine hydrochloride 10 mg - or –
iii. dicyclomine hydrochloride 10 mg / doxylamine succinate 10 mg - or -
iv. dicyclomine hydrochloride 10 mg / pyridoxine hydrochloride 10 mg - or -
v. doxylamine succinate 10 mg - or -
vi. dicyclomine hydrochloride 10 mg - or -

vii. pyridoxine hydrochloride 10 mg - or -
viii. placebo

at bedtime for 7 nights and if necessary 1 additional tablet in the morning and mid-afternoon.

Physicians were asked to evaluate the efficacy of the therapy overall, and for improvement in nausea and vomiting. Patients were also asked to evaluate the efficacy of their therapy. For all therapies, statistical significance was assessed compared to placebo.

Results:

Table 11 Efficacy results of the Doxylamine succinate and pyridoxine hydrochloride arms of the DESI-8 study among pregnant women with Nausea and Vomiting of Pregnancy

Primary Endpoints	Doxylamine Succinate + Pyridoxine Hydrochloride	Placebo	*P*-value
Physician's evaluation of % effectiveness (moderate to excellent)	78	57	<0.01
Physician's evaluation of % improvement in nausea	75	52	<0.01
Physician's evaluation of % improvement in vomiting	73	66	0.17
Patient's evaluation of % reduction in daily hours nausea	64	31	<0.01
Patient's evaluation of % with no vomiting on 5 or more treatment days	48	28	<0.01

The doxylamine succinate 10 mg / pyridoxine hydrochloride 10 mg group showed statistically significant improvement in symptoms as evaluated by physicians and patients compared to the placebo group (Table 11). Doxylamine was the most effective of these active ingredients for the treatment of nausea and vomiting and pyridoxine had an added effect on nausea. Dicyclomine was found to be ineffective for either nausea or vomiting in this study. Based on the demonstration of effectiveness in this study, Bendectin was reformulated with doxylamine and pyridoxine only as active ingredients.

Conclusion
The results of this study appear to show sufficient evidence to demonstrate the clinical contributions of doxylamine succinate and pyridoxine hydrochloride in the proposed fixed dose combination (FDC). Therefore, the findings of this study may be considered to partially address the issue of compliance with the current European regulatory guidelines, although the demonstration of superiority of the FDC against its mono-components is not possible from this 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 and the latest available NVP rates. However, it should be noted that due to the age of the innovator product, many of the older references are still considered important.

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.

Furthermore, supportive evidence generated from current clinical practice has been provided.

Overall conclusion on efficacy
The data submitted fulfils the fixed dose combination requirements (EMA/CHMP/158268/2017).

While the results of the single pivotal study regarding the demonstration of efficacy is considered largely borderline, these findings can be viewed in the context of the submitted additional data described above, which the applicant has generated from various sources including current clinical practice. These additional data particularly an Irish study, appear to show that the combination may be effective in a substantial proportion of pregnant women presenting with nausea and vomiting.

In addition, the results of the DESI study appear to show sufficient evidence to support the clinical contributions of each of the monocomponents in the fixed dose combination.

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 Xonvea for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

IV.4 Clinical Safety

The safety profile of doxylamine 10 mg/pyridoxine 10 mg fixed dose combination is well-established. No new or unexpected safety concerns arose from this application.

Diclectin has been marketed in Canada by Duchesnay since 1983, and in the US under the trade name Diclegis, since 2013, with no reported safety concerns.

The evidence of the safety for Xonvea is supported by the clinical pharmacokinetic and clinical efficacy studies discussed above, published data, as well as post marketing data. The applicant has supplied data, derived from several sources, to support the safety of Diclectin:

1. The Diclectin clinical programme including the Phase III pivotal efficacy trial, DIC-301
2. Global literature data on doxylamine succinate/pyridoxine hydrochloride combination products marketed under other trade names
3. Global post-marketing experience on doxylamine succinate/pyridoxine hydrochloride combination products marketed under other trade names
4. Diclectin post-marketing experience in Canada and the US.

The safety data submitted to support use of the proposed formulation for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management is summarised below.

Deaths
No study subject deaths occurred in any of the clinical studies.

Serious Adverse Events

Study DIC-301

There were nine subjects with serious adverse events and 7 additional subjects that discontinued the study drug due to treatment-emergent adverse events (TEAEs) that were not serious.

Serious adverse events (SAE) were collected from the time of the first dose until 30 days after the subject had either discontinued study medication or started on compassionate medication. As presented in Table 12. A total of nine serious adverse events were reported for this study with 3.0% (4/133) in the Diclectin 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). Rates of fetal death were the same in both arms and in all 8 cases the event was considered unrelated to study drug. There were 4 subjects (2 Diclectin, 2 placebo) that discontinued study drug due to their SAEs: missed abortion (Diclectin), spontaneous abortion (Diclectin), spontaneous abortion (placebo) and bile duct stone (placebo). None of the nine reported SAEs required unblinding of the study drug. Eight of the SAEs were considered unrelated to the study drug and one SAE was considered unlikely to be related to the study drug.

Table 12 Study DIC-301 Serious Treatment Emergent Adverse Events in the Study for ITT-S subjects

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, puerperium 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.

Studies 02163, 02191, 70294, 70381 and 160286

No serious adverse events were reported for these studies.

Common Adverse Events

The following section summarises the adverse events for studies in the Diclectin clinical study programme.

Study DIC-301

The incidence of treatment-emergent adverse events (TEAEs) was similar for both treatment and placebo groups. Of the 261 ITT-S subjects, 74 (55.6%) Diclectin-treated and 66 (51.6%) placebo-treated subjects experienced at least one adverse event during the study. For both treatment groups, most TEAEs were considered mild in severity.

There were 40 (30.1%) Diclectin-treated and 32 (25.0%) placebo-treated subjects with at least one TEAE considered related to study drug (possibly, probably or definitely related). This difference was not

statistically significant (P=0.359).

Related events (> 2% in either treatment group) were: somnolence [19 (14.3%) Diclectin, 15 (11.7%) placebo]; abdominal pain [1 (0.8%) Diclectin, 3 (2.3%) placebo]; dry mouth [4 (3.0%) Diclectin, 1 (0.8%) placebo]; fatigue [6 (4.5%) Diclectin, 5 (3.9%) placebo]; dizziness [6 (4.5%) Diclectin, 5 (3.9%) placebo]; and headache [8 (6.0%) Diclectin, 8 (6.3%) placebo]. Other related events (≤2% in either treatment group) were: constipation, diarrhoea, dyspepsia, feeling jittery, increased alanine aminotransferase, increased blood amylase, increased appetite, myalgia, ageusia, migraine, syncope, insomnia, mood swings, nasal congestion, and hot flush. There were 3 severe TEAEs considered related to study medication including fatigue (Diclectin, possible), fatigue/exhaustion (Diclectin, probable), and headache (placebo, possible).

Study 70294
A total of 52 treatment emergent adverse events (TEAEs) were reported by 26 of the 44 subjects who received at least one dose of the study medication (safety population). The most commonly reported TEAE in the safety population were headache (13.6%; n=6), catheter site pain (13.6%; n=6), and somnolence (11.4%; n=5).

Study 70381
A total of 109 treatment-emergent adverse events were reported by 17 of the 18 subjects who received at least one dose of the study medication (safety population). Of the 109 adverse events reported, 82 were graded as mild, 25 were graded as moderate, and 2 were graded as severe. The severe adverse events were vomiting (intermittent) and a sensation of chest tightness, both with onset on Day 22 (after the last drug administration). The most frequently occurring adverse events were mild in intensity and included nausea (50%) and headache (44%).

Study 02163
A total of 74 treatment-emergent adverse events (TEAEs) occurred during this study. The most commonly reported adverse events were headache and nausea.

Of the 74 TEAEs reported, 38 were graded as mild and 33 were graded as moderate. The severity at onset of the remaining adverse events (n=3) could not be assessed as they were associated with clinically significant post-study laboratory results.

Of the 74 TEAEs reported, the relationship of 2 adverse events was judged as “probable”, 15 as “possible”, 37 as “remote”, and 20 as “unrelated”. One adverse event judged as probable with relation to the study medication was associated with each of the two treatments (tablets and oral solution); nine and six adverse events judged to be possible in relation to the study medication were associated with treatments A (tablets) and B (oral solution), respectively.

Study 02191
A total of 51 treatment-emergent adverse events occurred during the study, of which 49 can be analysed per treatment group. The remaining TEAEs (n=2) were clinically significant abnormal laboratory results and could not be assigned to a treatment group (exact time and date of onset unknown). The most commonly reported adverse event was headache.

Of the 51 TEAEs reported, 38 were graded as mild and 10 were graded as moderate. The severity at onset of the remaining adverse events (n=3) could not be assessed as they were associated with clinically significant post-study laboratory results or the severity was not graded at onset.

Of the 51 post-dose adverse events reported, the relationship of 3 adverse events was judged as “probably”, 16 as “possible”, 23 as “remote”, and 9 as “unrelated”. Eight adverse events judged to be possible with relation to the study medication were associated with each of the two treatments (fed and fasted); 1 and 2 adverse events judged probably related to the study medication were associated with

treatments A (fed) and B (fasted), respectively.

Discontinuation due to adverse events
Study DIC-301
Overall, there were 11 subjects that discontinued study drug due to adverse events. Of the subjects who had an adverse event causing discontinuation of study drug, 6 (4.5%) were in the Diclectin treatment group and 5 (3.9%) were in the placebo treatment group.

Of the events leading to study drug withdrawal, 7 non-serious events (4 Diclectin, 3 placebo) were considered related to study drug and included somnolence, syncope, and dizziness for the Diclectin-treated subjects, and dyspepsia, somnolence and abdominal pain for placebo-treated subjects. There were 4 events (2 Diclectin, 2 placebo) of the 11 events leading to early discontinuation of study drug that were considered serious and included missed abortion and spontaneous abortion for Diclectin-treated subjects and spontaneous abortion and bile duct stone for placebo-treated subjects. Three of the SAEs leading to study drug discontinuation were considered unrelated to the study drug and 1 was considered unlikely related to study drug.

Studies 02163, 02191, 70294, 70381 and 160286
No other significant adverse events were reported for these studies conducted with healthy non-pregnant women.

Safety related to interactions
No studies were conducted with Diclectin to examine potential drug-drug interactions. Theoretical drug-drug interactions for doxylamine succinate and pyridoxine hydrochloride are summarised in the tables below.

Table 13 Theoretical drug-drug interactions for doxylamine succinate

Drugs	Effect	Clinical Comment
Monoamine Oxidase Inhibitors (MAOIs)	Enhance	MAOIs may prolong and intensify the anticholinergic effects of doxylamine succinate[1,2]
Antimuscarinic drugs	Additive	There is an increased risk of antimuscarinic side effects when doxylamine is given with other antimuscarinic drugs[1,3]
Solid potassium dose forms	Enhance	Doxylamine succinate anticholinergic effects may slow the gastrointestinal transit and increase local exposure to high potassium concentration, increasing risks of ulcerative/stenotic lesions[4]
Opioids	Additive	May increase risk of severe constipation/paralytic ileus, CNS depression and psychomotor impairment[4]
Dronabinol, Nabilone	Additive/ Synergistic	May increase risk of tachycardia, drowsiness, CNS depression and psychomotor impariment[4]
Ezogabine	Additive	May increase risk of urinary retention, CNS depression and psychomotor impairment.[4]
Metoclopramide	Antagonistic/Additive	May decrease gastrointestinal prokinetic effect and increase risk of CNS depression[4]
Pramlintide	Additive	Anticholinergic effect of doxylamine may further delay gastric emptying (slow gastrointestinal transit)[4]
Cevimeline	Antagonistic	May decrease efficacy of both doxylamine and cevimeline[4]
Pilocarpine	Antagonistic	May decrease efficacy of both doxylamine and pilocarpine.[4] If pilocarpine ophthalmic is used doxylamine may decrease the efficacy of the ophthalmic pilocarpine[4]
Loperamide	Additive	May increase risk of severe constipation/paralytic ileus[4]
Mirabegron	Additive	May increase risk of urinary retention[4]
Zonisamide	Additive	Use with drugs possessing anticholinergic effect may increase risk of oligohidrosis, hyperthermia and heat stroke (especially in children)[4]

Drugs	Effect	Clinical Comment
Alcohol and CNS depressants (barbiturates, hypnotics, narcotic analgesics, anxiolytic sedatives and anti-psychotics; other first generation antihistamines; acrivastine, cetirizine or levocetirizine)	Additive	Doxylamine succinate may increase the risk of CNS depressant effects[1,2]

Table 14 Theoretical drug-drug interactions for pyridoxine hydrochloride

Drugs	Effect	Clinical Comment
Levodopa	Reduces effectiveness	Pyridoxine enhances peripheral decarboxylation of levodopa reducing the effectiveness of levodopa[1,2] Concomitant administration of carbidopa with levodopa prevents the reversal by pyridoxine of levodopa's effects. Pyridoxine hydrochloride should not be administered in dosages greater than 5 mg daily to patients receiving levodopa alone.[1]
Altretamine	Reduced response to altretamine	Data from a randomized trial evaluating altretamine and cisplatin with and without pyridoxine in the treatment of ovarian cancer found that pyridoxine administration adversely affected the response duration of these agents. These results suggest that pyridoxine should not be coadministered with altretamine.

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 55 years in over 33 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. Based on the latest PSUR information, Diclectin has been used by over an estimated 5 million women in North America. Annual PSURs continue to support a positive benefit-risk assessment for Diclectin. Furthermore, numerous published clinical data have demonstrated the safety and tolerability of Diclectin for pregnant women. In addition, this product combination has been the subject of many epidemiological studies designed to detect possible teratogenicity. Results from these studies negate an association with fetal abnormalities.

Adverse reactions identified during the post-marketing period are listed alphabetically below. Pyridoxine is a vitamin that is generally recognised as having no adverse effects. These reactions are reported voluntarily from a population of uncertain size; therefore it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: dyspnoea, palpitation, tachycardia
Ear and labyrinth disorders: vertigo
Eye disorders: vision blurred, visual disturbances
Gastrointestinal disorders: abdominal distension, abdominal pain, constipation, diarrhoea
General disorders and administration site conditions: chest discomfort, fatigue, irritability, malaise
Immune system disorders: hypersensitivity
Nervous system disorders: dizziness, headache, migraines, paresthesia, psychomotor, hyperactivity
Psychiatric disorders: anxiety, disorientation, insomnia, nightmares
Renal and urinary disorders: dysuria, urinary retention
Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus, rash, rash maculopapular

Published Safety Studies

Safety of higher than standard doses of Diclectin was evaluated in 225 pregnant women with NVP in an observational, prospective study. A total of 123 women received standard doses of up to 4 tablets a day and 102 women received a higher than standard dose ("supradose") of 5 to 12 tablets/day. The dose ranged from 1 to 12 tablets (0.1 – 2.0 mg/kg/d). Diclectin was given for a mean of 15.4 ±10 weeks in the supradose and 17.2 ±10.3 weeks in the standard dose groups. Two to four weeks following initiation of Diclectin therapy women were interviewed and adverse effects recorded according to a structured questionnaire. Pregnancy outcome was recorded in an additional interview after birth at which time inquiries were also made about the highest dose used as well as length of the NVP symptoms and need for hospitalisation.

Despite a 2-fold greater mean maximal dose of Diclectin, women receiving the supradose did not report more prevalent adverse effects of Diclectin. In the supradose group, 32% (31/97) reported sleepiness, tiredness and/or drowsiness compared with 35% (42/122) among the standard dose recipients. Not all endpoints were available from all subjects. There was no association between the dose per kg and rates of reported maternal adverse effects with doses ranging from 0.1 mg/kg to 2.0 mg/kg (1-12 tablets).

Two pregnancies were diagnosed with major malformations (anencephaly and ventricular septal defect), of which one with anencephaly was terminated. Both occurred in the standard dose group. The authors noted that these findings were consistent with rates of birth defects in the general population.

In a prospective comparison study of the new versus old formulations (2004), 150 women with NVP counselled by Motherisk in 2002, using the original preparation of Diclectin and a similar number of women recruited in March 2003 or later, using the new formulation of Diclectin were randomly selected and their characteristics as well as 109 adverse events were compared. The overall rate of adverse events was similar between the years [89 in 2002 (59.3%) and 86 in 2003 (57.3%)], as shown in Table 13. Since patients could have more than one reported adverse event (AE), the number of patients with at least one AE was compared, detecting 74 patients (49.3%) in 2002 and 73 patients (48.7%) in 2003.

Table 13 Symptoms for patients taking Diclectin in 2002 versus 2003

Symptom as described by the patient	2002 (n=150)	2003 (n=150)
Drowsiness	20	20
Dopiness	2	6
Tiredness	20	22
Sluggish	1	-
Dizziness	10	10
Sleepiness	25	20
Fatigue	3	1
Dry mouth	3	2
Tremor	1	-
Blurred vision	1	-
Bradycardia	2	1
Agitation	-	3
Grogginess	1	1
Total	**89**	**86**

Birth outcomes:

Table 14 Pregnancy outcomes of included patients, Motherisk NVP Disease Management and Surveillance Helpline, January 1, 1996 to August 27, 2014

Characteristic	Anti-emetic Polytherapy[a] N=1148	Diclectin Monotherapy[b] N=128
Live Birth	1104 (96.2)	124 (96.9)
Miscarriage	33 (2.9)	1 (0.8)
Elective Termination	8 (0.7)	2 (1.6)
Fetal Death	3 (0.3)	1 (0.8)
Yes, Major	16 (1.4)	3 (2.3)
Yes, Minor	39 (3.4)	6 (4.7)
Genetic or developmental disorder	7 (0.6)	1 (0.8)
Unable to assess	5 (0.4)	2 (1.6)
Mean ± SD	38.7 ± 2.5	39.0 ± 2.4
Median	39	40
Mean ± SD	3371 ± 639	3461 ± 590
Median	3413.5	3487

[a] Consists of patients who were exposed to Diclectin in addition to other antiemetics and medications
[b] Consists of patients who were exposed to Diclectin as an antiemetic and did not use any other pharmacological or non-pharmacological therapy other than prenatal multivitamins or nutritional supplements such as Boost or Ensure. These patients are a subset of the Antiemetic Polytherapy Group.

Overall conclusion on clinical safety
Taking into account long duration of clinical use of the combination, the safety data demonstrate an acceptable safety profile for this combination product, in accordance with the FDC requirements.

IV.5 Risk Management Plan

The MAH has submitted a Risk Management Plan (RMP), 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 Xonvea.

A summary of safety concerns is listed in the table below:

Table 15 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Somnolence
Important potential risks	Drug interaction with MAOIs Drug interaction with CNS depressants
Missing information	Use in breast-feeding women Use in pregnant adolescent females (< 18 years) Use in hepatic impaired women Use in renal impaired women

Routine pharmacovigilance and risk minimisation activities are planned for all safety concerns, which is considered acceptable.

IV.6 Discussion of the clinical aspects

Xonvea was found to be effective and the benefit/risk assessment positive in the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. It is recommended that a Marketing Authorisation is granted, from a clinical point of view.

V. USER CONSULTATION

A user consultation with target patient groups on the patient information leaflet (PIL) has been conducted 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 PIL was English.

The results show that the PIL 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

The quality of the product is acceptable and no new non-clinical safety concerns have been identified.

It is acknowledged that the combination has been in clinical use for many years. However, this has to be balanced with the requirements of the current CHMP guidelines which state that the clinical study data must show superiority of the fixed dose combination (FDC) against each of the monocomponents. In addition, the guideline stipulates that the trial should demonstrate the clinical contribution to the combination of each component.

The submitted single pivotal efficacy study did not include monotherapy arms, thereby precluding an ability to assess the contribution of each component to the claimed effects of the combination.

The applicant has submitted published data from the DESI study which was carried out in the 1970's. The results of this study appear to show that there may be sufficient evidence to support the effectiveness of the combination of doxylamine succinate and pyridoxine hydrochloride for the treatment of nausea and vomiting of pregnancy. Therefore, the findings of this study may be considered to provide the required evidence in compliance with the current European regulatory guidelines.

Taking into consideration the long history of clinical use of the combination and the absence of demonstrable safety concerns, in totality the submitted clinical information may be considered adequate to support the application.

Therefore, the overall benefit/risk ratio of Xonvea (Diclectin) is considered positive.

The grant of Marketing Authorisation is, therefore, recommended.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website. The current labelling is provided below.


92 mm
ALLIANCE
Xonvea®
10mg / 10mg
gastro-resistant tablets
doxylamine succinate/
pyridoxine hydrochloride
BN: XXXXX
EXP: YYYY-MM-DD
84 mm
6 mm
84 mm

Xonvea 10 mg/10 mg gastro-resistant tablets

(doxylamine succinate and pyridoxine hydrochloride)

UK Licence No: PL 16853/0147

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome