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EMA/29245/2018
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Rotigotine Mylan

International non-proprietary name: rotigotine

Procedure No. EMEA/H/C/004286/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

%CV	Percent coefficient of variation
AE	Adverse event
AUCL/AUCt	Area under the plasma concentration-time curve from time zero to the last quantitative concentration
AUCI/AUCINF/AUC0-α	Area under the plasma concentration-time curve from time zero to infinity
AUCTAU	Area under plasma drug concentration-time curve from time zero to time tau over a dosing interval at steady state, where tau is the dosing interval
AUC (0-24),ss	Area under the plasma concentration-time curve from time zero to 24 hours at steady state
AUC(0-tz)	Area under the concentration-time curve from zero up to the last concentration ≥LOQ
β-HCG	Beta-human chorionic gonadotropin
BMI	Body mass index
CAV(SS), CSS	Average drug concentration at steady state
CFR	Code of Federal Regulations
Cmax,ss/CPEAK(SS)	Maximum or peak plasma concentration at steady state
CPEAK/Cmax	Maximum or peak plasma concentration
CMIN(SS)	Minimum drug concentration within the last dosing interval during steady state
CNS	Central Nervous System
Ct	Concentration at the end of the dosing interval
Cτ (SS)	Concentration at the end of the dosing interval at steady-state
CYP	Cytochrome
D/DA	Dopamine
ECG	Electrocardiogram
EMA	European Medical Agency
EU	European Union
FLUCT1, %FLUCTUATION	One of the fluctuation parameters, where FLUCT1=100% (CPEAKCMIN)/CSS, provided that CSS does not = 0.
FLUCT2	One of the fluctuation parameters, where FLUCT2=100% (CPEAKCMIN)/CMIN, provided that CMIN does not = 0.
GCP	Good Clinical Practice

K2EDTA	Potassium ethylenediaminetetraacetic acid
HALFLIFE	Half-life
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
Kel/KEL	Apparent elimination rate constant
LNAUCINF/LNAUCI/LNAUC0-α	Natural log transformed AUCINF/AUCI/AUC0-α
LNAUCL/LNAUCT	Natural log transformed AUCL/AUCT
LNAUCTAU	Natural log transformed AUCTAU
LNCPEAK/LNCMAX	Natural log transformed CPEAK/CMAX
LSMEANS	Least square means
LQC	Last quantifiable plasma concentration
mg/d	Milligram/day
n/a	Not applicable
ng/ml	Nanogram/Millilitre
PD	Parkinson Disease
QoL	Quality of Life
RLS	RestLess Legs Syndrome
SD	Standard deviation
SmPC	Summary of Product Characterstics
TBD	To be determined
TAU, Tau, tau, τ	Drug dosing interval
TPEAK/TMAX	Time at which CPEAK occurs
TPEAK/TMAX,ss	TPEAK/TMAX at Steady State
THALF, t1/2	Terminal Elimination Half-Life
TDDS	Transdermal Drug Delivery System
US	United States

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the generic application for Rotigotine Mylan 1 mg/24 h, 2 mg/24 h, 3mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h transdermal patch in the claimed indications Parkinson's disease and moderate-to-severe primary restless legs syndrome , is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objection precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality

- Pharmaceutical development
- Manufacture - Process validation and/or evaluation
- Control of drug product - Batch analyses

Clinical

- In vivo skin adhesion has been investigated only in healthy young adults, no results in the elderly have been provided. While Restless Legs Syndrome may begin at any age, Parkinson's disease typically occurs in people over the age of 60. Skin structural changes due to the aging process could have an effect on the adhesion properties. The applicant is requested to provide an adequate justification on the absence of an adhesion study in the "elderly population".

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

Deficiencies arising from concerns over the confidential (ASM - Active Substance Manufacturer restricted) part of the DMF are mentioned in the appendix (this appendix is not supplied to the MAA). These concerns will be conveyed in confidence to the holder of the ASMF.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

The CHMP has requested an inspection of the manufacturing facilities in accordance with Article 19(3) of Regulation (EC) No 726/2004 and Article 111(1) of Directive 2001/83/EC.

GCP inspection(s)

No trigger for inspection was identified from the data provided for the BE-studies.

2. Executive summary

2.1. Problem statement

This marketing authorisation application for Rotigotine Mylan 1 mg/24 h, 2 mg/24 h, 3 mg/24 h, 4 mg/24 h, 6 mg/24 h,8 mg/24 h transdermal patch is based upon „essential similarity" to the reference

medicinal product Neupro 1mg/24h, 2mg/24h, 3mg/24h, 4mg/24h, 6mg/24h, 8mg/24h transdermal patches (UCB Manufacturing Ireland Ltd) in accordance with Article 10.1 of Directive 2001/83/EC, as amended.

The application is supported by 3 bioequivalence studies, all of them conducted in healthy volunteers: A single dose study in fasting state with integrated adhesion study, a multiple dose study under fasting conditions and also a dermal irritation and sensitization study.

The claimed indications are the same as for the reference product, i.e. Parkinson's disease and moderate-to-severe primary restless legs syndrome.

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons in the substantia nigra in the brain. Parkinson's disease is a slowly progressive disease, characterised clinically by bradykinesia, resting tremor, rigidity and postural reflex impairment. The cause of PD is presently unknown.

Pharmacological intervention of PD is symptomatic. Initial treatment is typically with the anti-parkinson medication L-DOPA (levodopa), with dopamine agonists being used once levodopa becomes less effective. Diet and some forms of rehabilitation have shown some effectiveness at improving symptoms. Surgery to place microelectrodes for deep brain stimulation has been used to reduce motor symptoms in severe cases when drugs are ineffective.

PD typically occurs in people over the age of 60, of which about one percent is affected. Males are affected more often than females. The average life expectancy following diagnosis is between 7 and 14 years.

Restless Legs Syndrome is a neurological sensory-motor disorder, characterized by five essential diagnostic criteria defined by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 and updated in 2012. Patients report an irresistible leg movement often accompanied by creeping sensations deep in the limbs. The symptoms of RLS are not confined to the legs, but can also occur in the upper limbs, the majority of symptoms occurring in the evening and at night. Lying down in bed is associated with increased paresthesia and an irresistible urge to move, often accompanied by periodic limb movements which interfere with sleep onset and consolidation of sleep.

Treatment includes lifestyle changes, such as stopping alcohol and tobacco, and sleep hygiene. Medications used include levodopa or a dopamine agonist.

Restless Legs Syndrome is one of the most frequent neurological diseases, with an estimated prevalence of 7% to 11% of the general population.

2.2. About the product

This centralised marketing authorisation application concerns Rotigotine Mylan 1 mg/24 h, 2 mg/24 h, 3mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h transdermal patches.

Rotigotine is a nonergolinic dopamine agonist, with high potency at human dopamine D1, D2 and D3 receptors and a lower potency at D4 and D5 receptors (Wood M, Dubois V, Scheller D, et al. 2015).

Rorigotine transdermal patch is indicated for the treatment of moderate-to-severe primary restless legs syndrome and for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on-off" fluctuations).

The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown, although it is thought to be related to its ability to stimulate dopamine receptors within the caudate putamen in the brain. The precise mechanism of action of rotigotine as a treatment for Restless Legs Syndrome is unknown but is thought to be related to its ability to stimulate dopamine receptors.

Pharmacotherapeutic group: Anti-parkinson drugs, dopamine agonists

ATC code: N04BC09

The chemical name of rotigotine is (6S)-6-{propyl [2-(2-thienyl) ethyl] amino}-5, 6, 7, 8- tetrahydro-1-naphthalenol. The empirical formula is C19H25NOS. The molecular weight is 315.48.

2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

In order to show essential similarity with the originator product Neupro 1mg/24h, 2mg/24h, 3mg/24h, 4mg/24h, 6mg/24h, 8mg/24h transdermal patches, Mylan conducted 3 bioequivalence studies, all of them in healthy volunteers:

A single dose study in fasting state with integrated adhesion study, a multiple dose study under fasting conditions and also a dermal Irritation and Sensitization study.

The applicant largely followed the following CHMP guidance:

- Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, commonly "BE-Guideline")
- Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)

The submitted dermal safety study ROTI-12128 was designed based on *Draft FDA Guidance for Rotigotine Transdermal Systems (Recommended June 2012/Revised October 2016)*.

Analytical method (Study ROTI-15074 and ROTI-15035): The validation(s) were performed according to the requirements of the *Guidance for Industry. Bioanalytical Method Validation (U.S. Food and Drug Administration, May 2001);* no reference was made to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009).

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

In order to confirm GMP compliance, the CHMP has requested an inspection of the manufacturing facilities in accordance with Article 19(3) of Regulation (EC) No 726/2004 and Article 111(1) of Directive 2001/83/EC.

GLP:

N/A

GCP

The applicant confirms that the studies [ROTI-15074, ROTI-12128 and ROTI-15035] were conducted according to Good Clinical Practice (GCP). The study reports contain a signed statement declaring compliance with GCP, the protocol and applicable regulations.

Furthermore the applicant confirms that “clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC”. A copy of the declaration signed by the sponsor’s representative is provided.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This marketing authorisation application (MAA) for Rotigotine Mylan 1 mg/24 h, 2 mg/24 h, 3 mg/24 h, 4 mg/24 h, 6 mg/24 h,8 mg/24 h transdermal patch is based upon „essential similarity“ to the reference medicinal product Neupro 1mg/24h, 2mg/24h, 3mg/24h, 4mg/24h, 6mg/24h, 8mg/24h transdermal patches (UCB Manufacturing Ireland Ltd) in accordance with Article 10.1 of Directive 2001/83/EC, as amended.

The reference medicinal product was first authorised for use in the European Union on 15th February 2006 (EU/1/05/331/001-002-015-018).

- Comments on the dossier

Both, the non-clinical and the clinical overview are based on appropriate scientific literature and are considered largely adequate. However, the following inconsistencies have been found in the Clinical Overview, which need to be clarified and corrected, respectively:

- Section 2.5.1.2 “*Application for Rotigotine Trandermal Patch*”: On page 11 of the Overview it says that this application is for a generic form of rotigotine transdermal system available as 2 mg, 4 mg, 6 mg and 8 mg of rotigotine per 24 hours. Information to the 1mg/24h and 3mg/24 patches is missing.
- Section 2.5.2.1 “Justification for Biowaiver”:On page 31 of the Overview information regarding the 1mg/24h and 3mg/24 patches is missing as well:” *UCB Pharma Limited’s Neupro Transdermal patches are available as Neupro 2mg/24h, 4mg/24h, 6mg/24h and 8mg/24h Transdermal patch. Mylan intends to market the generic versions of Neupro (rotigotine) Transdermal patches for strengths of 2mg/24h, 4mg/24h, 6mg/24h and 8mg/24h…..*”

Furthermore, information provided in section 1.9 of the dossier *„Information relating to Clinical trials”* is considered incomplete. The applicant refers only to one bioequivalence study:” *The bioequivalence study supporting this application was conducted in 2016…*” Section 1.9 should comprise information on all clinical trials conducted.

- Reference medicinal product

The reference medicinal product Neupro underwent a major quality variation (WS/0886/G) quite recently, a grouped variation including changes of composition, manufacturing process etc.

The BE studies in this generic application were carried out in April/May 2016 (single dose study ROTI 15074) and August/September 2016 (multiple dose study ROTI 15035) with the "old version" of the originator. There is no EMA/CHMP guidance/policy that establishes a cut-off date from which the applicant for a generic product would have to use the "new version" of the originator in the BE studies. From a regulatory viewpoint, the legal requirement for generic application is to provide a bioequivalence study versus the reference medicinal product.

In the present case, it is important to ensure that the quality issues that led to an Art. 20 procedure for Neupro (EMEA/H/626/A20/0023) with the requirement to reformulate due to a possible crystallisation process, do not occur with the generic, and to ensure that the reformulation of the originator did not lead to changes in the way the originator is to be used (e.g. posology, etc).

- The risk of crystal formation that was seen in the Neupro patch is sufficiently addressed. The risk appears low, based on the information provided.
- The reformulation of the originator did not lead to changes in the way the originator is to be used.

Therefore, from a regulatory viewpoint, it is deemed acceptable that the bioequivalence studies were carried out with the "old version" of the originator.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

This application concerns a centralised procedure according to Regulation (EC) No 726/2004. The application is submitted in accordance with Article 10(1) generic application of the Directive 2001/83/EC. Reference medicinal product is “Neupro” transdermal patch, in the strengths 1 mg/ 24 h, 2 mg/24 h, 3 mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg /24 h, authorised February 2006. The build-up of the transdermal patch, which is a three layer matrix system, consists of a release liner, the adhesive matrix (including the drug substance) and the coloured backing layer.

3.1.2. Active Substance

General Information

The drug substance Rotigotine is not mentioned in the current European Pharmacopoeia or in the USP.

Rotigotine is soluble in acetone and insoluble in water. It has one asymmetric center and 2 stereoisomers exist. Rotigotine exhibits polymorphism. The material manufactured is consistently form-II.

All information is provided in an ASMF.

Manufacture, characterisation and process controls

A brief description of the manufacturing process and a flow chart of the five stage process are provided. Some information is missing in the open part and should be transferred from the closed part to the open part of the dossier.

For detailed information regarding the manufacturing process (provided in the closed part of the ASMF) please see annex 1 to this report.

The structure of the drug substance is elucidated in detail and a mainly appropriate discussion on impurities is provided. Some details regarding carry over of reagents and the use of a solvent are missing. A further discussion on mutagenic impurities covering the whole synthesis including the potential impurities from the starting materials is missing and should be provided.

Specification

The specification of Rotigotine is with the exception of the limit for total impurities acceptable; a limit for total residual solvents is not given, but covered by “loss on drying”. The analytical methods are described sufficiently and the validations of the methods are all adequate.

Sufficient batch data are provided for three consecutive batches, but one question is raised regarding the definition of the batch size.

In-house synthesized material is used as reference standard and the currently working standard is qualified against this reference.

The primary container closure system material is in conformance to regulation 10/2011 and therefore acceptable.

Stability

Stability data for up to 24 months for long term stability and 6 month for accelerated stability are provided and the proposed retest period of 24 months without storage restrictions is acceptable.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

A view in the details of the composition show that the generic product is similar with the Neupro composition of batches with an expiry date October 2017 (1 mg/24 h and 6 mg/24 h), October 2016 (2 mg/24 h), September 2017 (3 mg/24h), November 2017 (4 mg/24 h), March 2017 (8 mg/ 24 h).

A detailed comparison of the composition (per patch) was provided showing an increase of certain excipients as well as for the used adhesives. This difference, for most of the excipients and drug substance, is explained by the respective increased area of the Mylan patch. Comparison of the compositions of Mylan transdermal patch and Neupro transdermal patch, each strength, is provided. Exhaustive updates of all dossier sections, corrections and clarifications are needed. The Release Liner and Backing Film are compared only by their superficial qualitative composition. The weight per square meter of the films and areas of the films per patch should be provided.

The difference in patch area activity between Mylan and Neupro patch is acceptable from a quality point of view.

A comparison of in-vitro dissolution and in-vitro skin permeation is provided. The applicant mentioned that in-vitro dissolution studies showing a significant difference (e.g. Mylan patch 100% dissolution after 1.5, where the Neupro patch showing 100% dissolution after 2 – 2.5 hours). In-vitro dissolution proportionality for the different strength of the Mylan patch is questionable from a quality point of view. Similarity factors could be acceptable (see clinical assessment) but scatter even if same intermediates of the laminates are used (N.B. different strengths are manufactured by using different patch areas of the laminate). Additionally, possibly important information is missing on the batches of some strengths regarding similarity. A rough estimation of batches that were not included for similarity determination leads to similarity factors below 50 (**MO**). The in-vitro skin permeation study method is not provided and the validity of this study is questionable.

Bioequivalence studies regarding pharmacokinetics (ROTI-15045and ROTI 15074) and adhesion (ROTI 15074) are provided using the same composition as used for the product to be market. Several questions are raised by the assessor if the manufacturing process used for these batches is a commercial process or not. The applicant follows the FDA's Draft Guidance on Rotigotine transdermal patch bioequivalence recommendations for assessment of bioequivalence, as well as for the adhesion study. The use of the FDA draft guidance instead of the use of the EU-guidance is questionable and results in several queries by the CHMP.

In the development section relevant information is missing. This risk assessment is based upon prior knowledge and experience from related processes and information gained during the development of Rotigotine Mylan transdermal patch, generic to Neupro. The risk assessment should also be based on (initial) experimental data. Relevant data should be provided and included in this section. Evaluation of this risk assessment should be possible also for the CHMP. In the view of this risk assessment, the range (design space) of process parameters should be from sufficient relevace and process parameter ranges should be clearly defined based on data. These data, sufficient to use a Qualiy by Design (QbD) approach, should be provided as well. Ratio: The risk assessment of the applicant is based on a defined target interval or Normal Operating Range (NOR), this is not sufficient for the CHMP for this drug product and a design space should be defined as well. (**MO**)

In addition, the intention of the applicant to use continuous process validation and furthermore scale-up is therefore not be given for this complex dosage form manufactured by a non-standard process. Pertinence to follow the European guidance EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev.1, Corr.1 is pointed out here.

The risk of crystal formation as seen in the Neupro patch is sufficiently addressed. The risk is acceptable to be low, based on this information (but not finally be shown by data – see stability). Nevertheless, other factors like residual solvents content could possibly have also an influence on crystal formation. In the risk assessment of the drug substance, the applicant identified the risk of residual solvents in the drug substance to be low on the Drug Product CQAs e.g. Peel Strengths, Adhesion, Tack, Cold Flow and Drug Release. Ratio by the applicant is that the residual solvents are substantially below the ICH Q3C levels. A view in the drug substance specification shows that 7 solvents are mentioned with ICH Q3C limits in total of 27,070 ppm, theoretical of cause (please see also questions to drug substance). The CHMP opinion is that such a high (theoretical) limit could possibly result in an influence of the final drug product in respect to the CQAs mentioned above and in special in in-vivo adhesion and in-vivo release behaviours. Thus the relative risk of residual solvents in the drug substance should be ranked as high and therefore further investigations of the residual solvents impact of the drug product CQAs should be provided or a more rigid limitation should be done.

Finally, the parameter “Microscopy” in the release and shelf-life specifications would be sufficient to control the crystallinity in the drug product, but the limit set is not acceptable. For the Finished Product Specification, it is not acceptable that the microscopy test permits the presence of crystals. The effect of the reservoir system properties on *in vitro* dissolution and permeation was studied. The applicant was asked to provide information on the batch compositions used in these studies and clarify how different reservoir systems with different properties were manufactured. Definite differences in flux rates are shown in the figures. It is not understood by the CHMP, why these differences are discussed to be negligible by the applicant. Clarification should be given on that topic and in addition the analytical method for in-vitro skin permeation study should be provided.

Initial and updated risk assessment is mainly justified by “based on knowledge”. To support this knowledge, the applicant should provide data of former transdermal drug products including relevant information of the drug substance, authorisation data and marketing area (European market, US market, etc.).

The blending process is discussed to be a low risk on CQA (on the final drug product). A justification is based for example on the mixing time. The time for example is not limited in the process. A target is mentioned only (15 min) and a maximum limit is set (not more than 30 min). Data should be provided to define the range, where homogeneity is assured. Furthermore, the applicant mentioned to specify a timed rate of addition of the stabiliser excipient into the induction mixer for future manufacture. Future specifications are not sufficient for the CHMP to justify a low risk.

The coating and drying process is defined as low risk with respect to process variables. The outcome of some aspects is questionable for the CHMP. First of all the applicant justified uniformity and thickness by the weight, which is controlled by the slot die coating system. Differences in weight, between single measurements, are not an accurate and reproducible process in the view of the quality CHMP. Discussion is needed to verify this range. In addition, the parameters for the slot die pump speed and line speed should be provided and included in the dossier. Data for these parameters should be provided as well. The drying process is shown to be independent of the temperature and line speed. It is mentioned here by the CHMP that the drying process independency is only defined in specific temperature range and line speed. With respect to the line speed, the meaning of mpm should be clarified (e.g. measures per minutes, miles per minutes, meters per minute…) and a correction of the dossier in the view of consistent use of metric units could be useful to avoid misunderstandings. With respect to the laminating process intermediate batch results of the laminate are provided. In the risk assessment of the drug manufacturing process, the applicant justified the low risk, for example, by the fact that the removal of solvents during coating is a robust process. Data are missing for this justification and should be provided.

Manufacture of the product and process controls

The bulk and finish product manufacturer is stated.

The applicant provides batch formulas described as “exhibit batches” and “production batches”. In addition the applicant differentiates between intermediate batch size and production batch size, where the intermediate batch size defines the intermediate before die-cutting. The (exhibit) intermediate batch size was stated and the amount of patches, which varies depending on the strengths, has been defined. Higher strengths result in lower patch amounts than lower strengths. For the CHMP it is not clear what the definition of an “exhibit batch” is. The use of commonly used definitions like “lab scale batch”, “pilot scale batch” and “production scale batch” should be used instead to comply with the wording used in the EU guidelines and to avoid misunderstandings.

A brief description of the manufacturing process was provided and details of the process are requested by the assessor. The manufacturing process could be graduated in dispensing and blending, coating, drying and laminating, slitting (slit master laminate) and finally die cutting and packaging (final patch of different strength).

The widths of the coated rolls are mentioned in the flow chart. The length of the master or jumbo rolls should be also provided.

The “Die Cutting and Packaging”-process is irreproducible for the CHMP and should be clearly described. In particular the removal, slitting and re-laminating of the release liner should be described in more detail. As described in the packaging leaflet, the release-liner consists of a break, where the liner is opened to peel off (for removal convenience by the patient). More details should be provided e.g. is the break completely cut, is the break a line or a curve, orientation of the slit. Regarding the slitting or cut, the applicant should satisfyingly describe how the slitting of the release liner is centred in respect to the patch. Used machinery equipment in the view of die cutting and kiss-cut should be mentioned in the dossier.

In addition, in-process parameters (IPCs) are missing or not limited adequately to be quality relevant. A justification of setting the IPC limits is not provided and should be included in the relevant section of the dossier.

For the specification of the intermediate Rotigotine Blend, a justification should be provided that the parameters selected are able to control the quality of the intermediate sufficiently. Secondly, the set

limits should be justified, possibly on batch results. It should be mentioned here that the CHMP did not accept the limit range of the viscosity for the blend.. Furthermore, the assay limit of the blend intermediate is also of non-acceptance.

The preparation of the intermediate Rotigotine blend is a critical process that should ensure that the drug substance is present in a solution. A highly homogenous mix is expected. It should be confirmed by the applicant that the active substance is dissolved during the preparation of intermediate Rotigotine blend. The process and specification should include a check that the active substance is completely dissolved. The specification limits for uniformity should be significantly tightened, in line with batch data. A test for the dispersion of the drug solution in the adhesive mix should be included and a limit/range for certain parameters should be specified, in line with batches for which satisfactory bioequivalence has been demonstrated.

Regarding the process validation the CHMP's perspective is that the manufacturing process of the blend as well as of the laminate is considered complex (non-standard), to produce a complex dosage form (transdermal patch). Therefore process validation data should be provided for this manufacturing process by a minimum of three batches, using the same equipment as for the production scale, before authorisation of the drug product. The size of these three batches would be defined by the jumbo rolls - before slitting. The process validation results of the three batches would be acceptable to fulfil the guidelines in the view of the CHMP. The definition of other batch sizes and/or the use of other equipment (Line 2, (Dispensing), Line 5 (Mixing) and Line P (Coating)) are not acceptable for the CHMP. Please note as well that the used equipment and batch size stick on the bioequivalent studies regarding *in vivo* efficacy and in-vivo adhesion, for this complex dosage form manufactured by a non-standard process (**MO**).

Under the headline "Product Lifecycle Management and Continual Improvement" the applicant mentioned that manufacturing process validation will be done during drug product lifecycle. This approach is justified based on the FDA process validation guidance: U.S. Food and Drug Administration. Guidance for Industry. Process Validation: General Principles and Practices. January 2011. The CHMP addresses here that this guideline is not effective for the European market. Instead the "Guideline on process validation for finished products - information and data to be provided in regulatory submissions – EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev.1, Corr.1" should be used. Based on this guideline, traditional process validation should be used and it is considered necessary to provide production scale validation data in the marketing authorisation dossier at the time of regulatory submission for a complex dosage form produced by a non-standard process. It should be mentioned here as well that continuous process verification, as described in the guideline, is not possible due to a massive gap of information.

Excipients

Both adhesives are no novel excipients in the view of the relevant guidelines. Ratio: Silicone Adhesives, used in various drug products and in special in transdermal patches. Differences between various adhesives are a result of end capping or not (standard and amine-compatible), difference in polarity (silanol content), the solids content, resin/polymer ratio and therefore in viscosity. The characteristics of the final adhesive could be completely different in respect to adhesion and release but the excipients do not vary significant in respect to toxicological aspects.

The section should be updated and should include composition details for the silicone adhesives (e.g. ratio of resin/polymer, absolute amounts of the resin, polymer, methylating agent hexamethyldisilazane, catalyst ammonia and non-volatile content, including the name of the solvents used).

For the backing layer the coat weight is specified. This range is regarded to be too large to produce a transdermal patch of a consistent quality (in respect to *in vivo* behaviours of adhesion and drug release). If not sufficiently shown by data (*in vivo*) the range should be tightened.

Product specification

A specification is provided including more or less all relevant parameters. Tightening of most of the limits is requested, because these limits are not set data driven and the exhaust of such ranges could possibly result in a massive change of in-vivo release and adhesion properties.

Assay release range is not justified. Batch data were provided. In accordance with the relevant regulation for release a tighter limit range should be set. The shelf-life assay range is also not justified. Batch data provided for 6 months showing tighter values if stored at 25°C/65% RH. Under accelerated conditions only one result is below 95.0% (94.7% at time point 6 months).

The limit for “Total impurities” should be set data driven by the maximum value found in the release batches and the maximum value found in the stability batches under long term conditions for 6 months and at accelerated conditions.

The limits set for drug release are not in-line with the relevant guidance in Europe. Normally, the permitted range in mean release at any given time point should not exceed a total numerical difference of ±10% of the labelled content of active substance (i.e. a total variability of 20%: a requirement of 50±10% thus means an acceptable range from 40-60%), unless a wider range is supported by a bioequivalence study. Wider limits may be accepted only if satisfactorily explained and justified on quality reasons and supported by a bioequivalence study.

It is pointed out that the limits should be set based on the release results of the bioequivalence test batch.

The type of excipient used as an antioxidant should be specified. The study shows a reduction of the antioxidant after 3 months and after 6 months. Studies under long term conditions are not provided. Based on these results the CHMP recommended including an assay parameter for this antioxidant in the shelf-life specification.

Cold flow is specified in the specification. The limit seems to be appropriate, but a worst case calculation by the CHMP came to the result that a small increase of the patches, could possibly result in a significantly increased patch area. In accordance to these calculation results by the CHMP, which should be verified by the applicant, the cold flow limit should be set to be strength independent (e.g. use of percentage instead of an absolute value, or to set own limit values for each strength). To avoid misunderstandings regarding this behaviour, an extent of the patch area as calculated above is not acceptable for the CHMP. Such an extent of patch area needs *in vivo* release studies. Tightening of the limit is also mandatory based on the release batch results and stability results. From a quality perspective a split of limits for release and shelf-life seems to be mandatory as well if not otherwise justified. It should be noticed here as well by the CHMP, that the drug product do not tent to cold flow, based on the data provided.

All limits given in the specification are identical with respect to release and shelf-life, except for assay. For some parameters it would be a quality requirement to distinguish between release and shelf-life. The CHMP requests therefore to choose independent limits for release and shelf-life for the following parameters: “Related compounds – Total impurities”, “Peel strength”, “Adhesion”.

The applicant provides for each patch strengths release data. For the smallest (1 mg/24 h) and the highest strength (8 mg/24 h) three batches are provided. Based on information given in other sections

(e.g. 3.2.P.3), the patches are produced from three laminate batches. The release data provided are therefore sufficient for the CHMP.

Stability of the product

Bulk/intermediate stability: The applicant defined the blend to be stable for at least up to 4 days and the laminate is stable for at least up to 17 days in master roll form and at least 31 days in slit roll form. It is not obvious for the CHMP, which conditions (e.g. temperature, equipment and/or packaging material, use of nitrogen, …) are used during the test. The maximum storage time and conditions should be part of the dossier.

The applicant provided stability data (exhibit batch size) under long term conditions (25°C/60%RH) and accelerated conditions (40°C/75%RH) for six months. One batch of each strength is used for stability; for the lowest and highest strength three batches are provided additionally. Three intermediate batches of Rotigotine Laminate 4.50 g/m^2 are the basis of these strengths used in the stability studies. It should be mentioned here by the CHMP that based on the stability studies and in accordance with the relevant guidance a maximum shelf-life of only 12 months is possible right now. The submission of ongoing stability studies is requested. The applicant asked for storage conditions "not more than 30°C". These conditions are not justified by the stability data provided (data at 25°C and at 40°C). In addition, the Ph.Eur. monograph for transdermal patches (01/2008:1011) state "Store at room temperature, unless otherwise indicated." From the CHMP's point of view storage conditions of not more than 25°C should be used. Ratio: At 40°C a slight degradation increase of total impurity) of the drug substance is observed, stability studies under ambient conditions are missing and the Ph.Eur. monograph recommended to store at room temperature. Aside from the fact that only 6 months data are provided and crystallisation could not be excluded during shelf-life.

Comparability exercise for Finished Medicinal Drug Product

Not applicable

Adventitious agents

Not applicable

3.1.4. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the assessment of the quality documentation, the application for Rotigotine Mylan Transdermal patches 1mg/24 h, 2mg/24 h, 3mg/24 h, 4mg/24 h, 6mg/24 h, 8mg/24 h is presently not approvable from a quality point of view. Adequate responses have to be provided to the concerns addressed in the list of questions (**more than 100 OC**), some of which are considered to be major issues (**3 MO**).

3.2. Non clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Rotigotine are well known. As Rotigotine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview is based on up-to-date and adequate scientific literature.

3.2.1. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. In the expert report, the author states that the absence of an environmental risk assessment can be justified for a generic; however the guideline states that an ERA is required for all new MAA regardless of its legal basis. The statement that "*Rotigotine…is aimed at replacing rather than increasing prescriptions of Neupro*" is inadequate justification for the absence of data as, in particular for a first generic; the overall use of the active substance can increase. The guideline states that there are situations where the introduction of a generic can lead to an increase in exposure. The applicant should refer to the Q & A document EMA/CHMP/SWP/44606/2010 Rev 1.

3.2.2. Discussion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of rotigotine are well known. The applicant provided a non-clinical overview that is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The applicant's justification for omission of an environmental risk assessment is currently not agreed on.

3.2.3. Conclusion on non-clinical aspects

There are no objections to approval of Rotigotine Mylan 1 mg/24 h, 2 mg/24 h, 3mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h transdermal patch from a non-clinical point of view. An OC concerning the ERA has been identified.

3.3. Clinical aspects

A clinical overview on human pharmacology, efficacy and safety has been provided by the applicant. Human pharmacology, efficacy and safety of rotigotine are known from the experience with Neupro 1mg/24h, 2mg/24h, 3mg/24h, 4mg/24h, 6mg/24h, 8mg/24h transdermal patches. The clinical overview is based on up-to-date and adequate scientific literature. Overall, the clinical overview is deemed acceptable.

The clinical aspects of the generic product's SmPC are in accordance with the SmPC of the reference product.

Exemption

A) Biowaiver for additional strengths

UCB Pharma Limited's Neupro Transdermal patches are available as Neupro 1mg/24h, 2mg/24h, 3 mg/24h, 4mg/24h, 6mg/24h and 8mg/24h Transdermal patch. Mylan intends to market the generic versions of Neupro (rotigotine) Transdermal patches for strengths of 1mg/24h, 2mg/24h, 3mg/24h, 4mg/24h, 6mg/24h and 8mg/24h.

According to the current Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr 1) for TDDS, a bioequivalence study investigating only one strength may be acceptable provided that:

- the qualitative composition is the same for all strengths;
- the strengths are proportional to the effective surface area of the patch and the lower dose strengths can be considered as ''partial'' areas of the highest dose strength;

- dissolution/release profiles are similar.

The bioequivalence study should be performed with the highest/most sensitive strength. In case of safety/tolerability limitations at the highest strength, the use of a lower strength is acceptable for size proportional formulations.

- **Qualitative and Quantitative Composition of the Test Product**

The data submitted by the Applicant showed that the qualitative composition is the same for all strengths, both for the active substance and the inactive ingredients. Therefore, prerequisite “same qualitative composition of the different strengths” fulfilled.

- **Proportionality of the different dosage strengths**

According to the table directly above, Mylan´s rotigotine transdermal patches are proportional in formulation, i.e. composition is the same and the strength is proportional to the effective surface area of the patch. →Prerequisite “strengths proportionality” fulfilled.

- **In-vitro Dissolution Data for Biowaiver Request for Different Strengths**

Dissolution studies were performed in 3 different pH media (1.2, 4.5, and 6.8) in order to confirm the adequacy of waiving additional in vivo bioequivalence testing referring to the 6 different strengths of Rotigotine Mylan.

In addition, dissolution studies in the medium intended for drug product release (QC Medium: Phosphate Buffer, pH 4.5) were also performed. Phosphate Buffer pH=4.5 was chosen as QC dissolution medium as the pH of it is the closest to the pH of the skin where absorption occurs. The surface of healthy skin can be characterised by acidic pH, oscillating between 4.0 and 6.0 (Boer, M et al., 2016).

f2 values > 50 have been provided for the QC Medium (Phosphate Buffer, pH 4.5), suggesting that the dissolution profiles are similar.

However, a rough estimation of f2 values for the batches R616006, R616009, R616004 and R616010 by the quality assessor results in f2 factors lower than 50. A comparison with the dissolution profiles of the above mentioned batches to the 2 mg/24 h strength (R616001) should thus be provided and similarity factors should be calculated .

No f2 value calculation was submitted for the other dissolution media. According to the current guideline on the investigation of bioequivalence, dissolution profiles may be accepted as similar without further mathematical evaluation, where more than 85% of the drug is dissolved within 15 minutes. This does not apply to Rotigotine Mylan Transdermal patch and the applicant is requested to provide f2 values for the additional media, although a pH of 4.5 appears to be most relevant pH in the case of transdermal systems.

For the sake of completeness, graphical diagrams of the comparison of the different strengths should be provided.

The temperature used for the dissolution studies (32°C) is in accordance with recommendations made in the Ph.Eur. section 2.9.4. “Dissolution test for transdermal patches” and thus accepted.

Prerequisite “similar dissolution profiles” is currently **not** fulfilled.

- **Justification for use of lower strength**

Dopamine agonists can affect the regulation of blood pressure resulting in orthostatic hypotension, particularly during dose escalation. Syncope has also been reported in patients using dopamine agonists. Rotigotine may also cause general somnolence and falling asleep during daily activities.

According to the Summary of Product Characteristics, 2016 of the originator Neupro® dosing should be started at a low dose and up-titrated based on clinical effect and adverse events.

The applicants justification for not using the largest patch size for transdermal bioequivalence studies due to safety reasons is acceptable according to the EMA Guidance, "Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr 1)".

Furthermore, Rotigotine exhibits over the therapeutic dose range linear pharmacokinetics.

- **General waiver criteria** according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98)

Linearity

Rotigotine exhibits over the therapeutic dose range linear pharmacokinetics. →Prerequisite "linearity in pharmacokinetics" fulfilled.

Same manufacturer and manufacturing process

The applicant assured that the pharmaceutical products are manufactured by the same manufacturing process. → Prerequisite "sahuman plasmae manufacturing process" fulfilled.

B) Comparative Dissolution Studies

Dissolution profiles have been generated for the European reference product and the generic product. Rotigotine Mylan Transdermal Patch showed dissimilar dissolution results (f2 < 50) from the EU reference product in all three dissolution media (pH 1.2, pH 4.5, pH 6.8). The applicant argues conclusively that this is caused by the use of different silicone adhesive for their product compared to the reference product.

The "Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (section 4.2.1) specifies that in case the results of comparative in vitro dissolution of the biobatches do not reflect bioequivalence as demonstrated in vivo, the latter prevails. Therefore, no issue is raised on the comparative dissolution results

- ***Tabular overview of clinical studies***

TYPE OF STUDY	STUDY IDENTIFIER	LOCATION OF STUDY REPORT	OBJECTIVE(S) OF THE STUDY	STUDY DESIGN AND TYPE OF CONTROL	TEST PRODUCT (S); DOSAGE REGIMEN; ROUTE OF ADMINISTRATION	NUMBER OF SUBJECTS	HEALTHY SUBJECTS OR DIAGNOSIS OF PATIENTS	DURATION OF TREATMENT	STUDY STATUS; TYPE OF REPORT
BE Adhesion	ROTI-15074	5.3.1.2	Compare Mylan formulation and RLD	Fasting Crossover	Test: Rotigotine Transdermal System Ref: Neupro® Transdermal System 2 mg/24 hours Single Dose Transdermal	72	Healthy Subjects	Single Dose	Complete, Full
BE	ROTI-15035	5.3.1.2	Compare Mylan formulation and RLD	Crossover	Test: Rotigotine Transdermal System Ref: Neupro® Transdermal System 2 mg/24 hours; 3 consecutive applications Transdermal	39	Healthy Subjects	Multiple Dose: 3 applications	Complete, Full
Cumulative Irritation and Sensitization	ROTI-12128	5.3.1.2	Compare Mylan formulation and RLD	Subject wore each treatment	Test: Rotigotine Transdermal System Ref: Neupro® Transdermal System 2 mg/24 hours; 21 same site applications – induction; 1 application - challenge Transdermal	240	Healthy Subjects	Multiple Dose: 21 applications – induction; 1 application - challenge	Complete, Full

3.3.1. Pharmacokinetics

To support the application, the applicant has submitted a single dose bioequivalence study, a multiple dose (steady-state) bioequivalence study and also a dermal adhesion study on the strength, 2 mg/24 hours.

Study Number: ROTI-15074

Title: Single-Dose Bioequivalence and Adhesion Study of Rotigotine Transdermal System (2 mg/24 hours; Mylan), Neupro® Transdermal System (2 mg/24 hours; UCB) and Neupro® Transdermal Patch (2 mg/24 hours; UCB UK) in Healthy Adult Volunteers.

Methods

Study design

This study was an irritation evaluator-blinded, single-dose, randomized, three-period, three-treatment crossover study to investigate the bioequivalence and adhesion of Mylan's rotigotine transdermal systems, 2 mg/24 hours to UCB's Neupro® Transdermal System, 2 mg/24 hours and UCB UK's Neupro® Transdermal Patch, 2 mg/24 hours in seventy-two (72) healthy, adult subjects under fasting conditions

Treatment A (Test) = Rotigotine Transdermal System, 2 mg/24 hours (Mylan)
Treatment B
Treatment C (EU-Reference) = Neupro® Transdermal Patch 2 mg/24 hours (UCB UK)

The clinical part of the study took place from 23-Apr-2016 till 26-May-2016: Group 1 subjects checked into the clinical facility on 22-Apr-2016 for Period 1, on 29-Apr-2016 for Period 2 and on 06-May-2016 for Period 3. Group 2 subjects checked into the clinical facility on 09-May-2016 for Period 1, on 16-May-2016 for Period 2 and on 23-May-2016 for Period 3.

Subjects arrived at the clinical site at least 15 hours prior to patch application for each study period. Subjects received dinner the evening prior to dosing. Following an overnight fast of least 10 hours each of the enrolled 72 subject received one of the three rotigotine transdermal system treatments (treatment A, B or C) applied to a clean, dry area of the skin on the right or left side of the abdomen according to the randomization scheme. The randomization scheme utilized a three-treatment, three-period crossover design and was generated prior to the first dosing period.

Upon removing the patch from the protective liner, any residual adhesive on the liner was evaluated. Once the patch was applied, it was held in place with the palm of the hand for 30 seconds. Each patch application site was documented and diagrammed for each subject.

Each transdermal system was worn for 24 hours on the abdomen. Following an 6-day washout period between the last patch removal in Period 1 and the first patch application in Period 2, and a 6-day washout period between the last patch removal in Period 2 and the first patch application in Period 3, subjects returned to the clinical facility to be dosed with the alternative treatment as per the randomization.

On the day of dosing, subjects received a standard meal approximately 4 hours post-dose followed by an evening meal approximately 10 hours after dosing. Subjects consumed 240 mL of ambient temperature water beginning at 1.25 hours before dosing and 1 hour after dosing. Water was not permitted for 1 hour before and until 1 hour after dosing, but was allowed at all other times.

Serial *blood samples* (1 x 6 mL) were collected in K2 EDTA tubes at pre-dose (within 120 minutes prior to dosing), 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 36 and 48 hours post-dose.

Subjects were allowed to leave the clinical site after the 36 hour post dose blood draw and were asked to return to the clinical site before the remaining blood sample.

The blood sampling points are acceptable, albeit more frequent sampling around predicted tmax (~15-18 hours after patch application) would have been advisable.

The sampling period of 48 hours is sufficient to characterize the plasma concentration-time profile; AUC (0-t) covers at least 80% of AUC (0-∞).

The washout period of 6 days (144 hours) is regarded as long enough, since it covers more than the requested at least 5 elimination half-lives ($t^1_{/2}$=5-7 hours after removal of the patch according to Originator´s SmPC).

The products (test and reference) were administered to 72 subjects, divided into two groups: 62 subjects were dosed in the first group, 10 subjects in the second group. According to the applicant two groups were necessary to enrol the required number of subjects. The study was not designed as a two stage design and Mylan confirmed that no interim analysis was performed. This confirmation is supported by the fact that patients randomized to group Nr. 2 have already completed period 1 before the analytical part of the study has started (end of period 1, group 2: 12-May-2016, start of analytical phase: 17-May-2016). The option of “multiple cohorts” was predefined in the protocol and the statistical analysis was done only on the combined data, therefore the two groups are accepted and the statistical analysis does not require an adjustment for multiplicity of testing.

The study was conducted under fasting conditions. This is acceptable as it is considered to be the most sensitive condition to detect a potential difference between formulations. As rotigotine is administered transdermally food does not affect absorption and the patch may be applied regardless of meals.

According to the EMA guidance, the bioequivalence study should be conducted at the highest/most sensitive strength in case the marketing authorisation of multiple strengths is required. Dopamine agonists can affect the regulation of blood pressure resulting in orthostatic hypotension, particularly during dose escalation. According to the SmPC of the reference medicinal product a single daily dose should be initiated at 2 mg/24 h rotigotine for the treatment of Parkinson´s disease and then increased weekly. The selected strenght is adequately justified and dose selection is accepted.

Adhesion properties were assessed at 4, 8, 12, 16, 20 and 24 hours after patch application by trained clinical staff utilizing a 100% scale, with 100% being completely adhered and 0% being completely detached.

In general, it is accepted that the skin adhesion investigation for Mylan’s rotigotine transdermal system was an integrated part of the single dose PK study, as this is in line with the applicable EMA guideline EMA/CPMP/EWP/280/96 Corr1. However, according to the EMA guidance, adhesion studies should be performed "in the intended population." Neupro is indicated for the treatment of idiopathic Parkinson's disease and for the treatment of Restless Legs Syndrome. While Restless Legs Syndrome may begin at any age, Parkinson's disease typically occurs in people over the age of 60. Thus, in order to ensure comparable adhesion properties between test and reference product in the elderly population, the applicant needs to provide additional adhesion data in elderly subjects, unless otherwise justified.

The clinical staff for adhesion assessment was not blinded. Blinding of the personnel for adhesion assessment is recommended whenever possible. However, in this case blinding was not possible, since the appearance of test and reference patch revealed the identity of the products. The use of an overlay or a cover is not justified for the purpose of blinding because an overlay may affect the product’s

performance. Therefore it is considered acceptable that the clinical staff for adhesion assessment was not blinded.

Legibility of the printing on the back of the patch was examined every at the time of patch application and every 4 hours after patch application.

At patch removal, application sites were examined for any ***residual adhesive on the skin*** site. After patch removal, patches and alcohol wipes were heat-sealed and sent to Mylan Technologies Inc. for residual drug analysis.

Acute dermal irritation was assessed 30 to 45 minutes following patch removal by trained clinical staff blinded to the randomization scheme.

Test and reference products

Detailed information of test and reference product was provided as requested in the D80 Clinical AR Guidance document. The test product is furthermore identical to the proposed commercial formulation.

Population(s) studied

A total of **72 subjects** were **included** and dosed in this study. Study population consisted of non-tobacco using, male (55) and non-pregnant, non-lactating female (17) volunteers, between the ages of 19 and 62, with a BMI from 19 to 30 kg/m^2 who were judged healthy based on a medical history, ECG, laboratory evaluation, physical examination and vital signs measurements. 56 were White, 11 Black, 1 Asian, 1 American Indian or Alaska Native, 3 Other.

Subjects 15 (treatment sequence: CBA) and 59 (ACB) withdrew consent during Period 1 due to an adverse event. Subject 55 (BAC) withdrew consent during Period 1 due to personal reasons. Subjects 10 (CBA) and 67 (ABC) withdrew consent due to personal reasons prior to Period 2 dosing. Subject 40 (BCA) withdrew consent due to an adverse event prior to Period 2 dosing. Subject 61 (ABC) did not report to clinic for Period 2. Subject 29 (CAB) withdrew consent due to personal reasons prior to Period 3 dosing. Subject 30 (ABC) was discontinued due to positive urine drug screen at Period 3 check-in. Subject 19 (CAB) withdrew consent due to personal reasons during Period 3.

Therefore, **sixty-two (62) subjects completed the study**.

Pharmacokinetic Population

The plasma samples for Subjects 15 (CBA), 40 (BCA) and 59 (ACB) were assayed per EMEA guidance but are not included in the pharmacokinetic analysis.

According to the study protocol subjects must have completed at least two periods of the study (with one being test product) and have had an adhesion score $\geq$ 80% at the end of the wear period to be included in the pharmacokinetic analysis. The evaluation of a possible effect on PK results, when including the subjects in PK analysis with a greater than 20% lift of patch, is however regarded to be relevant in order to demonstrate comparable in vivo performance, i.e. similarity in terms of efficacy. The provision of AUC results including the values of the above mentioned subjects is thus requested.

Based on the criteria mentioned above, Subjects 10, 15, 19, 20, 22, 23, 26, 27, 29, 40, 50, 55, 59, 61, 67 are excluded and, therefore there are **fifty-seven (57) subjects included in the primary US analysis**. Subjects 10, 15, 20, 22, 23, 26, 30, 34, 35, 40, 50, 55, 59, 61, 67 are excluded and, therefore, **fifty-seven (57) subjects included in the EU pharmacokinetics analysis.**

Subjects excluded from US pharmacokinetic analysis

Subject Number	Time of Discontinuation	Reason for Discontinuation
10	Period 1	Subject withdrew consent due to personal reasons prior to Period 2 dosing.
15	Period 1	Subject withdrew consent to an adverse event (headache) during Period 1.
19	Period 3	Subject withdrew consent due to personal reasons during Period 3.
20	Period 3	Subject had adhesion score < 80% at end of wear period
22	Period 1/3	Subject had adhesion score < 80% at end of wear period
23	Period 1/3	Subject had adhesion score < 80% at end of wear period
26	Period 3	Subject had adhesion score < 80% at end of wear period
27	Period 3	Subject had adhesion score < 80% at end of wear period
29	Period 2	Subject withdrew consent due to personal reasons prior to Period 2 dosing.
40	Period 1	Subject withdrew consent to an adverse event (influenza) prior to Period 2 dosing.
55	Period 1	Subject withdrew consent due to personal reasons during Period 1.
59	Period 1	Subject withdrew consent to an adverse event (lightheadedness) during Period 1.
61	Period 1	Subject did not report to clinic for Period 2 dosing.
67	Period 1	Subject withdrew consent due to personal reasons prior to Period 2 dosing.

Subjects excluded from EU pharmacokinetic analysis

Subject Number	Time of Discontinuation	Reason for Discontinuation
10	Period 1	Subject withdrew consent due to personal reasons prior to Period 2 dosing.
15	Period 1	Subject withdrew consent to an adverse event (headache) during Period 1.
20	Period 3	Subject had adhesion score < 80% at end of wear period
22	Period 1/3	Subject had adhesion score < 80% at end of wear period
23	Period 1/3	Subject had adhesion score < 80% at end of wear period
26	Period 3	Subject had adhesion score < 80% at end of wear period
30	Period 2	Subject was discontinued due to a positive urine drug screen at Period 3 check-in
34	Period 3	Subject had adhesion score < 80% at end of wear period
35	Period 1	Subject had adhesion score < 80% at end of wear period
40	Period 1	Subject withdrew consent to an adverse event (influenza) prior to Period 2 dosing.
50	Period 2	Subject had adhesion score < 80% at end of wear period
55	Period 1	Subject withdrew consent due to personal reasons during Period 1.
59	Period 1	Subject withdrew consent to an adverse event (lightheadedness) during Period 1.
61	Period 1	Subject did not report to clinic for Period 2 dosing.
67	Period 1	Subject withdrew consent due to personal reasons prior to Period 2 dosing.

According to the above tables, Subject Nr. 29 (male, white, age: 22 years) with the assigned treatment sequence “CAB” withdrew his consent due to personal reasons prior to period 2 dosing and thus was excluded from US PK analysis, but not from EU PK analysis. As plasma concentration data

following treatment C and A are available for patient 29 (study report section 16.2.6.5.1), this is considered an inconsistency in reporting and the applicant is asked to provide adjusted tables.

Adhesion Analysis

64 subjects were included in the EU Adhesion Analysis.

Safety Population

The safety population includes all **seventy-two (72) subjects** who received at least one dose of study medication during the study.

Analytical methods

Study description ROTI-15074: Single-Dose Bioequivalence and Adhesion Study of Rotigotine Transdermal System (2 mg/24 hours; Mylan), Neupro® Transdermal System (2 mg/24 hours; UCB) and Neupro® Transdermal Patch (2 mg/24 hours; UCB UK) in Healthy Adult Volunteers

Number of subjects: Seventy-two (72) volunteers were enrolled in the study. Subjects 15 and 59 withdrew consent during Period 1 due to an adverse event. Subject 55 withdrew consent during Period 1 due to personal reasons. Subjects 10 and 67 withdrew consent prior due to personal reasons prior to Period 2 dosing. Subject 40 withdrew consent prior due to an adverse event prior to Period 2 dosing. Subject 61 did not report to clinic for Period 2. Subject 29 withdrew consent prior due to personal reasons prior to Period 3 dosing. Subject 30 was discontinued due to a positive urine drug screen at Period 3 check-in. Subject 19 withdrew consent prior due to personal reasons during Period 3. Therefore, sixty-two (62) subjects completed the study. The plasma samples for Subjects 15, 40 and 59 were assayed per EMEA Guidance but are not included in the pharmacokinetic analysis.

Subjects must have completed at least two periods of the study (with one being test product) and have had an adhesion score ≥ 80% at the end of the wear period to be included in the pharmacokinetic analysis. Based on these criteria, subjects 10, 15, 19, 20, 22, 23, 26, 27, 29, 40, 50, 55, 59, 61, 67 are excluded and, therefore there are fifty-seven (57) subjects included in the primary US analysis. Subjects 10, 15, 20, 22, 23, 26, 30, 34, 35, 40, 50, 55, 59, 61, 67 are excluded and, therefore, fifty-seven (57) subjects included in the EU pharmacokinetics analysis. As a secondary US analysis, all subjects regardless of adhesion will be included in bioequivalence analysis for US submission. Subjects 10, 15, 19, 29, 40, 55, 59, 61, 67 are excluded and, therefore, there are sixty-three (63) subjects included in the secondary US pharmacokinetic analysis.

Sponsor of the study: Mylan Pharmaceuticals Inc.

Clinical center: West Virginia University Hospitals Inc., Clinical Laboratories

1 Medical Center Drive

Morgantown, WV 26506, USA

Bioanalytical center: Mylan Pharmaceuticals Inc.

Bioanalytical Department

3711 Collins Ferry Rd.

Morgantown, WV 26505, USA

The analytical part of the study lasted from 17.05.2016 till 23.06.2016; study samples were obtained stored at a nominal temperature of -70ºC and -15°C.

3676 samples from 65 subjects (19 time-points per subject, 3 periods) were analysed, the theoretical amount of samples is 3705.

Analytical Methods

The analyte was Rotigotine. A liquid chromatography a with tandem mass spectrometry detector was used.

Quantitation is determined by peak area ratio method.

Validation of the analytical methods

Comments on study ROTI-15074

Sample reassays for Rotigotine were done on 33 samples (0.9 %). All reassays are in accordance with the presented SOP and the relevant guideline.

Incurred sample reanalysis (ISR) of Rotigotine has been performed on 333 samples for each subject and study period (~ 10% of total samples analysed); 330 out of 330 evaluable ISR samples (100 %) were within 20% from the mean value.

Representative chromatograms (subjects 1-9, 11-14 and 16, >20 %) were provided.

The analytical method for the determination of Rotigotine in human plasma as well as respective validations (including partial validations) are described adequately; the validation(s) were performed according to the requirements of the Guidance for Industry. Bioanalytical Method Validation (U.S. Food and Drug Administration, May 2001), but no reference was made to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009). Consequently the acceptance criteria are mainly in a plausible range and were fulfilled, but full compliance to the EMA guideline is probably not given. The applicant should confirm full compliance to the EMA guideline of the BE-study ROTI-15074.

No data regarding a potential carry-over of the analyte could be found in the method validation. Adequate data should be provided.

Pharmacokinetic variables

Single-dose pharmacokinetic parameters for rotigotine were calculated using non-compartmental techniques. The maximum concentration (CPEAK) and the time at which it occurred relative to the administered dose (TPEAK) were determined from the observed plasma concentration-time profile over the sampling time interval. The elimination rate constant (KEL) was determined by linear regression of the terminal linear phase of the log plasma concentration-time profile. Area under the plasma concentration-time curve (AUCL) was the sum of the linear trapezoidal estimation of the areas from the time of dosing to the time of the last quantifiable concentration.

Area under the plasma concentration-time curve from zero to infinity (AUCINF) was calculated as: AUCINF = AUCL + LQC/KEL where LQC is the last quantifiable concentration. The elimination half-life (HALFLIFE) was calculated as HALFLIFE = 0.693/KEL.

The **primary pharmacokinetic variables** for assessment of bioequivalence are **CPEAK**, **AUCL**, and **AUCINF** for rotigotine. The pharmacokinetic variables are considered adequate.

Statistical methods

Determination of Sample Size

Assuming a true ratio between 92%-108% and an intrasubject variability of 23%, a minimum of thirty-five (35) subjects were required to conclude bioequivalence with approximately 80% power. In order to determine differences in adhesion between the test formulation and the reference formulations, seventy-two (72) subjects were randomized and dosed in order to complete a minimum of sixty (60) subjects for the adhesion analysis.

Statistical Analysis - Pharmacokinetics

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tested for treatment effects in the parameter means at an alpha level of 0.05. The parameters: TPEAK, KEL and HALFLIFE were analyzed statistically using the non-transformed data. The natural log transformed parameters: LNAUCL, LNAUCINF and LNCPEAK were also analyzed. The tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed using the two one-sided tests procedure.

Statistical Analysis – Adhesion for EU Submission

The source data for the analysis of patch adhesion is the patch adhesion score recorded following visual evaluation of the test patch. A one-sided hypothesis test was used to determine if the adhesion scores of Mylan's rotigotine transdermal patches were equivalent to or better than UCB UK's Neupro® transdermal systems (for the reference product). However, the available data are indicating non-inferiority but not superiority. The applicant is asked to comment.

For the adhesion score at the end of the wear period, the null and alternative hypotheses are:

$$H_0: \mu_1-\mu_2 < -10$$

$$H_1: \mu_1-\mu_2 \geq -10$$

where μ_1 is the mean adhesion score for the test product and μ_2 is the mean adhesion score for the reference product. The null hypothesis H_0 was rejected when the lower limit of the 90% confidence interval is ≥ -10.

Statistical Analysis – Acute Dermal Irritation for EU Submission

The source data for the analysis of acute dermal irritation is the irritation score recorded following visual evaluation of the patch sites. Transdermal system irritation scores (=dermal scores only and the sum of the dermal response and other effects Scores) are presented in a frequency table by treatment. No formal statistical analyses were performed for the acute dermal irritation scores.

Statistical Analysis – Print Legibility

No formal statistics was performed. A frequency table indicating the legibility of each patch (yes/no) is presented.

Statistical Analysis – Residue

No formal statistics was performed. A table indicating the amount of adhesive residue found on the protective liner and the skin application site is presented

Sample size calculation considered not only the pharmacokinetic endpoints but also the hypothesis of adequate adhesion.

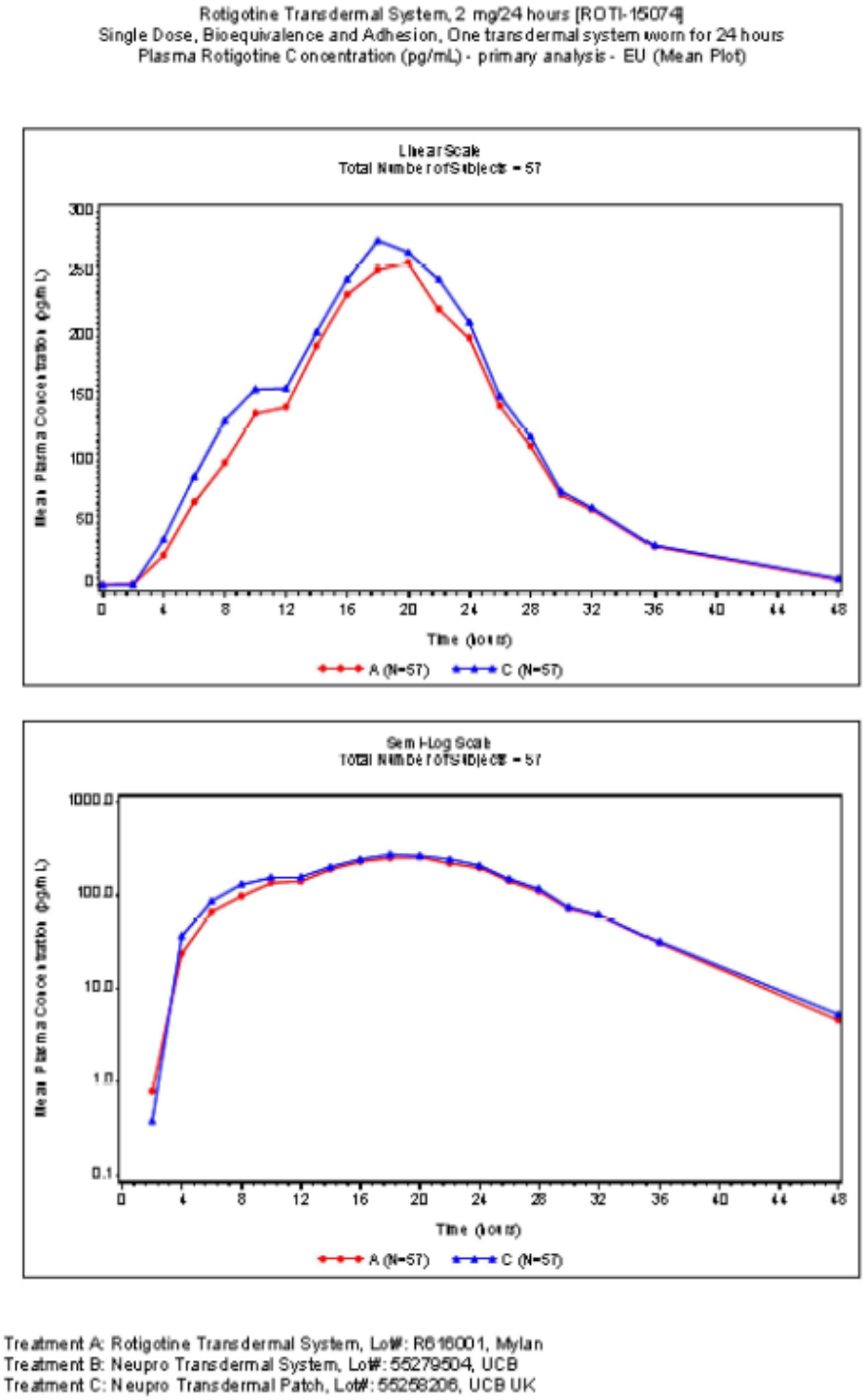
Results

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	arithmetic mean	CV%
$AUC_{(0-t)}$ (pg•hr/mL)	4658	58.41	5107	53.66
$AUC_{(0-\infty)}$ (pg•hr/mL)	4837	57.22	5291	52.56
C_{max} (ng/mL)	285.5	50.92	310.9	53.45
T_{max}* (hr)	18.49	14.64	19.37	13.11
KEL (hr^{-1})	0.1419	24.13	0.1393	27.66
HALFLIFE (hr)	5.197	26.46	5.425	32.89

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)
KEL	apparent elimination rate constant

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	0.91	85.42% – 96.39%	
C_{max}	0.93	85.68% – 100.04%	
$AUC_{(0-\infty)}$	0.91	85.90% – 96.02%	

* estimated from the Residual Mean Squares



Treatment A: Rotigotine Transdermal System, Lot#: R616001, Mylan
Treatment B: Neupro Transdermal System, Lot#: 55279504, UCB
Treatment C: Neupro Transdermal Patch, Lot#: 55258206, UCB UK

Figure 1: Mean Graphical Presentation of rotigotine Plasma Consentrations – EU

The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are within the bioequivalence acceptance range of 0.80-1.25.

The results of the pharmacokinetic and statistical analysis including 57 subjects indicate that the reference and test product are bioequivalent. However, 7 subjects have been excluded from PK analysis due to a greater than 20% lift of patch. The estimation of the effect on the final results is of interest. AUC results including the values of these subjects should thus be provided.

Adhesion Results

Patch adhesion was assessed as the percentage of the area that remained adhered at 4, 8, 12, 16, 20 and 24 hours (± 10 minutes) after patch application.

The patch adhesion assessment results indicate that Mylan`s Transdermal patch is not-inferior to the corresponding innovator Neupro®.

The methodology used for adhesion assessment is not exactly described in the protocol. The applicant is asked to provide a detailed description of the technique used for adhesion evaluation. Furthermore a possible effect on adhesion due to physical manipulation during adhesion assessment should be discussed (e.g. unintentional pressing of the patch,…).

On the graphical representation of the results (see graph below) it is noticeable that the adhesion score and especially the proportion of subjects achieving greater than 90% adherence continuously declines over time but rises again after 20 hours. As result the adhesion after 24 hours is higher than after 20 hours.

The applicant is requested to provide an explanation for the increased adhesion score of the patches with increasing exposure (the time frame between 20-24 hours). The results should be seen also in the context that adhesion assessment of the study was not blinded.

In vivo skin adhesion has been investigated only in healthy young adults, no results in elderly have been provided. Per EMA Guidance, "*Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms*" (EMA/CPMP/EWP/280/96 Corr 1), adhesion studies should be performed "in the intended population", which implies that different studies may be necessary for the adhesion and the pharmacokinetic studies. Neupro is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease and for the treatment of moderate to severe primary Restless Legs Syndrome. While Restless Legs Syndrome may begin at any age, Parkinson's disease typically occurs in people over the age of 60. Age related skin structural changes such as e.g. wrinkles could have a negative effect on the adhesion properties of the patch. Lack of adhesion is a critical efficacy and safety issue, a possible accidental transfer of a patch to the skin of a non- patch wearer has to be prevented in all circumstances. On the other hand, an adhesive which is too sticky can tear or irritate elderly subjects' fragile skin. Therefore, demonstrating acceptable adhesion characteristics in individuals with similar skin conditions as the expected patients (elderly people) is considered essential in order to minimize adhesion related risks.

Adhesion Results – EU Submission (n=64):

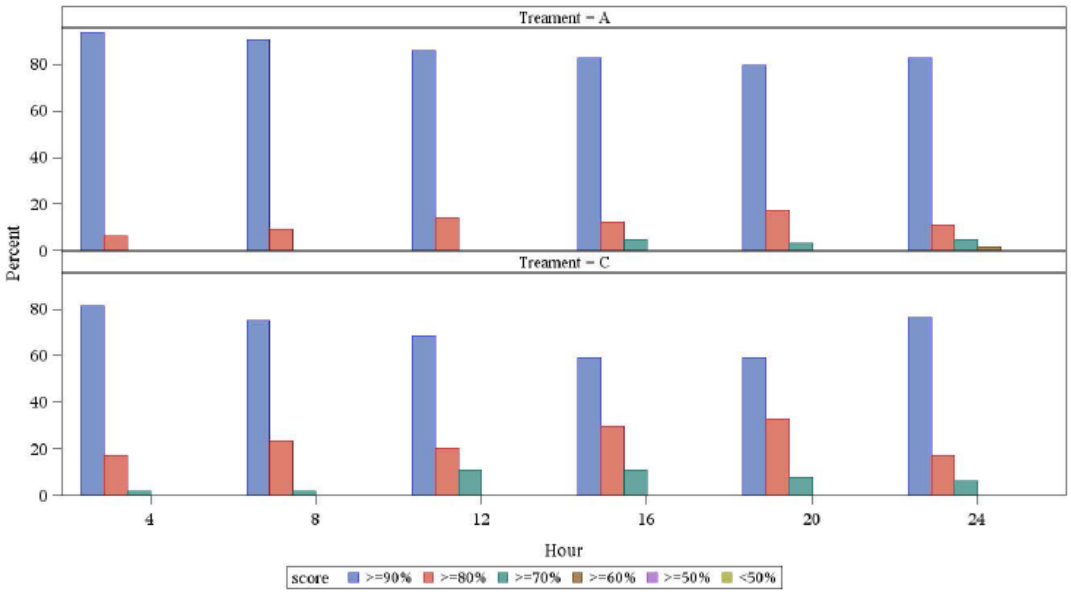
Time (hr)	A = Mylan Mean (%CV)^	C = Neupro® UK Mean (%CV)^
4	97.20 (4.39)	94.92 (6.31)
8	96.30 (4.79)	93.77 (7.03)
12	94.27 (5.45)	91.09 (8.14)
16	93.66 (6.65)	89.84 (8.67)
20	93.00 (6.59)	89.70 (8.14)
24	93.56 (7.11)	92.92 (8.25)
Cumulative	94.66 (4.96)	92.04 (6.93)

^ Scores based on 100% scale, with 100% being completely adhered and 0% being completely detached

Least-Squares Mean			
Treatment A Mylan	Treatment C Neupro® UK	$\mu_1-\mu_2$[1]	90% Confidence Interval[2]
93.08	92.55	0.5344	-1.453 – 2.522

[1] Estimated as Mylan least-squares mean – Neupro® UK least-squares mean.
[2] Lower limit of the 90% confidence interval ≥ -10 indicates Mylan is non-inferior to Neupro® UK.

	4 hr		8 hr		12 hr		16 hr		20 hr		24 hr	
Adherenc	Treat A	Treat C	Treat A	Treat C	Treat A	Treat C	Treat A	Treat C	Treat A	Treat C	Treat A	Treat C
>=90%	60 93.8%	52 81.3%	58 90.6%	48 75.0%	55 85.9%	44 68.8%	53 82.8%	38 59.4%	51 79.7%	38 59.4%	53 82.8%	49 76.6%
>=80%	4 6.25%	11 17.2%	6 9.38%	15 23.4%	9 14.1%	13 20.3%	8 12.5%	19 29.7%	11 17.2%	21 32.8%	7 10.9%	11 17.2%
>=70%	0 0%	1 1.56%	0 0%	1 1.56%	0 0%	7 10.9%	3 4.69%	7 10.9%	2 3.13%	5 7.81%	3 4.69%	4 6.25%
>=60%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	1 1.56%	0 0%
>=50%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
<50%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%



Treatment A: Rotigotine Transdermal System, Lot#: R616001, Mylan
Treatment B: Neupro Transdermal System, Lot#: 55279504, UCB
Treatment C: Neupro Transdermal Patch, Lot#: 55258206, UCB UK

Acute Irritation Results

The scoring system reflected in the EMA Guidance, "Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr 1)" has been applied. After thirty minutes, the mean (± SD) irritation score (dermal response score only) was 1.55 ± 1.02 and 1.56 ± 0.774 for Mylan's rotigotine transdermal system, 2 mg/24 hours and UCB UK's Neupro® Patch, 2 mg/24 hours, respectively, the mean (± SD) irritation score (dermal response score + other effects score) was 1.81 ± 1.21 and 1.75 ± 0.797 for Mylan's rotigotine transdermal system, 2 mg/24 hours and UCB UK's Neupro® Patch, 2 mg/24 hours, respectively.

According to the above mentioned EMA Guidance, a dermal response score of 3-7 or any dermal score combined with other effects rating of 4 or greater is defined as a "strong" reaction. Among Mylan treatment 7 out of 64 subjects developed strong reactions, compared to 4 out of 64 subjects among subjects receiving Neupro® Patch. In the Mylan treatment group, one patient experienced even a grade 7 irritation score. The applicant is requested to adequately discuss these findings.

Table 1: Acute Irritation Frequency Table – EU Submission

Summary of the Overall Acute Irritation Scores Observed Thirty Minutes Following Transdermal System Removal							
Treatment	Acute Irritation Score*						Total
	0	1	2	3	4	6	
Mylan	9	21	27	6	0	1	64
Neupro® UK	5	23	32	3	1	0	64
Total	14	44	59	9	1	1	128

*Scores represent the Dermal Response.

Summary of the Overall Acute Irritation Scores Observed Thirty Minutes Following Transdermal System Removal								
Treatment	Acute Irritation Score*							Total
	0	1	2	3	4	5	7	
Mylan	9	12	32	8	1	1	1	64
Neupro® UK	4	17	35	7	1	0	0	64
Total	13	29	67	15	2	1	1	128

*Scores represent the sum of the Dermal Response score and the Other Effects score

SKIN IRRITATION EVALUATION SCORING SYSTEM

Dermal Response

Scale	Irritation
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test (i.e., application) site

Other Effects

Scale	Appearance
1	Slightly glazed appearance
2	Marked glazed appearance
3	Glazing with peeling and cracking
4	Glazing with fissures
	Film of dried serous exudates covering all or part of the patch site
	Small petechial erosions and/or scabs

Print Legibility Results

Print legibility of the Mylan rotigotine transdermal system was similar to the innovator products.

Table 2: Print Legibility Table

Print Legibility During 24 Hour Wear Period						
Time (hr)	A = Mylan		B = Neupro® US		C = Neupro® UK	
	Yes	No	Yes	No	Yes	No
0	68	0	66	0	66	0
4	68	0	66	0	66	0
8	68	0	66	0	66	0
12	67	0	65	0	65	0
16	67	0	63	1	65	0
20	66	1	63	0	65	0
24	66	1	63	0	65	0

Residue Results

Adhesive residue left on release liner at application or on skin site after patch removal ranged from none to a partial ring.

Protocol Deviations

The reported Protocol Deviations comprised: Blood sample collection time, meal deviations, water consumption, vital signs measurement, time of adhesion assessment, irritation assessment, time of patch removal, print legibility assessment and weight measurement.

The blood sample collection time point deviations should not have any impact on the outcome of the study as the actual blood sample collection times were utilized for pharmacokinetic analysis if the collection times were outside the protocol-defined window.

The protocol deviations reported for the subjects included in the analysis are judged to have no significant impact on the bioequivalence assessment or subject's safety.

Safety data

Adverse events

Seventy (70) subjects experienced a total of eight (8) pre-dose and three hundred thirty-three (333) post-dose adverse events (AEs) over the course of the study. The AEs were mild in severity. No SAEs were reported.

There were sixty-nine (69) AEs (application site irritation [58], application site pruritus [11]) considered definitely related; forty (40) AEs (asthenia, cold sweat, dizziness [8], feeling hot [3], headache [6], hiccups [2], hypoaesthesia, nausea [11], paraesthesia, pruritus [2], tremor [2], vomiting [2]) that were considered probably related; seven (7) AEs (dizziness [3], epistaxis, headache, hiccups, tinnitus) considered possibly related and two (2) AEs (catheter site pain, rhinorrhea) considered unrelated to the application of Mylan's rotigotine transdermal system, 2 mg/24 hours.

There were seventy-two (72) AEs (application site irritation [62], application site pruritus [8], application site pain, nausea) that were considered definitely related; thirty-eight (38) AEs (abdominal pain upper, asthenia, cold sweat, decreased appetite, dizziness [12], feeling hot, flushing, headache [5], hyperhidrosis [2], nausea [11], vomiting [2]) considered probably related; three (3) AEs (dizziness, nausea, vomiting) considered possibly related and one (1) AE (abdominal distention) considered unlikely related to the application of UCB UK's Neupro® Transdermal Patch (UK), 2 mg/24 hours.

One (1) AE (blood uric acid increased) occurred at study exit but cannot be definitively attributed to any treatment as chemistry testing was performed only at screening and study exit. In addition, there were eight (8) AEs (dizziness [5], hypoaesthesia, nausea, syncope) reported prior to Period 1 dosing and therefore considered unrelated to any treatment.

The most frequently reported adverse event (AE) following application of Mylan's rotigotine transdermal system, 2 mg/24 hours, was application site irritation which was reported by 58/68 (85.29%) subjects.

Application site irritation was also the most frequent AE experienced by subjects following application of Neupro® Transdermal System (US), 2 mg/24 hours, and Neupro® Transdermal Patch (UK), 2 mg/24 hours, and was reported by 58/66 (87.88%) and 61/66 (92.42%) subjects, respectively.

Overall, the two formulations showed no apparent differences in safety.

Clinical laboratory evaluation:

The HIV antibody, hepatitis B surface antigen, and hepatitis C antibody screens were nonreactive for all subjects. The serum pregnancy screen at the screening visit, each check-in, and study exit was negative for all female subjects over the course of the study.

Repeat hematology testing was not requested at study exit.

There was one clinically significant change in the clinical laboratory measurements over the course of the study which could have been reasonably associated with the formulations under investigation. Subject 42 experienced one (1) AE (blood uric acid increased (9,2mg/dl)) that occurred at study exit. Subject 42 failed to return for repeat chemistry testing.

Study Number: ROTI-15035

Title: Multiple-Dose Bioequivalence Study of Rotigotine Transdermal System (2 mg/24 hours; Mylan) and Neupro® Transdermal Patch (2 mg/24 hours; UCB) in Healthy Adult Volunteers Under Steady-State Conditions.

Methods

Study design

This was an irritation evaluator-blinded, randomized, **two-treatment**, **two-period**, multiple-dose crossover study to investigate the bioequivalence of Mylan's rotigotine transdermal systems 2 mg/24 hours to UCB's Neupro® Transdermal System, 2 mg/24 hours in thirty nine (39) healthy, adult subjects under steady-state conditions.

Treatment A = Rotigotine Transdermal System 2 mg/24 hours

Treatment B = Neupro® Transdermal Patch 2 mg/24 hours

The clinical part of the study took place from 25-Aug-2016 till 11-Sep-2016

Subjects arrived at the clinical site at least 15 hours prior to patch application for each study period.

Subjects received dinner the evening prior to dosing. A light breakfast was served prior to the first patch application. A standard meal was provided at least 5 hours and 10 hours after dosing and at appropriate times thereafter. Water was allowed ad libitum.

Beginning on Day 1, each subject received either three consecutive applications of Mylan`s rotigotine transdermal system, 2mg/24 hours or UCB`s Neupro® Transdermal System, 2 mg/24 hours applied to a clean, dry area of the skin on abdomen according to the randomization scheme. Once a patch was applied it was held in place with the palm of the hand for 30 seconds to ensure good contact with the application site, especially around the edges.

Each transdermal system was worn for 24 hours on the abdomen and subjects received three consecutive applications. Adhesion of the patch was assessed prior to each patch removal. If there was observed lift of the patch >15%; the subject was discontinued from the study. The exclusion from subjects due to a lift of patch is considered inappropriate in this case, since demonstrating comparable in vivo performance (including comparable adhesion) is essential for generic TDDS.

An eleven-day washout separated the last patch removal from Period 1 and the first patch application for Period2. The washout period is considered adequate since the recommended time between two test periods is 5 times the half-life (which is 5-7 hours for rotigotine).

Serial *blood samples* (1 x 6 mL) were collected in K_2 EDTA tubes at pre-dose (within 30 minutes prior to dosing) and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hours after the third patch application.

After patch removal, patches and alcohol wipes were heat-sealed and sent to Mylan Technologies Inc. for *residual drug analysis*.

Acute dermal irritation was assessed 30 to 45 minutes following patch removal by trained clinical staff blinded to the randomization scheme.

The justification for the administered dose (2mg/24hrs) of the medicinal product is based on safety considerations. Since a trial with higher dose might put a non-justifiable risk on the study population, dose selection is acceptable.

Test and reference products

The information regarding test and reference products provided by the applicant is appropriate. The batch size is adequate. Test product is identical to the formulation which is intended for MA.

Population(s) studied

Forty (40) volunteers were originally planned for enrolment. Study population consisted of **thirty nine (39)**, non-tobacco using, males (29) and non-pregnant, non-lactating females (10) between the ages of 20 and 59, with a BMI from 21 to 30 kg/m^2 who were judged healthy based on a medical history, ECG, laboratory evaluation, physical examination and vital signs measurements were accepted into the clinical phase of this study. 28 were White, 10 Black, 1 Asian.

Subjects 25, 30 and 36 withdrew consent during Period 1 due to an adverse event (nausea). Subjects 30 and 36 were assigned to treatment sequence AB, subject 25 to sequence BA. Subject 6 had less than 85% patch adhesion during Period1 and was discontinued from the study. It is noted that subject Nr.6 received Neupro® Transdermal Patch 2 mg/24 hours during period 1 (treatment sequence BA). Subjects 5 and 12 withdrew consent due to personal reasons prior to Period 2 dosing. Subject 26 was discontinued due to a positive urine drug screen at Period 2 check-in. Subject 29 withdrew consent due to personal reasons during Period 2.

Pharmacokinetic Population

Therefore, **thirty-one (31)** subjects completed the study and are included in the pharmacokinetic analysis. The plasma samples for Subjects 25, 30 and 36 were assayed per EMEA Guidance but are not included in the pharmacokinetic analysis.

Safety Population

The safety population includes all thirty-nine **(39) subjects** who received at least one dose of study medication during the study.

Analytical methods

Study No.: ROTI-15035

Study description ROTI-15035: This was an irritation evaluator-blinded, randomized, two-treatment, two-period, multiple-Dose Bioequivalence Study of Rotigotine Transdermal System (2 mg/24 hours; Mylan) and Neupro® Transdermal Patch (2 mg/24 hours; UCB) in Healthy Adult Volunteers under Steady-State Conditions

Number of subjects

Forty (40) volunteers were originally planned for enrollment and thirty-nine (39) subjects were dosed in the study. Subjects 25, 30 and 36 were discontinued during Period 1 due to an adverse event (nausea). Subject 6 had less than 85% patch adhesion during Period 1 and was discontinued from the study. Subjects 5 and 12 withdrew consent due to personal reasons prior to Period 2 dosing. Subject 26 was discontinued due to a positive urine drug screen at Period 2 check-in. Subject 29 withdrew consent due to personal reasons during Period 2. Therefore, thirty-one (31) subjects completed the study and are included in the pharmacokinetic analysis. The plasma samples for Subjects 25, 30 and 36 were assayed per EMEA Guidance but are not included in the pharmacokinetic analysis.

Sponsor of the study: Mylan Pharmaceuticals Inc.

Clinical center: West Virginia University Hospitals Inc., Clinical Laboratories

1 Medical Center Drive

Morgantown, WV 26506, USA

Bioanalytical center: Mylan Pharmaceuticals Inc.

Bioanalytical Department

3711 Collins Ferry Rd.

Morgantown, WV 26505, USA

The analytical part of the study lasted from 06.10.2016 till 19.10.2016; study samples were obtained stored at a nominal temperature of -70ºC.

933 samples from 34 subjects (15 time-points per subject, 2 periods) were analysed, the theoretical amount of samples is 1020 (see “number of subjects” above).

Analytical Methods

The analyte was Rotigotine.A liquid chromatograph, with a tandem mass spectrometry detector was used.

Quantitation is determined by peak area ratio method.

Comments on Study ROTI-15035

Sample reassays for Rotigotine were done on 21 samples (2.3 %). All reassays are in accordance with the presented SOP and the relevant guideline.

Incurred sample reanalysis (ISR) of Rotigotine has been performed on 102 samples for each subject and study period (~ 10% of total samples analysed); 98 out of 98 evaluable ISR samples (100%) were within 20% from the mean value.

Representative chromatograms (subjects 1-4 and 7-10, >20 %) were provided.

The analytical method for the determination of Rotigotine in human plasma as well as respective validations (including partial validations) are described adequately; the validation(s) were performed according to the requirements of the Guidance for Industry. Bioanalytical Method Validation (U.S. Food and Drug Administration, May 2001), but no reference was made to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009). Consequently the acceptance criteria are mainly in a plausible range and were fulfilled, but full compliance to the EMA guideline is probably not given. The applicant is advised to confirm full compliance to the EMA guideline of the BE-study ROTI-15035.

No data regarding a potential carry-over of the analyte could be found in the method validation. Adequate data should be provided.

Pharmacokinetic variables

Multiple-dose (steady-state) pharmacokinetic parameters for rotigotine were calculated using non-compartmental techniques. The maximum concentration at steady-state ($C_{PEAK(SS)}$), the minimum concentration at steady-state ($C_{MIN(SS)}$), and the times at which they occurred relative to the administered dose ($T_{PEAK(SS}$) and $T_{MIN(SS)}$) were determined from the observed plasma concentration-time profile over the sampling time interval. Area under the plasma concentration-time curve (AUC_{TAU}) was the sum of the linear trapezoidal estimation of the areas over the dosing interval (i.e. 24 hrs). The pre-dose concentrations were determined to assess whether steady-state has been achieved. Three consecutive pre-dose concentrations were determined. The concentration at the end of the dosing interval at steady-state ($C_{\tau,ss}$) was determined from the observed plasma concentration-time profile. Fluctuation (expressed as a percentage) was determined as the range of concentrations divided by the average steady-state concentration: %FLUCTUATION (FLUCT1), calculated as $[C_{PEAK}-C_{MIN})]/[Css])$ x 100, where the average steady-state concentration, Css = AUC_{TAU}/Tau.

The **primary pharmacokinetic variables** for assessment of bioequivalence are **AUCTAU, CPEAK(SS)** and **C_{τ}(SS)** for rotigotine.

The chosen pharmacokinetic variables and methods are considered adequate.

Statistical methods

Determination of Sample Size

Assuming a true ratio between 92%-108% and an intra-subject variability of 20%, a minimum of thirty-six (36) subjects were required to conclude bioequivalence with approximately 90% power. To account for subject withdrawal and dropouts due to adverse events, non-compliance or personal reasons, forty (40) subjects were randomized. Sample size calculation can be followed from the

technical perspective. However, the drop-out rate (20%) was double compared to what was estimated (10%). The applicant is asked to comment on this issue.

Subjects who fail to complete the study (drop-outs) were not replaced without written authorization from the Sponsor.

Statistical Analysis - Pharmacokinetics

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tested for treatment effects in the parameter means at an alpha level of 0.05. The parameters: TPEAK(SS) and %FLUCTUATION were analyzed statistically using the nontransformed data. The natural log transformed parameters: LNAUCTAU, LNCT,ss, and LNCPEAK(SS) were also analyzed.

Attainment of steady-state was investigated separately for each formulation. Trough plasma concentrations were compared statistically by linear regression analysis using the SAS procedure MIXED. A 90% confidence interval was calculated for the slope of the regression line. The null hypothesis (H0) will be that the slope of the regression line equals zero (0) (slope = 0). The alternative hypothesis (H1) will be that the slope of the regression line does not equal zero (0) (slope $\neq$ 0). If the 90% CI for the slope includes the value 0, it will be assumed that the null hypothesis is true i.e. that steady-state has been achieved. The -48 hr trough levels were all 0, therefore the 24 hr trough level was added to the analysis for determination of steady-state.

Tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed using the two one-sided tests procedure.

Statistical methods chosen for the analysis of pharmacokinetic data can in general be considered suitable.

Statistical Analysis – Acute Dermal Irritation

The source data for the analysis of acute dermal irritation is the irritation score recorded following visual evaluation of the patch sites. Transdermal system irritation scores (=dermal scores only and the sum of the dermal response and other effects Scores) are presented in a frequency table by treatment. No formal statistical analyses were performed for the acute dermal irritation scores.

Results

Pharmacokinetic parameters

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	arithmetic mean	CV%
AUC_{TAU} (pg•hr/mL)	4132	46.48	4223	40.74
$C_{PEAK(SS)(pg/mL)}$	240.4	47.79	249.5	41.19
$C\tau_{(SS)\ (pg/mL)}$	180.9	44.38	183.1	38.74
$C_{min(SS)\ (pg/mL)}$	101.4	56.62	106.0	46.41
$T_{PEAK(SS)\ (hr)}$	16.97	26.52	17.55	25.61
$T_{min(SS)\ (hr)}$	4.452	36.15	3.935	44.47
FLUCT1 (%)	84.82	29.36	85.06	35.24
AUC_{TAU} area under the plasma concentration-time curve from time zero to time tau over a dosing interval				

Pharmacokinetic	Test	Reference
	at steady state, where tau is the dosing interval	
$C_{PEAK(SS)}$	maximum or peak plasma concentration at steady state	
$C\tau_{(SS)}$	concentration at the end of the dosing interval at steady-state	
$C_{min(SS)}$	minimum plasma concentration obtained directly from the data without interpolation	
$T_{PEAK(SS)}$	time for maximum concentration	
$T_{min(SS)}$	time for minimum concentration	
FLUCT1 (%)	one of the fluctuation parameters, where FLUCT1=100% (C_{PEAK}-C_{MIN})/C_{SS}, provided that C_{SS} does not = 0	

Statistical analysis for <analyte> (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC_{TAU} (pg•hr/mL)	0.97	89.62% – 104.05%	
$C_{PEAK(SS)(pg/mL)}$	0.96	87.51% – 106.09%	
$C\tau_{(SS)\,(pg/mL)}$	0.97	87.71% – 106.48%	
* estimated from the Residual Mean Squares			

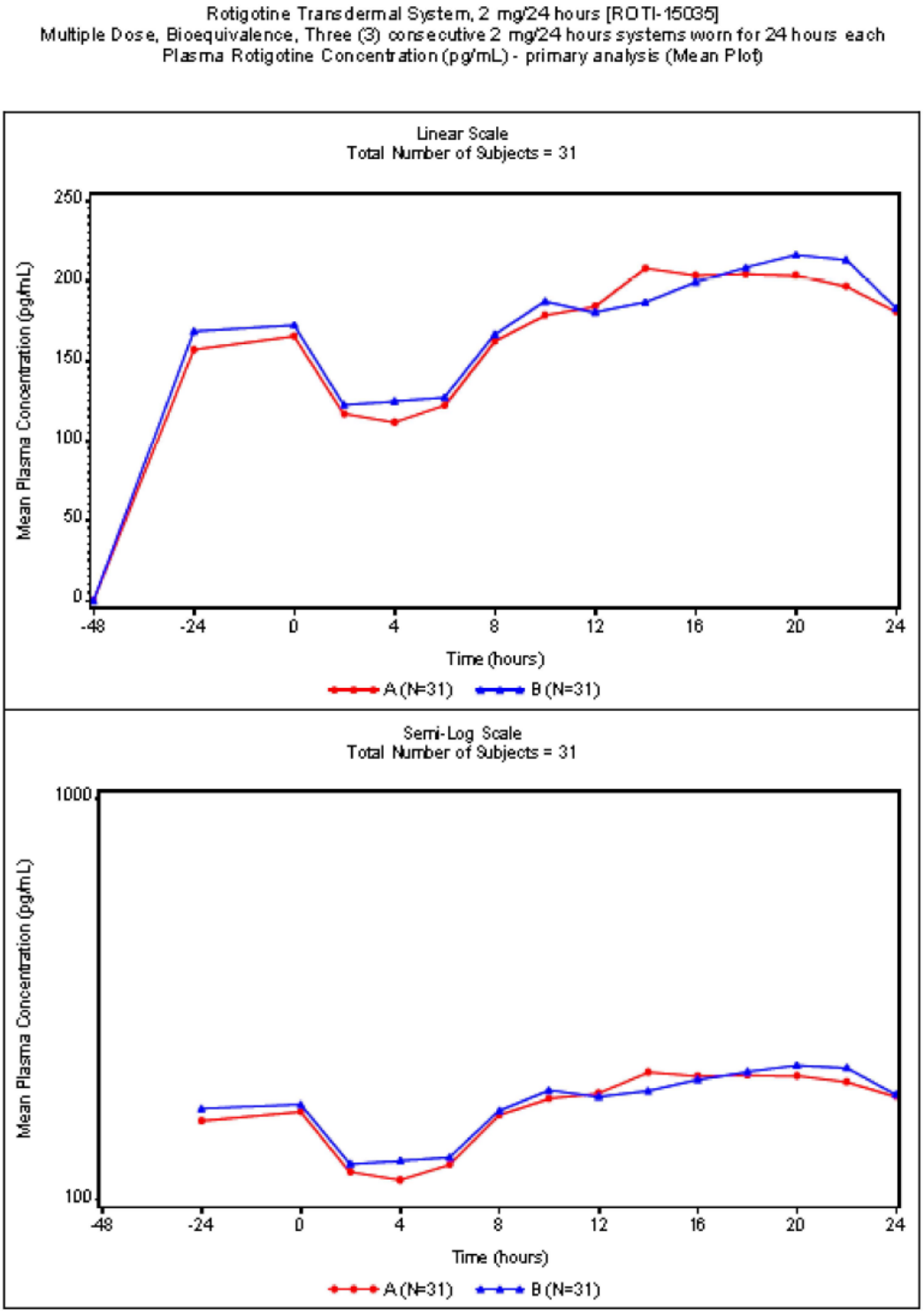


Figure 2: Mean Graphical Presentation of rotigotine Plasma Concentrations

The 90% confidence intervals calculated for AUC_{TAU}, $C_{PEAK(SS)}$ and $C_{T(SS)}$ are within the 0.80 – 1.25 range. Based on these pharmacokinetic data, it can be concluded that the pharmacokinetic profile of Rotigotine Transdermal System (2 mg/24 hours; Mylan) is comparable with that of the reference product Neupro® Transdermal Patch (2 mg/24 hours; UCB) under steady-state conditions with respect

to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance (EMA/CPMP/EWP/280/96 Corr1).

Per study protocol, if any transdermal systems did not maintain at least 85% adhesion over the wear period, the subject was discontinued from the study. The evaluation of a possible effect on PK results, when including the subjects in PK analysis with a greater than 15% lift of patch, is however regarded to be of relevance in order to demonstrate comparable in vivo performance, i.e. similarity in terms of efficacy. Only one (1) subject had less than 85% adhesion throughout the study and was excluded from study. This subject received the reference product in period 1. Therefore a possible influence on the PK results is considered minimal.

Protocol deviations

Protocol deviations have been made during blood sampling times, but are considered acceptable, since actual sampling time points are taken for PK analysis.

With regard to other protocol deviations, subject 25 only consumed 34% (period 1, application1) of standard meal and subject 23 consumed 55%(period 1, application2), 70% (period 2, application1) and 65%(period 2, application1) of standard meal.

The protocol deviations reported for the subjects included in the analysis were judged to have no significant impact on the bioequivalence assessment or subject's safety, and this is deemed acceptable by the assessor.

Adhesion and Acute Irritation Results

Per protocol, if any transdermal systems did not maintain at least 85% adhesion over the wear period, the subject would be discontinued from the study. Only one (1) subject had less than 85% adhesion throughout the study. Generally, patches maintained good skin contact throughout the wear period.

Skin irritation was evaluated at 30 to 45 minutes after each patch removal.

Barely perceptible erythema to definite erythema (on average) was seen with both treatments a half hour after patch removal. This is thought to be of little clinical relevance.

Rotigotine Transdermal System, 2 mg/24 hours [ROTI-15035]
Multiple Dose, Bioequivalence, Three (3) consecutive 2 mg/24 hours systems worn for 24 hours each
Irritation Evaluation primary analysis

The FREQ Procedure

Frequency

Table of treat by scorec										
	scorec(Combined Irritation Score)									
treat	0(A)	0(N)	1(A)	1(C)	1(N)	2(A)	2(N)	3(A)	3(N)	Total
A	2	11	30	1	22	25	9	3	1	104
B	2	11	28	0	25	16	15	3	0	100
Total	4	22	58	1	47	41	24	6	1	204

Dermal Response		Other Effects	
Scale	Irritation	Scale	Appearance
0	No evidence of irritation	A (0)	Slightly glazed appearance
1	Minimal erythema, barely perceptible	B (1)	Marked glazed appearance
2	Definite erythema, readily visible; or minimal edema; or minimal papular response	C (2)	Glazing with peeling and cracking
3	Erythema and papules	F (3)	Glazing with fissures
4	Definite edema	G (3)	Film of dried serous exudates covering all or part of the patch site
5	Erythema, edema, and papules	H (3)	Small Petechial erosions and/or scabs
6	Vesicular eruption	None	No Other Effects observed
7	Strong reaction spreading beyond test (i.e., application) site		

Safety data

Adverse events

No deaths, serious adverse events (AE) or other significant AEs were reported. There was one (1) pre-dose and two hundred forty-six (246) post-dose AEs reported by thirty-nine (39) subjects over the course of the study. All AEs were mild in severity. There were one hundred three (103) AEs (application site irritation [93], application site pruritus [10]) considered definitely related; nine (9) AEs (dizziness [2], flushing, headache [2], nausea [3], vomiting) considered probably related; two (2) AEs (dizziness, headache) considered possibly related and three (3) AEs (pain in jaw [3]) considered unlikely related to the application of Mylan's rotigotine transdermal system, 2 mg/24 hours.

There were ninety-nine (99) AEs (application site irritation [89], application site pruritus [9], pruritus) considered definitely related; seventeen (17) AEs (abnormal dreams, dizziness, feeling abnormal, headache [2], hyperhidrosis, nausea [4], vomiting [7]) considered probably related; twelve (12) AEs (dizziness, flushing, headache [2], hyperhidrosis, nasal congestion, nausea [2], pain in extremity [4]) considered possibly related; one (1) AE (pain in jaw) considered unlikely related to the application of UCB's Neupro® Transdermal Patch, 2 mg/24 hours. In addition, there was one (1) AE (headache) reported by one subject prior to Period 1 dosing and therefore considered unrelated to either treatment.

Overall the safety profile of the test product was comparable with the reference product.

Table 3: Disposition for all Dosed Subjects by Treatment

	Treatment	
	A	B
Number of subjects who received at least one patch application	36	35
Number of subjects who withdrew consent due to AEs	0	0
Number of subjects who were withdrawn per Investigator and/or Sponsor due to AEs	1	1
Number of subjects with AEs	36	34
Total number of AEs*	117	129

*There was one (1) pre-dose AE that is unrelated to either treatment.
Treatment A: Rotigotine Transdermal System, 2 mg/24 hours, (Lot No.: R616001)
Treatment B: Neupro® Transdermal Patch 2 mg/24 hours, (Lot No.: 55258206)

Clinical laboratory evaluation

The HIV antibody, hepatitis B surface antigen, and hepatitis C antibody screens were nonreactive for all subjects. The serum pregnancy screen at the screening visit, each check-in, and study exit was negative for all female subjects over the course of the study.

There were no clinically significant changes in the clinical laboratory measurements over the course of the study which could be reasonably associated with the formulations under investigation.

Study Number: ROTI-12128

Title: Comparative Evaluation of the Cumulative Irritation and Sensitization of Rotigotine Transdermal System (2 mg/24 hours; Mylan), Neupro® Transdermal System (2 mg/24 hours; UCB) and Neupro® Transdermal Patch (2 mg/24 hours; UCB UK) in Healthy Adult Volunteers.

Methods

Study design

This was an open-label, irritation evaluator blinded, multiple-dose, randomized application site, three-treatment, three-phase, one-period human dermal safety study investigating the cumulative irritation and contact sensitization potential of Mylan's Rotigotine Transdermal System, UCB's Neupro® Transdermal System and UCB UK's Neupro® Transdermal Patch after repetitive placement of each treatment to the same skin site in up to two hundred and forty (240) healthy volunteers.

The clinical part of the study took place from 08-Apr-2015 till 20-Jun-2015.

Treatment A (Test): Rotigotine Transdermal System, 2 mg/24 hours

Treatment B

Treatment C (EU-Reference) Neupro® Transdermal Patch 2 mg/24 hours

Subjects were dosed in one group. Subjects checked into the clinical facility and were dosed daily for 21 days beginning on April 8, 2015 for the *Induction Phase*. The *Challenge Phase* was dosed on May 13, 2015 and the *Re-Challenge Phase*, if needed, was dosed on June 15, 2015.

Each check-in occurred no later than 1.5 hours prior to transdermal system application at their scheduled time. On Day 1, subjects remained at the clinical site for approximately 4 hours after patch application for monitoring of side effects. On all other days, subjects remained at the site until completion of all scheduled study procedures then were allowed to leave and return as needed.

Treatment Groups

The randomization scheme used to assign each subject number to a treatment sequence was generated by Mylan Inc. The randomization scheme utilized a three-treatment, randomized application site, one-period design and was generated prior to dosing. Mylan's rotigotine transdermal system, UCB's Neupro® Transdermal System and UCB UK's Neupro® Transdermal Patch were placed during the induction applications on the site indicated by the subject's randomization scheme, beginning with the right abdomen, middle abdomen, then the left abdomen. Alternate naïve sites may have been used if limiting irritation occurred. These sites could have been on the abdomen, thigh, hip, flank, upper arm, shoulder. The Challenge applications were placed below the induction application site.

Blinding

This was an open-label study. The randomization code was available to clinical staff for dosing, and to the statisticians and medical writers for report writing purposes. However, individuals performing irritation evaluations were blinded to the randomization scheme at the time of the evaluation.

Induction Phase

Subjects reported to the clinic no later than 1.5 hours prior to the first patch application. On Day 1, subjects remained at the clinical site for 4 hours after patch application for monitoring of side effects. On all other days, subjects remained at the site until completion of all scheduled study procedures then were allowed to leave and return as needed. Each subject received a 2.0 cm^2 die-cut of one (1) 2 mg/24 hours Mylan Rotigotine Transdermal System, a 1.67 cm^2 die-cut of one (1) 2 mg/24 hours Neupro® Transdermal System and a 1.67 cm^2 die-cut of one (1) 2 mg/24 hours Neupro® Transdermal Patch applied to a clean, dry area of the skin on the abdomen according to the randomization scheme. Subjects wore each treatment for 24 hours. Patches were re-applied to the same skin site every 24 hours for 21 consecutive days (for a total of 21 patch application per treatment). If a subject developed an irritation score of 3 or greater, the subject did not have any further patches applied to the same application site during the Induction phase of the study. In this case, any re-applications for Induction were made at a designated alternate site and appropriately documented and diagrammed. All other treatment applications continued as scheduled. Adhesion was assessed within 1 hour prior to each patch removal by trained clinical staff. Acute dermal irritation was assessed 30 to 45 minutes following each patch removal by trained clinical staff blinded to the randomization scheme.

A *rest phase* of at least 14 days followed the removal of the last Induction phase patch.

Challenge Phase

Following the rest phase, a challenge application of a 2.0 cm^2 die-cut of one (1) 2 mg/24 hours Mylan Rotigotine Transdermal System, a 1.67 cm^2 die-cut of one (1) 2 mg/24 hours Neupro® Transdermal System and a 1.67 cm^2 die-cut of one (1) 2 mg/24 hours Neupro® Transdermal Patch applied to a clean, dry area of the skin on the abdomen according to the randomization scheme took place. Patches were removed 48 hours after application. Irritation was assessed at 0.5, 24, 48 and 72 hours after removal of each patch by a trained a dermatologist or other trained individual blinded to the randomization scheme.

The submitted dermal safety study ROTI-12128 was designed based on Draft FDA Guidance for Rotigotine Transdermal Systems (Recommended June 2012/Revised October 2016).

FDA recommendations on the dermal safety study design are slightly different in comparison to the EMA recommendations:

The EMA Guideline suggests an active- and placebo-controlled, multiple-dose, three-phase, parallel-group design. Within Group 1 subjects should apply test, reference, and placebo patches daily for 21 consecutive days, whereas Group 2 subjects should apply the patches three times a week over the period of 21 days (a total of nine applications).

The FDA recommends a 1 group design. Subjects should apply test and reference patches daily for 21 consecutive days. Placebo/negative control is considered optional.

Since the daily application is in line with treatment recommendations made in the SmPC of Neupro®, the testing of only one scheme (daily for 21 consecutive days) is considered acceptable.

The main issue should be to show non-inferiority to the reference product, with respect to irritation and sensitization; thus for this case, the absence of a placebo arm is considered acceptable.

This study was conducted using healthy subjects randomized to wear a die-cut of the test product and a die-cut of each reference product on the abdomen, so the total rotigotine delivery per day was 1 mg.

The above mentioned FDA Draft Guidance on Rotigotine (June 2012), states that there is lack of current safety data to support the use of more than 1 mg/24 hour rotigotine delivery on the same

subject during a 21- day cumulative irritation and sensitization study. Guidance also states that if both the reference and test product are a matrix design, then the patches may be cut and both products worn simultaneously on separate skin sites.

The EMA Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms however does not mention a possible use of die-cut of patches. In case simultaneous application of test and reference is impossible as doubled amount of API might have life-threatening consequences the use of a lower strength is recommended for size proportional formulations.

Therefore, the applicant is requested to clearly point out and discusswhether and how the results could possibly be influenced by the use of die-cut of the patches instead of intact, whole patches.

Test and reference products

The test product is not identical to the formulation which is intended for MA with regard to size of drug matrix area (10cm² compared to 11cm²). The composition is however proportional. For further details, please refer to the above table.

Population(s) studied

The study population consisted of **two hundred forty (240)** non-smoking to light smoking (< 1 pack per day) male (104) and non-pregnant, non-lactating female (136) volunteers between the ages of 18 and 64, with a BMI from 19 to 34 kg/m^2 who were judged healthy based on a medical history, ECG, laboratory evaluation, physical examination and vital signs measurements were accepted into the clinical phase of this study. 133 were Black, 106 White, 1 Asian.

Two hundred forty (240) volunteers were enrolled in the study. Subjects 12, 18, 27, 32, 33, 53, 104, 105, 124, 127, 180, 211 and 214 withdrew consent during the study. Subjects 146 and 171 were discontinued from the study due to protocol non-compliance. Subjects 35, 96, 142 and 185 were discontinued by the Principal Investigator due to limiting skin irritation. Therefore, two hundred twenty-one **(221) subjects completed** the clinical portion of the study (Induction and Challenge Phases) for at least one treatment. Two hundred thirty-six (236) subjects and two hundred twenty-three (223) subjects are included in the statistical analysis of cumulative irritation and sensitization for US submission, respectively. Two hundred thirty-five (**235**) subjects and two hundred twenty-three (**223**) subjects are included in the statistical analysis of cumulative irritation and sensitization for EU submission, respectively.

Table 4: Summary of Subject Disposition

	Sequence						Total
	ABC	ACB	BAC	BCA	CAB	CBA	
Subjects Randomized	40	40	40	40	40	40	240
Subjects Successfully Completed	37	36	36	36	39	37	221
Subjects Who Withdrew Consent	3	2	3	2	0	3	13
Subjects Discontinued by the Investigator	0	2	1	2	1	0	6
Subjects Discontinued by Sponsor	0	0	0	0	0	0	0
Subjects Included in Irritation Analysis - US	38	39	40	40	40	39	236
Subjects Included in Irritation Analysis - EU	38	39	40	39	40	39	235
Subjects Included in the Sensitization Analysis - US	37	37	37	36	39	37	223
Subjects Included in the Sensitization Analysis - EU	37	37	37	36	39	37	223

Statistical methods

Determination of Sample Size

In order to determine possible contact sensitization reactions in the test and reference formulations, at least two-hundred (200) healthy male and female subjects were needed to complete all study procedures.

Statistical Analysis – Cumulative Irritation for EU Submission

A one-sided hypothesis test was used to determine if the cumulative irritation score of Mylan's rotigotine transdermal system was equivalent to or better than UCB UK's Neupro® Transdermal Patch (for the reference product). The available data however are indicating non-inferiority but not superiority. The applicant is asked to comment.

For the mean cumulative irritation scores, the null and alternative hypotheses were: H_0: $\mu_1/\mu_2 > 1.25$; H_1: $\mu_1/\mu_2 \leq 1.25$, which (assuming $\mu_2 > 0$) can be written as: H_0: $\mu_1 - 1.25\mu_2 > 0$; H1: $\mu_1 - 1.25\mu_2 \leq 0$, where μ_1 is the mean response for the test product and μ_2 is the mean response for the reference product.

The null hypothesis H_0 was rejected when the upper limit of the 90% confidence interval (that is the 95% upper confidence bound) for the quantity $\mu_1 - 1.25\mu_2$ is ≤ 0. If H_0 is rejected, then Mylan's rotigotine transdermal system was considered to be non-inferior to UCB UK's Neupro® Transdermal Patch with regard to cumulative irritation.

EU analysis was performed on both the dermal responses scores and the sum of the dermal response and other effects scores.

Statistical Analysis – Contact Sensitization for EU Submission

For EU submission, a subject was considered potentially sensitized if the combined Dermal Response + Other Effects score of 2 or greater was recorded during the Challenge Phase. There were no formal statistics performed on the sensitization data.

Results

The results of the statistical analysis indicate that the cumulative irritation for Mylan's rotigotine transdermal system 2 mg/24 hours is no worse than (i.e. non-inferior to) UCB UK's Neupro® Patch over repeated 24-hour applications for 21 consecutive days.

Cumulative Irritation Results – EU Submission (n =235)

Dermal Response Score Only

Least-Squares Mean Cumulative Irritation			
Treatment A Mylan	**Treatment C Neupro® (UCB UK)**	**μ_1-1.25μ_2[1]**	**90% Confidence Interval[2]**
1.368	1.347	-0.3158	-0.3898 - -0.2418

[1]Estimated as Mylan least-squares mean – 1.25 x Neupro® (UCB UK) least-squares mean
[2] Upper 90% confidence interval < 0 indicates Mylan is non-inferior to Neupro® (UCB UK)

Combined Dermal Response and Other Effects Score

Least-Squares Mean Cumulative Irritation			
Treatment A Mylan	**Treatment C Neupro® (UCB UK)**	**μ_1-1.25μ_2[1]**	**90% Confidence Interval[2]**
3.463	3.087	-0.3952	-0.5431 - -0.2473

[1]Estimated as Mylan least-squares mean – 1.25 x Neupro® (UCB UK) least-squares mean
[2] Upper 90% confidence interval < 0 indicates Mylan is non-inferior to Neupro® (UCB UK)

Table 5: Frequency of Irritation Scores and Cumulative Irritation Statistical Analysis – EU Submissions Dermal Scores

Frequency of Irritation Scores* Observed In Two Hundred Thirty-Five Healthy Males and Females Following Repeat Application of 2.0 cm^2 Die-Cut Rotigotine Transdermal Systems, 2 mg/24 hours and 1.67 cm^2 Neupro® Transdermal Systems, 2 mg/24 hours Every 24 Hours for 21 Days														
Time after Initial Patch Application	Treatment A Mylan Rotigotine Transdermal System, 2 mg/24 hours							Treatment C Neupro® Patch, 2 mg/24 hours						
Score	0	1	2	3	4	5	6	0	1	2	3	4	5	6
Day 2^	207	24	4	0	0	0	0	209	22	4	0	0	0	0
Day 3	178	45	12	0	0	0	0	182	40	13	0	0	0	0
Day 4	149	60	26	0	0	0	0	154	64	17	0	0	0	0
Day 5	137	50	45	1	0	2	0	144	51	36	2	0	2	0
Day 6	117	52	57	4	1	4	0	129	55	45	2	0	3	1
Day 7	96	43	85	6	1	4	0	118	45	61	5	2	3	1
Day 8	84	35	104	6	1	4	1	101	49	73	6	2	3	1
Day 9	69	26	126	6	1	4	3	81	45	96	6	2	3	2
Day 10	62	33	126	6	1	4	3	70	51	100	6	2	3	3
Day 11	52	34	135	6	1	4	3	54	53	113	6	2	3	4
Day 12	38	43	140	6	1	4	3	34	55	131	6	2	3	4
Day 13	29	46	146	6	1	4	3	30	45	145	6	2	3	4
Day 14	30	27	164	6	1	4	3	30	28	162	6	2	3	4
Day 15	30	21	170	6	1	4	3	22	25	173	6	2	3	4
Day 16	30	20	171	6	1	4	3	26	19	175	6	2	3	4
Day 17	28	22	171	6	1	4	3	23	17	179	7	2	3	4
Day 18	27	23	171	6	1	4	3	23	14	182	7	2	3	4
Day 19	26	23	172	6	1	4	3	20	17	182	7	2	3	4
Day 20	29	20	172	6	1	4	3	22	15	182	7	2	3	4
Day 21	27	22	172	6	1	4	3	20	18	181	7	2	3	4
Day 22	29	20	172	6	1	4	3	23	14	181	7	2	3	5

*Scores represent the Dermal Response Scores. Source: Appendix 16.2.6.3; ^Note Day 2 = day of patch removal for patch application #1, this is also Visit 3

Sensitization Results - EU Submission

Based on the criteria outlined in EU guidance, the number of subjects that were considered sensitized is 52 subjects for Mylan rotigotine transdermal system and 54 subjects for the UCB UK Neupro® Transdermal Patch. The development of sensitization was comparable between the two groups. In general, the sensitized subjects had reactions at both treatment sites, suggesting the reaction was caused by rotigotine, not by any formulation differences. However, the applicant is asked to discuss whether certain populations (age, gender, race,…) were affected more frequently.

Rotigotine Transdermal System, 2 mg/24 hours [ROTI-12128]
Multiple Dose, Cumulative Irritation and Sensitization, One transdermal system worn 24 hours for 21 days
Irritation Evaluation (Challenge Phase-Combined Score)

The FREQ Procedure

Frequency	Table 1 of hour by score								
	Controlling for EXTRT=A								
	score(Sum of dermal response and other effects)								
hour	2	3	4	5	6	7	8	10	Total
0.5	22	4	3	4	1	0	0	0	34
24	18	6	12	4	7	0	0	1	48
48	11	8	8	4	7	1	0	0	39
72	6	16	4	6	7	0	1	0	40
Total	57	34	27	18	22	1	1	1	161

Frequency	Table 2 of hour by score								
	Controlling for EXTRT=C								
	score(Sum of dermal response and other effects)								
hour	2	3	4	5	6	7	8	10	Total
0.5	22	1	6	3	1	0	0	0	33
24	18	9	7	2	10	0	0	0	46
48	14	9	6	3	6	1	0	0	39
72	9	16	3	5	8	0	1	0	42
Total	63	35	22	13	25	1	1	0	160

Treatment A: Rotigotine Transdermal System, 2 mg/24 hours - die-cut to 2.0 cm^2, Lot#: R615001, Mylan
Treatment B: Neupro Transdermal System, 2 mg/24 hours - die-cut to 1.67 cm^2, Lot#: 55187502, UCB
Treatment C: Neupro Transdermal Patch, 2 mg/24 hours - die-cut to 1.67 cm^2, Lot#: 55191205, UCB UK

Safety data

The safety assessment includes information for all two hundred forty (240) subjects who received at least one dose of study medication during the study.

Adverse events

No serious adverse events were reported. Two hundred forty (240) subjects experienced a total of two thousand three hundred eleven (2,311) adverse events (AEs) over the course of the study. The AEs were mild to severe in severity.

Per the product labeling, Neupro® should be applied to a different skin site every day. The patch should not be applied to the same area of skin more than one time every 14 days. Therefore, the development of numerous application site reactions is unsurprising following same-site applications every 24 hours for 21 consecutive days.

There were seven hundred ninety-four (794) AEs (application site irritation [665], application site discolouration [116], application site pruritus [10], application site exfoliation, application site pain, application site vesicles) considered related to the Mylan rotigotine transdermal system.

There were seven hundred thirty-seven (737) AEs (application site irritation [622], application site discolouration [104], application site pruritus [8], application site pain [2], application site oedema) considered related to the UCB Neupro® Transdermal System.

There were seven hundred twenty-eight (728) AEs (application site irritation [613], application site discolouration [104], application site pruritus [7], application site exfoliation, application site oedema,

application site pain, application site vesicles) considered related to the UCB UK Neupro® Transdermal Patch.

The most frequently reported adverse event (AE) following application of Treatment A and Treatment C was application site irritation which was reported by 224/240 (93.33%) and 223/240 (92.92%) subjects, respectively.

A clear table, which shows the distribution of the AEs in terms of severity between Treatment A and C, is however missing and should be provided.

As subjects received the test and the references patches simultaneously, AEs that were not localized to the application site of a particular patch could not be directly attributed to a specific patch type.

There were fifty-two (52) AEs that could not be attributed to a specific treatment. Twenty-eight (28) AEs (chest pain, constipation [2], dizziness, fatigue [3], headache [10], nausea [5], somnolence [4], vomiting [2]) were considered to be drug related. Twenty-four (24) AEs (abdominal pain, amenorrhoea, anaemia, back pain, cellulitis, cough, dysmenorrhea [3], fatigue [3], haematuria, headache [2], hypersensitivity, hypertension, malaise, musculoskeletal pain, nasal congestion, oropharyngeal pain, otitis externa, pyuria, toothache) was considered not related to treatment.

Overall, exposure to rotigotine was well tolerated following daily 1 mg/24 hours doses for 21 consecutive days.

Table 6: Disposition for all Dosed Subjects by Treatment

	Treatment^			
	A	B	C	A/B/C
Number of subjects who received study treatment	240	240	240	240
Number of subjects who withdrew consent due to AEs	0	0	0	0
Number of subjects who were withdrawn per Investigator and/or Sponsor due to AEs	4	4	4	4
Number of subjects with AEs	227	224	225	38
Total number of AEs	794	737	728	52

Treatment A: Rotigotine Transdermal System, 2 mg/24 hours, (Lot No.:R615001)
Treatment B: Neupro® Transdermal System, 2 mg/24 hours, (Lot No.:55187502)
Treatment C: Neupro® Patch, 2 mg/24 hours, (Lot No.:55191205)
^Only application site-related AEs could be attributed to a particular treatment; since three of each treatment were worn simultaneously, any systemic AEs could only be attributed to rotigotine itself (A/B/C), not a particular treatment

Clinical laboratory evaluation

The HIV antibody, hepatitis B surface antigen, and hepatitis C antibody screens were nonreactive for all subjects.

All urine drug screen results were negative throughout the study, except for Subject 171, who had a positive urine drug screen at the Re-challenge Visit and was discontinued from the study due to non-compliance.

According to the signed Consent Forms, women agreed to use effective contraception (a barrier method with spermicide in addition to their current contraceptive method) in order to prevent pregnancy during treatment. Nevertheless it is noted, that 5 women had a positive pregnancy test at Study Exit and a corresponding abortion in most cases:

Subject 12 had a positive pregnancy test at Study Exit; elected to have an abortion; Subject 32 had a positive pregnancy test at Study Exit, it was outside the 30 day window from last patch removal so no further follow-up required per protocol; Subject 41 had a positive pregnancy test at Study Exit; elected to have an abortion; Subject 142 had a positive pregnancy test at Study Exit; elected to have an

abortion; Subject 201 had a positive pregnancy test at Study Exit; gave birth to healthy female baby on 26 Dec 2016.

There were no clinically significant changes in the clinical laboratory measurements over the course of the study which could be reasonably associated with the formulations under investigation.

3.3.2. Pharmacokinetic conclusion

Based on the presented bioequivalence studies (ROTI-15074, ROTI-15035) Neupro® Transdermal Patch (2 mg/24 hours; UCB UK) is considered bioequivalent with Rotigotine Transdermal System (2 mg/24 hours; Mylan). However, in both studies subjects were excluded from PK analysis when they had a greater than 15% or 20% lift of patch, respectively. The estimation of the effect on the final results is of interest especially for study ROTI-15074. AUC results including the values of these subjects should thus be provided. (see LoQ)

Concerning the biowaiver of the remaining strengths, please refer to section 3.3. “Exemption”.

3.3.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

3.3.4. Additional data

Based on the provided dermal safety study the development of sensitization and local irritation was comparable between the Mylan’s product and the two Neupro® products.

A subject was considered potentially sensitized if the combined Dermal Response + Other Effects score of 2 or greater was recorded during the Challenge Phase.

In general, sensitized subjects had reactions at all treatment sites, suggesting the reaction was caused by rotigotine, not by any formulation differences.

The skin adhesion for Mylan’s rotigotine transdermal system has been investigated as an integrated part of the single dose PK study. This is in accordance with the EMA guideline EMA/CPMP/EWP/280/96 Corr1. However, according to that EMA Guidance, adhesion studies should be performed "in the intended population." Neupro® is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease and for the treatment of moderate to severe primary Restless Legs Syndrome. While Restless Legs Syndrome may begin at any age, Parkinson's disease typically occurs in people over the age of 60. Thus, in order to ensure comparable adhesion properties between test and reference product in the elderly population, the applicant will need to provide additional adhesion data in elderly subjects, unless otherwise justified.

3.3.5. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

3.3.6. Discussion on clinical aspects

According to the relevant EMA guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1), equivalence testing of TDDS should comprise both comparable or better adhesion properties and bioequivalence. Bioequivalence of TDDS should generally be assessed after single dose as well as after multiple dose application. The test product

should furthermore demonstrate a similar or lower degree of local irritation, phototoxicity and sensitization. In order to ensure equivalence in terms of safety, comparative state-of-the-art studies are required to investigate cutaneous tolerability, irritation and sensitisation, the potential to produce phototoxic reactions and adhesion characteristics.

To support the application, the applicant has submitted a single dose bioequivalence study with integrated adhesion study, a multiple dose (steady-state) bioequivalence study and also a dermal Irritation and Sensitization study on the strength, 2 mg/24 hours.

These studies largely fulfil the requirements of the relevant EMA guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) for TDDS and could in principle be adequate for showing in-vivo bioequivalence between the test and reference products.

Nevertheless, at present there are several open issues, including also one major objection regarding the adhesion assessment, which need to be adequately addressed and resolved:

- Based on the presented bioequivalence studies (ROTI-15074, ROTI-15035) Neupro® Transdermal Patch (2 mg/24 hours; UCB UK) is considered bioequivalent with Rotigotine Transdermal System (2 mg/24 hours; Mylan). However, in both studies subjects were excluded from PK analysis when they had a greater than 20 or 15% lift of patch, respectively. The evaluation of a possible effect on PK results, when including these subjects in PK analysis is deemed to be of relevance in order to demonstrate comparable in vivo performance, i.e. similarity in terms of efficacy. The provision of AUC results including the values of the above mentioned subjects is thus requested.
- The skin adhesion for Mylan's rotigotine transdermal system has been investigated as an integrated part of the single dose PK study. This is in accordance with the EMA guideline EMA/CPMP/EWP/280/96 Corr1. However, according to that EMA Guidance, adhesion studies should be performed "in the intended population" - in individuals with similar skin conditions as the expected patients. Neupro is indicated for the treatment of Parkinson's disease and for the treatment of Restless Legs Syndrome. While Restless Legs Syndrome may begin at any age, Parkinson's disease typically occurs in people over the age of 60. The Applicant has shown adequate adhesion properties for Rotigotine Mylan patch in healthy young adults, but no *in vivo* performance has been shown in the elderly population. Age related skin structural changes such as e.g. wrinkles could have a negative effect on the adhesion properties of the patch. Lack of adhesion is a critical efficacy and safety issue, a possible accidental transfer of a patch to the skin of a non- patch wearer has to be prevented in all circumstances. On the other hand, an adhesive which is too sticky can tear or irritate elderly subjects' fragile skin. Therefore, demonstrating acceptable adhesion characteristics in elderly people is considered essential.
- The results of the submitted dermal safety study ROTI-12128 indicate that the local irritation and sensitization was comparable between the Mylan's product and UCB UK's Neupro® Patch.

  However, ROTI-12128 was designed based on Draft FDA Guidance for Rotigotine Transdermal Systems (Recommended June 2012/Revised October 2016). FDA recommendations on the dermal safety study are slightly different in comparison to the EMA recommendations with regard to study design. The EMA Guideline suggests an active- and placebo-controlled, multiple-dose, three-phase, parallel-group design. Within Group 1 subjects should apply test, reference, and placebo patches daily for 21 consecutive days, whereas Group 2 subjects should apply the patches three times a week over the period of 21 days (a total of nine applications). The FDA recommends a 1 group design. Subjects should apply test and reference patches daily for 21 consecutive days. Placebo/negative control is considered optional.

Since the daily application is in line with treatment recommendations made in the SmPC of Neupro®, the testing of only one scheme (daily for 21 consecutive days) could be considered acceptable. The absence of a placebo arm is also acceptable for this case, as the main issue should be to show non-inferiority to the reference product.

Furthermore, the study was conducted in healthy subjects randomized to wear a die-cut of the test product and a die-cut of each reference product on the abdomen, resulting in total rotigotine delivery of 1 mg per day. The above mentioned FDA Draft Guidance on Rotigotine (June 2012), states that there is lack of current safety data to support the use of more than 1 mg/24 hour rotigotine delivery on the same subject during a 21- day cumulative irritation and sensitization study. Guidance also states that if both the reference and test product are a matrix design, then the patches may be cut and both products worn simultaneously on separate skin sites.

The EMA Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms however does not mention the possibility of using die-cut of patches. In case simultaneous application of test and reference is impossible (as doubled amount of API might have life-threatening consequences) the use of a lower strength is recommended for size proportional formulations. Therefore, the applicant is requested to discuss whether and how the results could possibly be influenced by the use of die-cut of the patches instead of intact, whole patches.

- Furthermore it is noticed, that the applicant has not provided any data/results on phototoxicity testing, as requested in the EMA guidance. These data need to be provided, unless otherwise justified.
- Mylan is requesting a biowaiver for the additional strengths. According to the current Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr 1) for TDDS, a bioequivalence study investigating only one strength may be acceptable provided that:

- the qualitative composition is the same for all strengths;
- the strengths are proportional to the effective surface area of the patch and the lower dose strengths can be considered as ''partial'' areas of the highest dose strength;
- dissolution/release profiles are similar.

The provided data show that the qualitative composition is the same for all strengths and that Mylan´s rotigotine transdermal 1mg/24h, 2mg/24h, 3mg/24h 4mg /24h, 6mg/24h and 8mg/24h patches are proportional in formulation, i.e. composition is the same and the strength is proportional to the effective surface area of the patch.

f2 values > 50 have been presented for the QC Medium(Phosphate Buffer, pH 4.5), suggesting that the dissolution profiles are similar. No f2 value calculation was submitted for the other dissolution media. According to the current Guideline on the Investigation of bioequivalence dissolution profiles may be accepted as similar without further mathematical evaluation, where more than 85% of the drug is dissolved within 15 minutes. This does not apply to Rotigotine Mylan Transdermal system and the applicant is requested to provide f2 values for the additional media.

Regarding safety, a comparable safety profile has been demonstrated across all 3 studies.

3.3.7. Conclusions on clinical aspects

This marketing authorisation application (MAA) for Rotigotine Mylan 1 mg/24 h, 2 mg/24 h, 3 mg/24 h, 4 mg/24 h, 6 mg/24 h,8 mg/24 h transdermal patch is based upon „essential similarity“ to the

reference medicinal product Neupro 1mg/24h, 2mg/24h, 3mg/24h, 4mg/24h, 6mg/24h, 8mg/24h transdermal patches (UCB Manufacturing Ireland Ltd) in accordance with Article 10.1 of Directive 2001/83/EC, as amended.

Article 10(1) of European Directive 2001/83/EC (as amended) states that the applicant shall not be required to provide the results of clinical testing if it can be demonstrated that the product is essentially similar to a product which has been authorised within the European Union for 6-10 years (depending on territory) provided that the product is intended for the same therapeutic use at the same dosage and route of administration as the existing authorised product:

- The reference medicinal product was first authorised for use in the European Union on 15th February 2006.
- Rotigotine Mylan transdermal patches have the same active ingredient, Rotigotine, and the same amount of active substance released per unit time as compared to the reference TDDS, Neupro®. Furthermore, Rotigotine Mylan transdermal patches are intended for the same therapeutic use at the same dosage and route of administration as the reference product.
- In order to show essential similarity with the reference product in terms of safety and efficacy, pharmacokinetic studies (single-dose and multiple-dose) and clinical adhesion, cumulative irritation and sensitization studies have been conducted.
- The proposed SmPC for the applicant's rotigotine transdermal system is based on the UCB Pharma Limited SmPC for Neupro® (rotigotine) transdermal patch.
- An adequate clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of Rotigotine based on published literature has been provided. This expert report is compliant with the format outlined in Volume 2B of Notice to applicants, Medical products for human use, Presentation and format of the dossier Module 2, July 2003.

In principle, the submitted studies (single-dose and multiple-dose PK studies, clinical adhesion, cumulative irritation and sensitization studies) could be adequate for showing in-vivo bioequivalence between the test and reference products. However, as the adhesion study was an integrated part of the single dose PK study (conducted in healthy young adults), comparable adhesion has not been demonstrated in the elderly population. Parkinson's disease typically occurs in people over the age of 60. Thus, in order to ensure comparable adhesion properties between test and reference product in the elderly population, the applicant will need to provide additional data, unless otherwise justified. This is in accordance with the relevant EMA guideline EMA/CPMP/EWP/280/96 Corr1.

At present there are several open clinical issues, including also one major objection regarding the adhesion assessment, which need to be adequately addressed and solved (see section "Discussion on clinical aspects").

The measures necessary to address the clinical issues are detailed in the *List of questions.*

3.4. Risk management plan

Safety concerns

The applicant identifies the following safety concerns

Table 7: Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Application site skin reactions - Sleep attacks and somnolence - Postural/orthostatic hypotension
Important potential risks	- Cardiovascular fibrosis (bases on data on other dopamine agonists) - Effect on retina (based on non-clinical data) - Neuroleptic malignant syndrome after abrupt withdrawals (class effect)
Missing information	- Use in patients with severe hepatic impairment

The Committee considers that the following issues should be addressed:

In line with the reference product, the Rapporteur considers that the following should also be safety concerns:

As important identified risks:

- Impulse control and compulsive disorders
- Augmentation in RLS

As important potential risk:

- Rebound in RLS

In line with the reference product, the Rapporteur considers that the following should not be a safety concern:

- Cardiovascular fibrosis (bases on data on other dopamine agonists)

In line with the reference product, instead of “sleep attacks and somnolence” the wording “sleep attacks/sudden onset of sleep” should be used throughout the RMP.

Pharmacovigilance plan

The applicant has discussed how the safety concerns from module SVIII are proposed to be addressed within the pharmacovigilance plan. For all the safety concerns proposed by the applicant in the Summary of safety concerns it is proposed routine pharmacovigilance, to closely monitor, evaluate and further characterize the risk.

The applicant states that the routine pharmacovigilance system will ensure compliance with regulatory agency for pharmacovigilance responsibilities and will be sufficient to address and monitor the safety profile of rotigotine.

Committee comment:

The applicant proposes only routine pharmacovigilance activities for all the listed safety concerns which is endorsed.

Summary of planned additional PhV activities from RMP

Not applicable, since no additional pharmacovigilance studies/activities are conducted or planned by Mylan SAS for its product of Rotigotine Mylan, 1 mg/24h, 2 mg/24h, 3 mg/24h, 4 mg/24h, 6 mg/24h and 8 mg/24h, transdermal patch, under centralised marketing authorisation application in the EU.

Committee comment:

No additional Pharmacovigilance activities are proposed or deemed necessary.

Additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures

No such risk minimisation measures are planned for the above listed safety concerns of the applicant's products of Rotigotine Mylan, 1 mg/24h, 2 mg/24h, 3 mg/24h, 4 mg/24h, 6 mg/24h and 8 mg/24h, transdermal patch, under centralised marketing authorisation application which would require the use of non-routine pharmacovigilance activities to measure the effectiveness.

Committee comment:

No additional pharmacovigilance activities to assess the effectiveness of risk minimization measures are deemed necessary for any of the proposed safety concerns.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that, in line with the reference product, for all proposed safety concerns routine PhV is considered sufficient and no additional pharmacovigilance activities are required.

The PRAC Rapporteur also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Proposal from applicant for risk minimisation measures:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: application site skin reactions	Section 4.4 of the SPC contain adequate information on application site skin reactions Section 4.8 of the SPC contain adequate information on application site skin reactions	None
Sleep attacks and somnolence	Section 4.4 of the SPC contain adequate information on sleep attacks and somnolence Section 4.8 of the SPC contain adequate information on sleep attacks and somnolence	None
Postural/orthostatic hypotension	Section 4.4 of the SPC contain adequate information on postural/orthostatic hypotension Section 4.8 of the SPC contain adequate information on postural/orthostatic hypotension	None
Important potential risks: Cardiovascular fibrosis (based on data on other dopamine agonists),	Section 4.4 of the SPC contain adequate information on cardiovascular fibrosis	None
Effect on retina (based on non-clinical data),	Section 4.4 of the SPC contain adequate information on effect on retina Section 4.8 of the SPC contain adequate information on effect on retina	None
Neuroleptic malignant syndrome after abrupt withdrawal (class effect).	Section 4.4 of the SPC contain adequate information on neuroleptic malignant syndrome after abrupt withdrawal	None
Missing information: Use in patients with severe hepatic impairment	Sections .2 and 5.2 of the SPC contain adequate information on severe hepatic impairment patients.	None

Committee comment:

Routine risk minimisation measures for the proposed safety concerns are adequate and correct. The applicant, however, has not mentioned all the routine RMMs to address:

- '**Application site skin reactions**' - in addition to the warnings in section 4.4 and being listed in section 4.8, this risk has also important information concerning method of administration in **section 4.2**;

- '**Sleep attacks and somnolence**' - in addition to the warnings in section 4.4 and being listed in section 4.8, this risk has a warning concerning the possible additive effects with the concomitant use of sedating medicinal products, other CNS depressants or alcohol in **section 4.5,** and also a warning concerning driving and engaging other activities that may place patient at risk in **section 4.7**.

Therefore the relevant table should be updated to include those references. All other relevant parts of the RMP should be updated accordingly.

Additionally, for the missing information "**Use in patients with severe hepatic impairment"** the table should also be amended as there is a typo regarding one of the sections that contains important information to minimize this risk (should mention section **4.2** and 5.2 instead of .2 and 5.2).

Additional risk minimisation measures

The applicant proposed only routine risk minimisation measures for the proposed safety concerns.

Committee comment:

For all proposed safety concerns, we agree that no additional risk minimisation measures are deemed necessary.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted, was of the opinion that:

In line with the reference product, the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications provided that the applicant updates the table of risk minimisation measures to include reference to all SmPC sections with important information to minimise the following risks:

- 'Application site skin reactions' - in addition to the warnings in section 4.4 and being listed in section 4.8, this risk has also important information concerning method of administration in section 4.2;

- 'Sleep attacks and somnolence' - in addition to the warnings in section 4.4 and being listed in section 4.8, this risk has a warning concerning the possible additive effects with the concomitant use of sedating medicinal products, other CNS depressants or alcohol in section 4.5, and also a warning concerning driving and engaging other activities that may place patient at risk in section 4.7.

Additionally, for the missing information "**Use in patients with severe hepatic impairment"** the table should also be amended as there is a typo regarding one of the sections that contains important information to minimize this risk (should mention section **4.2** and 5.2 instead of .2 and 5.2).

All relevant sections of the RMP should be updated accordingly.

Conclusion

The RMP could be acceptable provided an updated RMP and satisfactory responses to the list of questions below is submitted.

The PRAC Rapporteur having considered the data submitted was of the opinion that, in line with the reference product, for all proposed safety concerns, routine PhV is considered sufficient and no additional pharmacovigilance activities are required.

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications, provided that the applicant, in line with the reference product, updates the table of risk minimisation measures to mention all the SmPC sections with important information to minimise the proposed safety concerns.

The RMP Part III-VI could be acceptable provided an updated RMP and satisfactory responses to the list of questions (section 3).

The Applicant has provided a RMP in support of its application for a generic product, which is not different from the reference product Neupro/Leganto in terms of dose, formulation or indication that would have any implications for safety.

3.5. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

As the pharmacovigilance system summary has not been dated, an update should be provided.

4. Benefit/risk assessment

The application contains adequate non-clinical data; the quality and clinical data, however, are inadequate.

Currently the clinical data are considered inadequate as bioequivalence has not been sufficiently shown in terms of comparable adhesion properties. The raised major quality issues concern the pharmaceutical development, the manufacture - process validation and/or evaluation and the batch analyses.

The aspects that are inadequately demonstrated are outlined in the body of this document.

A benefit/risk ratio comparable to the reference product can therefore not be concluded at present.

4.1. Conclusions

The overall B/R of Rotigotine Mylan 1 mg/24 h, 2 mg/24 h, 3mg/24 h, 4 mg/24 h, 6 mg/24 h and 8 mg/24 h transdermal patch is currently negative.

5. Recommended conditions for marketing authorisation and product information in case of a positive benefit risk assessment

*5.1. Proposed list of post-authorisation measures**

N/A at present

Post-authorisation measure(s)	Motivation
Proposed post-authorisation measure 1 with proposed classification:	Motivation/Background information on measure, including due date:
1.	
Proposed post-authorisation measure 2 with proposed classification:	Motivation/Background information on measure, including due date:
2.	
Proposed post-authorisation measure 3 with proposed classification:	Motivation/Background information on measure, including due date:
3.	
Proposed post-authorisation measure X with proposed classification:	Motivation/Background information on measure, including due date:
X.	

* Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other studies reflected only in the RMP (non-clinical, PK, PASS)

Proposed list of recommendations:

N/A at present

5.2. Other conditions

N/A at present

5.3. Summary of product characteristics (SmPC)

The SmPC, Labelling and Package Leaflet are largely in line with the respective documents of the Originator..

5.4. Labelling

As above.

5.5. Package leaflet (PL)

As above.

User consultation

The applicant is asked to provide the QRD form for submission and assessment of user testing bridging proposals [EMA/355722/2014]. All sections of this form should be completed by the applicant and submitted for assessment.

Quick Response (QR) code

N/A