LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Cernitol Novum, film-coated tablet

[Dry extract of crude pollen of *Secale cereale* L. (Rye), *Phleum pratense* L. (Timothy) and *Zea mays* L. (Maize)
and
Soft extract of crude pollen of *Secale cereale* L. (Rye), *Phleum pratense* L. (Timothy) and *Zea mays* L. (Maize)]

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This module reflects the scientific discussion for the approval of Cernitol Novum, film-coated tablets. The procedure was finalised January 13 2014. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

LAY SUMMARY

The Medical Products Agency (Läkemedelsverket, MPA) has granted AB Cernelle, Sweden a marketing authorisation for the herbal medicinal product Cernitol Novum, film-coated tablets. The product is available without prescription and can be bought from pharmacies and other outlets.

Cernitol Novum is a double strength film-coated tablet of the already authorised Cernitol, tablet (authorised since 2012).

Cernitol has an extensive medicinal use in the EU for treatment of symptoms of benign prostatic hyperplasia (BPH) with a dosage corresponding to the dosage for Cernitol Novum. The active ingredients are two different extracts of crude pollen from *Secale cereale* L. (rye), *Phleum pratense* L. (timothy) and *Zea mays* L. (maize).

The Medical Products Agency has concluded that the active substances in Cernitol Novum have a well-established medicinal use with a recognised efficacy and acceptable level of safety.

The chemical/pharmaceutical quality of the product is acceptable and no new or unexpected safety concerns have been identified during the assessment. It was therefore decided that Cernitol Novum could be granted a marketing authorisation as a herbal medicinal product.

I. INTRODUCTION

AB Cernelle has applied for a marketing authorisation for Cernitol Novum, film-coated tablets. The active substances are a soft and a dry extract of crude pollen from *Secale cereale* L. (Rye), *Phleum pratense* L. (Timothy) and *Zea mays* L. (Maize).

For approved indications, see the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

Cernitol Novum is presented in the form of film-coated tablets containing 40 mg of genuine dry extract, corresponding to 200 mg dried crude pollen, and 6.6 mg genuine soft extract which corresponds to approximately 120 mg of dried crude pollen.

The excipients are: microcrystalline cellulose, maltodextrin, croscarmellose sodium, colloidal anhydrous silica, polyvinyl alcohol, titanium dioxide, hydrophobic colloidal silica, macrogols and talc.

The film-coated tablets are packed in plastic jars.

All manufacturers involved in the production operate in accordance with EU-GMP, or where relevant, GACP (Good Manufacturing Practise, respectively Good Agricultural and Collection Practice).

II.2 Drug Substance

Herbal substances:

- *Secale cereale* L. (rye) dried crude pollen (Swedish: torkat råpollen från råg)
- *Phleum pratense* L. (timothy) dried crude pollen (Swedish: torkat råpollen från timotej)
- *Zea mays* L. (maize) dried crude pollen (Swedish: torkat råpollen från majs)

None of the herbal substances have monographs in the European Pharmacopoeia but are controlled using in-house specifications.

Herbal preparations (active substances):

- *Secale cereale* (rye) / *Phleum pratense* (timothy) / *Zea mays* (maize), dried crude pollen, soft extract (12-28:1) acetone (Cernitin GBX)
- *Secale cereale* (rye) / *Phleum pratense* (timothy) / *Zea mays* (maize), dried crude pollen, dry extract (2.7-7.5:1) water:acetone:sodium laurilsulphate (96:4:0.022) (Cernitin T60).

The herbal substances are collected from cultivations. Relevant information on growing conditions and controls of the herbal substances has been provided.

The herbal substances are dried and milled. The extraction process is a multistep extraction. First the mixture of herbal substances is extracted with water/acetone/sodium laurilsulphate. The filtrate is dried and, for manufacturing reasons, excipients are added. This yields the

extract Cernitin T60. After the first extraction, the pollen husks are removed after filtration, dried and extracted again with acetone. The resulting extract is concentrated to the soft extract Cernitin GBX.

The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials and solvents.

The specifications for both the herbal substances and the herbal preparation include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Cernitol Novum, film-coated tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetal origin and hence, safe with view to possible TSE/BSE risk.

The manufacturing process has been sufficiently described and critical steps identified. A process validation, according to a submitted validation plan will be performed prior to marketing.

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 under ICH conditions have been performed and data presented support the shelf life and storage conditions claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

There is no community monograph issued by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) for either the single herbal preparations or the mixture of them.

The evaluation is based on evidence of well-established use submitted by the applicant in conjunction with the assessment of Cernitol, tablets to which this application is an extension application. No new assessment of non-clinical data has been done at this stage.

III.2 Pharmacology

The Cernitin pollen extracts are a mixture of natural components such as amino acids, carbohydrates, lipids and minerals. Phytosterols and secalosides are believed to be important constituents in the extract. It is presently not known which compound or compounds are primarily responsible for the clinical efficacy.
Antiinflammatory activity, particularly of Cernitin GBX, has been demonstrated both *in vivo* and *in vitro*. Anti-proliferative effects of Cernitin T60, Cernitin GBX and the mixture of these

extracts have been demonstrated in several experiments. There is thus some non-clinical pharmacological support for the approved indication for Cernitol, tablet.
The safety pharmacological studies did not reveal any serious negative effects of Cernitin total extract or its fractions on the central nervous system, the cardiovascular system, the respiratory system and the urinary system.

III.3 Pharmacokinetics

Constituents responsible for the therapeutic effect of the extracts are not entirely known, and thus pharmacokinetic studies are neither possible nor relevant.

III.4 Toxicology

The toxicity studies performed indicate a low toxicity. Studies on reproductive and developmental toxicity as well as on embryo-foetal development have not been performed but should not be necessary as the product is only intended for male patients. The Cernitin pollen extract did not show any potential to cause gene mutation *in vitro*, neither in bacteria nor in mammalian (V79) cells. Furthermore, the *in vivo* test in rat bone marrow gave no evidence for induced chromosomal structural damage. It can be concluded that in the tests performed the extracts in Cernitol showed no genotoxic potential.
The inactive ingredients in Cernitol, microcrystalline cellulose, maltodextrin, croscarmellose sodium, colloidal anhydrous silica, polyvinyl alcohol, titanium dioxide, hydrophobic colloidal silica, macrogols and talc do not constitute any safety concern. The applicant has stated that none of the compounds are of animal origin.

The non-clinical file submitted in conjunction with assessment of the previously approved Cernitol is considered sufficient to fulfil the requirements for granting a marketing authorisation for Cernitol Novum, film-coated tablet as a herbal medicinal product with a well-established use.

There are no non-clinical objections from granting Cernitol Novum, film-coated tablet a marketing authorisation as a herbal medicinal product.

III.5 Ecotoxicity/environmental risk assessment

Cernitol Novum is a herbal medicinal product. According to *Guideline on the environmental risk assessment of medicinal products for human use* (EMEA/CHMP/SW4447/00), herbal medicinal products are exempted from the obligation to present an environmental risk assessment due to the nature of their constituents.

III.6 Discussion on the non-clinical aspects

Cernitin extracts have been in medicinal use in the Community for a long period of time. The extracts in Cernitol Novum are recognised to have a well established medicinal use with an acceptable level of safety in the European Community.
No serious safety concerns have been identified.

IV. CLINICAL ASPECTS

IV.1 Introduction

No community monograph has been issued by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) for either the single herbal preparations or the mixture of them.

The evaluation is based on evidence of well-established use submitted by the applicant in conjunction with the assessment of Cernitol, tablets to which this application is an extension application. No new assessment of clinical data has been done at this stage.

IV.2 Pharmacokinetics

There are no studies concerning pharmacokinetics. The lack of pharmacokinetic data is acceptable since constituents responsible for the therapeutic effect of the extracts are not entirely known, and thus pharmacokinetic studies are neither possible nor relevant.

IV.3 Pharmacodynamics

The mechanism of therapeutic action cannot be considered clarified at present.
The entire extracts are regarded as being the active constituents of Cernitol Novum.

IV.4 Clinical efficacy

Indication Benign Prostatic Hyperplasia (BPH)
The applicant has presented evidence that products containing Cernitin extracts of the same composition as that contained in Cernitol Novum have been used in the EU and outside Europe for more than 40 years for the indication BPH.
Based on evidence of long-term medicinal use and published results from clinical studies, approval of Cernitol Novum as a herbal medicinal product with a well-established use for the treatment of symptoms of benign prostatic hyperplasia (BPH), e.g.pollakisuria and nocturia is recommended with respect to clinical efficacy.

There are no clinical objections from granting Cernitol Novum, film-coated tablet a marketing authorisation as a herbal medicinal product.

IV.5 Clinical safety

The clinical safety documentation on Cernitol Novum indicates no signals of safety concern. Approval of Cernitol Novum as a herbal medicinal product with well-established use for treatment of symptoms of benign prostatic hyperplasia (BPH) is therefore recommended with respect to clinical safety.

There is no relevant indication for the use in children, adolescents or women. Nor is there any data on the effects on male fertility.

The PSA-concentration in serum may decrease slightly during treatment with Cernitol Novum. Changes in the PSA-value during treatment with Cernitol Novum should thus be interpreted with caution.

There are no new signals of safety concern in the submitted product specific documentation relating to Cernitol Novum.

IV.6 Discussion on the clinical aspects

Cernitol Novum is a herbal medicinal product available without prescription for the treatment of symptoms of benign prostatic hyperplasia (BPH).

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The adverse reactions reported during an extensive use of pollen from rye, timothy and maize are no cause for safety concern. No new safety signals have been identified in the submitted product specific documentation relating to Cernitol Novum. The benefits of Cernitol Novum should outweigh the potential risks.

The risk/benefit ratio is considered positive and Cernitol Novum, film-coated tablets is recommended for approval.

VI. APPROVAL

Cernitol Novum, film-coated tablets was approved in the national procedure on 2014-01-13.

LÄKEMEDELSVERKET
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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se