LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Neqlofol

(beclometasone dipropionate (anhydrous), formoterol fumarate dihydrate)

SE/H/2687/01-02/DC

This module reflects the scientific discussion for the approval of Neqlofol. The procedure was finalised on 2025-05-07. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Neqlofol, 100 microgram/6 microgram/dose, 200 microgram/6 microgram/dose, pressurised inhalation, solution.

The active substances are beclometasone dipropionate (anhydrous) and formoterol fumarate dihydrate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Neqlofol, 100 microgram/6 microgram/dose, 200 microgram/6 microgram/dose, pressurised inhalation, solution, is a Hybrid Art. 10(3) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and these CMSs: HR

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Foster, 100 microgram/6 microgram/dose pressurised inhalation, solution authorised in DE since 2006, with Chiesi GmbH as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
The Pharmacodynamic, pharmacokinetic and toxicological properties of beclomethasone and formoterol are well known. As these active substances are well-known and widely used, no further studies are required, nor does the applicant provide any. A Non-clinical Overview based on literature review is, thus, appropriate. A show overview of the non-clinical properties – with the toxicological focus being on genotoxicity, carcinogenicity, and DART - is provided below. No novel constituents (excipients) are part of the proposed product. Impurities are assessed in the Quality assessment.

Pharmacology
The proposed medicinal product has two active substances. Beclometasone dipropionate (BDP) is a synthetic corticosteroid that is a diester of beclometasone and is constitutes as a prodrug (the active metabolite being beclometasone 17-monopropionate (17-BMP). It has a glucocorticoid anti-inflammatory action within the lungs. The second active substance, formoterol (more specifically formoterol fumarate dihydrate), is a selective beta2-adrenergic agonist – a long-acting beta-2 agonist (or LABA) - that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The combination of active substances target different aspects of asthmatic disease. BDP suppress the chronic inflammation and reduces airway hyperresponsiveness whereas formoterol has bronchodilatory effects, inhibit mast cell mediator release and plasma exudation.

Pharmacokinetics
In rat studies, after intravenous (IV) administration of BDP, 95.4% of BDP was converted to 17-BMP, while after pulmonary delivery of BDP, 46.6% of deposited BDP was absorbed as BMP. Receptor occupancies in the lung were more pronounced than those in the systemic circulation after pulmonary delivery of BDP or BMP. Studies in dogs found that approximately 15% of the inhaled BDP dose was present in the respiratory tract, two-thirds of which was in the lung and the remainder deposited in the larynx, trachea, and main bronchi of dogs immediately after exposure. Corresponding values at 30 minutes post exposure were 4% and 1 % respectively. No similar non-clinical inhalation-based absorption information for formoterol was included in the Non-clinical overview. In-vitro studies with BDP indicate that CYP3A4 and CYP3A5 metabolize BDP to inactive metabolites and it has been speculated that differences in the expression or function of these enzymes in the lung and/or liver could influence BDP disposition. Formoterol is widely metabolized, and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. The glucuronide acid conjugates are pharmacologically inactive. A second major metabolic pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. No non-clinical information has been provided on elimination & excretion.

Toxicology
In Non-clinical toxicology, BDP is generally linked to immuno-suppressive effects. Formoterol is known to generate cardiovascular toxicity in dogs. BDP is not considered to be genotoxic or carcinogenic (based on a 95-week duration rat study, mixed inhalation- and oral exposure up to 2.4 mg/kg/day). Formoterol is not considered genotoxic. Genotoxicity studies performed with a beclomethasone dipropionate/formoterol combination do also not indicate mutagenic potential.
A two-year formoterol carcinogenicity study in rat and mouse did not find any clear increase of neoplasms in mouse and mesovarial leiomyomas in rat (benign neoplasms are typically associated with long-term treatment of rats at high doses of beta-2-adrenergic drugs). Rats also demonstrate increased incidences of ovarian cysts and benign granulosa/theca cell tumours but the clinical relevance remains unclear. The combination of active substances has not been assessed in carcinogenicity studies.

In DART-studies in rat, the combination of BDP and formoterol is associated with reduced female fertility, embryofoetal toxicity, impaired foetal ossification, decreased perinatal survival of pups, and impaired reproductive function of the female offspring. With regard to fertility, it can be noted that BDP is known to inhibit the estrous cycle in dogs (at 25x the maximum daily inhalation dose based on mg/m2 scaling). BDP is a corticosteroid which, as a class and at higher doses, is linked to teratogenic effects such as cleft palate and intra-uterine growth retardation. BDP inhalation-exposure of pregnant rats in known to generate gross injury (characterized by red foci) of the adrenal glands in foetuses at 180x the maximum daily inhalation dose. In mouse teratogenic studies, using SC-exposure at 0.75x of the maximum daily inhalation dose, cleft palate effects were generated. In rabbits, BDP SC-exposure at 0.75x of the maximum daily inhalation dose generated external and skeletal malformations) and embryolethal effects (increased foetal resorptions). For formoterol alone, no fertility effects have been observed in rats. In teratogenic rat studies, wavy ribs have been observed in the foetuses. Such skeletal findings have not been observed in PND21 pups. Formoterol has also been shown to cause stillbirth and neonatal mortality in rats at oral doses of 6 mg/kg and above (approximately 2000x the maximum recommended daily inhalation dose in humans) exposed for several days at the end of pregnancy. In rabbits, formoterol has been reported to cause a decrease in the number of viable foetuses at 500 mg/kg.

Environmental Risk Assessment (ERA)
Neqlofol is a generic product (Art 10(3)), and an ERA document has been provided that is in line with the 2024 CHMP ERA GL. A reference ERA has been identified (reference product Foster) and a LeA for that ERA has been received.

It can be noted that there has been a clear increase during recent years in consumption/sales (late 2010's, early 2020's) in some member states for products containing both active substances. It is also noted that beclomethasone is a glucocorticoid, a class of steroid hormones considered to be endocrine active substances (EAS) in an ERA context. These aspects have been covered by the reference ERA. Secondary poisoning assessment has been discussed and is not necessary. With regard to the triggering of Phase IIB terrestrial assessment according to the 2024 CHMP ERA GL (based on a combination of PECsw and Kfoc for sludge), a Kfoc value was not generated in the reference ERA, but triggering Phase IIB requires, due to a low PECsw, a Kfoc > 10 000 L/kg and the related compounds cortisol and budesonide are known to have experimental Kfoc below ~1500 L/kg – which makes it unlikely that beclomethasone would trigger such an assessment. As the pharmaco-toxicological mechanism of action involves interaction with glucocorticoid receptors, which are generally not present in the model organisms tested in the terrestrial assessment, it is also considered very unlikely that toxic effects would manifest in terrestrial ERA studies. Taken together, reasonable arguments have been provided that the conclusions of the reference ERA (no environmental risk, no PBT/vPvB) are also applicable for the present product.

Overall conclusions
There are no non-clinical objections to approval of Neqlofol.

IV. CLINICAL ASPECTS

Pharmacokinetics
According to the Guideline for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev.1, 2009), a step-wise approach should be considered when demonstrating therapeutic equivalence for an orally inhaled product. The first step consists of pharmaceutical data, the second step of pharmacokinetic data and the third step is represented by pharmacodynamic/clinical efficacy and safety data.

No pharmacokinetic studies have been submitted as the applicant claims that therapeutic equivalence can be concluded based on in vitro data only.

Pharmacokinetic properties of the active substances

Absorption: Beclomethasone dipropionate has an absolute bioavailability following inhalation of 2 % and 62% of the nominal dose of unchanged beclomethasone dipropionate and beclomethasone-17 monopropionate, respectively.
Elimination: The terminal half-life is 0.5 hours and 2.7 hours for beclomethasone dipropionate and beclomethasone-17 monopropionate, respectively. For formoterol, the half-life following oral administration is 2-3 hours. Following inhalation a half-life of 10 hours was estimated.

Discussion and overall conclusion
Therapeutic equivalence has been demonstrated using in vitro data (see Quality part). The absence of pharmacokinetic studies can be accepted in line with the OIP guideline.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Neqlofol.

Part II Safety specification
Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 28.10.2024 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The full user test for *100 microgram/6 microgram, SE/H/2583/01/DC* and the bridging for *200 microgram/6 microgram, SE/H/2583/02/DC* were assessed and accepted at day 70.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Neqlofol, is found adequate. There are no objections to approval of Neqlofol, from a non-clinical and clinical point of view. Therapeutic equivalence between the test and reference product has been adequately demonstrated based on in vitro-data. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Neqlofol, 100 microgram/6 microgram/dose, 200 microgram/6 microgram/dose, pressurised inhalation, solution was positively finalised on 2025-05-07.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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