Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

BELNIFREM 1.5 mg film-coated tablets (cytisinicline)

PL 46579/0008

APC Instytut Sp. z o.o.

LAY SUMMARY

BELNIFREM 1.5 mg film-coated tablets (cytisinicline)

This is a summary of the Public Assessment Report (PAR) for BELNIFREM 1.5 mg film-coated 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 Belnifrem in this lay summary for ease of reading.

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

What is Belnifrem and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Tabex 1.5 mg film-coated tablets.

Belnifrem is used in smoking cessation and reduction of nicotine cravings in smokers who are willing to stop smoking.

The treatment goal of Belnifrem is the permanent cessation of the nicotine-containing products use.

How does Belnifrem work?
Belnifrem contains the active substance cytisinicline, also known as cytisine. Using of the medicinal product Belnifrem allows to gradually decrease nicotine dependence and disaccustom of tobacco smoking without nicotine withdrawal symptoms (e.g., depressed mood, irritability, anxiety, difficulty concentrating, insomnia, increased appetite).

How is Belnifrem used?
The pharmaceutical form of this medicine is a film-coated tablet, and the route of administration is oral (taken by mouth). It should be taken with a suitable amount of water according to the following schedule.

Smoking should be stopped no later than on the fifth day of treatment. Smoking should not be continued during treatment as this may aggravate adverse reactions. In case of treatment failure, the treatment should be discontinued and may be resumed after two to three months.

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

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Belnifrem have been shown in studies?
As Belnifrem is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Belnifrem?
As Belnifrem is a generic medicine and is bioequivalent to the reference medicine, its and possible side effects are considered to be the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

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 https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Belnifrem approved?
It was concluded that, Belnifrem has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, 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 Belnifrem?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Belnifrem. The RMP details the important risks of Belnifrem, how these risks can be minimised, any uncertainties about Belnifrem (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Belnifrem.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Belnifrem are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

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

Other information about Belnifrem
A marketing authorisation for Belnifrem was granted in the United Kingdom (UK)/Great Britain (GB, consisting of England, Scotland and Wales)/Northern Ireland (NI) on 05 June 2023.

The full PAR for Belnifrem follows this summary.

This summary was last updated in August 2023.

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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 BELNIFREM 1.5 mg film-coated tablets (PL 46579/0008) could be approved. The product will be called Belnifrem 1.5 mg film-coated tablets in the remainder of this report.

The product is approved for the following indication:

- Smoking cessation and reduction of nicotine cravings in smokers who are willing to stop smoking.

  The treatment goal of Belnifrem 1.5 mg film-coated tablets is the permanent cessation of the nicotine-containing products use.

The active substance in this product, cytisinicline (also known as cytisine), is a plant alkaloid cytisine (found, among others, in seeds of golden chain, genus Laburnum), with a chemical structure similar to nicotine. It has an effect on acetylcholine nicotinic receptors. The action of cytisine is similar to that of nicotine, but in general weaker. Cytisine competes with nicotine for the same receptors and gradually displaces nicotine due to its stronger binding. It has lower ability to stimulate nicotinic receptors, mainly α4β2 subtype (it is their partial agonist) and less than nicotine passes into the central nervous system. It is hypothesised that in the central nervous system cytisine acts on the mechanism involved in nicotine dependence and on the release of neurotransmitters. It prevents nicotine-dependent full activation of the mesolimbic dopamine system and moderately increases level of dopamine in the brain, what alleviates the central symptoms of nicotine withdrawal. In the peripheral nervous system, cytisine stimulates and then infects the autonomic ganglia of the nervous system, causes a reflex stimulation of breathing and secretion of catecholamines from the core part of the adrenal gland, raises blood pressure and prevents peripheral symptoms of nicotine withdrawal.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Tabex 1.5 mg film-coated tablets, that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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 application and are satisfactory.

A marketing authorisation for Belnifrem 1.5 mg film-coated tablets was granted in the United Kingdom (UK) on 05 June 2023.

II QUALITY ASPECTS

II.1 Introduction

This product contains 1.5 mg of cytisinicline in each film-coated tablet.

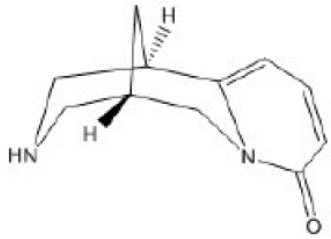
In addition to cytisinicline, this product also contains the excipients hypromellose, mannitol, maize starch, magnesium aluminometasilicate type A, silica colloidal anhydrous and magnesium stearate in the tablet core. The film-coat contains Aqua Polish P green [hypromellose (E464), cellulose microcrystalline (E460), talcum (E553b), glycerol (E422), titanium dioxide (E171), quinoline yellow Al-lake (E104), indigo carmine (blue 2) Al-lake (E132)], menthol flavour powder (SC552873) and aspartame (E951).

The finished product is packaged in polyvinylchloride/polyvinylidene chloride/aluminium (PVC/PVDC/Aluminium) blisters, in a pack size of 100 film-coated tablets.

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 ACTIVE SUBSTANCE

rINN: Cytisinicline
Chemical Name: (1R,5S)-1,2,13,4,5,6-Hexahydro-1,5-methano-8H-pyrido[1,2a][1,5]diazocin-8-one
Molecular Formula: $C_{11}H_{14}N_2O$
Chemical Structure:



Molecular Weight: 190.24 g/mol
Appearance: White or pale yellowish crystalline powder
Solubility: Freely soluble in water and in ethanol (96 per cent), and soluble in chloroform and acetonitrile.

Cytisine is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

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 was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

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

No excipients of animal or human origin are used in the final 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, 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 3 years, with the storage conditions ‘Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage conditions.’, 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 was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of cytisinicline are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology

No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of cytisinicline are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study:

Bioequivalence study (single-dose, fasting conditions)

This study was a randomised, open-label, single dose, two period, cross-over bioequivalence study comparing the test product Cytisine, film-coated tablets, 1.5 mg versus the reference product Tabex 1.5 mg film-coated tablets in healthy volunteers under fasted conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose (1.5 mg; 1 film-coated tablet) of either treatment with approximately 240 ml of water. Blood samples were taken pre-dose and up to 24 hours post-dose, with a washout period of seven days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1 Bioequivalence evaluation

Parameter	Total ISCV%	Geometric LSmeans		Test-to-Reference GMR(%)	90%CI
		Test	Reference		
C_{max}	15.0	22572.90	20616.01	109.49	103.40 – 115.94
AUC_{0-t}	4.1	114117.16	107534.27	106.12	104.47 – 107.80
$AUC_{0-\infty}$	4.2	116985.72	110379.69	105.98	104.30 – 107.69

LSmeans values are given in pg/mL for C_{max} and pg.h/mL for AUC

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for this application, and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application, and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

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
The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION
A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Tabex 1.5 mg film-coated tablets, (MA no. 03425, authorised in Poland to Sopharma Warszawa Sp. Z o.o.). The bridging report submitted by the applicant is acceptable.

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. Extensive clinical experience with cytisinicline 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), PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

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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, is 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**