Public Assessment Report

UKPAR

Indoramin 20 mg Tablets

(Indoramin hydrochloride)

UK Licence No: PL 41830/0043

NRIM Limited
LAY SUMMARY

Indoramin 20 mg Tablets
(Indoramin hydrochloride, tablets, 20 mg)

This is a summary of the Public Assessment Report (PAR) for Indoramin 20 mg Tablets (PL 41830/0043). It explains how Indoramin 20 mg Tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Indoramin 20 mg Tablets.

For practical information about using Indoramin 20 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Indoramin 20 mg Tablets and what are they used for?
Indoramin 20 mg Tablets is a ‘generic medicine’. This means that Indoramin 20 mg Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Limited).

Indoramin 20 mg Tablets are used for:
- A condition where your prostate becomes bigger, called ‘benign prostatic hyperplasia’ or BPH. The prostate is a gland found underneath the bladder in men. It surrounds the tube (called the urethra) which carries urine from the bladder to the outside of the body.

If the prostate gland becomes bigger, it may squeeze on the urethra and make it hard for the patient to pass urine.
When the patient’s prostate grows:
- the flow of their urine may be weaker or they may have to pass urine more often than before
- this can happen during the day or the patient can find they have to get up more often during the night
- the patient may have to wait for the flow of their urine to start
- the patient may find it difficult to stop the flow of their urine completely
As men get older their prostate grows in size and some men will suffer these symptoms.

- Patients who do not need or want an operation and also for patients waiting for an operation.

How do Indoramin 20 mg Tablets work?
Indoramin 20 mg Tablets contain the active ingredient indoramin (as the hydrochloride), which belongs to a group of medicines called ‘alpha-blockers’ (also called alpha adrenoceptor antagonists). They work by relaxing the muscles in the patient’s bladder, prostate gland and the tube that carries urine from the bladder to the outside of the body. This will help the patient’s urine flow better.

How are Indoramin 20 mg Tablets used?
The pharmaceutical form of Indoramin 20 mg Tablets is a tablet and the route of administration is oral.

The patient must always take indoramin exactly as their doctor has told them to. The patient must check with their doctor or pharmacist if they are not sure.

The recommended dose is one tablet (20 mg) twice a day. The tablet should be swallowed with water. Some elderly patients may need just one tablet at night.
The patient’s doctor may increase their dose to a maximum total daily dose of 100 mg. The patient must not take more than their doctor has recommended.
The patient must not stop taking indoramin without talking to their doctor first. If the patient stops taking their tablets, their symptoms may come back.

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

This medicine can only be obtained with a prescription.

**What benefits of Indoramin 20 mg Tablets have been shown in studies?**

As Indoramin 20 mg Tablets is a generic medicine, studies in patients have been limited to tests to determine that the tablets are similar to the reference medicine, Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Indoramin 20 mg Tablets?**

Because Indoramin 20 mg Tablets is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with Indoramin 20 mg Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why was Indoramin 20 mg Tablets approved?**

It was concluded that, in accordance with EU requirements, Indoramin 20 mg Tablets have been shown to have comparable quality and to be bioequivalent to Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Ltd). Therefore, the MHRA decided that, as for Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Limited) the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Indoramin 20 mg Tablets?**

A risk management plan (RMP) has been developed to ensure that Indoramin 20 mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Indoramin 20 mg Tablets 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/healthcare professionals will be monitored/reviewed continuously.

**Other information about Indoramin 20 mg Tablets**

A Marketing Authorisation was first granted in the UK on 08 December 2014.

The full PAR for Indoramin 20 mg Tablets follows this summary.

For more information about treatment with Indoramin 20 mg Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2015.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted NRIM Limited, a marketing authorisation for the medicinal product Indoramin 20 mg Tablets (PL 41830/0043). The product is a prescription-only medicine (POM) indicated in adults for conditions in which alpha blockade is indicated and the management of urinary outflow obstruction due to benign prostatic hyperplasia.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross-referring to Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets which was originally licensed on 21 January 1988 in the UK to Smithkline & French Laboratories Limited (PL 00002/0168) and subsequently underwent a change of ownership procedure on 03 March 2008 to the current Marketing Authorisation Holder (MAH) Chemidex Pharma Limited (PL 17736/0089).

The active ingredient, indoramin, is an alpha adrenoreceptor blocking agent. It acts selectively and competitively on post-synaptic alpha-1 receptors, causing a decrease in peripheral resistance. It also produces relaxation of hyperplastic muscle in the prostate.

One bioequivalence study was submitted to support this application comparing the applicant’s test product Indoramin 20 mg Tablets with the reference product Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Limited) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical Practises (GCP) requirements.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on a product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Indoramin 20 mg Tablets outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 22 mg of the active ingredient indoramin hydrochloride equivalent to 20 mg of indoramin. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, magnesium stearate, polacrillin potassium and the tablet film coat Opadry yellow 02B520014 (which consists of hypromellose, titanium dioxide (E 171), polyethylene glycol, yellow iron oxide (E172) and black iron oxide (E172)). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is packed into polyvinyl chloride (PVC)/polyvinliden chloride (PVDC)-aluminium blisters containing 60 tablets per carton. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance
INN: Indoramin hydrochloride
Structural formula:

![Indoramin Hydrochloride Structural Formula](image)

Molecular formula: $\text{C}_{22}\text{H}_{26}\text{ClN}_{3}\text{O}$
Molecular mass: 383.5 g/mol
Appearance: A white to off-white crystalline powder.
Solubility: Weakly soluble in water and soluble in methanol.

Indoramin hydrochloride is 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.

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.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

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, film-coated tablets containing 20 mg indoramin (as the hydrochloride) per tablet that are bioequivalent to the reference product Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Limited). A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity and *in-vitro* dissolution profiles have been provided for the proposed and originator product.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of polacrilin potassium which is controlled to United States Pharmacopeia-National Formulary standards (USP-NF) and the tablet film coat Opadry yellow 02B520014 which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

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

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation on future commercial-scale batches.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. 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. The data from these studies support a shelf-life of 24 months with no special storage conditions.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Indoramin 20 mg Tablets is presented below:
Each tablet contains '20mg' of indoramin hydrochloride equivalent to '20mg' of indoramin.
Each film-coated tablet contains '172.5mg' of lactose (as lactose monohydrate).
For oral administration.
Read the package leaflet before use.
This medicinal product does not require any special storage conditions.
Keep out of the sight and reach of children.
Use as directed by your physician.

Indoramin Tablets
60 Tablets

92mm x 71mm
III  NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of indoramin are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report 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
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Indoramin 20 mg Tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV  CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of indoramin is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of indoramin.

Based on the data provided, Indoramin 20 mg Tablets can be considered bioequivalent to Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Limited).
IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY
An open label, balanced, randomised, two-treatment, two-sequence, two-period, two-group, single dose, two way crossover study to compare the pharmacokinetics of the applicant’s test product Indoramin 20 mg Tablets (NRIM Limited) versus the reference product, Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Limited), in healthy adult subjects under fasting conditions.

The subjects were administered a single dose (20 mg) of either the test or the reference product with 240 ml of water, after an overnight fast.

Blood samples were collected before and up to and including 72 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Geometric Least Squares Means and it’s ratio</th>
<th>Intra subject %CV</th>
<th>90% Confidence Interval</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product (A)</td>
<td>Reference Product (B)</td>
<td>(T/R)%</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>8.549</td>
<td>8.640</td>
<td>98.95</td>
<td>21.64</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (hr*ng/mL)</td>
<td>69.685</td>
<td>68.172</td>
<td>102.22</td>
<td>14.34</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (hr*ng/mL)</td>
<td>73.271</td>
<td>71.972</td>
<td>101.80</td>
<td>19.89</td>
</tr>
</tbody>
</table>

AUC<sub>0-inf</sub> area under the plasma concentration-time curve from time zero to infinity
AUC<sub>0-t</sub> area under the plasma concentration-time curve from zero to t hours
C<sub>max</sub> maximum plasma concentration

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC, and C<sub>max</sub> values for indoramin lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Limited).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (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 Indoramin 20 mg Tablets.

A summary table of safety concerns as approved in RMP is listed as follows:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Exacerbation of Parkinson's disease</td>
</tr>
<tr>
<td></td>
<td>• Exacerbation of heart failure</td>
</tr>
<tr>
<td></td>
<td>• Exacerbation of depression</td>
</tr>
<tr>
<td></td>
<td>• Exacerbation of epilepsy</td>
</tr>
<tr>
<td></td>
<td>• Use in liver impairment</td>
</tr>
<tr>
<td></td>
<td>• Use in renal impairment, including reduced renal clearance in the elderly</td>
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<tr>
<td></td>
<td>• Orthostatic hypotension and syncope</td>
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<tr>
<td></td>
<td>• Hypersensitivity reactions including rash and pruritus</td>
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<tr>
<td></td>
<td>• Interaction with - monoamine oxidase inhibitors</td>
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<tr>
<td></td>
<td>• Interaction with - anti-hypertensives or drugs with hypotensive properties such as diuretics,</td>
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<tr>
<td></td>
<td>beta blockers and mexitolysys</td>
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<tr>
<td></td>
<td>• Interaction with drugs which can induce drowsiness such as antidepressants, anxiolytics,</td>
</tr>
<tr>
<td></td>
<td>hypnotics, narcotic analgesics, antihistamines and alcohol</td>
</tr>
<tr>
<td></td>
<td>Important potential risks</td>
</tr>
<tr>
<td></td>
<td>• Intraoperative Floppy Iris Syndrome</td>
</tr>
<tr>
<td></td>
<td>• Interaction with herbal, vitamin and complementary medicines</td>
</tr>
</tbody>
</table>

| Missing information | Use in pregnancy and lactation |

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimisation activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td>Routine pharmacovigilance activities are considered sufficient and no further actions are required.</td>
<td>Important identified risks are adequately described in the product information. No further risk management activities are necessary.</td>
</tr>
<tr>
<td>Exacerbation of Parkinson's disease</td>
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<td>Exacerbation of heart failure</td>
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<tr>
<td>Interaction with herbal, vitamin and complementary medicines</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Missing information</strong></td>
<td>Routine pharmacovigilance activities are considered sufficient and no further actions are required.</td>
<td>Missing information is adequately described in the product information.</td>
</tr>
<tr>
<td>Use in pregnancy and lactation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety concern</strong></td>
<td>Proposed pharmacovigilance activities (routine and additional)</td>
<td>Proposed risk minimisation activities (routine and additional)</td>
</tr>
<tr>
<td></td>
<td>actions are required.</td>
<td>No further risk management activities are necessary.</td>
</tr>
</tbody>
</table>
The RMP for Indoramin 20 mg Tablets adequately documents the safety concerns for the product. Routine pharmacovigilance and risk minimisation are sufficient for the safety concerns in the RMP, given the established benefit-risk profile of indoramin and the information available to inform decisions on the balance of benefits and risks when it is used in clinical practice.

IV.7 Discussion on the clinical aspects

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Indoramin 20 mg Tablets and the reference product Doralese Tiltab Tablets 20 mg/Indoramin 20 mg Tablets (Chemidex Pharma Limited), under fasting conditions.

The grant of a marketing authorisation is recommended for this application.

V User consultation

The 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. The language used for the purpose of user testing the 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

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with indoramin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.