Public Assessment Report

UK PAR

Midotense 2.5 mg tablets
(Miodrine hydrochloride)

UK Licence No: PL 14308/0016

Transdermal Limited
LAY SUMMARY

Midotense 2.5mg tablets

(Midodrine hydrochloride)

The product may be referred to as ‘Midotense’ in this Lay summary.

This is a summary of the Public Assessment Report (PAR) for Midotense 2.5mg tablets (PL 14308/0016). It explains how the application for Midotense 2.5mg tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Midotense 2.5mg tablets.

The product may be referred to as ‘Midotense’ in this Lay summary.

For practical information about using Midotense, patients should read the package leaflet or contact their doctor or pharmacist.

What is Midotense and what is it used for?
Midotense is a ‘generic’ medicine. This means that Midotense is similar to a reference medicine already authorised in the European Union (EU) called Gutron 2.5mg, Tablets (Takeda, France). Midotense is used to treat certain severe forms of low blood pressure in adults when other treatments have not worked.

How does Midotense work?
Midotense contains the active substance midodrine hydrochloride, which belongs to a group of medicines called adrenergic and dopaminergic agents.

How is Midotense used?
Midotense is available as tablets and is taken by mouth (orally). This medicine may be taken with or without food.

Midotense can only be obtained with a prescription. This medicine should always be taken exactly as told by the doctor. The patient should check with the doctor or pharmacist if not sure.

The doctor will decide your dose and tell you how long you should take this medicine. The treatment is usually long-term.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

What benefits of Midotense has been shown in studies?
As Midotense is a generic medicine, studies have been limited to tests to determine that Midotense is bioequivalent to the reference medicine Gutron 2.5mg, Tablets (Takeda, France). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Midotense?
Because Midotense is a generic medicine and bioequivalent to the reference medicine Gutron 2.5mg, Tablets (Takeda, France), the possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Midotense, see section 4 of the package leaflet.
For the full list of restrictions, see the package leaflet.

**Why is Midotense approved?**
It was concluded that, in accordance with EU requirements, Midotense has been shown to have comparable quality and to be bioequivalent to Gutron 2.5mg, Tablets (Takeda, France). Therefore, the view was that, as for Gutron 2.5mg, Tablets (Takeda, France), the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Midotense?**
A Risk Management Plan has been developed to ensure that Midotense is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Midotense, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Midotense**
A Marketing Authorisation was granted in the UK on 23 May 2017.

The full PAR for Midotense follows this summary.

For more information about treatment with Midotense, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2017.
SCIENTIFIC DISCUSSION

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Scientific Discussion

I  **INTRODUCTION**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Transdermal Limited a Marketing Authorisation for the medicinal product Midotense 2.5mg tablets (PL 14308/0016) on 23 May 2017. The product is a Prescription Only Medicine (POM) indicated in adults for the treatment of severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate.

The product may be referred to as ‘Midotense’ in this Scientific discussion.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the originator medicinal product Gutron 2.5mg, Tablets (Takeda, France; original Marketing Authorisation to NYCOMED, France), which was first authorised on 16 June 1992 in the Community via the Centralised Procedure.

The active substance in Midotense 2.5mg tablets is midodrine hydrochloride. Midodrine hydrochloride is the pro-drug of the pharmacologically active desglymidodrine which is a sympathomimetic with a selective action on peripheral alpha1-adrenergic receptors. It is suggested that midodrine can raise blood pressure through an increase in vascular smooth muscle tone and peripheral arterial resistance.

One bioequivalence study was submitted to support this application, comparing the applicant’s test product Midodrine tablets, 2.5 mg (Actavis Group PTC ehf, Iceland) with the reference product Gutron (Midodrine) 2.5 mg tablets (NYCOMED, under fasting conditions. It is stated that the the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki.

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that the subject of this application is a generic medicinal product of an originator product that have been licensed for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of using Midotense outweigh the risks and a Marketing Authorisation was granted.

II  **QUALITY ASPECTS**

II.1  **Introduction**

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Midotense are white to off-white, 7 mm round, flat tablet with scoreline on one side. Each tablet contains 2.5 mg of midodrine hydrochloride.

The product also contains pharmaceutical excipients in the tablet core and coating, namely microcrystalline cellulose, pregelatinised starch, magnesium stearate, anhydrous silica colloidal and talc. Appropriate justification for the inclusion of each excipient has been provided.
The finished product is supplied in aluminium blisters in cartons of 30 or 90 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE
Midodrine hydrochloride

INN: Midodrine hydrochloride
Chemical name: (R,S)-2-Amino-N-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]acetamide hydrochloride 1-(2',5'-dimethoxyphenyl)-2-glycinamidoethanol hydrochloride.

Structural formula:

\[
\text{C}_{12}\text{H}_{18}\text{N}_{2}\text{O}_{4}\cdot\text{HCl}
\]

Molecular formula: \( \text{C}_{12}\text{H}_{18}\text{N}_{2}\text{O}_{4}\cdot\text{HCl} \)

\( M_r \): 290.74

Appearance: White crystalline powder, odourless

Solubility: Slightly soluble in methanol.

Midodrine hydrochloride is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable tablets, each containing 2.5 mg of midodrine hydrochloride, which were bioequivalent to Gutron 2.5mg, Tablets (Takeda, France). Suitable pharmaceutical development data have been provided for this application.
Comparative *in-vitro* dissolution profiles have been provided for this product and the reference product. The dissolution profiles were satisfactory.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

**Control of Finished Product**
The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that complies with the release specification. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with special storage instructions of ‘Store in the original package in order to protect from moisture,’ has been accepted. This medicinal product does not require any special temperature storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted for this application, from a quality point of view.

**III NON-CLINICAL ASPECTS**
**III.1 Introduction**
The pharmacodynamic, pharmacokinetic and toxicological properties of midodrine hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

**III.2 Pharmacology**
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.
III.3 Pharmacokinetics
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of already authorised product, it is not expected that environmental exposure of midodrine hydrochloride will increase following approval of the Marketing Authorisation for the proposed product. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction.
The clinical pharmacology of midodrine hydrochloride is well-known. With the exception of data from the bioequivalence study detailed in Section IV.2, Pharmacokinetics below, no new pharmacokinetic data is provided or required for this application.

IV.2 Pharmacokinetics
The clinical pharmacology of midodrine hydrochloride is well-known. In support of the application, the applicant submitted the following bioequivalence study:

An open-label, randomised, two-treatment, two-sequence, two-period, single-dose, crossover, bioequivalence study comparing the test product Midodrine tablets, 2.5 mg (Actavis Group PTC ehf, Iceland) versus the reference product Gutron (Midodrine) 2.5mg tablets(NYCOMED, France) in healthy adult subjects under fasting conditions.

Subjects were administered a single oral dose of either the test or reference product with 240 ml of water at room temperature after an overnight fast. Blood sampling was performed pre-dose and up to 12 hours post dose in each treatment period. A washout period of three days was kept between each consecutive dosing period. A summary of the pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Geometric Mean Ratio Test/Ref (%)</th>
<th>Confidence Intervals (%)</th>
<th>CV% (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;(0-t)&lt;/sub&gt;</td>
<td>103.26</td>
<td>98.29 to 108.49</td>
<td>11.28</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>96.08</td>
<td>84.00 to 109.89</td>
<td>31.31</td>
</tr>
</tbody>
</table>

**Bioequivalence Discussion and Conclusion**
The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80.00% to
125.00% for C\textsubscript{max} and AUC values. The results indicate that the bioequivalence criteria are met for midodrine as the AUC\textsubscript{(0-t)} and C\textsubscript{max} values lie within acceptance limits. Hence, the data from this study support the claim that the applicant’s test product is bioequivalent to the reference product, Gutron (Midodrine) 2.5mg tablets (NYCOMED, France), under fasting conditions.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of midodrine hydrochloride are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
The clinical efficacy of midodrine hydrochloride is well-known. No new efficacy data are presented or are required for an application of this type.

IV.5 Clinical Safety
No new safety data were submitted and none are required for an application of this type. No new or unexpected safety issues arose during the bioequivalence study.

IV.6 Risk Management Plan
The MAH has submitted a Risk Management Plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Midotense.

A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine hypertension</td>
</tr>
<tr>
<td></td>
<td>Reflex bradycardia</td>
</tr>
<tr>
<td></td>
<td>Drug interactions with sympathomimetic and other vasopressor agents</td>
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<tr>
<td></td>
<td>Drug interactions with digitalis, ergot derived dopamine agonists and ergot alkaloid vasocostrictors</td>
</tr>
<tr>
<td></td>
<td>Urinary retention</td>
</tr>
<tr>
<td></td>
<td>Increased intra-ocular pressure</td>
</tr>
<tr>
<td></td>
<td>Exacerbation of symptoms in patients with thyrotoxicosis</td>
</tr>
<tr>
<td></td>
<td>Exacerbation of symptoms in patients with phaeochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Toxicity due to accumulation in patients with severe renal impairment</td>
</tr>
<tr>
<td></td>
<td>Important potential risks</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Missing information</td>
<td>Use in Pregnancy and Lactation</td>
</tr>
<tr>
<td></td>
<td>Use in hepatic impairment</td>
</tr>
<tr>
<td></td>
<td>Use in children under &lt;18 years</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted, from a clinical point of view.
V. USER CONSULTATION
A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the package information leaflet (PIL) was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Midotense are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of midodrine hydrochloride are well-known, no additional data were required.

Efficacy
Bioequivalence has been demonstrated between the applicant’s test product and the reference product Gutron (Midodrine) 2.5mg tablets (NYCOMED, France), under fasted conditions.

SAFETY
No new data were submitted and none are required for an application of this type. As the safety profile of midodrine hydrochloride is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with midodrine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the marketed reference product. The overall benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
**Midotense 2.5mg tablets**

(Midodrine hydrochloride)

**PL 14308/0016**

### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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