LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Jimandin
# (sitagliptin)

# SE/H/1550/01-03/DC

**This module reflects the scientific discussion for the approval of Jimandin. The procedure was finalised on 2017-06-21. 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

# I. INTRODUCTION

The application for product Jimandin, 25mg, 50mg and 100mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Medochemie Ltd. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, CY, CZ, EE, EL, HR, LT, LV, MT, RO and SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Januvia, 25mg, 50mg and 100mg, film-coated tablets authorised in the union since 2007, with Merck Sharp & Dohme Ltd as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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

# 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

## III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

No bioequivalence study has been submitted since the applicant applies for a BCS class I biowaiver.

From a pharmacokinetic point of view, a BCS-class I based biowaiver is acceptable for an immediate release drug product if the drug substance has proven to exhibit complete absorption and the excipients that might affect bioavailability are qualitatively and quantitatively the same. It should also be confirmed that the substance is not a narrow therapeutic index drug.

The extent of absorption of sitagliptin is >85 % and the absorption/permeability criteria for a BCS class I biowaiver is fulfilled. The qualitative composition of the test and reference products is identical and none of the excipients are known to affect the bioavailability. In addition sitagliptin is not considered to be a narrow therapeutic index drug.
Hence, the justification for a BCS class I (Biopharmaceutics Classification System) based biowaiver can be accepted from a clinical point of view.

## IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

## IV.3 Risk Management Plan

The Applicant has submitted an updated risk management plan (version 2.1 with DLP 31.03.2017), 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 Jimandin.

Safety specification

*Summary of safety concerns*

| | |
|---|---|
| **Important identified risks** | Gastrointestinal disorders, including nausea, constipation, diarrhoea, upper abdominal pain, flatulence and related terms (dyspepsia, gastritis, and abdominal pain)<br><br>Hypersensitivity reactions, including anaphylactic reaction, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation, and Stevens-Johnson |

| | |
|---|---|
| | syndrome<br>Hypoglycemia with concomitant sulfonylurea<br>Hypoglycemia with concomitant insulin<br>Musculoskeletal disorders: Osteoarthritis, pain in extremity, and related terms (e.g. arthralgia, myalgia, myopathy)<br>Pancreatitis |
| **Important potential risks** | Neurotoxicity, including tremor, ataxia, and balance disorders<br>Suicidal ideation/suicide, including depression<br>Skin reactions: contact dermatitis<br>Infections: URTI, nasopharyngitis and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis)<br>Impaired renal function, including acute renal failure (sometimes requiring dialysis)<br>Pancreatic cancer<br>Rhabdomyolysis |
| **Missing information** | Exposure in paediatric population<br>Exposure during pregnancy and lactation<br>Theoretic carcinogenic potential |

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

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

*Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed in RMP (ver 2.1)*

| **Safety Concern** | **Routine Risk Minimisation Measures** | **Additional Risk Minimisation Measures** |
|---|---|---|
| **Important Identified Risks** | | |
| Gastrointestinal disorders, including nausea, constipation, diarrhoea, upper abdominal pain, flatulence and related terms (dyspepsia, gastritis, and abdominal pain) | Proposed text in SmPC sections 4.8<br>Prescription only medicine | None proposed |
| Musculoskeletal disorders: Osteoarthritis, pain in extremity, and related terms (e.g. arthralgia, myalgia, myopathy) | Proposed text in SmPC sections 4.8<br>Prescription only medicine | None proposed |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| Hypoglycaemia with concomitant sulfonylurea | Proposed text in SmPC sections 4.4<br>Prescription only medicine | None proposed |
| Hypoglycaemia with concomitant insulin | Proposed text in SmPC sections 4.4<br>Prescription only medicine | None proposed |
| Hypersensitivity reactions, including anaphylactic reaction, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation, and Stevens-Johnson syndrome | Proposed text in SmPC sections 4.4, 4.8<br>Prescription only medicine | None proposed |
| Pancreatitis | Proposed text in SmPC sections 4.4, 4.8<br>Prescription only medicine | None proposed |
| **Important Potential Risks** | | |
| Neurotoxicity, including tremor, ataxia, and balance disorders | Proposed text in SmPC sections 5.3<br>Prescription only medicine | None proposed |
| Suicidal ideation/suicide, including depression | Prescription only medicine | None proposed |
| Infections: URTI, nasopharyngitis and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis) | Proposed text in SmPC sections 4.8<br>Prescription only medicine | None proposed |
| Impaired renal function, including acute renal failure (sometimes requiring dialysis) | Proposed text in SmPC sections 4.4<br>Prescription only medicine | None proposed |
| Pancreatic cancer | Prescription only medicine | None proposed |
| Skin reactions: contact dermatitis | Skin reactions: contact dermatitis | Skin reactions: contact dermatitis |
| Rhabdomyolysis | Prescription only medicine | None proposed |
| **Missing Information** | | |
| Exposure in paediatric population | Proposed text in SmPC sections 4.2, and 5.2.<br>Prescription only medicine | None proposed |
| Exposure during pregnancy and lactation | Proposed text in SmPC sections 4.6<br>Prescription only medicine | None proposed |
| Theoretic carcinogenic potential | Prescription only medicine | None proposed |

Summary of the RMP

The RMP is acceptable.

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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Januvia in EMEA/H/C/000722 (content) and Encapia in NL/H/2497/001/DC (layout). The bridging report submitted by the applicant has been found acceptable.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Jimandin, is found adequate. There are no objections to approval of Jimandin, from a non-clinical and clinical point of view. The product information is acceptable.

The application is therefore recommended for approval.

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

N/A

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

N/A

# VII. APPROVAL

The Decentralised procedure for Jimandin, 25mg, 50mg and 100mg, film-coated tablets was positively finalised on 2017-06-21.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| | | | | | |

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

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