Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Pyridoxine hydrochloride 50mg tablets

(pyridoxine hydrochloride)

PL 15764/0153

Strandhaven Limited t/a Somex Pharma

LAY SUMMARY

Pyridoxine hydrochloride 50mg tablets
pyridoxine hydrochloride

This is a summary of the Public Assessment Report (PAR) for Pyridoxine hydrochloride 50mg tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as pyridoxine tablets in this lay summary for ease of reading.

For practical information about using pyridoxine tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are pyridoxine tablets and what are they used for?
This application is for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the UK for at least 10 years, with recognised efficacy and an acceptable level of safety.

This medicine is used to treat low levels of Vitamin B6 in the body and in the treatment of a condition called idiopathic sideroblastic anaemia where the red cells in the blood do not form properly.

Pyridoxine tablets can also be used to treat damage to the nerves (peripheral neuritis) caused by isoniazid, a drug used to treat tuberculosis.

How do pyridoxine tablets work?
Pyridoxine hydrochloride is Vitamin B6. Vitamin B6 plays an important role in the body. It is needed to maintain the health of nerves, skin, and red blood cells.

How are pyridoxine tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is by mouth (oral).

The patient’s doctor will decide the dose which is best for their patient. The patient should always follow the doctor's instructions completely, and also follow any special instructions or warnings which the pharmacist has put on the dispensing label.

The patient should contact their doctor if their symptoms worsen or do not improve. If the patient does not understand their treatment or condition, or has any doubt, they should ask their doctor or pharmacist.

Unless the patient is instructed differently, pyridoxine tablets should be taken with a glass of water. The score line is only there to help break the tablet if the patient has difficulty swallowing the tablet/s whole.

Dose
For the treatment of low levels of Vitamin B6 in the body, the usual dose in adults is 50 to 150mg daily in divided doses.

For the treatment of idiopathic sideroblastic anaemia, the usual dose in adults is 100 to 400mg daily in divided doses

For the treatment of nerve damage (peripheral neuritis) caused by isoniazid, the usual adult dose is 50mg three times a day. In adults, this dosage form is not suitable for prophylaxis.

Elderly
Elderly patients will require similar doses to those given above.

Children
Pyridoxine tablets are not recommended for use in children.

For further information on how pyridoxine tablets are used, refer to the PIL and Summary of Product Characteristics (SmPC(s)) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them.

What benefits of pyridoxine tablets have been shown in studies?
As the active substance pyridoxine tablets has/have been in clinical use for over 10 years, data were provided in the form of literature references to show that pyridoxine tablets are a safe and efficacious treatment for

- conditions caused by with low levels of Vitamin B6 in the body,
- and in the treatment of a condition called idiopathic sideroblastic anaemia where the red cells in the blood do not form properly.
- to treat damage to the nerves (peripheral neuritis) caused by isoniazid, a drug used to treat tuberculosis.

What are the possible side effects of pyridoxine tablets?
Like all medicines pyridoxine tablets can cause side effects, although not everybody gets them. If the patient takes large doses of pyridoxine tablets for a long time, they may develop problems with their nerves (peripheral neuritis). One of the symptoms of peripheral neuritis can be pins and needles.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why were pyridoxine tablets approved?
It was concluded that the data provided from literature references had shown that pyridoxine tablets is effective in the treatment of:

- conditions caused by with low levels of Vitamin B6 in the body,

- and in the treatment of a condition called idiopathic sideroblastic anaemia where the red cells in the blood do not form properly.
- to treat damage to the nerves (peripheral neuritis) caused by isoniazid, a drug used to treat tuberculosis.

Furthermore, the well-established use of the active substance pyridoxine tablets has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of pyridoxine tablets?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for pyridoxine tablets The RMP details the important risks of pyridoxine tablets, how these risks can be minimised, any uncertainties about pyridoxine tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for pyridoxine tablets:
Important identified risks

- Development of severe peripheral neuritis
- Hypersensitivity to any of the ingredients

Potential Risk

- Interaction with other medicines

Missing information

- None

The RMP and a summary of the pharmacovigilance system have been provided with this application are satisfactory.

Other information about pyridoxine tablets

A Marketing Authorisation for Pyridoxine hydrochloride 50mg tablets was granted in the United Kingdom (UK), consisting of England, Scotland,Wales, and Northern Ireland on 25 March 2022

The full PAR for pyridoxine tablets follows this summary.

This summary was last updated in May 2022.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Pyridoxine hydrochloride 50mg tablets (PL 15764/0153) could be approved.

The product is approved for the following indications:

Pyridoxine hydrochloride is indicated for adults and children over 12 years old in the treatment of isoniazid-induced peripheral neuritis, idiopathic sideroblastic anaemia and Vitamin B6 deficiency states.

The name of the active substance is pyridoxine hydrochloride.

Pyridoxine hydrochloride is Vitamin B6. It is converted to pyridoxal phosphate which is the co-enzyme for a variety of metabolic transformations. It is essential for human nutrition.

This application was approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this/these application and are satisfactory.

A national marketing authorisation was granted in the United Kingdom (UK) consisting of England, Scotland,Wales, and Northern Ireland on 25 March 2022
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II QUALITY ASPECTS

II.1 Introduction

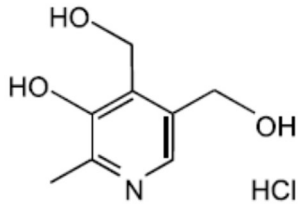
The active substance in pyridoxine tablets is pyridoxine hydrochloride. Each tablet contains 50mg of the active substance. The other ingredients are calcium phosphate dibasic anhydrous, starch maize, sodium lauryl sulphate, and magnesium stearate.

The finished product is packaged in OPA/ALU/PVC blister of 10 or 14 tablets in pack sizes: 10, 14, 20, 28, 30, 40, 50, 56, 60, 70, 80, 84, 90 and 112 tablets. Not all pack sizes may be marketed.

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

II.2 Pyridoxine hydrochloride

rINN:	**Pyridoxine hydrochloride**
Other name:	Vitamin B6
Chemical names:	2-methyl-3-hydroxy-4,5-bis(hydroxymethyl)pyridine hydrochloride; 5-hydroxy-6-methyl-3,4-pyridinedimethanol hydrochloride; 5-hydroxy-6-methyl-3,4-pyridinecarbinol hydrochloride; 4,5-bis(hydroxymethyl)-2-methylpyridine-3-ol hydrochloride
Description:	White or almost white crystalline powder
Solubility:	Freely soluble in water, slightly soluble in ethanol (96%)
Molecular formula:	$C_8H_{11}NO_3.HCl$
Structural formula:	



Molecular weight: 205.6 g/mol

Pyridoxine hydrochloride is the subject of a European Pharmacopoeia monograph.

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

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product(s), along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with the storage conditions store below 25°C, store in the original blister in order to protect from light and moisture, is acceptable.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

This application was submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology

Brief summary

Pyridoxine is a water-soluble vitamin. Pyridoxine is composed of three forms (vitamers), pyridoxine, pyridoxal and pyridoxamine, the cofactor forms of pyridoxine are pyridoxal-5'-phosphate and pyridoxamine-5'-phosphate. Pyridoxal phosphate is involved as a cofactor particularly in the metabolic transformation of amino acids, including decarboxylation, transamination and racemisation.

III.3 Pharmacodynamics

The pharmacology of the active substance is adequately discussed in the applicant's non-clinical overview and is only briefly summarised below.

Pyridoxine hydrochloride

Pyridoxine deficiency in the adult male rat leads to true arterial hypertension, which is reversed within 24 hours by pyridoxine treatment possibly through the mechanism of general sympathetic stimulation.

Two trials were carried out to determine the effects of added dietary pyridoxine or thiamine (vitamin B1) on growth performance of weanling pigs. These results suggest that adding 3.3 mg/kg of pyridoxine (7.1 to 7.9 mg/kg of total pyridoxine) to diets fed from day 0 to 14 after weaning can improve pig growth performance.

The Coenzyme form of pyridoxine, pyridoxal phosphate inhibited the platelet aggregation and prolonged the clotting time in vitro.

Rats fed a diet deficient in pyridoxine all exhibited severe microcytic hypochromic anaemia after 40 to 50 weeks. This anaemia responded promptly to pyridoxine administration.

It was found that pyridoxine at concentrations of 10-3 M, or greater significantly inhibited rat mast cell degranulation and histamine release induced by phospholipase A, compound 48/80, antigen (egg albumin) or a mixture of dextran and phosphatidyl serine, respectively. The modifications of ventricular action potentials and of frequency were coupled with a decrease of vitamin B6 in the heart. Ventricular action potentials of pyridoxine-supplemented rats appeared to be largely restored to their normal parameters by pyridoxine administration. Pyridoxine-supplementation had also a remarkable effect upon frequency of the pyridoxine deficient hearts since it reversed bradycardia to a striking tachycardia.

Assessor's overall conclusions on pharmacology

The primary and secondary pharmacology of pyridoxine hydrochloride has been reviewed adequately in the applicant's non-clinical overview. As the drug substance has been in use for many years, further discussion of non-clinical data is not warranted.

III.4 Pharmacokinetics

Pyridoxine hydrochloride

Pyridoxine is absorbed rapidly from the upper intestine regardless of the size of the dose given. Absorption may also occur from the ileum and to a small extent from the colon. There is a linear relationship between oral dose and the amount absorbed in normal animals and in those in which the distal small intestine has been resected. These observations suggest the possibility that pyridoxine may be absorbed by diffusion. Labelled pyridoxal, pyridoxal- and pyridoxine-phosphate were found in the intestine and liver, although labelled pyridoxine could not be detected in the peripheral blood, substantial amounts of labelled pyridoxal and pyridoxal-phosphate were found in the blood. The results suggest that the liver and intestine play major role in converting dietary pyridoxine to circulating pyridoxal which is taken up and phosphorylated by other organs. Most of blood pyridoxal was shown to be located in the plasma.

Pyridoxine is rapidly converted in the liver to pyridoxine phosphate, pyridoxal phosphate and pyridoxamine phosphate via oxidation. This causes the release of pyridoxal and some pyridoxal phosphate to the general circulation where it reaches other organs chiefly as circulating pyridoxal. The biliary excretion studies of vitamin B-6 in the intact rat and isolated perfused rat liver suggest that pyridoxine and its metabolites are released separately by the hepatocytes into the bile and the perfusate and that paracellular transport of vitamin B-6 is not the predominant pathway for the biliary excretion of this vitamin. In urine, pyridoxine was excreted primarily unchanged with a small amount of only one metabolite, most likely 4-pyridoxic acid.

It has been demonstrated in a rat intestinal absorption model that the intestinal absorption of isoniazid could be significantly inhibited by pyridoxine, although the pharmacokinetics do not appear to be adversely affected.

Assessor's overall conclusions on pharmacokinetics
The pharmacokinetic properties of pyridoxine hydrochloride have been reviewed adequately in the applicant's non-clinical overview. As this drug substance has been used extensively in the clinic the findings from non-clinical species are superseded by the human findings.

III.5 Toxicology
The toxicology properties of pyridoxine hydrochloride are discussed in detail in the applicant's non-clinical overview. The summaries of these findings are presented below.

Pyridoxine hydrochloride:
Acute toxicity studies are reported in rats and mice suggested the development of ataxia, tremor, and convulsions at high doses ranging from 5600 mg/kg to 7800 mg/kg.

Chronic toxicity studies revealed the loss of axons and myelin due to potential neurotoxicity, resulting in ataxia, muscle weakness and loss of balance in dogs given 200 mg/kg (40-75 days). Similar findings were observed in dogs administered up to 150 mg/kg for approximately 100 days.

A mutagenicity test on pyridoxine hydrochloride was performed using Saccharomyces cerevisiae (strain D4) and S. typhimurium (strains TA 100, TA 1535, TA 1537, TA 1538, and TA 98) as indicator organisms. The substance did not exhibit mutagenic activity (in presence and absence of S9).
No carcinogenicity data has been retrieved. There is some evidence presented on the effect of vitamin B6 on the growth of transplanted tumour and characteristics of ascitic tumour cells in

vitamin B6 deficiency were examined cytologically. There was no clear evidence to suggest a carcinogenic response due to chronic exposure to vitamin B6.

High doses of pyridoxine (500 mg/kg) in male rats for 2 weeks showed decreased weights of reproductive organs like epididymis and reduced spermatid counts. After 6 weeks of administration resulted in similar decrease in reproductive organs observed. Pyridines have also been shown to cross the placental barrier in rats and cause premature delivery, miscarriages and stillbirths. Pyridoxal crosses the placenta and is distributed into breast milk.

Excipients
No toxicological concerns are raised in respect to use of excipients

III.6 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product containing an active substance of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing authorisation for the proposed product.

III.7 Discussion on the non-clinical aspects
The pharmacological, pharmacokinetic and toxicological properties of pyridoxine hydrochloride have been well characterised. New non-clinical studies are not required, and the applicant has not conducted any. A literature review is, therefore, appropriate. The Applicant has provided a discussion of the literature on the pharmacology, pharmacokinetics, and toxicity of pyridoxine hydrochloride.

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

IV.2 CLINICAL PHARMACOLOGY
IV.2.1 Pharmacokinetics
The assessment of the clinical pharmacokinetics of pyridoxine is based on the information and references presented in the submitted clinical overview.

Absorption and metabolism
Pyridoxine is readily absorbed from the gastrointestinal tract following oral administration and is converted to the active forms of pyridoxal phosphate and pyridoxamine phosphate, which are stored in the liver. The absorption of the ingested vitamin B6 occurs in the jejunum through unsaturable passive diffusion (Hamm et al., 1979). However, in vitro experiments with human intestinal epithelial Caco-2 cells showed evidence that vitamin B6 absorption also occurs through a saturable pH dependent carrier-mediated and proton-coupled process (Said et al., 2003). The principal excretory product is 4-pyridoxic acid, which is formed by the action of hepatic aldehyde oxidase on free pyridoxal and are excreted in the urine.

In the diet, vitamin B6 compounds exist in the free and phosphorylated forms; the latter form is hydrolysed to the free form prior to absorption. Earlier studies on the mechanism of

intestinal vitamin B6 absorption concluded that the process is non-saturable. However, more recent studies using the enterocyte-like human intestinal epithelial Caco-2 cells, mouse-derived colonic epithelial cells and purified human colonic apical membrane vesicle preparations, isolated from the colon of organ donors, as models and proper physiological conditions have shown the existence of a specific acidic pH (but not Na+)-dependent carrier-mediated mechanism for pyridoxine uptake.

The active forms of B6 appeared in red cells immediately after oral administration of pyridoxine. pyridoxine was taken up by the red cells, where it was converted to pyridoxal phosphate and then to pyridoxal, followed by a gradual release of a proportion of pyridoxal into the plasma. This suggested that pyridoxine may be converted to pyridoxal phosphate in red cells by the pathway demonstrated in liver homogenates, and finally to pyridoxal before release into plasma. It was also claimed that pyridoxine could be converted directly to pyridoxal by an alternative but much slower pathway in the liver. The possibility of a small contribution via this pathway in the red cells cannot be excluded.

Distribution
PLP and PL are the main constituents of plasma B6 (Okada et al 1998), but the majority of B6 is stored in muscle as PLP in conjunction with glycogen phosphorylase (Bowling, 2011; Okada et al., 1998). Body storage of B6 is reported to be around 1000 µmol (206 mg PN-HCl), with the assumption that 80% of B6 stores are located in the muscle (Coburn et al., 1988). Stored B6 is released from body stores at a slow rate (Lui et al 1985). The rate of phosphorylating PN, PM and PL to PLP by PL kinase to stay in the cell is higher than converting PNP and PMP to PL by PNP oxidase for the eventual conversion to PLP to be released from liver into circulation. This would indicate a slower release of PLP originating from PN or PM rather than PL (Merrill Jr. & Henderson, 1990). Due to slow storage release and a lack of consensus on which B6 vitamer is the best indication of B6 body stores, it has been difficult to accurately determine B6 status among the population. B6 can be measured directly through analysis of plasma, blood cells and urine, or indirectly through functional enzyme tests and methionine loading (Institute of Medicine, 1998; Miller et al 1994).

Vitamin B6 is transferred through the blood brain barrier via facilitated diffusion, although the exact mechanism is not fully elucidated (Spector & Johanson, 2007). Studies in healthy adults demonstrated that, compared with plasma, the concentration of vitamin B6 in the cerebrospinal fluid is almost the same or slightly lower (Albersen et al. 2014). The homoeostasis of vitamin B6 in the central nervous system is not well maintained and low dietary intake of vitamin B6 can result in a disturbed brain function (i.e. abnormal electroencephalograms and seizures) (Borschel, 1995; Kretsch et al 1995). The mechanism of vitamin B6 placental transfer is unclear. Studies have reported up to five times higher plasma PLP concentration in the umbilical cord of the new-born or foetus than in maternal blood in pregnancy or at delivery, suggesting an active placental transfer of PLP from the mother to the foetus (Shane and Contractor, 1980; Zempleni et al., 1992) .

Excretion
Vitamin B6 is excreted through the urine, mainly as its catabolic product 4- pyridoxic acid (4- PA), but also the active forms of vitamin B6 can be found in the urine. In a study in humans, 85–90% of vitamin B6 ingested or administered intravenously could be recovered as urinary 4-PA (Lui et al., 1985, Hansen et al 1996), which suggests that urine is the main route for elimination of vitamin B6. Most of the excreted active forms of vitamin B6 are reabsorbed in the kidney tubules.

PK in special populations

Liver impairement

Merrill et al 1986 stated that patients with cirrhosis and other hepatic diseases frequently exhibit lower concentrations of plasma pyridoxal 5′-phosphate (PLP), which is derived primarily from liver.

In order to determine the biochemical basis for this abnormality, the enzymes of vitamin B6 metabolism [(pyridoxal kinase, pyridoxine (pyridoxamine) 5′-phosphate oxidase, PLP phosphatase(s), and pyridoxal oxidase(s)] were analysed in liver. The activities of the two biosynthetic enzymes, pyridoxal kinase and pyridoxine (pyridoxamine) 5′-phosphate oxidase were similar for both. The phosphatase activities were significantly higher (9.55 ± 8.03 versus 3.97 ± 2.36 nmol min mg protein, $p < 0.05$) for cirrhotics. Pyridoxal oxidase activities appeared slightly lower for cirrhotic. There was considerable variation in many indices of liver function, which suggests that the defects contributing to altered vitamin metabolism may be complex and individualistic. These analyses have shown that cirrhotic are capable of apparently normal PLP synthesis and that increased hepatic dephosphorylation may be responsible for low levels of plasma PLP.

Renal impairment

A discussion has been provided regarding the effect of renal impairment on the pharmacokinetics of pyridoxine, and the content of this discussion was acceptable.

During Lactation

Chang & Kirksey 1990 assessed vitamin B6 status, by measuring plasma pyridoxal phosphate (PLP) concentrations, and vitamin B6 concentrations in breast milk in 47 lactating mothers supplemented with different amounts of pyridoxine HCl during pregnancy and the first 6 PLP months of lactation.

PLP concentrations in cord blood and maternal plasma at 2 day postpartum and vitamin B6 concentration in colostrum were positively correlated with the amount of pyridoxine supplementation prenatally ($p < 0.001$; $p < 0.001$; $p < 0.001$, respectively). Correlations between the amounts of pyridoxine supplementation postnatally and plasma PLP concentrations increased with the length of supplementation. Plasma PLP concentrations were also correlated with vitamin B6 concentrations of milk samples, which were obtained on the same day as plasma. pyridoxine supplements between 2.5 and 4.0 mg/d (2.1-3.4 mg Pyridoxin equivalents) ensured vitamin B6 adequacy of the mother and maintained relatively saturated concentrations of vitamin B6 in breast milk.

Pyridoxine-drugs interactions

Roio-Sebastian et al 2020 investigated the role of L-DOPA/carbidopa (CD) therapy on vitamin B6 levels in patients with Parkinson disease (PD). The study showed that Vitamin B6 could play an important role in PD and its levels seem to be influenced by LDOPA/ CD. Plasma vitamin B6 levels should be monitored in patients receiving high LDOPA/ CD doses, especially those treated with intraduodenal infusion.

Sievers et al 1981 emphasizes the efficacy of high-dose pyridoxine hydrochloride (vitamin B6) treatment of acute isoniazid overdose. They stated that more than 150 patients with isoniazid overdose have been successfully treated with intravenous (IV) administration of pyridoxine in doses equivalent to the estimated amount of isoniazid ingested. In sufficient dosage, pyridoxine administered IV can reverse the severe toxic effects of isoniazid overdose and prevent death in humans and animals.

Tu et al 1963 described severe visual disturbance associated with lesions of the optic nerve developed in a Wilson's disease patient who had been receiving DL-penicillamine therapy for more than 2 years. Prompt relief was achieved with pyridoxine hydrochloride. These results suggest that the optic nerve lesions resulted from a penicillamine induced pyridoxine deficiency.

Cycloserine is a broad-spectrum antibiotic used to treat tuberculosis. In combination with pyridoxal phosphate, cycloserine increases urinary excretion of pyridoxine. The urinary loss of pyridoxine might exacerbate the seizures and neurotoxicity associated with cycloserine. Pyridoxine supplements can help prevent these adverse effects (Natural Medicines Comprehensive Database. Vitamin B6. 2011).

Antiepileptic Medications: Some antiepileptic drugs, including valproic acid, carbamazepine and phenytoin increase the catabolism rate of vitamin B6 vitamers, resulting in low plasma PLP concentrations and hyperhomocysteinemia. High homocysteine levels in antiepileptic drug users might increase the risk of epileptic seizures and systemic vascular events (Hansson & Sillanpaa 1976, Clayton 2006).

Levetiracetam: Preliminary evidence suggests that vitamin B6 supplementation at such doses as 50–350 mg/day in children and 50–100 mg/day in adults might reduce these side effects (Alsaadi et al 2015).

Theophylline: Patients treated with theophylline often have low plasma PLP concentrations, which could contribute to the neurological and central nervous system side effects associated with theophylline.

The pharmacokinetics of pyridoxine are well known and the applicant has presented a variety of drugs which may possibly interact with pyridoxine.

IV.3 Pharmacodynamics

Primary pharmacodynamics

Pyridoxine is involved in many physiological functions including maintaining the integrity of the nervous system, haemoglobin synthesis, tryptophan metabolism and sulphur containing amino acids.

In humans, an exogenous source of vitamin B6 is required for amino acid metabolism; the vitamin is also involved in carbohydrate and lipid metabolism. Pyridoxine, pyridoxal, and pyridoxamine are converted to the active forms of the vitamin, pyridoxal phosphate and pyridoxamine phosphate, which act as coenzymes in a wide variety of reactions in intermediary metabolism. The active forms of the vitamin are involved in transamination of amino acids and in the conversion of tryptophan to niacin. Pyridoxine appears to be essential in the synthesis of GABA within the CNS and in the synthesis of haeme.

The active form of the vitamin is pyridoxal phosphate, which is a coenzyme that is recognised as being required for the function of dozens of enzymes involved with transamination, deamination, decarboxylation or desulfuration reactions. Hence, the pharmacological property of pyridoxine is strongly connected with its oxidation to pyridoxal phosphate (PLP), the active
form of pyridoxine.

PLP plays a vital role in the function of over 100 enzymes that catalyse essential chemical reactions in the human body (da Silva et al 2012). PLP-dependent enzymes have been classified into five structural classes known as Fold Type I-V (Eliot & Kirsch 2912): The many biochemical reactions catalysed by PLP-dependent enzymes are involved in essential biological processes, such as haemoglobin and amino acid biosynthesis, as well as fatty acid metabolism. Of note, PLP also function as coenzyme for glycogen phosphorylase, an enzyme that catalyses the release of glucose from stored glycogen. Much of the PLP in the human body is found in muscle bound to glycogen phosphorylase. PLP is also a coenzyme for reactions that generate glucose from amino acids, a process known as gluconeogenesis (Leklem 1999).

Secondary pharmacodynamics
Pyridoxine deficiency results in the accumulation and urinary excretion of xanthurenic acid (an intermediate metabolite of tryptophan) and in decreased glutamic oxaloacetic transaminase activity in erythrocytes; measurement of either of these may be used to diagnose pyridoxine deficiency. For determination of xanthurenic acid excretion, an oral loading dose of 2–10 g of tryptophan is usually given; urine is collected for 8 hours and then analysed for xanthurenic acid. Urinary excretion of vitamin B6 or 4-pyridoxic acid can also be analysed to determine pyridoxine deficiency.

Nutritional deficiency disease is extremely rare, although a significant proportion of the population shows biochemical evidence of inadequate status, despite apparently adequate levels of intake. Average intakes of vitamin B6 in Britain are significantly above RNI, and even people in the lowest 2.5 centile meet the RNI. However, several studies show that a significant proportion of adults have biochemical evidence of inadequate vitamin B6 nutrition by one or other of the two criteria most commonly used: plasma concentration of PLP or erythrocyte transaminase activation coefficient. This suggests that current estimates of vitamin B6 requirements may be too low, although there is little evidence that marginal plasma concentrations of PLP or marginally elevated transaminase activation coefficients have any functional significance

Pyridoxine deficiency in adults principally affects the peripheral nerves, skin, mucous membranes, and the hematopoietic system. In children, the CNS is affected. The usual clinical symptoms of vitamin B6 deficiency are seborrheic dermatitis, microcytic anaemia, seizures, and depression and confusion. Administration of pyridoxine completely reverses symptoms of deficiency. A hereditary syndrome of pyridoxine dependency in which unusually large amounts of pyridoxine are needed to prevent seizures has been identified in infants. Xanthurenic aciduria, cystathioninuria, hyperoxaluria, and primary homocystinuria resulting from genetic abnormalities have responded to pyridoxine administration. A pyridoxine-responsive, hereditary, sideroblastic anaemia not related to pyridoxine deficiency has also been identified.

Assessor's comment
The pharmacodynamics of pyridoxine are well known and in the overview the applicant has provided literature reviews of the possible physiological influence of pyridoxine in a variety of clinical conditions.

IV.4 Clinical efficacy

Introduction

In general, dietary related pyridoxine deficiency is rare and most of the known conditions that are known to be associated with pyridoxine deficiency are acquired. Different

mechanisms have been proposed. Sideroblastic pyridoxine responsive anaemia caused by genetic mutations is recognised with their molecular genetic mostly uncovered.

Pyridoxin deficiency
Vitamin B6 deficiency is uncommon with adequate diets, including B6 sources from fish, organ meats, poultry, potatoes, grains, legumes, and non-citrus fruits. Isolated B6 deficiency is rare and usually found in association with other B vitamin deficiencies such as folic acid and B12.

Low plasma levels of active B6 are found in chronic alcohol dependence, with obese states, protein-energy malnutrition. Pregnancy, pre-eclampsia, and eclampsia, and malabsorptive states such as celiac, inflammatory bowel disease, and bariatric surgery.

Additional at-risk groups with inadequate intake or increased metabolic requirements may become functionally deficient in B6. Included in this group are those with renal impairment, autoimmune disorders, and chronic alcohol use. Patients with chronic renal failure, especially those receiving haemodialysis or peritoneal dialysis, have low plasma levels of B6.

Autoimmune diseases, such as rheumatoid arthritis, have increased catabolism of B6, resulting in higher demand for dietary supplementation of B6 (Brown et al 2020).

The patients with impaired renal function, patients on dialysis, and the patient who have undergone renal transplants are more at risk of Vitamin B6 deficiency. The pathophysiology behind this is low serum PLP concentrations in such patients. They exhibit similar signs and symptoms of B6 deficiency as compared to other individuals and usually respond well to oral or parenteral B6 therapy (Jankowska et al 2013, Joyce et al 2018).

Of clinical importance in toxicology is that drug antagonists to vitamin B6 occurs with the tuberculosis medicine isoniazid. Also, penicillamine and levodopa, as well as some anticonvulsant medications, may interfere with B6 metabolism (Bhagavan & Brin 1983). Vitamin B6 deficiency may present with seizures in the young. Severely deficient adults commonly present with rashes and mental status changes. Additional clinical findings of deficiency may include normocytic anaemia, a nonspecific pruritic rash, cheilitis with scaly lip skin and cracks in the corner of the mouth, and glossitis (swelling of the tongue). Depression is associated with a severe B6 deficiency as well.

Current studies are evaluating the role of B6 deficiency in heart disease, cancer, and cognitive decline as medical conditions that may respond to supplementation. To date, there is no clear evidence to support supplement use beyond the normal dietary intake. However, some studies indicate a reduction of symptoms in the premenstrual syndrome with supplementation of B6, particularly a decrease in moodiness, irritability, and forgetfulness. The American College of Obstetrics and Gynecology recommend vitamin B6 supplementation (1.9 mg per day) for hyperemesis gravidarum (Rollon et al 2015).

Groups at Risk of Vitamin B6 Inadequacy

Individuals with Impaired Renal Function
People with poor renal function, including those with end-stage renal disease and chronic renal insufficiency, often have low vitamin B6 concentrations. Plasma PLP concentrations are also low in patients receiving maintenance kidney dialysis or intermittent peritoneal dialysis, as well as those who have undergone a kidney transplant, perhaps due to increased

metabolic clearance of PLP. Patients with kidney disease often show clinical symptoms similar to those of people with vitamin B6 deficiency (Merrill & Henderson 1997, Mackey et al 2005).

Individuals with Autoimmune Disorders
People with rheumatoid arthritis often have low vitamin B6 concentrations, and vitamin B6 concentrations tend to decrease with increased disease severity. These low vitamin B6 levels are due to the inflammation caused by the disease and, in turn, increase the inflammation associated with the disease. Although vitamin B6 supplements can normalize vitamin B6 concentrations in patients with rheumatoid arthritis, they do not suppress the production of inflammatory cytokines or decrease levels of inflammatory markers.

Patients with celiac disease, Crohn's disease, ulcerative colitis, inflammatory bowel disease, and other malabsorptive autoimmune disorders tend to have low plasma PLP concentrations. The mechanisms for this effect are not known. However, celiac disease is associated with lower pyridoxine absorption, and low PLP concentrations in inflammatory bowel disease could be due to the inflammatory response (Merrill & Henderson 1987, Mackey et al 2005).

People with Alcohol Dependence
Plasma PLP concentrations tend to be very low in people with alcohol dependence. Alcohol produces acetaldehyde, which decreases net PLP formation by cells and competes with PLP in protein binding. As a result, the PLP in cells might be more susceptible to hydrolysis by membrane-bound phosphatase. People with alcohol dependence might benefit from pyridoxine supplementation (Institute of Medicines 1998, Mackey et al 2005).

Alcoholics have low plasma PLP concentrations, and this reduced B6 status is distinct from that caused by liver disease or poor diet. Acetaldehyde but not ethanol decreases net PLP formation by cells and is thought to compete with PLP for protein binding. This may make cellular PLP more susceptible to hydrolysis by membrane-bound phosphatase (Lumeng & Li, 1974). The extent to which this causes an increased B6 requirement is not known.

Effect of hormonal contraceptives on pyridoxine body status
Bermond 1982 discussed the accumulative evidence confirming an impaired status in women using hormonal contraception (OCA). Disturbances in the metabolism of tryptophan have been shown to be responsible for such symptoms as depression, anxiety, decrease of libido and impairment of glucose tolerance occurring in some of the OCA users. Administration of 40 mg of vitamin B6 daily not only restores normal biochemical values but also relieves the clinical symptoms in those vitamin B6 deficient women taking OCA's.

A number of studies have reported decreases in B6 status indicators in women receiving highdose oral contraceptives (Lumberg et al 1974, Rose, 1978). Plasma PLP concentrations are decreased but the decrease is quite small. Normalization of the tryptophan load test in subjects receiving oral contraceptives requires very high levels of PN, up to 25 mg (Rose, 1978). This probably reflects hormonal stimulation of tryptophan catabolism rather than any deficiency of B6 per se. These studies were conducted when the level of estrogen in oral contraceptive agents was three to five times higher than it is currently.

Pathophysiological implications related to vitamin B6/pyridoxine deficiency
Since vitamin B6 is present in almost all foods, B6 deficiency due to insufficient dietary supply is rare. Additionally, isolated vitamin B6 deficiency is uncommon; it usually occurs in combination with deficiencies of other B-complex vitamins. Often PN deficiency is caused

by absorption disorders, genetic factors, interactions with drugs or elevated requirements. Because of its wide variety of functions in the body, clinical pyridoxine deficiency results in a broad spectrum of impaired features. The most common pathophysiological implications related to pyridoxine deficiency are the followings (Spinneker et al 2007).

Hypochromic, microcytic, iron-refractory anaemia B6 -deficiency anaemia
Essentially, a defect in heme formation is responsible for the appearance of the hypochromic anaemia seen in B6 deficiency, since B6 is necessary for the synthesis of protoporphyrins on one hand and probably for the incorporation of iron on the other. It has been observed a strong inhibition of iron incorporation into the heme of erythrocytes in a patient with a pyridoxine sensitive anaemia. Yamada & Ogawa 1957 reported decrease iron incorporation in bone marrow culture from B6 deficient animals. This can be produced by cycloserine and isoniazid (INH).

Vitamin B6 deficiency or a genetic defect of the enzyme aminolevulinate synthase, can lead to an iron refractory, microcytic anaemia. In humans, vitamin B6 deficiency anaemia is rare. Therefore, literature is very scarce. In the seventies, Ofori-Nkansah et al. 1975 reported that the prevalence is higher in men than in women. Fishman et al 2000 suggest that a treatment with B6 may be effective in correcting the haematological abnormalities of sideroblastic anaemia. Meier et al 1981 found that the activity of delta-aminolevulinic acid synthetase (ALAS), the rate-limiting enzyme in heme synthesis was markedly reduced (13% of controls) in erythroblasts of a patient with acquired, primary sideroblastic anaemia. Administration of vitamin B6 (pyridoxin, 200-600 mg/d) resulted in complete reconstitution of erythroblastic ALAS-activity with concomitant disappearance of all hematologic abnormalities. The findings show that the therapeutic efficacy of pyridoxin in primary sideroblastic anaemia is due to its effect on defective ALAS.

Pyridoxine and sideroblastic anaemia
The sideroblastic anaemias are a heterogeneous group of disorders whose two distinctive features are ringed sideroblasts in the bone marrow (abnormal erythroblasts with excessive iron accumulation in the mitochondria) and impaired hembiosynthesis (Bottomley 1982, May & Fitzsimons 1994). Most commonly, the sideroblastic anaemias are classified as hereditary or acquired conditions. The acquired sideroblastic anaemias are far more common than the hereditary varieties. Acquired sideroblastic anaemia usually develops because of alcohol consumption, toxin exposure, substance abuse, and myelodysplastic syndrome-refractory anaemia with ring sideroblasts (MDS-RARS).

Inherited sideroblastic anaemia has a heterogeneous inheritance pattern including X-linked, autosomal, and mitochondrial entities. X-linked sideroblastic anaemia (XLSA) is the most common type, constituting about 40% of inherited sideroblastic anaemia. Most cases of XLSA result from deficiency of delta-aminolevulinate synthase 2 (ALAS2), an erythroid-specificenzyme involved in the heme biosynthetic pathway (Moon et al 2014).

Isoniazid and the development of sideroblastic anaemia
Isoniazid is a pyridoxine antagonist, both *in vitro* and *in vivo*, and many of its side effects can be attributed to interference with the proper action of this vitamin. It occupies a key position in the therapy of tuberculosis.

Although the occurrence of anaemia is quite uncommon during INH therapy, two patients have been reported who developed anaemia responsive to pyridoxine administration during treatment of tuberculosis with INH. A third patient, whose anaemia originally responded to small doses of pyridoxine, suffered a recurrence of anaemia during therapy of tuberculosis with INH. When administration of this drug was stopped and relatively small doses of pyridoxine (5 mg./day, i.m.) were given, there was a reticulocytosis followed by marked hematologic improvement. It is the purpose of this paper to describe three additional patients who had pyridoxine-responsive anaemia while being treated for tuberculosis with INH (McCurdy & Donohoe 1966).

The mechanism of isoniazid induced SA is an inhibition of the δ-aminolevulinate synthase-(Pasanen 1981) resulting in a depletion of haem synthesis (Chalevelakis et al 1989). Pyridoxine acts as a co-factor in synthesis of δ-aminolevulinate and is inhibited by isoniazid (Horrigan & Harris 1964). Substitution of pyridoxine is recommended during treatment with isoniazid (American Thoracis Society 2003).

Convulsive seizures
Vitamin B6 is an abundant cofactor in amino acid- and neurotransmitter metabolism. Physiologic availability depends on dietary supply, intact absorption and conversion of pyridoxamine and pyridoxine into the only active cofactor, pyridoxal-5'-phosphate (PLP) in liver.

PN deficiency is known to cause convulsive seizures in humans and experimental animals. Hence, a number of investigators reported disorders in central nervous system (CNS) activity in adults and infants. The neurological disorders in the infants manifested itself within 6 weeks up to 4 months by convulsive seizures, hyperirritability, and abnormal acuteness of the sense of hearing. Two reviews from the eighties summarised research on causative factors responsible for convulsions during vitamin B6 deficiency. They propose two hypotheses explaining the onset of convulsive seizures. First, it has been shown that a particular nutritional deficiency leads to the accumulation of a potentially hazardous tryptophan metabolite, 3-HK in the CNS.

Kynurenine transaminases and kynureninase catalyse are the main routes of 3-HK catabolism and require PLP. Reductions in their activities should lead to a build-up of 3-HK in the body and brain. Experimentally produced B6 deficiency by Guilarte & Wagner 1986 caused a 200-fold increase in brain regional 3-HK levels. This increase led the authors speculate that such levels of 3-HK could be responsible for the convulsions that typically occur in infant B6 deficiency. Another possible cause could be changes in the concentration of the neurotransmitter GABA, a major inhibitory transmitter in the CNS. GABA concentrations are reported to be low in the brains of vitamin B6 deficient infant animals, and such animals are often seen to convulse. Furthermore, pharmacologic studies indicate that drugs diminishing GABA transmission in the CNS promote convulsions.

Pyridoxine responsive seizures (PDRs) are characterized by early-onset seizures and epileptic encephalopathy which respond to pyridoxine. Aldehyde dehydrogenase 7A1 (*ALDH7A1*; antiquitin) mutation is the most common and first known mutation seen in them. Some cases

of pyridoxine responsive children have *ALDH4A1* mutation related to hyper-prolinemia II. Many children with PDRs and *ALDH7A1* mutation have intellectual disability even if seizure free on pyridoxine. Differential diagnosis of PDRs includes pyridoxal phosphate (PLP) responsive epileptic encephalopathy due to pyridoxamine phosphate oxidase deficiency, neonatal/infantile hypo-phosphatasia, familial hyperphosphatasia, and yet undefined conditions. Recently a new gene, PLP homeostasis protein (PLPHP) has been associated with pyridoxine responsiveness. 5 Still, there are children with no known genetic (defect who respond to pyridoxine (Koul et al 2019).

Plecko et al 2009 stated that two of the four varients are caused by reduced synthesis/availability of PLP (Pyridox(am)in-phosphate oxidase (PNPO) deficiency and infantile hypophosphatasia) and two by increased utilization/inactivation (pyridoxinedependent epilepsy and hyperprolinemia type II). All patients with these conditions present with early-onset epilepsy that is resistant to conventional antiepileptic medications. Patients with three of the conditions respond to any form of vitamin B6. Only those with pyridoxine phosphate oxidase deficiency respond to PLP instead of pyridoxine (Wang & Kuo 2007).

Assessor's Comment
Pyridoxine deficiency in adults principally affects the peripheral nerves, skin, mucous membranes, and the hematopoietic system. In children, the CNS can also be affected. The vitamin has been used to treat a wide variety of conditions, which may or may not be related to inadequate intake. In some conditions, use of vitamin B6 administration has been purely empirical; in other conditions, there is a reasonable physiological or metabolic mechanism to explain why supplements of the vitamin may have therapeutic uses.

IV.5 Clinical safety

Introduction
Pyridoxine toxicity has been recognised. It affects mainly the central nervous system and occurs at excessive doses. It is rare to develop pyridoxine toxicity without supplementation. Excessive supplementation for chronic periods (months to greater than a year) has resulted in sensory neuropathies and movement disorders. The pyridoxine toxicity induces sensory polyneuropathy (neuronal damage, and sensory and motor effects) causes decreased touch, temperature, and vibration sensation and resulted in poor coordination (Vrolijk et al 2017). The severity of symptoms is dose and duration of use dependent.

Additional clinical findings of toxicity may include photosensitivity, GI symptoms such as nausea and heartburn, as well as painful dermatological eruptions. These symptoms resolve for the most part over time with the elimination of the pyridoxine administration. Increased intakes from supplements may interact with the action of drugs, including levodopa, phenobarbital, and phenytoin (Bhagavan & Brin 1983).

Neurotoxicity
As a water-soluble vitamin which is rapidly metabolised and excreted, B6 might be expected to have low toxicity. In fact, no adverse effects have been associated with high intake of vitamin B6 from food sources. Schaumburg et al 1983 reported the development of severe sensory neuropathy in 7 patients treated with 2-6 g of PN hydrochloride/day. Further, reports of peripheral sensory neuropathy associated with high-dose PN therapy (1 to 4 g/day) appeared also in the 1980s (Parry & Bredesen 1984, Bear 1984, de Zegher et al 1985, Friedman et al 1986). However, it is noteworthy that none of the published reviews of patients with vitamin B6 dependency syndromes, who are treated with 500-1,500 mg/day,

mentions the development of peripheral neuropathy (Sturman et al 1986). Some patients developed abnormally low plasma concentrations of PLP after high doses of vitamin B6 . This rebound avitaminosis presumably reflects induction of pyridoxal oxidase, and hence increased catabolism of the vitamin. Within 4 months, plasma concentrations of the vitamin return to normal without supplementation (Dalton & Dalton 1987). The limited data involving lower PN doses reveal that the risk of developing sensory neuropathy decreases rapidly at doses below 1 g/day. The safe upper limit for vitamin B6 has been set at 100 mg/day, taking into account a security factor of 5, because the lowest dose at which toxicity (sensory neuropathy) has been observed is 500 mg/day (Institute of Medicines- USA 1998). The evidence for neurotoxicity in humans due to vitamin B6 administration is largely related to a series of case reports of patients with severe effects associated with extremely high intakes. An important aspect of these cases is the duration of intake prior to the development of symptoms. Duration of intake is critical in the interpretation of the results of clinical trials that used vitamin B6 for premenstrual syndrome. The information available indicate that cases of clinical neuropathy occur after about 12 months or longer treatment with doses of 2 g/day or less, whereas neuropathy can develop in less than 12 months at doses greater than 2 g/day.

De Zegher et al 1985 detected sensory neuropathy when a 1-year old patient was treated with 1 g pyridoxine daily for hyperoxaluria, and these effects were reversed when the dose was reduced to 400 mg per day.

Friedman et al 1986 described a woman who had ingested 2 gm of pyridoxine daily for two years for menstrual water retention developed a subepidermal vesicular eruption on the dorsa of the hands and toes, as well as a sensory peripheral neuropathy (bilateral numbness). The cutaneous and neurologic manifestations subsided about two months after discontinuation of the pyridoxine and improved within eight months of cessation of pyridoxine intake.

Waterston and Gilligan 1987 reported a case of sensory neuropathy in a young woman who had been taking pyridoxine at a dose of 1000 mg/day for 12 months, and whose symptoms resolved on cessation of pyridoxine intake.

Berger et al 1992 studied the development of pyridoxine neurotoxicity vs the administered daily dose. They administered either 1 or 3 g/d of pyridoxine to five healthy volunteers and repeatedly followed serum pyridoxal phosphate levels, clinical symptoms and signs, quantitative sensory thresholds (QSTs), and sural nerve electrophysiology. Pyridoxine was discontinued at the first sign of either clinical or laboratory abnormality.

In all subjects, sensory symptoms and QST abnormalities occurred concurrently. Subjects receiving higher doses became symptomatic earlier than low-dose subjects. Elevation of thermal QSTs preceded or exceeded that for vibration in the three low-dose subjects; vibration and thermal QST became abnormal simultaneously in the higher-dose subjects. A reduction in
the amplitude of the sural sensory potential lagged behind QST changes in two of three subjects. Symptoms continued to progress ("coasting") for 2 to 3 weeks despite stopping pyridoxine administration and the return of serum pyridoxal phosphate levels to normal.

Summary of findings: The human data on the safety of pyridoxine suggest that oral administration of doses greater than 500 mg/day for a prolonged period of time can result in the development of sensory neuropathy. Doses less than 500 mg/day appear to be safe on the basis of reports where pyridoxine was administered for periods ranging from 6 months to 6

years. An inverse relationship between dose and duration of administration appeared to exist. The recorded neuropathy is reversible, although, it could be incomplete and takes a considerable amount of time in order for the affected part to show an improvement.

Non-neurological adverse effects
Reports of adverse effects of pyridoxine other than sensory neuropathy have occasionally appeared in the literature. Skin changes resembling those of porphyria cutanea tarda were reported for two subjects with peripheral neuropathy that had ingested 2-4 g/day of pyridoxine for 2-4 years (Friedman et al 1986). The designation 'subepiderma1 vesicular dermatosis due to pyridoxine abuse' was suggested for this syndrome (Friedman et al 1985). An anecdotal report indicated that ingestion of 500 mg/day was associated with increased pigmentation of hair in an l8 year-old woman (Shelley et al 1971).

Mulrow et al 1985 suggested that 100 mg/day of pyridoxine for four months enhanced photosensitivity reactions to amiodarone. This apparent effect was inferred from the incidence of photosensitivity in two relatively small groups of patients (n = 23) and was an observation incidental to the purpose of this study. Phocomelia was observed in the full-term infant of a mother who took 50 mg of pyridoxine daily during the first 7 months of pregnancy together with a prescribed multivitamin
preparation and an assortment of over-the counter vitamin and nutritional preparations, including unknown doses of lecithin (Gardner et al 1985). The relevance of this report is uncertain since only one subject was involved, and a variety of preparations had been taken in addition to vitamin.

Morimoto et al 1996 described a 35-year-old female patient with photosensitivity due to pyridoxine hydrochloride (200mg/day) in a multivitamin over-the-counter preparation. Photopatch and oral photochallenge tests using pyridoxine hydrochloride and UVA irradiation were positive. Baer 1984 reported cutaneous skin changes in a woman who had taken massive doses (4 g/day) for a period of 4 years.

Coleman et al 1985 treated 400 patients with Down's syndrome with vitamin B6 at pharmacological doses (35 mg/kg/day). Reported side effects included skin blisters that were related to sun exposure, vomiting and peripheral neuropathy; all patients who developed blisters did so after a minimum of four and a half years of treatment. Two patients developed motor and sensory polyneuropathy after 9 years administration of doses up to 50 mg/kg and their condition improved once vitamin B6 administration had stopped.

Molimard et al 1980 showed that the administration of doses of 100 or 500 mg B6 per day for 10 days to a group of 58 medical students resulted in significantly impaired memorisation at 500 mg/day, and a non-significant decrease at 100 mg/day. The study was designed to investigate further an earlier unpublished observation of a decrease in "brain performance" from a double-blind study in medical students conducted in 1961. The study of Molimard et al. (1980) recruited 69 first year medical students who were randomly allocated to receive identical tablets of 50 mg or 250 mg pyridoxine or placebo to be taken twice per day for 10 days. Those who declared that they did not take the tablets were treated as a separate group. The subjects were given a simple digit coding test prior to treatment, immediately after treatment and 14 days later. In addition, the subjects underwent a test on the medical physiology that had been taught during the treatment period, plus some simple numerical problems at the end of the treatment period. A total of 58 subjects completed all 3-digit coding tests, which showed a highly significant improvement with time (a learning effect) in all groups. There were no significant differences in the uncorrected scores, but evidence of a

dose-related decrease in the learning effect, with a highly significant difference between the placebo group and 500mg/day group (P<0.002).

Use in pregnancy
Xonvea® is a delayed-release tablet containing doxylamine succinate 10 mg (an antihistamine) and pyridoxine hydrochloride 10 mg. In July 2018, it was granted a marketing authorisation by the MHRA for treating nausea and vomiting of pregnancy in women (aged 18 years or older) who do not respond to conservative management. Doxylamine/pyridoxine is taken every day and not on an as needed basis.

Evidence was from 2 randomised, double-blind, placebo-controlled multicentre trials in the US (Koren et al. 2010 and the Drug Efficacy Study Implementation (DESI-USA) study, which was undertaken in 1975 and reported by Zhang & Persaud 2017). In the key licensing study by Koren et al 2010, symptoms of nausea and vomiting were evaluated using the Pregnancy unique quantification of emesis (PUQE) score. Small but statistically significant improvements in PUQE scores were seen with doxylamine/pyridoxine compared with placebo at days 3, 4, 5 and 15. The MHRA concluded that the improvements are clinically important for women suffering from nausea and vomiting of pregnancy. The supporting study (the DESI study reported by Zhang & Persaud. 2017) also found that, overall, doxylamine/pyridoxine improved symptoms of nausea and vomiting compared with placebo.

Extensive data suggest that doxylamine/pyridoxine is safe for pregnant women to use, and that it is relatively well tolerated. The results of epidemiological studies designed to detect possible teratogenicity show no association with foetal abnormalities.

Drug Interactions
Many drugs may alter the metabolism or bioavailability of pyridoxine, including isoniazid, penicillamine and oral contraceptives, which may increase the requirements for pyridoxine. Pyridoxine hydrochloride may reduce the effect of levodopa, a drug used in the treatment of Parkinson's Disease unless a dopa decarboxylase inhibitor is also given

Pyridoxine reduces the activity of altretamine. It has also been reported to decrease serum concentrations of phenobarbital and phenytoin. Many drugs may increase the requirements for pyridoxine; such drugs include hydralazine, cycloserine, isoniazid, penicillamine, and oral contraceptives.

Assessor's Comment
The safety profile of pyridoxine is well known. Although pyridoxine is a physiological compound, it cannot be assumed that it is without adverse effect when administered at pharmacological doses. However, this should be viewed under the background that pyridoxine preparations have been used for many years as therapeutic agents without untoward effects.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

Pyridoxine preparations for the treatment of isoniazid-induced peripheral neuritis and pyridoxine deficiency states have been available in the UK for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

The application complies with current regulatory guidance documents and the submitted publications contain adequate clinical study data. There are no indications in the light of current scientific knowledge that the proposed product differs significantly from the other similar medicinal products with regards to safety or efficacy. The product contains the widely used and well-known active substance: pyridoxine which has a long history of established favourable risk-benefit profile.

Therefore, the application is approvable from a clinical viewpoint.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. 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.

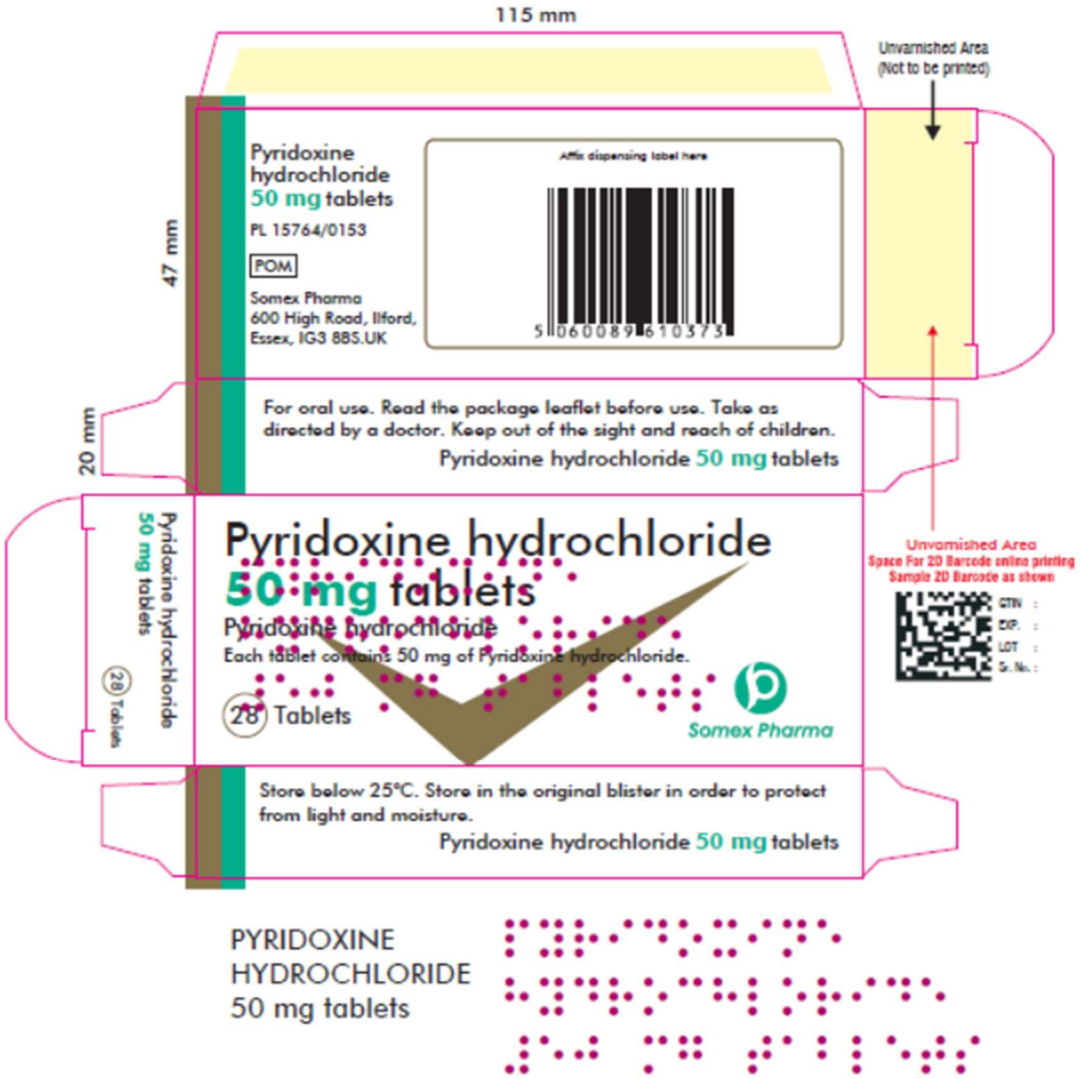
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with pyridoxine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

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

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.



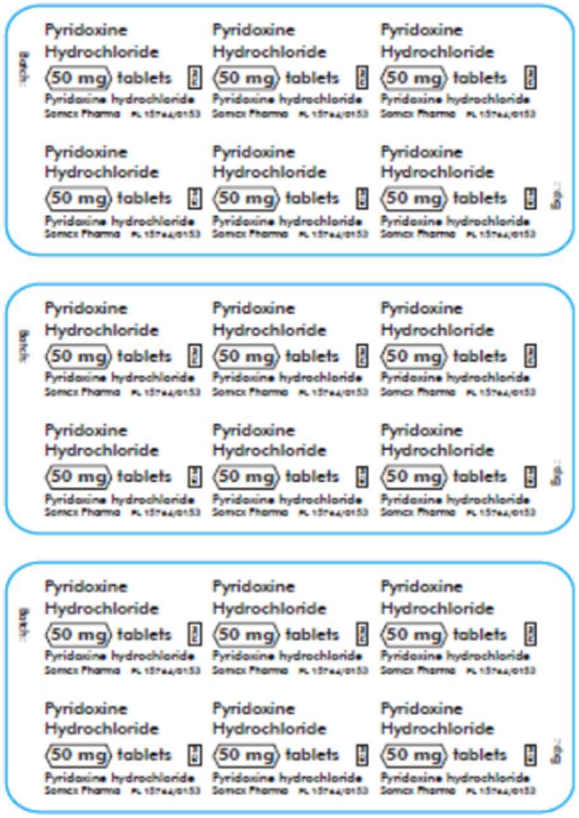

Pyridoxine Hydrochloride
50 mg tablets
Pyridoxine hydrochloride
Somex Pharma
PL 15764/0153

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**