UKPAR

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LORATADINE 10MG TABLETS
SELRIZ 10MG TABLETS
PL 33410/0078 & 0082

LAY SUMMARY

The MHRA granted licences for the medicinal products Loradine 10mg Tablets and Selariz 10mg Tablets (PL 33410/0078 & 0082) to APSLA Limited on 2 May 2012 and 30 April 2012, respectively. Loradine 10mg Tablets is a Pharmacy medicine (legal status ‘P’) and Selariz 10mg Tablets is a General Sales Licence medicine (legal status ‘GSL’). Both are indicated to relieve symptoms associated with allergic rhinitis (for example, hay fever), such as sneezing, runny or itchy nose, and burning or itchy eyes. These products may also be used to help relieve symptoms of urticaria (itching, redness and number and size of hives).

These products contain the active substance loradine, which belongs to a class of medicines known as antihistamines. Antihistamines help to reduce allergic symptoms by preventing the effects of a substance called histamine, which is produced in the body.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Loradine 10mg Tablets and Selariz 10mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
LORATADINE 10MG TABLETS
SELRIZ 10MG TABLETS
PL 33410/0078 & 0082

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Loratadine 10mg Tablets and Selariz 10mg Tablets (PL 33410/0078 & 0082) to APLSA Limited on 30 April 2012 and 2 May 2012, respectively. Loratadine 10mg Tablets is a Pharmacy medicine (legal status ‘P’) and Selariz 10mg Tablets is a General Sales Licence medicine (legal status ‘GSL’). Both are indicated for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.

These applications were submitted as generic applications, according to Article 10.1 of Directive 2001/83/EC, claiming to generic medicinal products of Clarityn 10mg Tablets (Schering-Plough Limited, UK), which has been licensed in the EU for over 10 years.

These products contain the active substance loratadine. Loratadine is a long-acting antihistamine agent, exhibiting partial selectivity for peripheral histamine H₁-receptors.

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

The data from one bioequivalence study, comparing the pharmacokinetics of these products with Clarityn 10mg Tablets (Schering-Plough Limited, UK) have been submitted with these applications. The study has been conducted in accordance with the principles of Good Clinical Practice (GCP).
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Loratadine

INN: Loratadine

Structure:

Molecular formula: C_{22}H_{23}ClN_{2}O_{2}
Molecular weight: 382.9
Appearance: A white to almost white crystalline powder. Soluble in acetone and methanol, practically insoluble in water

Loratadine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance is covered by a European Directorate for the Quality of Medicines Certificate of Suitability.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, maize starch, colloidal anhydrous silica, croscarmellose sodium, talc and magnesium stearate. All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of croscarmellose sodium (which complies with a US National Formulary monograph). Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients use materials sourced from animal or human origins. The suppliers of lactose monohydrate have confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. None of the excipients are sourced from genetically modified organisms.

Product development

The objective of the pharmaceutical development programme was to produce a safe, efficacious tablet formulation that could be considered a generic medicinal product of Clarityn 10mg Tablets (Schering-Plough Limited, UK).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative dissolution profiles of the proposed product and the brand leader product have been provided and are satisfactory.
**Manufacture**
A description and flow-chart of the manufacturing method have been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of finished product and the results appear satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The finished product is packaged in polyvinylchloride/aluminium blisters in pack sizes of 7 and 14 tablets for Selariz 10mg Tablets, and 30 tablets for Loratadine 10mg Tablets. The Marketing Authorisation Holder has stated that not all pack sizes may be marketed. However, they have confirmed that mock-ups of labelling will be submitted to the regulatory authorities for approval before marketing any pack size.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with current EU regulations regarding the contact of materials with foodstuff.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, with the storage instructions ‘Store in original package’.

**ADMINISTRATIVE**

**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SmPC)**
These are pharmaceutically satisfactory.

**Labelling**
These are pharmaceutically satisfactory.

**Patient Information Leaflet (PIL)**
These are pharmaceutically satisfactory.

The results of the PIL user testing have been submitted. These indicate that the PILs are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.
MAA Forms
These are pharmaceutically satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of loratadine are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As these products are intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of these products from a non-clinical viewpoint.
CLINICAL ASSESSMENT

Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product loratadine 10mg tablets versus the reference product Clarityn 10mg Tablets (Schering-Plough Limited, UK) in healthy adult subjects under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The two treatment arms were separated by a 14-day washout period.

The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) for loratadine and its active metabolite desloratadine are presented below:

<table>
<thead>
<tr>
<th>Loratadine Parameters (Units)</th>
<th>In-transformed Data</th>
<th>Geometric Least Squares Mean</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-B</td>
<td>Reference Product-A</td>
<td>Ratio (B/A)%</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>7.58</td>
<td>7.64</td>
<td>98.78</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.h/mL)</td>
<td>16.91</td>
<td>16.57</td>
<td>101.91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Desloratadine Parameters (Units)</th>
<th>In-transformed Data</th>
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<td>Test Product-B</td>
<td>Reference Product-A</td>
<td>Ratio (B/A)%</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>4.16</td>
<td>4.33</td>
<td>95.87</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.h/mL)</td>
<td>37.99</td>
<td>38.97</td>
<td>97.38</td>
</tr>
</tbody>
</table>

C_{max} – Maximum concentration
AUC – Area under the curve

The 90% confidence intervals for C_{max} and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

Efficacy
No new data on the efficacy have been submitted and none are required for these applications.

Safety
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.
**SmPC, PIL and Labels**
The SmPCs, PIL and labels are medically acceptable. The SmPCs are consistent with those for the originator products.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**
The grant of marketing authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Loratadine 10mg Tablets and Sellariz 10mg Tablets (PL 33410/0078 and 0082, respectively) 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 applications of this type. A suitable justification for non-submission of an Environmental Risk Assessment has been provided.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s product and the brand leader product Clarityn 10mg Tablets (Schering-Plough Limited, UK).

No new or unexpected safety concerns arose from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the brand leader product are interchangeable. Extensive clinical experience with loratadine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is therefore considered to be positive.
LORATADINE 10MG TABLETS
SELRIZ 10MG TABLETS
PL 33410/0078 & 0082

STEPS TAKEN FOR ASSESMENT

1. The MHRA received the marketing authorisation applications on 23 November 2009

2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 14 & 15 December 2009

3. Following assessment of the applications, the MHRA requested further information relating to the pharmaceutical dossier on 17 June 2010 and 27 April 2011, and clinical dossier on 23 April 2010

4. The applicant responded to the MHRA’s requests, providing further information relating to the pharmaceutical dossier on 19 April 2011 and 20 February 2012, and on the clinical dossier on 27 September 2010

5. The applications were determined on 30 April 2012 and 2 May 2012
LORATADINE 10MG TABLETS
SELRIZ 10MG TABLETS
PL 33410/0078 & 0082

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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

1 NAME OF THE MEDICINAL PRODUCT
Loratadine 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg loratadine.

Each Loratadine 10 mg tablet contains 72.50 mg of lactose monohydrate

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablets
White colored, circular, flat beveled uncoated tablets, with central breakline on one side and L on the other side.

The central break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Loratadine 10 mg tablets are indicated for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.

4.2 Posology and method of administration
Adults and children over 12 years of age:
10 mg once daily (one tablet once daily).
The tablet may be taken without regard to mealtime.

Children 2 to 12 years of age with:
Body weight more than 30 kg: 10 mg once daily (one tablet once daily).
The 10 mg strength tablet is not appropriate in children with a body weight less than 30 kg.

Efficacy and safety of Loratadine 10 mg tablets in children under 2 years of age has not been established. The use is therefore not recommended in these patients.

Patients with severe liver impairment should be administered a lower initial dose because they may have reduced clearance of loratadine. An initial dose of 10 mg every other day is recommended for adults and children weighing more than 30 kg.

No dosage adjustments are required in the elderly or in patients with renal insufficiency.

4.3 Contraindications
Loratadine 10 mg tablets are contraindicated in patients who are hypersensitive to the active substance or to any of the excipients in these formulations.

In children under 2 years (see section 4.2).

During pregnancy or lactation (see section 4.6)

4.4 Special warnings and precautions for use
Loratadine 10 mg tablets should be administered with caution in patients with severe liver impairment (see Section 4.2).

The administration of Loratadine 10 mg tablets should be discontinued at least 48 hours before skin tests since antihistamines may prevent or reduce otherwise positive reactions to dermal reactivity index.
These tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

There are no significant interactions between loratadine and food.

4.5 Interaction with other medicinal products and other forms of interaction
When administered concomitantly with alcohol, a Loratadine 10 mg tablet has no potentiating effects as measured by psychomotor performance studies.

Potential interaction may occur with all known inhibitors of CYP3A4 or CYP2D6 resulting in elevated levels of loratadine (see section 5.2), which may cause an increase in adverse events.

4.6 Pregnancy and lactation
Loratadine was not teratogenic in animal studies. The safe use of loratadine during pregnancy has not been established. The use of Loratadine 10 mg tablets during pregnancy is therefore not recommended.

Loratadine is excreted in breast milk, therefore the use of loratadine is not recommended in breast-feeding women.

4.7 Effects on ability to drive and use machines
In clinical trials that assessed driving ability, no impairment occurred in patients receiving loratadine. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

4.8 Undesirable effects
In clinical trials in a paediatric population children aged 2 through 12 years, common adverse reactions reported in excess of placebo were headache (2.7%), nervousness (2.3%), and fatigue (1%).

In clinical trials involving adults and adolescents in a range of indications including allergic rhinitis and chronic idiopathic urticaria, at the recommended dose of 10 mg daily, adverse reactions with loratadine were reported in 2% of patients in excess of those treated with placebo. The most frequent adverse reactions reported in excess of placebo were somnolence (1.2%), headache (0.6%), increased appetite (0.5%) and insomnia (0.1%). Other adverse reactions reported very rarely during the post marketing period are listed in the following table.

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<tr>
<td>General disorders and administration site condition</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

4.9 Overdose
Overdosage with loratadine increased the occurrence of anticholinergic symptoms. Somnolence, tachycardia, and headache have been reported with overdoses.

In the event of overdosage, general symptomatic and supportive measures are to be instituted and maintained for as long as necessary. Administration of activated charcoal as a slurry with water may be attempted. Gastric lavage may be considered. Loratadine is not removed by
haemodialysis and it is not known if loratadine is removed by peritoneal dialysis. Medical monitoring of the patient is to be continued after emergency treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other antihistamines for systemic use
ATC code: R06A X13

Loratadine, the active ingredient in Loratadine 10 mg tablets, is a tricyclic antihistamine with selective, peripheral H1-receptor activity.

Loratadine has no clinically significant sedative or anticholinergic properties in the majority of the population and when used at the recommended dosage.

During long-term treatment there were no clinically significant changes in vital signs, laboratory test values, physical examinations or electrocardiograms.

Loratadine has no significant H2-receptor activity. It does not inhibit norepinephrine uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity.

5.2 Pharmacokinetic properties
After oral administration, loratadine is rapidly and well absorbed and undergoes an extensive first pass metabolism, mainly by CYP3A4 and CYP2D6. The major metabolite-desloratadine (DL)- is pharmacologically active and responsible for a large part of the clinical effect.

Loratadine and DL achieve maximum plasma concentrations (Tmax) between 1-1.5 hours and 1.5-3.7 hours after administration, respectively.

Increase in plasma concentrations of loratadine has been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in controlled trials, but without clinically significant changes (including electrocardiographic).

Loratadine is highly bound (97% to 99%) and its active metabolite moderately bound (73% to 76%) to plasma proteins.

In healthy subjects, plasma distribution half-lives of loratadine and its active metabolite are approximately 1 and 2 hours, respectively. The mean elimination half lives in healthy adult subjects were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the major active metabolite.

Approximately 40% of the dose is excreted in the urine and 42% in the faeces over a 10 day period and mainly in the form of conjugated metabolites. Approximately 27% of the dose is eliminated in the urine during the first 24 hours. Less than 1% of the active substance is excreted unchanged in active form, as loratadine or DL.

The bioavailability parameters of loratadine and of the active metabolite are dose proportional.

The pharmacokinetic profile of loratadine and its metabolites is comparable in healthy adult volunteers and in healthy geriatric volunteers.

Concomitant ingestion of food can delay slightly the absorption of loratadine but without influencing the clinical effect.

In patients with chronic renal impairment, both the AUC and peak plasma levels (Cmax) increased for loratadine and its metabolite as compared to the AUCs and peak plasma levels (Cmax) of patients with normal renal function. The mean elimination half-lives of loratadine and its metabolite were not significantly different from that observed in normal subjects. Haemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite in subjects with chronic renal impairment.
In patients with chronic alcoholic liver disease, the AUC and peak plasma levels (Cmax) of loratadine were double while the pharmacokinetic profile of the active metabolite was not significantly changed from that in patients with normal liver function. The elimination half-lives for loratadine and its metabolite were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Loratadine and its active metabolite are excreted in the breast milk of lactating women.

5.3 Preclinical safety data
Preclinical data reveal no special hazard based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive toxicity studies, no teratogenic effects were observed. However, prolonged parturition and reduced viability of offspring were observed in rats a plasma levels (AUC) 10 times higher than those achieved with clinical doses.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
Maize starch
Silica, colloidal anhydrous
Croscarmellose sodium
Talc
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister strips comprising of clear PVC film with aluminium backing (with VMCH coating) containing 30 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0078

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/05/2012

10 DATE OF REVISION OF THE TEXT
02/05/2012
1 NAME OF THE MEDICINAL PRODUCT
Selariz 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg loratadine.

Each Selariz 10 mg tablet contains 72.50 mg of lactose monohydrate (see Section 4.4).

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablets
White colored, circular, flat beveled uncoated tablets, with central breakline on one side and L on the other side.

The central break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Selariz 10 mg tablets are indicated for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.

4.2 Posology and method of administration
Adults and children over 12 years of age:
10 mg once daily (one tablet once daily).

The tablet may be taken without regard to mealtime.

Children 2 to 12 years of age with:
Body weight more than 30 kg: 10 mg once daily (one tablet once daily).

The 10 mg strength tablet is not appropriate in children with a body weight less than 30 kg.

Efficacy and safety of Selariz 10 mg Tablets in children under 2 years of age has not been established. The use is therefore not recommended in these patients.

Patients with severe liver impairment should be administered a lower initial dose because they may have reduced clearance of loratadine. An initial dose of 10 mg every other day is recommended for adults and children weighing more than 30 kg.

No dosage adjustments are required in the elderly or in patients with renal insufficiency.

4.3 Contraindications
Selariz 10 mg Tablets are contraindicated in patients who are hypersensitive to the active substance or to any of the excipients in these formulations.

In children under 2 years (see section 4.2).

During pregnancy or lactation (see section 4.6)

4.4 Special warnings and precautions for use
Selariz 10 mg Tablets should be administered with caution in patients with severe liver impairment (see Section 4.2).

The administration of Selariz 10 mg Tablets should be discontinued at least 48 hours before skin tests since antihistamines may prevent or reduce otherwise positive reactions to dermal reactivity index.
These tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

There are no significant interactions between loratadine and food.

4.5 Interaction with other medicinal products and other forms of interaction
When administered concomitantly with alcohol, a Selariz 10 mg Tablet has no potentiating effects as measured by psychomotor performance studies.

Potential interaction may occur with all known inhibitors of CYP3A4 or CYP2D6 resulting in elevated levels of loratadine (see section 5.2), which may cause an increase in adverse events.

4.6 Pregnancy and lactation
Loratadine was not teratogenic in animal studies. The safe use of loratadine during pregnancy has not been established. The use of Loratadine 10 mg Tablets during pregnancy is therefore not recommended.

Loratadine is excreted in breast milk, therefore the use of loratadine is not recommended in breast-feeding women.

4.7 Effects on ability to drive and use machines
In clinical trials that assessed driving ability, no impairment occurred in patients receiving loratadine. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

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In clinical trials in a paediatric population children aged 2 through 12 years, common adverse reactions reported in excess of placebo were headache (2.7%), nervousness (2.3%), and fatigue (1%).

In clinical trials involving adults and adolescents in a range of indications including allergic rhinitis and chronic idiopathic urticaria, at the recommended dose of 10 mg daily, adverse reactions with loratadine were reported in 2% of patients in excess of those treated with placebo. The most frequent adverse reactions reported in excess of placebo were somnolence (1.2%), headache (0.6%), increased appetite (0.5%) and insomnia (0.1%). Other adverse reactions reported very rarely during the post marketing period are listed in the following table.

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Overdosage with loratadine increased the occurrence of anticholinergic symptoms. Somnolence, tachycardia, and headache have been reported with overdoses.

In the event of overdosage, general symptomatic and supportive measures are to be instituted and maintained for as long as necessary. Administration of activated charcoal as a slurry with water may be attempted. Gastric lavage may be considered. Loratadine is not removed by
haemodialysis and it is not known if loratadine is removed by peritoneal dialysis. Medical monitoring of the patient is to be continued after emergency treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other antihistamines for systemic use
ATC code: R06A X13

Loratadine, the active ingredient in Loratadine 10 mg tablets, is a tricyclic antihistamine with selective, peripheral H₁-receptor activity.

Loratadine has no clinically significant sedative or anticholinergic properties in the majority of the population and when used at the recommended dosage.

During long-term treatment there were no clinically significant changes in vital signs, laboratory test values, physical examinations or electrocardiograms.

Loratadine has no significant H₂-receptor activity. It does not inhibit norepinephrine uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity.

5.2 Pharmacokinetic properties
After oral administration, loratadine is rapidly and well absorbed and undergoes an extensive first pass metabolism, mainly by CYP3A4 and CYP2D6. The major metabolite-desloratadine (DL)- is pharmacologically active and responsible for a large part of the clinical effect. Loratadine and DL achieve maximum plasma concentrations (Tmax) between 1-1.5 hours and 1.5-3.7 hours after administration, respectively.

Increase in plasma concentrations of loratadine has been reported after concomitant use with ketoconazole, erythromycin, and cimetidine in controlled trials, but without clinically significant changes (including electrocardiographic).

Loratadine is highly bound (97% to 99%) and its active metabolite moderately bound (73% to 76%) to plasma proteins.

In healthy subjects, plasma distribution half-lives of loratadine and its active metabolite are approximately 1 and 2 hours, respectively. The mean elimination half lives in healthy adult subjects were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the major active metabolite.

Approximately 40% of the dose is excreted in the urine and 42% in the faeces over a 10 day period and mainly in the form of conjugated metabolites. Approximately 27% of the dose is eliminated in the urine during the first 24 hours. Less than 1% of the active substance is excreted unchanged in active form, as loratadine or DL.

The bioavailability parameters of loratadine and of the active metabolite are dose proportional.

The pharmacokinetic profile of loratadine and its metabolites is comparable in healthy adult volunteers and in healthy geriatric volunteers.

Concomitant ingestion of food can delay slightly the absorption of loratadine but without influencing the clinical effect.

In patients with chronic renal impairment, both the AUC and peak plasma levels (Cₘₐₓ) increased for loratadine and its metabolite as compared to the AUCs and peak plasma levels (Cₘₐₓ) of patients with normal renal function. The mean elimination half-lives of loratadine and its metabolite were not significantly different from that observed in normal subjects. Haemodialysis does not have an effect on the pharmacokinetics of loratadine or its active metabolite in subjects with chronic renal impairment.
In patients with chronic alcoholic liver disease, the AUC and peak plasma levels (Cmax) of loratadine were double while the pharmacokinetic profile of the active metabolite was not significantly changed from that in patients with normal liver function. The elimination half-lives for loratadine and its metabolite were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Loratadine and its active metabolite are excreted in the breast milk of lactating women.

5.3 Preclinical safety data
Preclinical data reveal no special hazard based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive toxicity studies, no teratogenic effects were observed. However, prolonged parturition and reduced viability of offspring were observed in rats a plasma levels (AUC) 10 times higher than those achieved with clinical doses.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
Maize starch
Silica, colloidal anhydrous
Croscarmellose sodium
Talc
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister strips comprising of clear PVC film with aluminium backing (with VMCH coating) containing 7, 14 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0082

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/04/2012

10 DATE OF REVISION OF THE TEXT
30/04/2012
UKPAR Loratadine/Selariz 10mg Tablets

PL 33410/0078 & 0082

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Loratadine 10 mg Tablets

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to take Loratadine 10 mg tablets carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Loratadine 10 mg Tablets are and what they are used for
2. Before you take Loratadine Tablets
3. How to take Loratadine Tablets
4. Possible side effects
5. How to store Loratadine Tablets
6. Further information

1. WHAT LORATADINE 10 MG TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Loratadine 10 mg Tablets. It will be referred to as Loratadine Tablets throughout this leaflet.

Loratadine Tablets belong to a class of medicines known as antihistamines. Antihistamines help to reduce allergic symptoms by preventing the effects of a substance called histamine, which is produced in the body.

Loratadine Tablets relieve symptoms associated with allergic rhinitis (for example, hay fever), such as sneezing, runny or itchy nose, and burning or itchy eyes.

Loratadine tablets may also be used to help relieve symptoms of urticaria (itching, redness and swelling of the hands and feet), and itching.

Relief of these symptoms lasts a full day and helps you to resume your normal daily activities and sleep.

2. BEFORE YOU TAKE LORATADINE TABLETS

DO NOT TAKE Loratadine Tablets
- if you are allergic (hypersensitive) to Loratadine or any of the other ingredients of Loratadine Tablets. An allergic reaction can include skin rash, itching, swelling or breathing difficulties.
- if you are pregnant or planning to become pregnant
- if you are breast-feeding currently.

Children under 2 years of age and/or under 30 kg of weight should not take this medicine.

Take special care with Loratadine Tablets
- if you have severe liver problems
- if you have been told that you have an intolerance to some sugars.
- if you are due to have skin tests since Loratadine could affect the results.

If any of the above applies to you, please tell your doctor or pharmacist.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Laboratory tests:

Antihistamines may prevent response to allergens in skin allergy testing, therefore this medicine should be stopped two days prior to such testing.

Taking Loratadine Tablets with food and drink

This medicine may be taken with or without food.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy: the safe use of loratadine during pregnancy has not been established. The use of Loratadine during pregnancy is therefore not recommended.

Breast feeding: Loratadine, the active substance in this medicine is excreted in breast milk; therefore the use of loratadine is not recommended in breast-feeding women.

Driving and using machines

At the recommended dose, Loratadine Tablets are not expected to cause you to be drowsy or less alert. However, very rarely some people experience drowsiness, which may affect their ability to drive or use machines. Please make sure you are not drowsy before performing these activities.

Important information about some of the ingredients of Loratadine tablets

Loratadine Tablets contain lactose (milk sugar). If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.
3. HOW TO TAKE LORATADINE TABLETS

Always take Loratadine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Try to get into the habit of taking your medicine at the same time every day. This will make it easier for you to remember.

The usual dose is

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and children over 12 years of age</td>
<td>10 mg once daily (swallow one tablet daily with water)</td>
</tr>
<tr>
<td>Children aged 2 to 12 years and weighing over 30 kg</td>
<td>10 mg once daily (swallow one tablet daily with water)</td>
</tr>
<tr>
<td>Children who are aged over 2 years old but do not weigh more than 30 kg</td>
<td>Should not take this medicine</td>
</tr>
<tr>
<td>Children under 2 years of age</td>
<td>Should not take this medicine</td>
</tr>
<tr>
<td>Patients with severe liver problems</td>
<td>Your doctor may prescribe a different dose for patients with severe liver problems</td>
</tr>
</tbody>
</table>

If you take more Loratadine Tablets than you should
If you may have taken more Loratadine than you should, talk to your doctor or pharmacist immediately. Overdose may cause sleepiness or a faster heart beat. Immediate medical attention should be sought in the event of an overdose; take your tablets along to show to your doctor, if possible.

If you forget to take Loratadine Tablets
If you have forgotten to take your tablet, take it as soon as you remember and continue as usual. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Loratadine can cause side effects, although not everybody gets them.

You must stop taking Loratadine Tablets immediately and consult your doctor if you develop any allergic reaction to this medicine. This can consist of:
- skin rash or rashes (including inside the mouth)
- itching
- swelling of the face, tongue, lips, hands, feet
- breathing difficulties

Other side effects
- The following side effects have been reported rarely with Loratadine use. They are generally mild and may go away on their own.

However, check with your doctor if they continue or are bothersome:
- nausea (feeling sick)
- fatigue
- headache
- nervousness
- dryness of the mouth, nose and throat
- hair loss

In addition, other side effects that have been reported when taking Loratadine Tablets are:
- dizziness
- rapid heartbeat
- palpitation (awareness of heartbeat/racing)
- irritation of the stomach lining (gastritis)
- increased appetite
- insomnia
- skin rash
- abnormal liver function.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LORATADINE TABLETS

Keep your tablets out of the reach and sight of children.
- Do not take Loratadine Tablets after the expiry date which is stated on the carton after “Exp.” The expiry date refers to the last day of that month.
- Store in the original package.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Loratadine Tablets contain
- The active substance is Loratadine 10 mg.
- The other ingredients are lactose monohydrate, colloidal silicon dioxide, croscarmellose sodium, talc and magnesium stearate.

What Loratadine Tablets look like and contents of the pack
Loratadine Tablets are white coloured, circular, flat bevelled uncoated tablets, with central breakline on one side and ‘L’ on other side. Loratadine Tablets are available in blister strips in pack size of 30 tablets.

Marketing Authorisation Holder
APSLA Limited, Bayview House, 49 North Strand Road, Dublin 3, Ireland.

Manufacturer:
APC Pharmaceuticals & Chemicals (Europe) Ltd., 9th floor, C.P. House, 97-107 Uxbridge Road, Enfield, London, W5 5TL

Distributed By:
APC Pharmaceuticals & Chemicals (Europe) Ltd., 9th floor, C.P. House, 97-107 Uxbridge Road, Enfield, London, W5 5TL

This leaflet was last revised in 10/2010.

UKPAR Loratadine/Selariz 10mg Tablets  PL 33410/0078 & 0082
UKPAR Loratadine/Selariz 10mg Tablets
PL 33410/0078 & 0082

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Selariz 10 mg Tablets
Loratadine

Read all of this leaflet carefully because it contains important information for you.
This medicine is available without prescription. However, you still need to take Loratadine 10 mg tablets carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Selariz 10 mg Tablets are and what they are used for
2. Before you take Selariz Tablets
3. How to take Selariz Tablets
4. Possible side effects
5. How to store Selariz Tablets
6. Further information

1. WHAT SELARIZ 10 MG TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Selariz 10 mg Tablets. It will be referred to as Selariz Tablets throughout this leaflet.

Selariz Tablets belong to a class of medicines known as antihistamines. Antihistamines help to reduce allergic symptoms by preventing the effects of a substance called histamine, which is produced in the body.

Selariz Tablets relieve symptoms associated with allergic rhinitis (for example, hay fever), such as sneezing, runny or itchy nose, and burning or itchy eyes.

Selariz tablets may also be used to help relieve symptoms of urticaria (itching, redness and number and size of hives).

Relief of these symptoms lasts a full day and helps you to resume your normal daily activities and sleep.

2. BEFORE YOU TAKE SELARIZ TABLETS

DO NOT TAKE Selariz Tablets:
- if you are allergic (hypersensitive) to loratadine or any of the other ingredients of Selariz Tablets. An allergic reaction can include skin rash, itching, swelling or breathing difficulties.
- if you are pregnant or planning to become pregnant
- if you are breast-feeding currently.

Children under 2 years of age and/or under 30 kg of weight should not take this medicine.

Take special care with Selariz Tablets:
- if you have severe liver problems
- if you have been told that you have an intolerance to some sugars.
- if you are due to have skin tests since loratadine could affect the results.

If any of the above applies to you, please tell your doctor or pharmacist.

Taking other medicines
Please tell your doctor or pharmacist if you are taking, or have recently taken any other medicines, including medicines obtained without a prescription.

Laboratory tests:
Antihistamines may prevent response to allergens in skin allergy testing, therefore this medicine should be stopped two days prior to such testing.

Taking Selariz Tablets with food and drink
This medicine may be taken with or without food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy: The safe use of loratadine during pregnancy has not been established. The use of loratadine during pregnancy is therefore not recommended.

Breast feeding: Loratadine, the active substance in this medicine is excreted in breast milk; therefore, the use of Selariz Tablets is not recommended in breast-feeding women.

Driving and using machines
At the recommended dose, Selariz Tablets are not expected to cause you to be drowsy or less alert. However, very rarely some patients experience drowsiness, which may affect their ability to drive or use machines. Please make sure you are not drowsy before performing these activities.

Important information about some of the ingredients of Selariz tablets:
Selariz Tablets contain lactose (milk sugar). If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.
3. HOW TO TAKE SELARIZ TABLETS

Try to get into the habit of taking it at the same
time every day. This will make it easier for you to
remember.

The usual dose is

<table>
<thead>
<tr>
<th>Age</th>
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</tr>
<tr>
<td>not weigh more than 30 kg</td>
<td>medicine</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>severe liver problems</td>
</tr>
</tbody>
</table>

However, check with your doctor if they continue or are bothersome:
- nausea (feeling sick)
- fatigue
- headache
- nervousness
- dryness of the mouth, nose and throat
- hair loss

In addition, other side effects that have been reported when taking Sellariz Tablets are:
- dizziness
- rapid heartbeat
- palpitation (awareness of heartbeat/racing)
- irritation of the stomach lining (gastritis)
- increased appetite
- insomnia
- skin rash
- abnormal liver function.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If you take more Sellariz Tablets than you should

If you may have taken more Loratadine than you should, talk to your doctor or pharmacist immediately. Overdose may cause sleepiness or a fast heart beat. Immediate medical attention should be sought in the event of an overdose; take your tablets along to show to your doctor, if possible.

If you forget to take Sellariz Tablets

If you have forgotten to take your tablet, take it as soon as you remember and continue as usual. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Sellariz Tablets can cause side effects, although not everybody gets them.

You must stop taking Sellariz Tablets immediately and consult your doctor if you develop any allergic reaction to this medicine. This can consist of:
- skin rash or eruptions (including inside the mouth)
- itching
- swelling of the face, tongue, lips, hands, feet
- breathing difficulties

Other side effects

The following side effects have been reported rarely with Loratadine use. They are generally non serious and may go away on their own.

However, check with your doctor if they continue or are bothersome:
- nausea (feeling sick)
- fatigue
- headache
- nervousness
- dryness of the mouth, nose and throat
- hair loss

In addition, other side effects that have been reported when taking Sellariz Tablets are:
- dizziness
- rapid heartbeat
- palpitation (awareness of heartbeat/racing)
- irritation of the stomach lining (gastritis)
- increased appetite
- insomnia
- skin rash
- abnormal liver function.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE SELARIZ TABLETS

Keep your tablets out of the reach and sight of children.
- Do not take Sellariz Tablets after the expiry date which is stated on the carton after “Exp”. The expiry date refers to the last day of that month.
- Store in the original package.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Sellariz Tablets contain
- The active substance is Loratadine 10 mg.
- The other ingredients are lactose monohydrate, colloidal anhydrous silica, crosslinkedmethylcellulose sodium, tio and magnesium stearate.

What Sellariz Tablets look like and contents of the pack
Sellariz Tablets are white coloured, circular, flat bevelled uncoated tablets, with central breakline on one side and ‘L’ on other side.
Sellariz Tablets are available in blister strips in pack size of 7 and 14 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder
APSA Limited, Bayview House, 49 North Strand Road, Dublin 3, Ireland.

Manufacturer:
APC Pharmaceuticals & Chemicals (Europe) Ltd., 9th floor, C.P. House, 97-107 Uxbridge Road, Ealing, London, W5 5TL

Distributed By:
APC Pharmaceuticals & Chemicals (Europe) Ltd., 9th floor, C.P. House, 97-107 Uxbridge Road, Ealing, London, W5 5TL
This leaflet was last revised in 01/2012.
UKPAR Loratadine/Selaniz 10mg Tablets

WARNING: DO NOT EXCEED THE STATED DOSE

Loratadine/Selaniz 10mg Tablets

Children and adults over 1 year of age weighing more than 40 kg: swallowed once a day. If you have severe liver problems you may need to take one tablet every other day. Ask your pharmacist or doctor if you think this applies to you. Do not give to children under the age of 7 years.

Dosage adults and children over 1 year of age weighing more than 40 kg: swallowed once a day. If you have severe liver problems you may need to take one tablet every other day. Ask your pharmacist or doctor if you think this applies to you. Do not give to children under the age of 7 years.

Do not use if you are pregnant or breast-feeding.

If symptoms persist consult your doctor or pharmacist.

Please read the package leaflet before use.

Store in the original package.

Keep out of the reach and sight of children.

Selariz 10 mg tablets

Loratadine

Each tablet contains 10 mg of Loratadine

Also contains lactose monohydrate.

For oral use.

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PL 33410/0082

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