COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mingerlan 6 mg/0.4 mg, modified-release tablets (solifenacin succinate and tamsulosin hydrochloride)

NL/H/5410/001-DC

Date: 9 February 2024

This module reflects the scientific discussion for the approval of Mingerlan 6 mg/0.4 mg, modified-release tablets. The procedure was finalised on 26 April 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDC	Fixed Dose Combination
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mingerlan 6 mg/0.4 mg, modified-release tablets, from G.L. Pharma GmbH.

The product is indicated for the treatment of moderate to severe storage symptoms (urgency, increased micturition frequency) and voiding symptoms associated with benign prostatic hyperplasia (BPH) in men who are not adequately responding to treatment with monotherapy.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Vesomni 6 mg/0.4 mg modified-release tablets (NL RVG 111622) which has been registered in the Netherlands by Astellas Pharma Europe B.V. since 6 May 2013 (original product) via the mutual recognition procedure NL/H/2968/001-MR.

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Czechia, Hungary, Poland and Romania.

II. QUALITY ASPECTS

II.1 Introduction

Mingerlan 6 mg/0.4 mg are red film-coated, round, biconvex tablets debossed with “T7S” on one side. Each modified-release tablet contains 6 mg solifenacin succinate, corresponding to 4.5 mg solifenacin and 0.4 mg tamsulosin hydrochloride, corresponding to 0.37 mg tamsulosin.

The excipients are:

Tablet core - calcium hydrogen phosphate, cellulose, microcrystalline (E460), croscarmellose sodium (E468), iron oxide red (E172), magnesium stearate (E470b), macrogol high-molecular mass and silica colloidal anhydrous.
Tablet coating - hypromellose (E464), iron oxide red (E172), macrogol and titanium dioxide (E171).

The modified-release tablets are packed in Oriented Polyamide/Aluminum/Polyvinyl chloride/Aluminum (OPA/Alu/PVC/Alu) blisters or OPA/Alu/PVC/Alu perforated unit-dose blisters.

II.2 Drug Substance

The drug product contains two active substances, tamsulosin hydrochloride and solifenacin succinate.

Tamsulosin hydrochloride
This is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is slightly soluble in water, is not hygroscopic and has no known polymorphism. Tamsulosin hydrochloride contains one chiral centre. For this product, the pure levorotatory form is consistently produced.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur. with additional requirement for residual solvent as stated in the CEP. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

Solifenacin succinate
This is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water, is not hygroscopic and has no known polymorphism. Different isomers of solifenacin succinate exist. For this product, a single-isomer form is consistently produced.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is

meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for five years. Based on the data submitted, a retest period could be granted of five years when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The aim of the development was to make a fixed dose combination (FDC) tablet consisting of two layers to result in drug release patterns similar to the already authorised reference product. During development, aspects of the product formulation and manufacturing process were evaluated that could affect the critical quality attributes and other characteristics of the drug product. Furthermore, a co-processed excipient was chosen. The MAH has submitted three bioequivalence studies under fed and fasting conditions. For the comparison studies of the dissolution profile of the reference and drug product, *in vitro* dissolution tests were developed. The QC dissolution methods have been adequately developed and are discriminatory. Comparative dissolution studies at different pH levels were performed to demonstrate similarity between the finalised FDC tablet and the reference product used in the bioequivalence studies. For tamsulosin hydrochloride, the dissolution profiles at pH 1.2, 4.5, 6.8 and using the QC method are similar (f_2 values between 50 and 100). For solifenacin succinate, the dissolution profiles of the test and reference product at pH 1.2, 4.5, 6.8 and using the QC method are not similar, although *in vivo* results show equivalence. This discrepancy between *in vitro* and *in vivo* has been adequately addressed. The biobatch used in the bioequivalence studies was representative of commercial batches (formulation and size).

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1, section 6.9), for generic oral formulations, *in vitro* studies of the release in alcohol solutions should be performed. Alcohol induced dose dumping has been investigated for this product. For this, dissolution tests at pH 1.2 and pH 6.8 media with 0%, 5%, 10% and 20% alcohol were performed. The dissolution profiles

between the test and reference products were found comparable in the tested media from 0 to 20 % (V/V) of alcohol.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for six commercial scaled batches (three batches of small size and three batches of large size) in accordance with the relevant European guidelines. The granulates for the solifenacin layer and the tamsulosin layer are manufactured separately by means of wet granulation. The bi-layered tablet is then compressed in stages on a bi-layered tablet press and the bi-layered cores are then film-coated. The manufacturing process is a non-standard manufacturing process due to the low unit dose concentration of Tamsulosin hydrochloride and the modified release principles.

Control of excipients

The excipients comply with relevant Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, residual solvents and for both drug substances: identity, assay, uniformity of dosage units, dissolution and related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamine risk assessment has been performed. Nitrosamine was detected but at levels consistently below 10% of the AI (acceptable intake limit). Therefore, test for the nitrosamine can be omitted from the specification.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial batches of the large size stored at 25°C/60%RH (12 months), 30°C/65%RH (12 months) and 40°C/75%RH (6 months). Additionally, stability data has been submitted for three commercial batches of the small size stored at 25°C/60%RH (24 or 36 months), 30°C/65%RH (15 months) and 40°C/75%RH (6 months). The batches were stored in OPA/Al/PVC-Al blisters. The stability was tested in accordance with applicable European guidelines. A significant change was observed at accelerated conditions regarding the assay of tamsulosin hydrochloride. Furthermore, out of specification for one impurity was found in two batches at a time point under intermediate condition. Hence, the shelf life should be based on the available long-term data. Photostability was studied according to ICH, the results show that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 12 months. The labelled storage conditions are store below 25 ℃.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Mingerlan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Mingerlan is intended for generic substitution, this will not lead to an increased exposure to the environment. In addition, a justification for non-submission of an ERA has been submitted by the MAH as requested, the justification is considered acceptable. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Vesomni which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Solifenacinesuccinaat/Tamsulosinehydrochloride are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Mingerlan 6 mg/0.4 mg, modified-release tablets, (G.L. Pharma GmbH, Austria) was compared with the pharmacokinetic profile of the reference product Vesomni 6 mg/0.4 mg modified-release tablets (Astellas Pharma Europe B.V., Bulgaria). The bioequivalence studies have been conducted to demonstrate appropriate bioavailability and bioequivalence (i.e., therapeutic equivalence). The test tablet has a potency of 101.3% for solifenacin and 100.5% for tamsulosin. The reference tablet has a potency of 98.2% for solifenacin and 99.3% for tamsulosin. The difference in potency between test and reference for solifenacin as well as for tamsulosin is within 5%. The submitted bioequivalence studies were a single dose study under fasting conditions, a single dose study under fed conditions and a multiple dose study, which is in accordance with the guidelines for modified-release formulations. The studies were all conducted in healthy volunteers.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence studies

Study 1, single-dose fasted conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label bioequivalence study was carried out under fasted conditions in 58 healthy adult male subjects, aged 18-60 years. Each subject received a single dose (tamsulosin hydrochloride 0.4 mg + solifenacin succinate 6 mg) of one of the two tamsulosin hydrochloride/solifenacin succinate formulations. The modified-release tablet was orally administered with 240 mL water after overnight fasting for at least 10 hours. Fasting continued for at least 4 hours following drug administration, after which a standardised lunch was served.

There were twee dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable.

Results

58 subjects were enrolled for the study. Two subjects were discontinued from the study, one subject had taken prohibited concomitant medication to treat an adverse event (AE) and one

subject was withdrawn from the study due to the COVID-19 protocol. A total of 56 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of solifenacin 6 mg under fasted conditions.

Treatment N=56	AUC_{0-t} (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	352 ± 95	9.1 ± 2.4	5.0 (2.5 – 8.0)
Reference	338 ± 86	8.7 ± 2.1	5.5 (2.0 - 10.0)
***Ratio (90% CI)**	1.04 (1.00 - 1.07)	1.04 (1.00 - 1.08)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tamsulosin 0.4 mg under fasted conditions.

Treatment N=56	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{0-tau} (ng.h/mL)	AUC_{0-tau}/ $AUC_{0-\infty}$ (%)	C_{max} (ng/mL)	t_{max} (h)
Test	142 ± 70	150 ± 76	91 ± 38	64 ± 11	6.45 ± 2.59	5.0 (2.5 – 16.0)
Reference	142 ± 73	151 ± 84	92 ± 38	65 ± 11	6.45 ± 2.39	5.0 (2.0 - 16.0)
***Ratio (90% CI)**	1.00 (0.93 - 1.08)	1.00 (0.93 - 1.09)	--	--	0.99 (0.92 - 1.06)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero t = 12 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

The tamsulosin ratio of $AUC_{0-tau}/AUC_{0-\infty}$ (%) is 64% and 65% for Test and Reference formulation respectively, indicating that accumulation will occur after multiple doses. Therefore, a study under steady state conditions is needed to show bioequivalence after multiple dosing. See study 3.

Study 2, single-dose fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label bioequivalence study was carried out under fed conditions in 54 healthy male subjects, aged 19-60 years. After overnight fasting for at least 10 hours, subjects consumed a standardised high-fat, high-calorie breakfast of 1011 kcal. Thirty minutes after the start of the breakfast, each subject received a single dose (tamsulosin hydrochloride 0.4 mg + solifenacin succinate 6 mg) of one of the two tamsulosin hydrochloride/solifenacin succinate formulations. The modified-release tablet was orally administered with 240 mL water. Fasting continued for at least 5 hours following drug administration, after this a standardised lunch was served. There were twee dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable.

Results

54 subjects were enrolled for the study. One subject was withdrawn from the study due to the COVID-19 protocol. 53 subjects received the treatment, three subjects were discontinued after period 1 with consent (blood samples were not obtained due to difficulty with the veins and two subjects had episodes of diarrhoea). A total of 51 subjects were eligible for pharmacokinetic analysis of solifenacin and 50 subjects for tamsulosin.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of solifenacin 6 mg under fed conditions.

Treatment N=51	**AUC_{0-t}** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	330 ± 110	8.4 ± 2.4	9.0 (3.0 – 24.0)
Reference	322 ± 93	8.0 ± 2.1	9.0 (3.0 - 36.0)
***Ratio (90% CI)**	1.01 (0.98 - 1.03)	1.05 (1.00 - 1.09)	--

$AUC_{0-\infty}$ Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max} Maximum plasma concentration
t_{max} Time after administration when maximum plasma concentration occurs
CI Confidence interval

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tamsulosin 0.4 mg under fasted conditions.

Treatment N=50	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	AUC_{0-tau} (ng.h/mL)	AUC_{0-tau}/ $AUC_{0-\infty}$ (%)	C_{max} (ng/mL)	t_{max} (h)
Test	172 ± 85	181 ± 93	118 ± 50	68 ± 9	10.19 ± 4.14	8.5 (1.0 – 16.0)
Reference	171 ± 78	179 ± 85	117 ± 48	68 ± 11	9.92 ± 3.88	7.5 (2.0 - 16.0)
***Ratio (90% CI)**	0.99 (0.93 – 1.05)	0.99 (0.93 - 1.05)	--	--	1.01 (0.95 - 1.09)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero t = 12 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

The tamsulosin ratio of $AUC_{0-tau}/AUC_{0-\infty}$ (%) is 68% and 68% for Test and Reference formulation respectively, indicating that accumulation will occur after multiple doses. Therefore, a study under steady state conditions is needed to show bioequivalence after multiple dosing. See study 3.

Study 3, multiple dose fasted conditions

Design

A multiple dose, open label, randomised, two-treatment, two-period, cross-over, bioequivalence study was carried out under fasted conditions in 66 healthy male subjects, aged 20-58 years. Each subject received a single dose (tamsulosin hydrochloride 0.4 mg + solifenacin succinate 6 mg) of both the test and reference tamsulosin hydrochloride/solifenacin succinate formulations once daily for 18 days. The tablet was orally administered with 240 mL water after overnight fasting for at least 10 hours.

For each subject there were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were taken at pre-dose at day 0, day 16, day 17 and day 18 and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, 20 and 24 hours after administration of the formulation.

The design of the study is acceptable.

Results

66 subjects were enrolled for the study. Three subjects were withdrawn before start of Period II due to a positive alcohol test. One subject withdrew before start of Period II for personal reasons. Another subject was withdrawn before start of period II due to the COVID-19 protocol. One subject was withdrawn before Period 2 due to non-compliance. One subject was withdrawn due to a mild adverse event (vomiting). A total of 59 subjects were eligible for pharmacokinetic analysis.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of solifenacin 6 mg at steady state, under fasted conditions.

Treatment N=59	$AUC_{0\text{-}tau}$ (ng.h/mL)	C_{tau} (ng/ml)	C_{avg} (ng/ml)	C_{max} (ng/mL)	t_{max} (h)	Fluctuation (%)
Test	597 ± 231	22.9 ± 9.5	24.9 ± 9.6	32.4 ± 11.6	5.0 (3.0 – 8.0)	51 ± 11
Reference	579 ± 222	22.3 ± 9.4	24.1 ± 9.3	31.5 ± 11.2	5.0 (2.0 - 8.0)	51 ± 11
***Ratio (90% CI)**	1.03 (1.01 - 1.05)	1.03 (1.00 - 1.05)	--	1.03 (1.00 - 1.05)	--	--

$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve from time zero t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tamsulosin 0.4 mg at steady state, under fasted conditions.

Treatment N=59	$AUC_{0\text{-}tau}$ (ng.h/mL)	C_{tau} (ng/ml)	C_{avg} (ng/ml)	C_{max} (ng/mL)	t_{max} (h)	Fluctuation (%)
Test	130 ± 63	3.8 ± 2.2	5.4 ± 2.6	9.7 ± 4.0	4.5 (2.0 – 10.0)	138 ± 53
Reference	127 ± 57	3.9 ± 2.3	5.3 ± 2.4	9.0 ± 3.6	4.5 (2.0 - 8.0)	127 ± 51
***Ratio (90% CI)**	1.02 (0.94 - 1.10)	0.97 (0.87 - 1.09)	--	1.07 (0.99 - 1.16)	--	--

$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve from time zero t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

Analytical/statistical methods

The analytical methods for the studies have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

As the tablets were dosed to individual groups at different dates (for study 1 there were three groups and for study 3 two groups), additionally statistic tests were submitted by the MAH as requested, to demonstrate that there is no group-by-treatment (formulation) effect present in the studies. For this, the FDA Model I was used. The results for both tamsulosin and solifenacin were found acceptable.

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} of solifenacin and AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of tamsulosin are within the bioequivalence acceptance range of 0.80 – 1.25 for both the study under fed and fasting conditions. Furthermore, the 90% confidence intervals calculated for AUC_{0-tau}, C_{max} and C_{tau} of solifenacin and tamsulosin for the steady state study are within the bioequivalence acceptance range of 0.80 – 1.25, the reference and test products are considered bioequivalent with respect to the extent and rate of absorption at steady state. Based on the submitted bioequivalence studies Mingerlan 6 mg/0.4 mg is considered bioequivalent with Vesomni 6 mg/0.4 mg.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Mingerlan 6 mg/0.4 mg.

Table 7. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity reactions, including anaphylactic reaction and angioedema • Urinary retention • QT prolongation /Torsade de Pointes • Glaucoma • Ileus • Intraoperative Floppy Iris Syndrome • Orthostatic hypotension
Important potential risks	• Concomitant administration with strong CYP3A4 inhibitors
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Vesomni 6 mg/0.4 mg. No new clinical studies were conducted. The MAH demonstrated through three bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Vesomni 6 mg/0.4 mg modified release (NL/H/2968/001-MR) for content and to Clozapine 12.5 mg orodispersible tablets for layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mingerlan 6 mg/0.4 mg, modified-release tablets has a proven chemical-pharmaceutical quality and is a generic form of Vesomni 6 mg/0.4 mg modified-release tablets. Vesomni is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Mingerlan 6 mg/0.4 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 April 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5410/1/ IB/001	Change in the specification parameters and/or limits of the finished product: - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material).	No	31-10-2023	Approved	N.A.
NL/H/5410/1/ IB/002	Change in the shelf-life or storage conditions of the finished product: - Extension of the shelf life of the finished product. As packaged for sale (supported by real time data).	Yes	20-12-2023	Approved	N.A.