Lorvacs XL 1.5 mg Prolonged-release Tablets

PL 27900/0001

UKPAR

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LORVACS XL 1.5 MG PROLONGED-RELEASE TABLETS

PL 27900/0001

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Lorvacs XL 1.5 mg Prolonged-release Tablets (Product Licence number: 27900/0001).

This medicine is a prolonged-release tablet containing indapamide as the active ingredient. It is intended to reduce high blood pressure (hypertension).

Lorvacs XL 1.5 mg Prolonged-release Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

LORVACS XL 1.5 MG PROLONGED-RELEASE TABLETS

PL 27900/0001

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Lorvacs XL 1.5 mg Prolonged-release Tablets (PL 27900/0001) to Renantos Pharmavertriebsgesellschaft mbH on 22 December 2009. This medicine is only available on prescription.

These are national, abridged applications submitted under Directive 2001/83/EC, Article 10.1. The applicant claims that Lorvacs XL 1.5 mg Prolonged-release Tablets is a generic version of Fludex® 1.5mg prolonged-release tablets, licensed to Les Laboratoies Servier, which was granted a Marketing Authorisation in France on 4 December 1994. The ten year rule is, therefore, complied with and the legal basis of this application is acceptable. A product identical to Fludex® 1.5mg prolonged-release tablets was licensed in the UK on 9 January 1996 to Servier Laboratories Ltd under the name Natrilix SR® (PL 05815/0010).

Lorvacs XL 1.5 mg Prolonged-release Tablets is indicated for the treatment of essential hypertension.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

All aspects of the manufacture and control of indapamide are supported by European Directorate for the Quality of medicines and Healthcare (EDQM) Certificates of Suitability from the active substance manufacturers. These certificates are accepted as confirmation of the suitability of indapamide for inclusion in medicinal products.

The method of manufacture of indapamide is appropriate.

The proposed drug substance specification and its justification, analytical procedures and their validation, batch analyses and reference standards used by the drug substance manufacturer are satisfactory.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Active indapamide is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting the retest period.

DRUG PRODUCT

Description and Composition

Tablets are white to off white, round, biconvex film-coated tablets. The excipients are lactose monohydrate, pregelatinised maize starch, hypromellose, silica, colloidal anhydrous, magnesium stearate, macrogol 6000, and titanium dioxide (E171) All ingredients comply with their respective Ph Eur monographs.

Dissolution and Impurity profiles

Dissolution and impurity profiles of the drug product were found to be similar to that of the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on product batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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 have been provided for any working standards used.

Container Closure System
The product is packed in PVC/aluminium blisters packs of 10, 14, 15, 20, 30, 50, 60, 90 or 100 tablets.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory.

Product literature
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is 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 it contains.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for applications of this type.

CLINICAL ASSESSMENT

INTRODUCTION

Indications
The only indication sought is “essential hypertension”.

Dose and Dose Regimen
Irrespective of the formulation (immediate or sustained release), the posology is one tablet daily, preferably in the morning to minimise disruption of sleep and avoid discomfort of diuresis.

Legal Status
Prescription only Medicine (POM)

CLINICAL PHARMACOLOGY

Pharmacokinetics

Introduction and overview
The clinical pharmacology has been well detailed and established for use of indapamide in essential hypertension. In some countries it is also advocated for use in oedematous states or in treatment of oedema.

Absorption
Indapamide is rapidly and completely absorbed from the gastrointestinal tract, peak blood levels occurring 0.5-2 hours after ingestion. It is strongly bound to red blood cells, having a 5.7:1 blood to plasma ratio with volumes of distribution of 25L and 110L, respectively. Indapamide in plasma is 76-79% protein-bound. Steady state blood levels are attained after four daily doses. Indapamide is extensively metabolised. Elimination is biphasic, with a half-life in whole blood of about 14 hours. About 60-70% of the dose is excreted in the urine, circa 16-23% in the faeces, but only about 5-7% is unchanged. The pharmacology of the metabolites has not been established, except that hydroxy-indapamide shares the free-radical scavenging property of the parent drug. Indapamide is not removed by haemodialysis but does not accumulate in patients with renal impairment, due to extensive hepatic metabolism.

The pharmacology of indapamide is well established and detailed adequately in the clinical overview. This applies whether it is part of a standard release or immediate release formulation, the major difference between them being a change in C_{max} achieved and time to maximum plasma concentration. There are no issues relating to the pharmacokinetics or dynamics.

Bioequivalence
To support the application, the applicant has submitted three bioequivalence studies comparing the proposed product to the reference product (Fludex LP 1.5 mg of Servier Laboratories, France).

Methods

Study design

1. Two-period, two sequence, cross-over single dose bioequivalence study in healthy male and female volunteers in fasting conditions
Two period, two sequence, cross-over single dose administration. Hospitalization of subjects until 24 hours post administration. Then they continued the study by visiting the study centre at scheduled time intervals.
Blood samples were collected before dose (0.0) and at 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0, 36.0, 48.0, 72.0, 96.0, 144.0 hours post dose, after each administration. Washout period: 11 days.

The bioequivalence study was conducted in line with the relevant EU-NfG documents ("NfG on investigation of bioavailability and bioequivalence, CPMP/ EWP/ QWP/ 1401/ 98", "NfG on modified release oral and transdermal dosage forms, CPMP/ EWP/ 280/ 96"). The design is acceptable.

Test and reference products
Lorvacs XL 1.5 mg Prolonged-release Tablets has been compared to Fludex LP 1.5 mg (Servier Laboratories Limited, France). The reference product is accepted.

Population(s) studied
A number of thirty-six healthy male and female volunteeres, aged 18-45, BMI within 19.0 and 29.0.

Analytical methods
Determination of indapamide by HPLC-MS/ MS. Quantification limit: LLOQ 0.312 ng/ ml. Sample analysis calibration curve range: 0.312 up to 40 000 ng/ ml. The results obtained in the different assays performed to validate this HPLC-MS/ MS method are described in the following:

LLOQ
Analytical data were obtained by analysing eight individual LLOQ samples together with eight blank plasma samples. No peak similar to indapamide was observed in blank samples and so far the peak response in LLOQ is adequate; also the LLOQ peak area precision is good being 6.796%. The mean precision and accuracy of the back-calculated indapamide LLOQ concentrations are within the requested limits: 8.403% and 100.592%, respectively.
Calibration curve: fitting, precision and accuracy
The precision and accuracy at all concentrations are satisfactory; the curve linearity is also optimal in the whole range with a correlation coefficient r= 0.99790.
Within-run precision and accuracy
The within-run precision and accuracy has been calculated from the QC data. Precision and accuracy are adequate for the validation.
Between-run precision and accuracy
The between run precision and accuracy has been calculated from the QC data. As it can be observed, the precision and accuracy are adequate for the validation.
Extraction recovery

The mean concentrations were determined in freshly extracted QC sets (control) in comparison with extracts of the same QC set stored 4 or 24 hours at room temperature. The results obtained showed that indapamide is stable in plasma extracts up to 16 hours at room temperature.

Specificity

The analyses performed on eight plasma samples from different donors, without addition of internal standard, did not put in evidence the presence of interfering peaks with HPLC behaviour similar to indapamide or the internal standard. The analyses performed in samples spiked with internal standard or indapamide did not put in evidence interfering peaks in any of the other chromatographic traces.

The analytical method is accepted. From the results reported it can be concluded that the present analytical method has adequate sensitivity, linearity, precision, accuracy, and specificity to quantitatively determine indapamide in plasma, at the concentration that can be expected in real samples.

Pharmacokinetic Variables

The following pharmacokinetic parameters were assessed:

$AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max} (as primary) ; T_{max} (as secondary); AUC% extra, T_{half} and MRT (as additional)

These parameters are in line with those proposed by the relevant EU-NfG ("NfG on investigation of bioavailability and bioequivalence, CPMP/ EWP/ QWP/ 1401/ 98") and are acceptable.

Statistical methods:

The following procedure was used:

- C_{max}, AUC $_{o\text{-}inf}$ and AUC $_{o\text{-}t}$, ANOVA after logarithmic transformation (model: treatments, sequences, subjects (sequence) and periods of administration), 90% confidence intervals according to Classic and Schuirmann (two one-sided parametric t-Test) for the intra-individual ratios.
- T_{max}, Kruskal Wallis test and Wilcoxon test
- T_{half} and MRT, ANOVA test
- Clinical laboratory parameters and vital signs at screening vs. follow-up, ANOVA test
- Vital signs measured before and after dosing, descriptive statistic (mean, standard deviation and range).

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**$AUC_{0\text{-}t}$** **ng/ml/h**	**$AUC_{0\text{-}\infty}$** **xg/ml/h**	**C_{max}** **xg/ml**	**t_{max}** **h**	**$T_{1/2}$** **h**
Test	226.578	241.481	6.279	21.039	16.082
Reference	217.624	232.429	6.523	15.606	16.583
***Ratio (90% CI)**	108.989 (97.778-121.485)	107.616 (97.667-118.580)	100.049 (89.891-111.354)		

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration
$T_{1/2}$	half-life

**ln-transformed values*

Safety results

Four non-serious adverse events, of which one was of mild intensity and three were of moderate intensity, occurred in three subjects in the present study. All these, three volunteers completely recovered before the end of the study.

ANOVA test analysis of clinical laboratory parameters follow-up vs. screening found six statistically significant differences regarding lower values of haemoglobin, red blood cells, hematocrit, monocytes and ALT and higher value of alkaline phosphatase. No statistically significant differences have been registered for vital signs at follow up and screening.

The key criterion AUC_{0-t} as well as the other criteria were within the predefined acceptance ranges as were the other relevant parameters. There were statistically significant differences with regard to the laboratory parameters in the single dose study.

Pharmacokinetic conclusion

Based on these results, it can be concluded that a single dose of the test Lorvacs XL 1.5 mg Prolonged-release Tablets is bioequivalent to a single oral dose of the reference product Fludex LP 1.5 mg (Servier Laboratories Limited, France), under fasting conditions.

2. Two-period, two-sequence, cross-over, controlled, block randomized, single dose bioequivalence study of Lorvacs XL 1.5 mg Prolonged-release Tablets vs. equal dose reference formulation in healthy male and female volunteers, in fed conditions

Study design

Two period, two sequence, cross-over single dose administration. Hospitalization of subjects until 24 hours post administration. Then they continued the study by visiting the study centre at scheduled time intervals.

Blood samples were collected before dose (0.0) and at 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0, 36.0, 48.0, 72.0, 96.0, 144.0 hours post dose, after each administration. Washout period: 10 days.

The bioequivalence study was conducted in line with the relevant EU-NfG documents ("NfG on investigation of bioavailability and bioequivalence, CPMP/ EWP/ QWP/ 1401/ 98", "NfG on modified release oral and transdermal dosage forms, CPMP/ EWP/ 280/ 96"). The design is acceptable.

Test and reference products

Lorvacs XL 1.5 mg Prolonged-release Tablets have been compared to Fludex LP 1.5 mg (Servier Laboratories Limited, France). The reference product is accepted

Population(s) studied

A number of 36 healthy male and female volunteers, aged 18-45, BMI within 19.0 and 29.0.

Analytical methods

Determination of indapamide by HPLC-MS/ MS. Quantification limit: LLOQ 0.312.
Sample analysis calibration curve range: 0.312 up to 40 000 ng/ ml.
The results obtained in the different assays performed to validate this HPLC-MS/ MS method are described in the following:

LLOQ

Analytical data were obtained by analysing eight individual LLOQ samples together with eight blank plasma samples. No peak similar to indapamide was observed in blank samples and so far the peak response in LLOQ is adequate; also the LLOQ peak area precision is good being 6.796%. The mean precision and accuracy of the back-calculated indapamide LLOQ concentrations are within the requested limits: 8.403% and 100.592%, respectively.

Calibration curve: fitting, precision and accuracy

The precision and accuracy at all concentrations are satisfactory; the curve linearity is also optimal in the whole range with a correlation coefficient r= 0.99790.

Within-run precision and accuracy

The within-run precision and accuracy have been calculated from the QC data. Precision and accuracy are adequate for the validation.

Between-run precision and accuracy

The between run precision and accuracy have been calculated from the QC data. As it can be observed, the precision and accuracy are adequate for the validation.

Extraction recovery

The mean concentrations were determined in freshly extracted QC sets (control) in comparison with extracts of the same QC set stored 4 or 24 hours at room temperature. The results obtained showed that indapamide is stable in plasma extracts up to 16 hours at room temperature.

Specificity

The analyses performed on eight plasma samples from different donors, without addition of internal standard, did not put in evidence the presence of interfering peaks with HPLC behaviour similar to indapamide or the internal standard.
The analyses performed in samples spiked with internal standard or indapamide did not put in evidence interfering peaks in any of the other chromatographic traces.

The analytical method is accepted. From the results reported it can be concluded that the present analytical method has adequate sensitivity, linearity, precision, accuracy, and specificity to quantitatively determine indapamide in plasma, at the concentration that can be expected in real samples.

Pharmacokinetic Variables

The following pharmacokinetic parameters were assessed:
$AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max} (as primary) ; T_{max} (as secondary); AUC% extra, T_{half} and MRT (as additional).
These parameters are in line with those proposed by the relevant EU-NfG (“NfG on investigation of bioavailability and bioequivalence, CPMP/ EWP/ QWP/ 1401/ 98”) and are acceptable.

Statistical methods:

The following procedure was used:

- C_{max}, AUC $_{o-inf}$ and AUC $_{o-t}$, ANOVA after logarithmic transformation (model: treatments, sequences, subjects (sequence) and periods of administration), 90% confidence intervals according to Classic and Schuirmann (two one-sided parametric t-Test) for the intra-individual ratios.
- T_{max}, Kruskal Wallis test and Wilcoxon test
- T_{half} and MRT, ANOVA test
- Clinical laboratory parameters and vital signs at screening vs. follow-up, ANOVA test
-Vital signs measured before and after dosing, descriptive statistic (mean, standard deviation and range).

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** xg/ml/h	**C_{max}** xg/ml	**t_{max}** h	**$T_{1/2}$** h
Test	208.769	223.280	7.728x	9.801	16.077
Reference	206.326	221.365x	8.197	9.230	15.726
***Ratio (90% CI)**	101.893 (96.614-107.461)	101.344 (96.178-106.788)	94.269 (84.910-104.783)		

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration
$T_{1/2}$	half-life

**ln-transformed values*

Safety results:

One not serious adverse event of moderate intensity occurred in one in the present study. The volunteer completely recovered before the end of the study.

ANOVA test analysis of clinical laboratory parameters follow-up vs. screening found eight statistically significant differences regarding lower values of neutrophils, lymphocytes, potassium, sodium, uric acid and glycaemia and higher values of eosinophils and monocytes. No statistically significant difference has been registered for vital signs at follow up vs. screening.

The key criterion AUC_{0-t} as well as the other criteria were within the predefined acceptance criteria as were the other relevant parameters.

Pharmacokinetic conclusion

Based on these results, it can be concluded that a single dose of the test Lorvacs XL 1.5 mg Prolonged-release Tablets is bioequivalent to a single oral dose of the reference product Fludex LP 1.5 mg (Servier Laboratories Limited, France) under fed conditions.

3. Two period two sequence, cross-over, controlled, block randomized, multi-dose bioequivalence study at steady state of Lorvacs XL 1.5 mg Prolonged-release Tablets vs. equal dose reference formulation in healthy male and female volunteers, in fasting conditions

Study design
Two period, two sequence, cross-over multiple dose (at steady state) administration. Hospitalization of subjects until 24 hours post administration. Then they continued the study by visiting the study centre at scheduled time intervals.

Product administered: 7 (days) x one Lorvacs XL 1.5 mg Prolonged-release Tablets or 7(days) x one Fludex LP 1.5 mg / day, in each study period.
Blood samples were collected before dose (0.0) for days 1-7 and at 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0, 36.0, 48.0, 72.0, 96.0, 144.0 hours post dose for day 7. Washout period: eight days.

Hospitalisation of subjects from the evening before the seventh administration until 24 hours post-administration.

The bioequivalence study was conducted in line with the relevant EU-NfG documents ("NfG on investigation of bioavailability and bioequivalence, CPMP/ EWP/ QWP/ 1401/ 98", "NfG on modified release oral and transdermal dosage forms, CPMP/ EWP/ 280/ 96). The design is acceptable.

Test and reference products
Lorvacs XL 1.5 mg Prolonged-release Tablets have been compared to Fludex LP 1.5 mg (Servier Laboratories Limited, France). The reference product is accepted.

Population(s) studied
A number of 36 healthy male and female volunteers, aged 18-45, BMI within 19.0 and 29.0.

Analytical methods
Determination of indapamide by HPLC-MS/ MS. Quantification limit: LLOQ 0.312 ng/ ml. Sample analysis calibration curve range: 40 ng/ ml.
The results obtained in the different assays performed to validate this HPLC-MS/ MS method are described in the following:

LLOQ
Analytical data were obtained by analysing eight individual LLOQ samples together with eight blank plasma samples. No peak similar to indapamide was observed in blank samples and so far the peak response in LLOQ is adequate; also the LLOQ peak area precision is good being 6.796%. The mean precision and accuracy of the back-calculated indapamide LLOQ concentrations are within the requested limits: 8.403% and 100.592%, respectively.
Calibration curve: fitting, precision and accuracy
The precision and accuracy at all concentrations are satisfactory; the curve linearity is also optimal in the whole range with a correlation coefficient r= 0.99790.
Within-run precision and accuracy
The within-run precision and accuracy have been calculated from the QC data. Precision and accuracy are adequate for the validation.
Between-run precision and accuracy
The between run precision and accuracy have been calculated from the QC data. As it can be observed the precision and accuracy are adequate for the validation.
Extraction recovery

The mean concentrations were determined in freshly extracted QC sets (control) in comparison with extracts of the same QC set stored 4 or 24 hours at room temperature. The results obtained showed that indapamide is stable in plasma extracts up to 16 hours at room temperature.

Specificity

The analyses performed on eight plasma samples from different donors, without addition of internal standard, did not put in evidence the presence of interfering peaks with HPLC behaviour similar to indapamide or the internal standard.

The analyses performed in samples spiked with internal standard or indapamide did not put in evidence interfering peaks in any of the other chromatographic traces.

The analytical method is accepted. From the results reported it can be concluded that the present analytical method has adequate sensitivity, linearity, precision, accuracy, and specificity to quantitatively determine indapamide in plasma, at the concentration that can be expected in real samples.

Pharmacokinetic Variables

The following pharmacokinetic parameters were assessed:

C_{max}, C_{min}, AUC_{ss}, %ptf (as primary); T_{max} (as secondary) and % swing, caverage, % extrapolated AUC, $t_{½}$, MRT (as additional).

Safety: laboratory data/ vital signs/ adverse events

These parameters are in line with those proposed by the relevant EU-NfG ("NfG on modified release oral and transdermal dosage forms, CPMP/ EWP/ 280/ 96") and are acceptable.

Statistical methods:

For the active compound (indapamide) the following procedure was used:

-C_{max}, C_{min}, AUC_{ss}, %ptf, ANOVA after logarithmic transformation (model: treatments, sequences, subjects and period of administration), classic 90% confidence intervals (shortest) for the intra-individual ratios and Schuirman's two one-sided parametric test for the null hypothesis of bioequivalence.

- T_{max} at SS, Kruskal Wallis test and Wilcoxon T-test
- % extrapolated AUC, T_{half} and MRT, only descriptive statistics
- clinical laboratory parameters screening vs. follow-up, ANOVA test
- vital signs measured before dosing in days 1 to 7 and in day 7 also after dosing, descriptive statistic (mean, standard deviation and range).

Results

Indapamide SR Tablets 1.5mg (Torrent Pharmaceuticals Limited, India)

Parameters	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (Hours)	AUCss (ng/ml*h)	% ptf (Hours)	% Swing	Thalf (Hours)
Mean	10.370	6.292	6.650	193.659	50.247	67.104	16.043
Std. Dev.	4.735	2.558	4.472	77.388	14.665	28.252	2.343

FLUDEX LP 1.5mg (Servier Laboratories Limited, France)

Parameters	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (Hours)	AUCss (ng/ml*h)	% ptf (Hours)	% Swing	Thalf (Hours)
Mean	10.490	6.524	7.529	198.766	50.700	68.068	15.701
Std. Dev.	5.030	3.291	5.344	93.496	20.125	38.777	2.500

Bioequivalence comparison, Primary parameters:

Test name	Parameter	Test value (test/ reference)	Lower 90% CI	Upper 90% CI
Classic 90% CI	AUC_{ss}	100.017	93.817	106.627
Classic 90% CI	Cmin	100.267	91.984	109.296
Classic 90% CI	Cmax	100.225	94.592	106.195
Classic 90% CI	%ptf	100.312	89.746	112.123

Safety results:
Eight non serious adverse events, of mild to moderate intensity occurred in this study in two subjects. One of them was considered a drop out due to an adverse event but both of them recovered before the end of the study. ANOVA test analysis of clinical laboratory parameters follow-up versus screening found seven statistically significant differences regarding higher values of glucose and lower values of haemoglobin, hematocrit, red blood cells, bilirubine, sodium and potassium. Two statistically significant differences have been registered for vital signs at follow-up versus screening, lower values of SAP and HR.

The primary pharmacokinetic parameters as well as the other criteria were well within the predefined acceptance criteria as were the other relevant parameters.
There were statistically significant differences with regard to the laboratory parameters in the multiple dose study. But these are not considered to be of clinical significance and, therefore, will not be pursued further

Assessors' overall conclusions on pharmacokinetics
It is considered that the applicant has fulfilled the requirement for an application for a generic product by conducting three bioequivalence studies. All studies conform to the acceptance criteria as established by the CHMP guidance note; CPMP/EWP/QWP/1401/98 and the modified relase guideline (CPMP/EWP/280/96) with studies in the fasted, fed and steady state studies. The results show some

differences to published literature with Natrilix bioequivalence studies but cross study comparisons are difficult and, moreover, within each two-period study bioequivalence has been established. For future reference, a four cross over study providing fasted-fed comparisons within a single study should be advocated in order to avaoid this pitfall.
Bioequivalence to the reference product is established.

PRODUCT LITERATURE
All product literature is medically satisfactory.

OVERALL CONCLUSION
Bioequivalence has been established with three studies. All product literature is medically satisfactory. The risk: benefit ratio is therefore considered positive and granting of a Marketing Authorisation is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Lorvacs XL 1.5 mg Prolonged-release Tablets 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

The efficacy of indapamide is well established.
The SPCs, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with indapamide. The risk: benefit ratio is therefore considered to be acceptable.

LORVACS XL 1.5 MG PROLONGED-RELEASE TABLETS

PL 27900/0001

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 18 May 2006
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 9 August 2006.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 24 November 2006 and the clinical dossier on 31 March 2007
4	The applicant responded to the MHRA's requests, providing further information on the clinical dossier on 22 June 2007 and the quality dossier on 15 October 2007
5	Following assessment of the response the MHRA requested further information relating to the quality dossier on 15 October 2007
6	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 18 October 2007
7	Following assessment of the response the MHRA requested further information relating to the quality dossier on 12 December 2008
8	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 27 April 2009
9	The application was determined on 22 December 2009

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lorvacs XL 1.5 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 1.5 mg indapamide.
Excipient: 144.22 mg lactose monohydrate/prolonged-release tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.
White to off-white, round shaped, biconvex, prolonged-release tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension.

4.2 Posology and method of administration

Oral use.
One tablet per 24 hours, preferably in the morning, to be swallowed whole with water and not chewed.
At higher doses the antihypertensive action of indapamide is not enhanced but the saluretic effect is increased.

Renal failure (see sections 4.3 and 4.4):
In severe renal failure (creatinine clearance below 30 ml/min), treatment is contraindicated.
Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired.

Elderly (see section 4.4):
In the elderly, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with Lorvacs XL 1.5 mg when renal function is normal or only minimally impaired.

Patients with hepatic impairment (see sections 4.3 and 4.4):
In severe hepatic impairment, treatment is contraindicated.

Children and adolescents:
Lorvacs XL 1.5 mg is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to indapamide, to other sulfonamides or to any of the excipients.

- Severe renal failure.
- Hepatic encephalopathy or severe impairment of liver function.
- Hypokalaemia.

4.4 Special warnings and precautions for use

Special warnings

When liver function is impaired, thiazide-related diuretics may cause hepatic encephalopathy, particularly in case of electrolyte imbalance. Administration of the diuretic must be stopped immediately if this occurs.

Photosensitivity:

Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Excipients:

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Special precautions for use

- **Water and electrolyte balance:**

• Plasma sodium:

This must be measured before starting treatment, then at regular intervals subsequently. Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be even more frequent in the elderly and cirrhotic patients (see sections 4.8 and 4.9).

• Plasma potassium:

Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. The risk of onset of hypokalaemia (< 3.4 mmol/l) must be prevented in certain high risk populations, *i.e*. the elderly, malnourished and/or polymedicated, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients. In this situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias.

Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as well as bradycardia, is then a predisposing factor to the onset of severe arrhythmias, in particular, potentially fatal *torsades de pointes.*

More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be obtained during the first week following the start of treatment.

Detection of hypokalaemia requires its correction.

• Plasma calcium:

Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism.
Treatment should be withdrawn before the investigation of parathyroid function.

- **Blood glucose:**

Monitoring of blood glucose is important in diabetics, in particular in the presence of hypokalaemia.

- **Uric acid:**

Tendency to gout attacks may be increased in hyperuricaemic patients.

- **Renal function and diuretics:**

Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired (plasma creatinine below levels of the order of 25 mg/l, *i.e*. 220 µmol/l in an adult). In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender.
Hypovolaemia, secondary to the loss of water and sodium induced by the diuretic at the start of treatment causes a reduction in glomerular filtration. This may lead to an increase in blood urea and plasma creatinine. This transitory functional renal insufficiency is of no consequence in individuals with normal renal function but may worsen preexisting renal insufficiency.

- **Athletes:**

The attention of athletes is drawn to the fact that this medicinal product contains a drug substance, which may give a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations that are not recommended:

Lithium:

Increased plasma lithium with signs of overdose, as with a salt-free diet (decreased urinary lithium excretion). However, if the use of diuretics is necessary, careful monitoring of plasma lithium and dose adjustment is required.

Combinations requiring precautions for use:

Torsades de pointes-inducing drugs:

- class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide),
- some antipsychotics :

phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),
benzamides (amisulpride, sulpiride, sultopride, tiapride)
butyrophenones (droperidol, haloperidol)
others: bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV.
Increased risk of ventricular arrhythmias, particularly *torsades de pointes* (hypokalaemia is a risk factor).

Monitor for hypokalaemia and correct, if required, before introducing this combination. Clinical, plasma electrolytes and ECG monitoring.
Use substances which do not have the disadvantage of causing torsades de pointes in the presence of hypokalaemia.

N.S.A.I.D.s (systemic route) including COX-2 selective inhibitors, high dose salicylic acid (3 g/day):
Possible reduction in the antihypertensive effect of indapamide.
Risk of acute renal failure in dehydrated patients (decreased glomerular filtration). Hydrate the patient; monitor renal function at the start of treatment.

Angiotensin converting enzyme (A.C.E.) inhibitors:
Risk of sudden hypotension and/or acute renal failure when treatment with an A.C.E. is initiated in the presence of preexisting sodium depletion (particularly in patients with renal artery stenosis).
In hypertension, when prior diuretic treatment may have caused sodium depletion, it is necessary:
- either to stop the diuretic 3 days before starting treatment with the A.C.E. inhibitor, and restart a hypokalaemic diuretic if necessary;
- or give low initial doses of the A.C.E. inhibitor and increase the dose gradually.

In congestive heart failure, start with a very low dose of A.C.E. inhibitor, possibly after a reduction in the dose of the concomitant hypokalaemic diuretic.
In all cases, monitor renal function (plasma creatinine) during the first weeks of treatment with an A.C.E. inhibitor.

Other compounds causing hypokalaemia: amphotericin B (IV), gluco- and mineralo-corticoids (systemic route), tetracosactide, stimulant laxatives:
Increased risk of hypokalaemia (additive effect).
Monitoring of plasma potassium and correction if required. Must be particularly borne in mind in case of concomitant digitalis treatment. Use non-stimulant laxatives.

Baclofen:
Increased antihypertensive effect.
Hydrate the patient; monitor renal function at the start of treatment.

Digitalis preparations:
Hypokalaemia predisposing to the toxic effects of digitalis.
Monitoring of plasma potassium and ECG and, if necessary, adjust the treatment.

Combinations to be taken into consideration:
Potassium-sparing diuretics (amiloride, spironolactone, triamterene):
Whilst rational combinations are useful in some patients, hypokalaemia (particularly in patients with renal failure or diabetes) or hyperkalaemia may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin:
Increased risk of metformin induced lactic acidosis due to the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics. Do not use metformin when plasma creatinine exceeds 15 mg/l (135 µmol/l) in men and 12 mg/l (110 µmol/l) in women.

Iodinated contrast media:
In the presence of dehydration caused by diuretics, increased risk of acute renal failure, in particular when large doses of iodinated contrast media are used.
Rehydration before administration of the iodinated compound.

Imipramine-like antidepressants, neuroleptics:
Antihypertensive effect and increased risk of orthostatic hypotension increased (additive effect).

Calcium (salts):
Risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

Ciclosporin, tacrolimus:
Risk of increased plasma creatinine without any change in circulating ciclosporin levels, even in the absence of water/sodium depletion.

Corticosteroids, tetracosactide (systemic route):
Decreased antihypertensive effect (water/sodium retention due to corticosteroids).

4.6 Pregnancy and lactation

Pregnancy
As a general rule, the administration of diuretics should be avoided in pregnant women and should never be used to treat physiological oedema of pregnancy. Diuretics can cause foetoplacental ischaemia, with a risk of impaired foetal growth.

Lactation
Breast-feeding is inadvisable (indapamide is excreted in human milk).

4.7 Effects on ability to drive and use machines

Indapamide does not affect vigilance but different reactions in relation with the decrease in blood pressure may occur in individual cases, especially at the start of the treatment or when another antihypertensive agent is added.
As a result the ability to drive vehicles or to operate machinery may be impaired.

4.8 Undesirable effects

The majority of adverse reactions concerning clinical or laboratory parameters are dose-dependent.

Thiazide-related diuretics, including indapamide, may cause the following undesirable effects ranked under the following frequency:
Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

Cardiac disorders:
Very rare:arrhythmia, hypotension

Blood and the lymphatic system disorders:
Very rare: thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia

Nervous system disorders:
Rare: vertigo, fatigue, headache, paresthesia

Gastrointestinal disorders:
Uncommon: vomiting
Rare: nausea, constipation, dry mouth
Very rare: pancreatitis

Renal and urinary disorders:
Very rare:renal failure

Skin and subcutaneous tissue disorders:
Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions:
- Common: maculopapular rashes
- Uncommon: purpura
- Very rare: angioneurotic oedema and/or urticaria, toxic epidermic necrolysis, Steven Johnson syndrome

Not known: possible worsening of pre-existing acute disseminated lupus erythematosus.

Cases of photosensitivity reactions have been reported (see section 4.4).

Hepatobiliary disorders:
Very rare: abnormal hepatic function
Not known: possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4)

Laboratory parameters:
During clinical trials, hypokalaemia (plasma potassium <3.4 mmol/l) was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.
Very rare:Hypercalcaemia
Not known:
- Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see section 4.4).
- Hyponatraemia with hypovolaemia responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight.
- Increase in plasma uric acid and blood glucose during treatment: appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes.

4.9 Overdose

Indapamide has been found free of toxicity at up to 40 mg, i.e. 27 times the therapeutic dose.

Signs of acute poisoning take the form above all of water/electrolyte disturbances (hyponatraemia, hypokalaemia) which are manifested as nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (due to hypovolaemia).

Initial measures involve the rapid elimination of the ingested substance(s) by gastric wash-out and/or administration of activated charcoal, followed by restoration of water/electrolyte balance to normal in a specialised centre.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, plain
ATC code: C03BA11
Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to thiazide diuretics, which acts by inhibiting the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Phase II and III studies using monotherapy have demonstrated an antihypertensive effect lasting 24 hours. This was present at doses where the diuretic effect was of mild intensity.

The antihypertensive activity of indapamide is related to an improvement in arterial compliance and a reduction in arteriolar and total peripheral resistance.

Indapamide reduces left ventricular hypertrophy.

Thiazide and related diuretics have a plateau therapeutic effect beyond a certain dose, while adverse effects continue to increase. The dose should not be increased if treatment is ineffective.

It has also been shown, in the short-, mid- and long-term in hypertensive patients, that indapamide:

- does not interfere with lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol;
- does not interfere with carbohydrate metabolism, even in diabetic hypertensive patients.

5.2 Pharmacokinetic properties

Lorvacs XL 1.5 mg is supplied in a prolonged release dosage based on a matrix system in which the drug substance is dispersed within a support which allows sustained release of indapamide.

Absorption
The fraction of indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract.
Eating slightly increases the rapidity of absorption but has no influence on the amount of the drug absorbed.
Peak serum level following a single dose occurs about 12 hours after ingestion, repeated administration reduces the variation in serum levels between 2 doses. Intra-individual variability exists.

Distribution
Binding of indapamide to plasma proteins is 79%.
The plasma elimination half-life is 14 to 24 hours (mean 18 hours).
Steady state is achieved after 7 days.
Repeated administration does not lead to accumulation.

Metabolism
Elimination is essentially urinary (70% of the dose) and faecal (22%) in the form of inactive metabolites.

High risk individuals
Pharmacokinetic parameters are unchanged in renal failure patients.

5.3 Preclinical safety data

The highest doses administered orally to different animal species (40 to 8000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of indapamide. The major symptoms of poisoning during acute toxicity studies with indapamide administered intravenously or intraperitoneally were related to the pharmacological action of indapamide, i.e. bradypnoea and peripheral vasodilation.

Indapamide has been tested negative concerning mutagenic and carcinogenic properties.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinised maize starch
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate
Macrogol 6000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This product does not require any special storage conditions.

6.5 Nature and contents of container
10, 14, 15, 20, 30, 50, 60, 90, 100 tablets in blisters (PVC/aluminium).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Renantos Pharmavertriebsgesellschaft GmbH
Beethovenstraße 10
89340 Leipheim, Germany
Tel.: +49 (0) 8221 916033-8
Fax: +49 (0) 8221 916033-9
e-mail: regulatory@renantos.com

8 MARKETING AUTHORISATION NUMBER(S)

PL 27900/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/12/2009

10 DATE OF REVISION OF THE TEXT

22/12/2009

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET:
INFORMATION FOR THE USER

Lorvacs XL 1.5 mg Prolonged-release Tablets

Indapamide

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT LORVACS XL 1.5 MG IS AND WHAT IT IS USED FOR

This medicine is intended to reduce high blood pressure (hypertension).
It is a prolonged-release tablet containing indapamide as the active ingredient.
Indapamide is a diuretic. Most diuretics increase the amount of urine produced by the kidneys.

2. BEFORE YOU TAKE LORVACS XL 1.5 MG

Do not take Lorvacs XL 1.5 mg
- if you are allergic (hypersensitive) to indapamide or any other sulphonamide or to any of the other ingredients of Lorvacs XL 1.5 mg,
- if you have severe kidney disease,
- if you have severe liver disease or suffer from a condition called hepatic encephalopathy (liver problems which affect the brain and central nervous system),
- if you have low potassium levels in your blood.

Take special care with Lorvacs XL 1.5 mg
- if you have liver problems,
- if you have diabetes,
- if you suffer from gout,
- if you have any heart rhythm problems or problems with your kidneys,
- if you need to have a test to check how well your parathyroid gland is working.

You should tell your doctor if you have had photosensitivity reactions.

Your doctor may give you blood tests to check for low sodium or potassium levels or high calcium levels.
If you think any of these situations may apply to you or you have any questions or doubts about taking your medicine, you should consult your doctor or pharmacist.

Athletes should be aware that this medicine contains an active ingredient, which may give a positive reaction in doping tests.

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.

You should not take Lorvacs XL 1.5 mg with lithium (used to treat depression) due to the risk of increased levels of lithium in the blood.

Make sure to tell your doctor if you are taking any of the following medicines, as special care may be required:
- medicines used for heart rhythm problems (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, ibutilide, dofetilide, digitalis),
- medicines used to treat mental disorders such as depression, anxiety, schizophrenia (e.g. tricyclic antidepressants, antipsychotic drugs, neuroleptics),
- bepridil (used to treat angina pectoris, a condition causing chest pain),
- cisapride (used to treat reduced movement of the gullet and stomach),
- diphemanil (used to treat gastric problems such as ulcers, too much acid, overactive digestive system),
- sparfloxacin, moxifloxacin (antibiotics used to treat infections),
- halofantrine (antiparasitic drugs used to treat certain types of malaria),
- pentamidine (used to treat certain types of pneumonia),
- mizolastine (used to treat allergic reactions, such as hay fever),
- non-steroidal anti-inflammatory drugs for pain relief (e.g. ibuprofen) or high doses of acetylsalicylic acid,
- angiotensin converting enzyme (ACE) inhibitors (used to treat high blood pressure and heart failure),
- oral corticosteroids used to treat various conditions including severe asthma and rheumatoid arthritis,
- stimulant laxatives,
- baclofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis),
- potassium-sparing diuretics (amiloride, spironolactone, triamterene),
- metformin (to treat diabetes),
- iodinated contrast media (used for tests involving X-rays),
- calcium tablets or other calcium supplements,
- ciclosporin, tacrolimus or other medicines to depress the immune system after organ transplantation, to treat autoimmune diseases, or severe rheumatic or dermatological diseases,
- tetracosactide (to treat Crohn's disease).

Pregnancy and breast-feeding

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

This medicine is not recommended during pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Please tell your doctor if you are pregnant or wish to become pregnant. The active ingredient is excreted in milk. Breastfeeding is not advisable if you are taking this medicine.

Driving and using machines

This medicine can cause side effects such as dizziness or tiredness due to lowering of the blood pressure (see section 4). These side effects are more likely to occur after initiation of the treatment and after dose increases. If this occurs, you should refrain from driving and other activities requiring alertness.

Important information about some of the ingredients of Lorvacs XL 1.5 mg

This medicine contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE LORVACS XL 1.5 MG

Always take Lorvacs XL 1.5 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one tablet each day, preferably in the morning. The tablets can be taken with or without food. They should be swallowed whole

with water. Do not crush or chew them. Treatment for high blood pressure is usually life-long.

If you take more Lorvacs XL 1.5 mg than you should

If you have taken too many tablets, contact your doctor or pharmacist immediately.

A very large dose of Lorvacs XL 1.5 mg could cause nausea (feeling sick), vomiting, low blood pressure, cramps, dizziness, drowsiness, confusion and changes in the amount of urine produced by the kidneys.

If you forget to take Lorvacs XL 1.5 mg

If you forget to take a dose of your medicine, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

If you stop taking Lorvacs XL 1.5 mg

As the treatment for high blood pressure is usually life-long, you should discuss with your doctor before stopping this medicinal product.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Lorvacs XL 1.5 mg can cause side effects, although not everybody gets them.

These can include:

Commonly (less than 1 patient in 10 but more than 1 in 100):
- Low potassium in the blood, which may cause muscle weakness, allergic reactions, mainly dermatological, such as skin rashes

Uncommonly (less than 1 patient in 100 but more than 1 in 1000):
- Vomiting, purpura (red pinpoints on skin) in subjects with a tendency to allergic and asthmatic reactions.

Rarely (less than 1 patient in 1000 but more than 1 in 10,000):
- Feeling of tiredness, dizziness, headache, pins and needles (paresthesia);
- Nausea (feeling sick), constipation, dry mouth;
- Increased risk of dehydration in the elderly and in patients suffering from heart failure.

Very rarely (less than 1 patient in 10,000):
- Heart rhythm irregularities (causing palpitations, feeling of the heart pounding), low blood pressure;
- Kidney disease (causing symptoms of tiredness, increased need to urinate, itchy skin, feeling sick, swollen extremities);
- Pancreatitis (inflammation of the pancreas which causes upper abdominal pain), abnormal liver function (with symptoms such as tiredness, loss of appetite, feeling or being sick, swollen extremities, yellow skin). In cases of liver failure, there is a possibility of getting hepatic encephalopathy (liver problems which affect the brain and central nervous system);
- Changes in blood cells, such as thrombocytopenia (decrease in the number of platelets which causes easy bruising and nasal bleeding), leucopenia (decrease in white blood cells which may cause unexplained fever, soreness of the throat or other flu-like symptoms – if this occurs, contact your doctor) and anaemia (decrease in red blood cells);
- Angioedema and/or urticaria, severe skin manifestations. Angioedema is characterised by swelling of the skin around the eyes, lips, hands or feet. It may cause swelling of the throat, tongue or airways resulting in shortness of breath or difficulty in swallowing. If this occurs, contact your doctor immediately.

If you suffer from systemic lupus erythematosus (a disorder of the immune system leading to inflammation and damage to the joints, tendons and organs with symptoms including skin rashes, tiredness, loss of appetite, weight gain and joint pain), this might get worse. Cases of photosensitivity reactions (change in skin appearance) after exposure to the sun or artificial UVA have also been reported.

Some changes may occur in your blood and your doctor may need to give you blood tests to check your condition. The following changes in your blood test results may occur:
- low potassium in the blood,
- low sodium in the blood that may lead to dehydration and low blood pressure,
- increase in uric acid, a substance which may cause or worsen gout - painful joint(s) especially in the feet,
- increase in blood glucose levels in diabetic patients,
- increase of calcium in blood.

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

5. HOW TO STORE LORVACS XL 1.5 MG

Keep out of the reach and sight of children.

Do not use this medicine after the expiry data which is stated on the carton and blister. The expiry date refers to the last day of that month.
This product does not require any special storage conditions.

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 Lorvacs XL 1.5 mg contains

The active substance is indapamide. Each tablet contains 1.5 mg of indapamide.
The other ingredients are lactose monohydrate, pregelatinised maize starch, hypromellose, silica colloidal anhydrous, magnesium stearate, macrogol 6000, titanium dioxide (E171).

What Lorvacs XL 1.5 mg looks like and contents of the pack

White to off-white, round shaped, biconvex, prolonged-release film-coated tablets which come in boxes of 10, 14, 15, 20, 30, 50, 60, 90 and 100. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

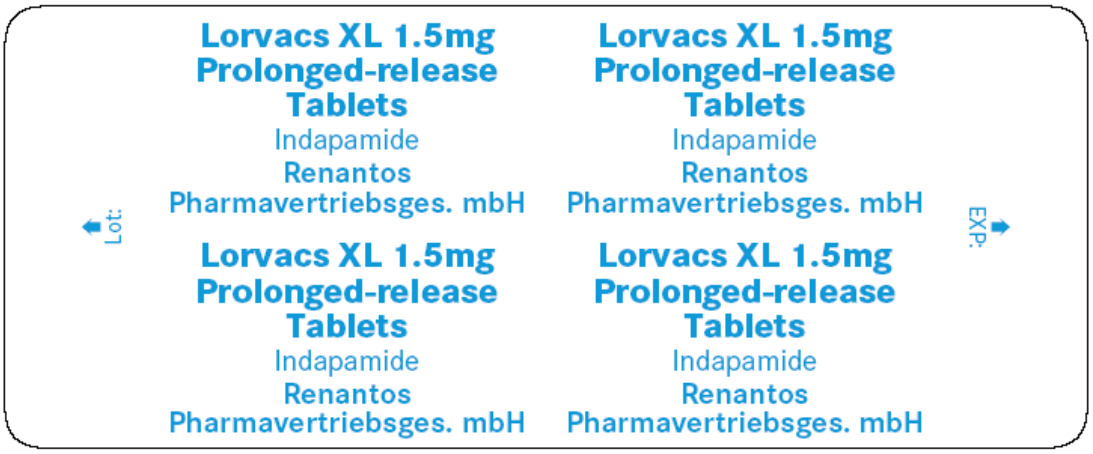
Marketing Authorisation Holder
Renantos Pharmavertriebsgesellschaft mbH
Beethovenstraße 10
89340 Leipheim
Germany

Manufacturer
Heumann Pharma GmbH & Co. Generica KG
Suedwestpark 50
90449 Nuremberg
Germany

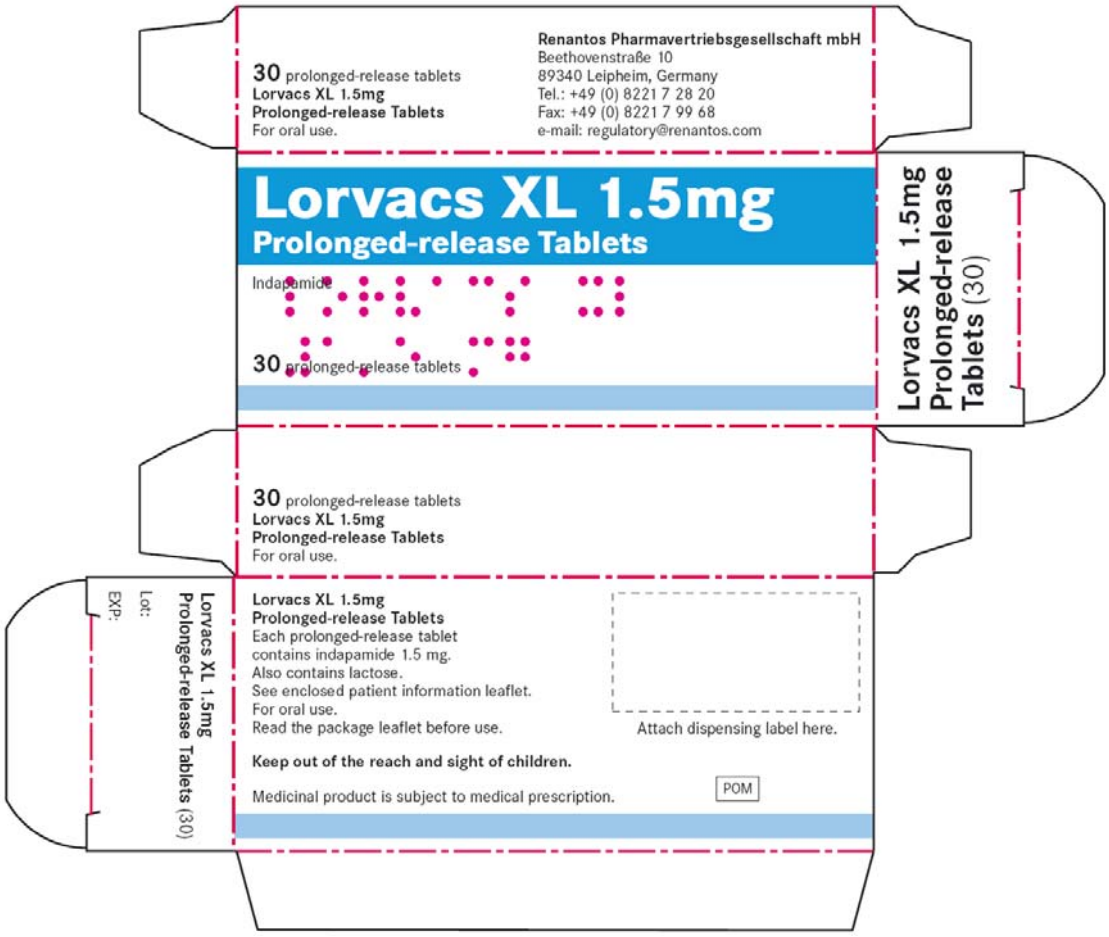
This leaflet was last approved in {MM/YYYY}.

LABELLING

Blister:



Carton:


30 prolonged-release tablets
Lorvacs XL 1.5mg
Prolonged-release Tablets
For oral use.
Renantos Pharmavertriebsgesellschaft mbH
Beethovenstraße 10
89340 Leipheim, Germany
Tel.: +49 (0) 8221 7 28 20
Fax: +49 (0) 8221 7 99 68
e-mail: regulatory@renantos.com
Lorvacs XL 1.5mg
Prolonged-release Tablets
Indapamide
30 prolonged-release tablets
Lorvacs XL 1.5mg Prolonged-release Tablets (30)
30 prolonged-release tablets
Lorvacs XL 1.5mg
Prolonged-release Tablets
For oral use.
Lot:
EXP:
Lorvacs XL 1.5mg Prolonged-release Tablets (30)
Lorvacs XL 1.5mg
Prolonged-release Tablets
Each prolonged-release tablet
contains indapamide 1.5 mg.
Also contains lactose.
See enclosed patient information leaflet.
For oral use.
Read the package leaflet before use.
Attach dispensing label here.
Keep out of the reach and sight of children.
Medicinal product is subject to medical prescription.
POM