TRANDOLAPRIL 0.5MG CAPSULES
PL 00289/0800
PL 00289/0804

TRANDOLAPRIL 1MG CAPSULES
PL 00289/0801
PL 00289/0805

TRANDOLAPRIL 2MG CAPSULES
PL 00289/0802
PL 00289/0806

UKPAR

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TRANDOLAPRIL 0.5MG CAPSULES
PL 00289/0800
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TRANDOLAPRIL 1MG CAPSULES
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PL 00289/0805

TRANDOLAPRIL 2MG CAPSULES
PL 00289/0802
PL 00289/0806

LAY SUMMARY

The MHRA granted TEVA UK Marketing Authorisations (licences) for the medicinal products Trandolapril 0.5mg Capsules (PL 00289/0800 and PL 00289/0804), Trandolapril 1mg Capsules (PL 00289/0801 and PL 00289/0805) and Trandolapril 2mg Capsules (PL 00289/0802 and PL 00289/0806). These are prescription-only medicines for the treatment of high blood pressure. The capsules may also be used to protect your heart after a heart attack.

Trandolapril Capsules contain the active ingredient trandolapril, which belongs to a group of drugs called angiotensin-converting enzyme inhibitors (ACE inhibitors). It works by relaxing the blood vessels making it easier for the heart to pump blood around the body. This helps to reduce blood pressure and relieve the strain on the heart muscle.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Trandolapril 0.5mg, 1mg and 2mg Capsules outweigh the risks; hence Marketing Authorisations have been granted.

TRANDOLAPRIL 0.5MG CAPSULES
PL 00289/0800
PL 00289/0804

TRANDOLAPRIL 1MG CAPSULES
PL 00289/0801
PL 00289/0805

TRANDOLAPRIL 2MG CAPSULES
PL 00289/0802
PL 00289/0806

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted marketing authorisations for the medicinal products Trandolapril 0.5mg Capsules (PL 00289/0800 & 00289/0804), Trandolapril 1mg Capsules (PL 00289/0801 & 00289/0805) and Trandolapril 2mg Capsules (PL 00289/0802 & 00289/0806) on 31st January 2008. The products are prescription-only medicines.

These are three strengths of trandolapril, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to the original products Odrik 0.5mg, 1mg and 2mg Capsules (Aventis Pharma Limited). The reference products were first authorised in the Ireland on 25th November1992 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient trandolapril. Trandolapril is a pro-drug, a non-peptide angiotensin converting enzyme (ACE) inhibitor. Trandolapril is rapidily absorbed and then non-specifically hydrolysed to its potent, long-lasting active metabolite, trandolaprilat. The beneficial effects of ACE inhibitors in hypertension and in heart failure appear to result primarily from the suppression of the plasma angiotensin aldosterone system.

Trandolapril 0.5mg, 1mg and 2mg Capsules are indicated for the treatment of hypertension and to help protect the heart after a heart attack.

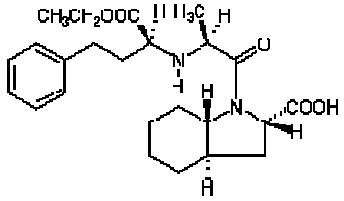
These applications were submitted at the same time and all three strengths depend on the bioequivalence study comparing the applicant's 2mg product with the reference product Odrik 2mg Capsules (Aventis Pharma Limited). Consequently, all sections of this Scientific Discussion refer to all products.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Trandolapril

INN: Trandolapril
Chemical Name: (2S,3aR,7aS)-1-[(S)-2-[[1-Ethoxycarbonyl-3-phenylpropyl]amino]propanoyl]octahydro-1H-indole-2-carboxylic acid
Structure:



Molecular formula: $C_{24}H_{34}N_2O_5$
Molecular weight: 430.54

Physical form: White or almost white powder
Solubility: Freely soluble in methanol and acetic acid
Soluble in ethanol
Slightly soluble in acetonitrile
Very slightly soluble in water
Melting range: 130-135^{o}C

At present there is no drug substance monograph for trandolapril in the Ph.Eur. An appropriate specification is provided for the active substance trandolapril.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

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

Batch analysis data are provided and comply with the proposed specification.

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

Appropriate stability data have been generated supporting a retest period of 24 months, with no specific storage instructions.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose anhydrous, sodium stearyl fumarate, erythosine FD & C red no.3 (E127), titanium dioxide E171, yellow iron oxide (E172), gelatine, quinoline yellow (E104), povidone K-30, industrial methylated

spirit, pregelatinised starch, capsule shell, shellac glaze, propylene glycol and black iron oxide. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exceptions of erythosine FD & C red no.3 (E127), yellow iron oxide (E172) and quinoline yellow (E104) which comply with in- house specifications, this is acceptable. Satisfactory certificates of analysis have been provided for all excipients.

The product contains two materials of animal origin – anhydrous lactose and gelatine. A declaration has been provided confirming that the anhydrous lactose is sourced from healthy animals under the same conditions as that for human consumption. Satisfactory TSE certificates have been provided for the suppliers of gelatine.

There were no novel excipients used and no overages.

Dissolution and impurity profiles
Dissolution and impurity profiles for all three strengths of the drug product were found to be similar to those for the reference products.

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 two pilot-scale batches of each capsule strength. 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
Product is packaged in aluminium- aluminium blisters. Specifications and certificates of analysis for the packaging type used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 14,20,28,30,50,60,98 and 100 capsules.

Stability
Stability studies were performed on pilot-scale batches of all strengths of finished product in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies on pilot batches were within specified limits. These data support a shelf-life of 24 months with the following storage conditions; “Do not store above 25 degrees” and “Store in original container”.

The Marketing Authorisation Holder has committed to providing stability data for the first three commercial-scale batches (each strength) of the finished product.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

Trandolopril 0.5mg, 1mg and 2mg Capsules and their duplicate licences have been shown to be generic medicinal products of Odrik 0.5mg, 1mg and 2mg Capsules. The proposed drug products correspond to the current EU definition of a generic product as they comply with the criteria of having the same qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence as the reference products.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1. BACKGROUND

Trandolapril belongs to the group of agents acting on the renin-angiotensin system, known as ACE inhibitors (ATC code C09A A 10).

2. INDICATIONS

Therapeutic indications

Mild or moderate hypertension.

Left ventricular dysfunction after myocardial infarction.

It has been demonstrated that Trandolapril improves survival following myocardial infarction in patients with left ventricular dysfunction (ejection fraction $\leq$ 35 percent), with or without symptoms of heart failure, and/or, with or without residual ischaemia. Long-term treatment with Trandolapril significantly reduces overall cardiovascular mortality. It significantly decreases the risk of sudden death and the occurrence of severe or resistant heart failure.

3. DOSE & DOSE SCHEDULE

Posology and method of administration

Adults

Mild or moderate hypertension

For adults not taking diuretics, without congestive heart failure and without renal or hepatic insufficiency; the recommended initial dosage is 0.5 mg as a single daily dose. A 0.5 mg dose will only achieve a therapeutic response in a minority of patients. Dosage should be doubled incrementally at intervals of 2 to 4 weeks, based on patient response, up to a maximum of 4 mg as a single daily does. The usual maintenance dose range is 1 to 2 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 4 mg Trandolapril combination therapy should be considered.

Left ventricular dysfunction after myocardial infarction

Following a myocardial infarction, therapy may be initiated as early as on the third day. Treatment should be initiated at a daily dose of 0.5 mg. The dose should be progressively increased to a maximum of 4 mg as a single daily dose. Depending upon the tolerability such as symptomatic hypotension, this forced titration can be temporarily suspended.

In the event of hypotension, all concomitant hypotensive therapies such as vasodilators including nitrates, diuretics, must be carefully checked and if possible their dose reduced.

The dose of Trandolapril should be lowered only if the previous measures are not effective or not feasible.

Elderly
The dose in elderly patients is the same as in adults. There is no need to reduce the dose in elderly patients with normal renal and hepatic function. Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to the need for the control of blood pressure.
Prior diuretic Treatment
In patients who are at a risk from a stimulated renin-angiotension system (eg patients with water and sodium depletion) the diuretic should be discontinued 2-3 days before beginning therapy with 0.5 mg trandolapril to reduce the likelihood of symptomatic hypotension. The diuretic may be resumed later if required.

Cardiac Failure
In hypertensive patients who also have congestive heat failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 0.5 mg Trandolapril once daily under close medical supervision in hospital.

Dosage Adjustment in Renal Impairment
For patients with mild or moderate renal impairment (creatinine clearance of 10-70 ml/min) the usual adult and elderly doses are recommended.

For patients with severe renal impairment (creatinine clearance of <10 ml/min) the usual adult and elderly starting doses are also recommended but the maximum daily dose should not exceed 2 mg. In these patients therapy should be under close medical supervision.

Dialysis
It is not known for certain if trandolapril or trandolaprilat are removed by dialysis. However, it would be expected that dialysis could remove the active moiety, trandolaprilat, from the circulation, resulting in a possible loss of control of blood pressure.Therefore careful monitoring of the patient's blood pressure during dialysis is required, and the dosage of trandolapril adjusted if needed.

Dosage Adjustment in Hepatic Impairment
In patients with severely impaired liver function a decrease in the metabolic clearance of the parent compound trandolapril and the active metabolite trandolaprilat results in a large increase in plasma trandolapril levels and to a lesser extent an increase in trandolaprilat levels. Treatment with Trandolapril should therefore be initiated at a dose of 0.5 mg once daily under close medical supervision.

Children
Trandolapril has not been studied in children and therefore use in this age group is not recommended.

5. TOXICOLOGY

No toxicology data has been submitted or is required for his type of application.

6. CLINICAL PHARMACOLOGY

The bioavailability of a single dose of 2mg Teva Trandolapril Capsules was compared with that of the reference product Odrik 2 mg Capsules (Aventis Pharma Ltd, UK) in a bioequivalence study.

Dissolution Profiles

The dissolution profiles of all strengths of Teva Trandolapril were similar to their equivalent strength of Odrik Capsules (UK).

Bioequivalence Study 20XX-YYY

This was a single dose randomised, two-period, two-sequence, two-treatment, crossover fasting study comparing the bioavailability of Trandolapril 2 mg Capsules with the reference Odrik 2mg Capsules (UK).

Results

The results obtained are shown in Table 1, below:

Table 1: Analyte: Trandolapril

Parameter	Geometric Arithmetic Treatment A	Means Means(CV%) Treatment B	Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
AUC_{0-t} (ng*h/mL)	**2.4263** **2.6291 (45)**	**2.3900** **2.6463 (51)**	**101.52**	**96.09 – 107.25**	**16**
AUC_{inf} (ng*h/mL)	**3.1977** **3.5464 (42)**	**3.2748** **3.8906 (40)**	**97.64**	**89.96 – 105.99**	**8**
C_{max} (ng/mL)	**2.0419** **2.2061 (42)**	**2.0622** **2.4034 (63)**	**99.01**	**88.04 – 111.36**	**35**

The mean relative bioavailability for trandolapril was 97.64%, with a 90% confidence interval of 89.96%- 105.99% for the ratio of log-transformed AUC_{0-inf} . The ratio of mean C_{max} log-transformed values was 99.01% with a confidence interval of 88.04 – 111.36%.

The mean T_{max} values were 0.66 and 0.75 hours for the Teva and reference products respectively.

Similarly, the mean relative bioavailability of trandolaprilat was within the required 80-125% for AUC and C_{max} parameters both for analyses with and without baseline adjustment for the pre-dose concentration of trandolaprilat concentrations for all subjects.

Table 2: Analyte: Trandolaprilat

Parameter	Geometric Arithmetic Treatment A	Means Means(CV%) Treatment B	Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
AUC_{0-t} (ng*h/mL)	**76.2417** **78.6904 (26)**	**76.3556** **78.5064 (25)**	**99.58**	**97.72 – 102.03**	**6**
C_{max} (ng/mL)	**2.5492** **2.6881 (34)**	**2.5845** **2.7165 (32)**	**98.63**	**95.29 – 102.10**	**10**
T_{max} (h)	**5.32 (33)**	**5.10 (35)**	-	-	-

It was found that the ratios (test/reference) of least-squares means and 90% confidence interval for trandolapril and trandolaprilat were within the 80-125% acceptance range.

Assessor's Comments on Bioequivalence Study 20XX-YYY

The results for this study showed all the parameters were within the limits of 80-125% as described in Notes for Guidance on Bioavailability and Bioequivalence CPMP/EWP/98.

Bioequivalence of 0.5mg and 1 mg doses of trandolapril with the Innovator product.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 2mg strength can be extrapolated to the 0.5mg and 1mg strength tablets.

Evidence of the linear kinetics of trandolapril

The company has submitted evidence of the dose linearity of trandolapril from literature reference Lenfant *et al*[1] and the Physician's Desk Reference.

1. Lenfant *et al*, carried out a pharmacokinetic study with a single oral doses of trandolapril 0.5mg, 1 mg, 2 mg and 4 mg in 12 healthy male volunteers. The results obtained for trandolapril are shown in Table 3, below:

Table 3. Plasma pharmacokinetic parameters of trandolapril after a single oral administration of 0.5, 2, and 4mg to 12 healthy volunteers (mean ± SEM)

	Dose of trandolapril				
	0.5 mg	1 mg	2 mg	4 mg	ANOVA
C_{max} (ng/ml)	0.43 ± 0.1	0.86 ± 0.1	1.68 ± 0.33	3.32 ± 0.56	-
C_{max}/ dose (ng/ml mg)	0.86 ± 0.2	0.86 ± 0.1	0.84 ± 0.17	0.83 ± 0.14	NS
T_{max-} (h)[4]	1	0.5	0.5	0.5	
(range)	(0.5 – 1)	(0.5 – 1)	(0.5 – 1)	(0.5 – 1)	NS[b]
AUC (ng/ml)	0.4 ± 0.11	0.95 ± 0.15	1.86 ± 0.3	3.64 ± 0.44	-
AUC/dose (ng h/ml mg)	0.8 ± 0.21	0.95 ± 0.15	0.93 ± 0.15	0.91 ± 0.11	NS
$T_{1/2}$ (h)	0.71 ± 0.08	0.74 ± 0.09	0.68 ± 0.05	0.76 ± 0.13	NS

ANOVA, dose factor, NS, p>0.05
[4]Median

The results and graphic representation of the data clearly illustrate the proportional relationship between the dose of trandolapril and the plasma concentration and area under the curve.

The results given below in Table 4 are for the active metabolite trandolaprilat.

Table 4. Dose-dependent pharmacokinetic parameters of trandolaprilat standardised to the dose following a single oral administration of 0.5, 1, 2 and 4 mg of trandolapril to 12 healthy volunteers (mean ± SEM)

	Dose of trandolapril				ANOVA Tukey Test
	0.5 mg	1 mg	2 mg	4 mg	
C_{max}/ dose (ng/ml mg)	1.92 ± 0.17	1.44 ± 0.12	1.40 ± 0.13	1.61 ± 0.14	**
					0.5 4 1 2
AUC_{0-96} hr/dose (ng/ml mg)	128.75 ± 14.16	92.82 ± 9.12	61.93 ± 3.94	38.70 ± 2.83	0.5 1 2 4 ***
AUC_{0-24} hr/dose (ng/ml mg)	35.99 ± 3.71	27.67 ± 2.55	22.86 ± 1.61	18.43 ± 1.36	0.5 1 2 4 ***
AUC_{0-12} hr/dose (ng h/ml mg)	17.81 ± 1.83	14.21 ± 1.28	12.80± 1.02	12.36 ± 1.01	0.5 1 2 4 ****
U_{0-96} hr/dose (ng/mg)	19.17 ± 6.60	83.92 ± 10.11	118.42 ± 11.65	144.27 ± 13.58	4 2 1 ****
U_{0-24} hr/dose (ng/mg)	12.00 ± 5.98	43.75 ± 4.96	84.46 ± 7.38	119.54 ± 10.84	4 2 1

ANOVA: Dose factor (a) dose factor only tested on doses 1, 2, 4mg Tukey test: the means are sorted in descending order, those underlined with the same line are not significantly different
0.05 ≥ p > 0.01; **0.01 ≥ p 0.001; ***p ≤0.001

The results show linear relationships between the C_{max}, AUC_{0-12} and dose for doses greater than 0.5mg. Some features of non-linearity were detected at low doses, which were attributed to saturable plasma ACE binding. The authors conclude that the pharmacokinetics of non-ACE bound trandolaprilat is probably linear.

Assessor's Comments on Dose linearity of Trandolapril and Bioequivalence of 0.5mg and 1 mg dosage strengths.
The applicant has provided a detailed review of the available literature to demonstrate that trandolapril demonstrates linear pharmacokinetics between 0.5-2 mg and that although trandolaprilat pharmacokinetics are non-linear at 0.5 mg, this is attributed to saturable ACE binding rather than non-linear pharmacokinetics as non-linearity is observed after 12 hours ie. in the elimination phase of trandolaprilat. This justification has since been accepted for several other applications where bioequivalence has been demonstrated on the basis of bioequivalence at the highest strength. Given that the biowaiver criteria apply for the 0.5 mg and 1 mg capsules, the 2 mg strength can be considered suitable for demonstrating bioequivalence for the remaining strengths.

7. EFFICACY
No new efficacy data is required for these applications.

8. SAFETY
No new safety data is required for these applications.

9. EXPERT REPORTS
The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

The Clinical Overview gives a comprehensive exposition of the pharmacology and therapeutics of trandolapril and discusses the bioequivalence study submitted with the dossier in support of these marketing authorisation applications. It concludes that the bioequivalence study presented for the 2mg dose is valid for the 0.5 mg and 1mg strengths as the percentage of the composition of the 3 strengths is similar, in line with Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

Medical Assessor's Comments
This assessor agrees with the Clinical Overview including the conclusion that the bioequivalence of the 2 mg strength with the reference product Odrik 2 mg (Aventis) has been demonstrated in a properly conducted study, the result of which can be extrapolated to the 0.5 mg and 1mg strengths.

10. SUMMARY OF PRODUCT CHARACTERISTICS
The SmPC of Teva trandolapril 0.5mg, 1 and 2 mg Hard Gelatine Capsules is identical to the brand leader, Odrik (Aventis).
There is no data to indicate any new undesirable effects likely to change the benefit/risk ratio. Therefore no change to the SPC is proposed.

This is satisfactory.

11. PATIENT INFORMATION LEAFLET

This is clinically satisfactory.

The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

12. LABELLING

This is clinically satisfactory.

13. MAA FORM

This is satisfactory.

14. RECOMMENDATION

The applicant has satisfactorily demonstrated bioequivalence for all three strengths of Trandopril. Marketing authorisations should be granted for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Trandopril 0.5mg, 1mg and 2mg Capsules 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

Bioequivalence has been demonstrated between the applicant's Trandolapril 2mg Capsules and the reference innovator product Odrik 2mg Tablets (Aventis). Given that linear kinetics apply between the 0.5mg, 1mg and 2mg capsules, that proportional formulae for the capsules have been used and that similar dissolution results have been shown for the three strengths, separate bioequivalence studies using the 1mg or 0.5mg capsules will not be considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Odrik capsules.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with trandolapril is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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PL 00289/0802
PL 00289/0806

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 31st December 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 24th January 2005.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 5th October 2005, 5th February 2007, 27th September 2007 and 20th November 2007 and further information relating to the clinical dossiers on 17th December 2007.
4	The applicant responded to the MHRA's requests, providing further information on 22nd October 2006, 27th September 2007, 8th October 2007, and 30th November 2007 for the quality sections, and again on 4th January 2008 for the clinical sections.
5	The applications were determined on 31st January 2008.

TRANDOLAPRIL 0.5MG CAPSULES
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TRANDOLAPRIL 2MG CAPSULES
PL 00289/0802
PL 00289/0806

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Trandolapril 0.5mg, 1mg and 2mg Capsules is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Trandolapril 0.5 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 mg trandolapril.

Excipient: 31.5 mg lactose/capsule

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Body : Rich yellow, Imprinting: TD0.5
Cap: Medium orange, Imprinting: TD0.5

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Mild or moderate hypertension.

Left ventricular dysfunction after myocardial infarction.

It has been demonstrated that Trandolapril improves survival following myocardial infarction in patients with left ventricular dysfunction (ejection fraction $\leq$ 35 percent), with or without symptoms of heart failure, and/or, with or without residual ischaemia. Long-term treatment with Trandolapril significantly reduces overall cardiovascular mortality. It significantly decreases the risk of sudden death and the occurrence of severe or resistant heart failure.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults

Mild or moderate hypertension
For adults not taking diuretics, without congestive heart failure and without renal or hepatic insufficiency; the recommended initial dosage is 0.5 mg as a single daily dose. A 0.5 mg dose will only achieve a therapeutic response in a minority of patients. Dosage should be doubled incrementally at intervals of 2 to 4 weeks, based on patient response, up to a maximum of 4 mg as a single daily dose. The usual maintenance dose range is 1 to 2 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 4 mg Trandolapril, combination therapy should be considered.

Left ventricular dysfunction after myocardial infarction
Following a myocardial infarction, therapy may be initiated as early as on the third day. Treatment should be initiated at a daily dose of 0.5 mg. The dose should be progressively increased to a maximum of 4 mg as a single daily dose. Depending upon the tolerability such as symptomatic hypotension, this forced titration can be temporarily suspended.

In the event of hypotension, all concomitant hypotensive therapies such as vasodilators including nitrates, diuretics, must be carefully checked and if possible their dose reduced.

The dose of Trandolapril should be lowered only if the previous measures are not effective or not feasible.

Elderly

The dose in elderly patients is the same as in adults. There is no need to reduce the dose in elderly patients with normal renal and hepatic function. Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to the need for the control of blood pressure.

Prior Diuretic Treatment
In patients who are at risk from a stimulated renin-angiotensin system (eg patients with water and sodium depletion) the diuretic should be discontinued 2-3 days before beginning therapy with 0.5 mg trandolapril to reduce the likelihood of symptomatic hypotension. The diuretic may be resumed later if required.

Cardiac Failure
In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 0.5 mg Trandolapril once daily under close medical supervision in hospital.

Dosage Adjustment in Renal Impairment
For patients with mild or moderate renal impairment (creatinine clearance of 10-70 ml/min) the usual adult and elderly doses are recommended.

For patients with severe renal impairment (creatinine clearance of <10 ml/min) the usual adult and elderly starting doses are also recommended but the maximum daily dose should not exceed 2 mg. In these patients therapy should be under close medical supervision.

Dialysis
It is not known for certain if trandolapril or trandolaprilat are removed by dialysis. However, it would be expected that dialysis could remove the active moiety, trandolaprilat, from the circulation, resulting in a possible loss of control of blood pressure. Therefore careful monitoring of the patient's blood pressure during dialysis is required, and the dosage of trandolapril adjusted if needed.

Dosage Adjustment in Hepatic Impairment
In patients with severely impaired liver function a decrease in the metabolic clearance of the parent compound trandolapril and the active metabolite trandolaprilat results in a large increase in plasma trandolapril levels and to a lesser extent an increase in trandolaprilat levels. Treatment with Trandolapril should therefore be initiated at a dose of 0.5 mg once daily under close medical supervision.

Children
Trandolapril has not been studied in children and therefore use in this age group is not recommended.

4.3 CONTRAINDICATIONS

Known hypersensitivity to trandolapril or any other ACE inhibitor or to any of the excipients.

History of angioneurotic oedema associated with administration of an ACE inhibitor.

Hereditary/idiopathic angioneurotic oedema.

Second and third trimester of pregnancy (see section 4.4 and 4.6).

Lactation.

Use in children.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Trandolapril should not be used in patients with aortic stenosis or outflow obstruction.

Assessment of Renal Function
Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment. Proteinuria may occur if renal impairment is present prior to therapy or relatively high doses are used.

Impaired Renal Function
Patients with severe renal insufficiency may require reduced doses of trandolapril; their renal function should be closely monitored. In the majority, renal function will not alter. In patients with renal insufficiency, congestive heart failure or unilateral or bilateral renal artery stenosis, in the single kidney as well as after renal transplantation, there is a risk of impairment of renal function and severe hypotension. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy. In these patients treatment should be started in hospital under close medical supervision with low doses and careful dose titration.

Renal failure in association with ACE inhibitors has mainly been reported in patients with severe heart failure or underlying renal disease, including renal artery stenosis.

Some hypertensive patients with no apparent pre-existing renal disease may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when trandolapril is given concomitantly with a diuretic. Dosage reduction of trandolapril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency the risk of hyperkalaemia should be considered and the patient's electrolyte status checked regularly.

Patients who are dialysed using high flux polyacrylonitrile membranes and treated with ACE inhibitors are likely to experience anaphylactoid reactions such as facial swelling, flushing, hypotension and dyspnoea within a few minutes of commencing haemodialysis. It is recommended to use an alternative membrane or an alternative anti hypertensive drug.

Patients with renovascular hypertension
There is an increased risk of severe hypotension and renal insufficiency when patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a solitary kidney are treated with ACE inhibitors. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis. In these patients treatment should be started in hospital under close medical supervision with low doses and careful dose titration. Diuretic treatment should be discontinued and renal function should be monitored during the first weeks of therapy.

Impaired Liver Function
Trandolapril is a prodrug metabolised to its active moiety in the liver. Thus particular caution and close monitoring should be applied to patients with impaired liver function as it may lead to elevated plasma levels, therefore dose adaptation may be required.

Symptomatic Hypotension
In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of Trandolapril as well as after increasing the dose of Trandolapril. ACE inhibitors may cause a profound fall in blood pressure. It has been reported mainly in patients with severe heart failure with or without renal insufficiency. It is also more likely to occur in patients who have been volume-and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. This is more likely to occur in patients on high dose loop diuretics, or those with hyponatraemia or functional renal impairment. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with Trandolapril. These patients should also be kept under very close medical supervision when starting treatment preferably in hospital with low doses and careful titration. These considerations also apply to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may

be necessary if there is associated bradycardia. Treatment with Trandolapril may usually be continued following restoration of effective blood volume and blood pressure. The appearance of hypotension after the initial dose does not preclude subsequent careful dose titration with drug after effective management.

Surgery/Anaesthesia
In patients undergoing surgery or during anaesthesia ACE inhibitors may cause hypotension or even hypotensive shock due to enhancement of agents producing hypotension. Trandolapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment. If it is not possible to withhold the ACE inhibitor, volume management should be handled with care.

Agranulocytosis and Bone Marrow Depression
In patients on angiotensin converting enzyme inhibitors, agranulocytosis and bone marrow depression have been seen rarely. They are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Therefore, regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (eg lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and antimetabolites.

Aortic stenosis/hypertrophic cardiomyopathy
ACE inhibitors should be used with caution in patients with an obstruction in the outflow tract of the left ventricle.

Proteinuria
It may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Hyperkalaemia
Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics, the concomitant use of agents to treat hypokalaemia, diabetes mellitus and/or left ventricular dysfunction after myocardial infarction. Potassium supplements or potassium sparing diuretics are generally not recommended, since they may lead to significant increases in plasma potassium. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with frequent monitoring of serum potassium.

Angioneurotic Oedema
Rarely, ACE inhibitors (such as trandolapril) may cause angioneurotic oedema that includes swelling of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx especially during the first week of treatment. However in rare cases severe angiodema may develop after long term treatment with an ACE inhibitor. Patients experiencing angioneurotic oedema must immediately discontinue Trandolapril therapy and given an agent belonging to another class of drugs and be monitored until oedema resolution.

Angioneurotic oedema to the face will usually resolve spontaneously. Oedema involving not only the face but also the tongue, glottis or larynx may be life-threatening because of the risk of airway obstruction.

Angioneurotic oedema involving the tongue, glottis or larynx requires immediate sub-cutaneous administration of 0.3-0.5 ml of adrenaline solution (1:1000) or slow intravenous adrenalin (1mg/ml), with control of ECG and blood pressure. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

Caution must be exercised in patients with a history of idiopathic angioneurotic oedema and Trandolapril is contraindicated if angioneurotic oedema was an adverse reaction to an ACE inhibitor (see Contraindications, section 4.3).

Cough
During treatment with an ACE inhibitor, a dry and non-productive cough may occur which disappears after discontinuation.

Elderly
Some elderly patients may be more responsive to an ACE inhibitor than younger patients. Administration of low initial doses and evaluation of renal function at the beginning of the treatment is recommended.

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Children
ACE inhibitors should not be administered to children unless safety and efficacy have been established.

This product contains 31.5 mg lactose.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Drug Interactions
Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to Trandolapril. Adrenergic-blocking drugs should only be combined with trandolapril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia particularly in renal failure. Trandolapril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

Antidiabetic Agents
As with all ACE-inhibitors, concomitant use of antidiabetic medicines (insulin or oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycaemia. Therefore, blood glucose should be closely monitored in diabetics treated with a hypoglycaemic agent and trandolapril, particularly when starting or increasing the dose of ACE-inhibitor, or in patients with impaired renal function.

Non-steroid anti-inflammatory medicinal products:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (ie acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Combinations Necessitating a Warning
In some patients already receiving diuretic treatment or are volume and/or salt depleted particularly if this treatment has been recently instituted, the fall in blood pressure on initiation of treatment with Trandolapril may be excessive. The risk of symptomatic hypotension may be reduced by stopping the diuretic a few days before starting treatment with Trandolapril. If

it is necessary to continue the diuretic treatment, the patient should be monitored, at least after the initial administration of Trandolapril. As with all antihypertensives, combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension. Trandolapril may reduce the elimination of lithium and serum levels of lithium should be monitored.

Anaphylactoid reactions to high-flux polyacrylonitrile membranes used in haemodialysis have been reported in patients treated with ACE inhibitors. As with other antihypertensives of this chemical class this combination should be avoided when prescribing ACE inhibitors to renal dialysis patients.

The effects of certain anaesthetics may be enhanced by ACE inhibitors.

Allopurinol, cytostatic or immunosuppresive agents, systemic corticosteroids or procainamide may increase the risk of leucopenia, if used concomitantly with ACE inhibitors.

The antihypertensive effect of ACE inhibitors may be reduced by the administration of NSAIDs. An additive effect on serum potassium increase has been described when NSAIDs and ACE inhibitors have been used concomitantly, while renal function may be reduced.

Antacids cause reduced bioavailability of ACE inhibitors.

The antihypertensive effects of ACE inhibitors may be reduced by sympathomimetics, patients should be carefully monitored.

No clinical interaction has been observed in patients with left ventricular dysfunction after myocardial infarction when Trandolapril has been concomitantly administered with thrombolytics, aspirin, beta blockers, calcium channel blockers, nitrates, anticoagulants, diuretics or digoxin.

Alcohol enhances the hypotensive effect.

4.6 PREGNANCY AND LACTATION

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation

Due to insufficient experience trandolapril is contra-indicated during lactation.

It is not known whether trandolapril is excreted in mother’s milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Given the pharmacological properties of Trandolapril, no particular effect is expected. However, in some individuals, ACE inhibitors may affect the ability to drive or operate machinery particularly at the start of treatment, when changing over from other medication or

during concomitant use of alcohol. Therefore, after the first dose, or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 UNDESIRABLE EFFECTS

The following adverse reactions have been reported in long-term hypertension clinical trials with trandolapril. Within each system organ class, the reactions are ranked under headings of frequency, using the following convention: common (>1/100 to 1/10), uncommon (>1/1000 to 1/100).

Adverse Reactions Reported In Long Term Hypertension Trials With Trandolapril (n = 1049) That Occurred At A Frequency Greater Than Or Equal To 0.5%

Body System	Preferred Term	Frequency
Nervous system disorders	Headache Dizziness	Common (2.3%) Common (1.7%)
Cardiac disorders	Palpitations	Uncommon (0.7%)
Vascular disorders	Hypotension	Uncommon (0.5%)
Respiratory, thoracic and mediastinal disorders	Cough	Common (3.9%)
Gastrointestinal disorders	Nausea	Uncommon (0.5%)
Skin and subcutaneous tissue disorders	Pruritus	Uncommon (0.5%)
General disorders and administration site conditions	Asthenia Malaise	Common (2.1%) Uncommon (0.5%)

The following adverse reactions have been reported in the post myocardial infarction clinical trial with trandolapril. Within each system organ class, the reactions are ranked under headings of frequency, using the following convention: common (>1/100, ≤ 1/10), uncommon (>1/1000, ≤ 1/100).

Adverse Reactions Reported With Trandolapril In Post Myocardial Infarction Patients In The TRACE Study (n = 876) That Occurred At A Frequency Greater Than Or Equal To 0.5%

Body System	Preferred Term	Frequency
Nervous system disorders	Dizziness	Common (1.9%)
Cardiac disorders	Heart failure	Uncommon (0.8%)
Vascular disorders	Hypotension	Common (2.1%)
Respiratory, thoracic and mediastinal disorders	Cough	Common (3.9%)
Investigations	Creatinine Increased	Uncommon (0.6%)

In addition, other significant adverse events seen in clinical trials and postmarketing surveillance seen with trandolapril and those reported with other ACE inhibitors are listed below:

Nervous system disorders:
Transient ischaemic attacks have been reported with the use of ACE inhibitors.

Cardiac disorders:
Tachycardia, arrhythmias, angina pectoris, and myocardial infarction have been reported in association with hypotension during ACE inhibitor treatment.

Vascular disorders:
Cerebral haemorrhage has been reported with the use of ACE inhibitors.

Respiratory, thoracic and mediastinal disorders:
Sinusitis, rhinitis, glossitis, and bronchospasm have been reported, but rarely in association with ACE inhibitor treatment. Dyspnoea and bronchitis have been observed with ACE inhibitors, including trandolapril.

Gastrointestinal disorders:
Vomiting, abdominal pain, diarrhoea, constipation and dry mouth have been reported with ACE inhibitors, including trandolapril. Indigestion and ileus have been occasionally reported with ACE inhibitor treatment. Pancreatitis has also been observed in postmarketing reports with trandolapril.

Hepatobiliary disorders:
There have been reports of individual incidents of cholestatic jaundice and hepatitis connected with the use of ACE inhibitors.

Skin and subcutaneous tissue disorders:
Allergic hypersensitivity reactions such as pruritus and rash have been reported. Urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis-like efflorescences, and alopecia, which may be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA (anti-nuclear antibody) -titres have been occasionally reported with ACE inhibitor treatment. Alopecia and sweating have also been observed in postmarketing reports with trandolapril.
In very rare cases, angioneurotic oedema has occurred. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with trandolapril must be discontinued and appropriate therapy instituted immediately.

Renal and urinary disorders:
Deterioration of renal function and acute renal failure have been reported with the use of ACE inhibitors.

Investigations:
Reversible (on stopping treatment) increases in blood urea and plasma creatinine may result, particularly if renal insufficiency, severe heart failure or renovascular hypertension are present. Decreased haemoglobin, haematocrit, platelets and white cell count, and individual cases of agranulocytosis or pancytopenia and serum bilirubin have been reported with ACE inhibitor treatment. Haemolytic anaemia has been reported in some patients with a congenital deficiency concerning G-6 PDH (glucose-6-phosphate dehydrogenase) during treatment with ACE inhibitors. Leucopoenia and elevated liver enzymes (including SGOT and SGPT) have also been observed in postmarketing reports with trandolapril.
There have been reports of individual incidents of cholestatic jaundice, hepatitis, pancreatitis and ileus connected with the use of ACE inhibitors.

4.9 OVERDOSE
Symptoms expected with ACE inhibitors are severe hypotension, shock, stupor, bradycardia, electrolyte disturbance and renal failure.

After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently.

Therapeutic measures depend on the nature and severity of the symptoms. Measurements to prevent absorption such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake and hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered, ACE inhibitors may be removed from the circulation by hemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: cardiovascular system – agents acting on the renin-angiotensin system – ACE inhibitors, plain, ATC code: C09A A 10.

Trandolapril capsules contain the prodrug trandolapril, a non-peptide angiotensin converting enzyme (ACE) inhibitor with a carboxyl group but without a sulphydryl group. Trandolapril is rapidly absorbed and then non-specifically hydrolysed to its potent, long-acting active metabolite, trandolaprilat.

Trandolaprilat binds tightly and in a saturable manner to ACE.

The beneficial effects of ACE inhibitors in hypertension and in heart failure appear to result primarily from the suppression of the plasma angiotensin aldosterone system.

The administration of trandolapril causes decreases in the concentrations of angiotensin II, aldosterone and atrial natriuretic factor and increases in plasma renin activity and concentrations of angiotensin I. Renin is an endogenous enzyme synthesised by the kidneys and released into the circulation where it converts angiotensinogen to angiotensin I. Angiotensin I is then converted by angiotensin converting enzyme to angiotensin II which is a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure, as well as for stimulation of the adrenal gland to secrete aldosterone. Inhibition of ACE results in a decreased plasma angiotensin II leading to decreased vasopressor activity and to reduced aldosterone secretion. The cessation of the negative feedback of angiotensin II on the renin secretion results in an increase of the plasma renin activity. ACE also degrades the potent vasodepressive kinin peptide bradykinin to inactive metabolites. Therefore inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin-system which contributes to peripheral vasodilation by activating the prostaglandin system. Trandolapril thus modulates the renin-angiotensin-aldosterone system which plays a major part in regulating blood volume and blood pressure and consequently has a beneficial antihypertensive effect.

The administration of usual therapeutic doses of Trandolapril to hypertensive patients produces a marked reduction of both supine and erect blood pressure. The antihypertensive effect is evident after 1 hour, with a peak effect between 8 and 12 hours, persisting for at least 24 hours.

The properties of trandolapril might explain the results obtained in the regression of cardiac hypertrophy with improvement of diastolic function, and improvement of arterial compliance in humans. In addition a decrease in vascular hypertrophy has been shown in animals.

Achievement of optimal blood pressure reduction may require several weeks of therapy in some patients. The antihypertensive effects are maintained during long term therapy.

The haemodynamic effects of ACE therapy in patients with heart failure result from both arteriolar and venodilatation. Systemic vascular resistance is decreased and venous capacity increased. Thus, pre - and after - load are reduced. Consequences are a decrease in left ventricular filling pressure/capillary wedge pressure and an increase in cardiac output; heart rate remains unchanged or may even decrease. Clinically, signs and symptoms of the heart failure will improve and exercise capacity will increase. These effects are maintained during long term treatment.

5.2 PHARMACOKINETIC PROPERTIES

Trandolapril is very rapidly absorbed after oral administration. The amount absorbed is equivalent to 40 to 60% of the administered dose and is not affected by food consumption.

The peak plasma concentration of trandolapril is observed 30 minutes after administration. Trandolapril disappears rapidly from the plasma with a half-life of less than one hour.

Trandolapril is hydrolysed to trandolaprilat, a specific angiotensin converting enzyme inhibitor. The amount of trandolaprilat formed is not modified by food consumption. The peak plasma concentration of trandolaprilat is reached after 4 to 6 hours.

In the plasma trandolaprilat is more than 80% protein-bound. It binds saturably, with a high affinity, to angiotensin converting enzyme. The major proportion of circulating trandolaprilat is also non-saturably bound to albumin.

After repeated administration of Trandolapril in a single daily dose, steady state is reached on average in four days, both in healthy volunteers and in young or elderly hypertensives. The effective half-life of trandolaprilat is between 16 and 24 hours. The terminal half life of elimination is between 47 and 98 hours, depending on dose. This terminal phase probably represents binding/dissociation kinetics of the trandolaprilat/ACE complex.

Trandolaprilat eliminated in the urine in the unchanged form accounts for 10 to 15% of the dose of trandolapril administered. After oral administration of the labelled product in man, 33% of the radioactivity is found in the urine and 66% in the faeces.

The renal clearance of trandolaprilat is proportional to the creatinine clearance. The plasma concentrations of trandolaprilat are significantly higher in patients with a creatinine clearance less than or equal to 30 ml/min. However, after repeated dosing in patients with chronic renal failure steady state is also reached on average in four days, whatever the degree of renal failure.

5.3 PRECLINICAL SAFETY DATA

Acute oral toxicity studies of trandolapril and its active metabolite, trandolaprilat, in rats and mice showed both compounds to be non-toxic with respective LD_{50} values of > 4000 mg/kg and > 5000 mg/kg.

Repeat dose oral toxicity was evaluated in the rat and dog with studies of up to 18 and 12 months duration respectively. The principal observations in these studies were of anaemia (doses of 20 mg/kg/day and above in the rat 30 day study and 25 mg/kg/day and above in the dog 6 month study), gastric irritation and ulceration (doses of 20 mg/kg/day and above in the rat 30 day study and 125 mg/kg/day in the dog 6 month study) and renal lesions (20 mg/kg/day and above in the rat 30 day study and 10 mg/kg/day in the dog 30 day study): renal lesions were also seen in the 6 month studies in the rat and dog (from doses of 0.25 and 25 mg/kg/day respectively) - these were reversible on cessation of treatment.

Reproduction toxicity studies showed effects on renal development in offspring with increased incidence of renal pelvic dilation; this was seen at doses of 10 mg/kg/day and above in the rat but these changes did not affect the normal development of the offspring.
Trandolapril was not mutagenic or carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule contents:
Povidone PVP K-30
Lactose anhydrous
Pregelatinised starch
Sodium stearyl fumarate

Capsule shell:
Erythrosin (E127)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Gelatin
Quinoline yellow (E104)

Printing ink:
Shellac
Iron oxide black (E172)
Propylene glycol

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Aluminium-aluminium blisters.
Blister packs of 14, 20, 28, 30, 50, 60, 98 & 100 capsules.
Calendar packs of 14, 28 capsules.
Hospital packs of 40, 50 & 200 (5x40) capsules.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0800
PL 00289/0804

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/01/2008

10 DATE OF REVISION OF THE TEXT
30/01/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Trandolapril 1 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 1 mg trandolapril.

Excipients:
31.0 mg lactose/capsule
Sunset yellow FCF (E110)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard.

Body : Light orange, Imprinting: TD1
Cap: Medium orange, Imprinting: TD1

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Mild or moderate hypertension.

Left ventricular dysfunction after myocardial infarction.

It has been demonstrated that Trandolapril improves survival following myocardial infarction in patients with left ventricular dysfunction (ejection fraction ≤ 35 percent), with or without symptoms of heart failure, and/or, with or without residual ischaemia. Long-term treatment with Trandolapril significantly reduces overall cardiovascular mortality. It significantly decreases the risk of sudden death and the occurrence of severe or resistant heart failure.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults

Mild or moderate hypertension
For adults not taking diuretics, without congestive heart failure and without renal or hepatic insufficiency; the recommended initial dosage is 0.5 mg as a single daily dose. A 0.5 mg dose will only achieve a therapeutic response in a minority of patients. Dosage should be doubled incrementally at intervals of 2 to 4 weeks, based on patient response, up to a maximum of 4 mg as a single daily dose. The usual maintenance dose range is 1 to 2 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 4 mg Trandolapril, combination therapy should be considered.

Left ventricular dysfunction after myocardial infarction
Following a myocardial infarction, therapy may be initiated as early as on the third day. Treatment should be initiated at a daily dose of 0.5 mg. The dose should be progressively increased to a maximum of 4 mg as a single daily dose. Depending upon the tolerability such as symptomatic hypotension, this forced titration can be temporarily suspended.

In the event of hypotension, all concomitant hypotensive therapies such as vasodilators including nitrates, diuretics, must be carefully checked and if possible their dose reduced.

The dose of Trandolapril should be lowered only if the previous measures are not effective or not feasible.

Elderly
The dose in elderly patients is the same as in adults. There is no need to reduce the dose in elderly patients with normal renal and hepatic function. Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to the need for the control of blood pressure.

Prior Diuretic Treatment
In patients who are at risk from a stimulated renin-angiotensin system (eg patients with water and sodium depletion) the diuretic should be discontinued 2-3 days before beginning therapy with 0.5 mg trandolapril to reduce the likelihood of symptomatic hypotension. The diuretic may be resumed later if required.

Cardiac Failure
In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 0.5 mg Trandolapril once daily under close medical supervision in hospital.

Dosage Adjustment in Renal Impairment

For patients with mild or moderate renal impairment (creatinine clearance of 10-70 ml/min) the usual adult and elderly doses are recommended.
For patients with severe renal impairment (creatinine clearance of <10 ml/min) the usual adult and elderly starting doses are also recommended but the maximum daily dose should not exceed 2 mg. In these patients therapy should be under close medical supervision.

Dialysis
It is not known for certain if trandolapril or trandolaprilat are removed by dialysis. However, it would be expected that dialysis could remove the active moiety, trandolaprilat, from the circulation, resulting in a possible loss of control of blood pressure. Therefore careful monitoring of the patient's blood pressure during dialysis is required, and the dosage of trandolapril adjusted if needed.

Dosage Adjustment in Hepatic Impairment
In patients with severely impaired liver function a decrease in the metabolic clearance of the parent compound trandolapril and the active metabolite trandolaprilat results in a large increase in plasma trandolapril levels and to a lesser extent an increase in trandolaprilat levels. Treatment with Trandolapril should therefore be initiated at a dose of 0.5 mg once daily under close medical supervision.

Children
Trandolapril has not been studied in children and therefore use in this age group is not recommended.

4.3 CONTRAINDICATIONS

Known hypersensitivity to trandolapril or any other ACE inhibitor or to any of the excipients.

History of angioneurotic oedema associated with administration of an ACE inhibitor.

Hereditary/idiopathic angioneurotic oedema.

Second and third trimester of pregnancy (see section 4.4 and 4.6).

Lactation.

Use in children.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Trandolapril should not be used in patients with aortic stenosis or outflow obstruction.

Assessment of Renal Function
Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment. Proteinuria may occur if renal impairment is present prior to therapy or relatively high doses are used.

Impaired Renal Function
Patients with severe renal insufficiency may require reduced doses of trandolapril; their renal function should be closely monitored. In the majority, renal function will not alter. In patients with renal insufficiency, congestive heart failure or unilateral or bilateral renal artery stenosis, in the single kidney as well as after renal transplantation, there is a risk of impairment of renal function and severe hypotension. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy. In these patients treatment should be started in hospital under close medical supervision with low doses and careful dose titration.

Renal failure in association with ACE inhibitors has mainly been reported in patients with severe heart failure or underlying renal disease, including renal artery stenosis.

Some hypertensive patients with no apparent pre-existing renal disease may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when trandolapril is given concomitantly with a diuretic. Dosage reduction of trandolapril and/or discontinuation

of the diuretic may be required. Additionally, in patients with renal insufficiency the risk of hyperkalaemia should be considered and the patient's electrolyte status checked regularly.

Patients who are dialysed using high flux polyacrylonitrile membranes and treated with ACE inhibitors are likely to experience anaphylactoid reactions such as facial swelling, flushing, hypotension and dyspnoea within a few minutes of commencing haemodialysis. It is recommended to use an alternative membrane or an alternative anti hypertensive drug.

Patients with renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a solitary kidney are treated with ACE inhibitors. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis. In these patients treatment should be started in hospital under close medical supervision with low doses and careful dose titration. Diuretic treatment should be discontinued and renal function should be monitored during the first weeks of therapy.

Impaired Liver Function

Trandolapril is a prodrug metabolised to its active moiety in the liver. Thus particular caution and close monitoring should be applied to patients with impaired liver function as it may lead to elevated plasma levels, therefore dose adaptation may be required.

Symptomatic Hypotension

In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of Trandolapril as well as after increasing the dose of Trandolapril. ACE inhibitors may cause a profound fall in blood pressure. It has been reported mainly in patients with severe heart failure with or without renal insufficiency. It is also more likely to occur in patients who have been volume-and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. This is more likely to occur in patients on high dose loop diuretics, or those with hyponatraemia or functional renal impairment. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with Trandolapril. These patients should also be kept under very close medical supervision when starting treatment preferably in hospital with low doses and careful titration. These considerations also apply to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with Trandolapril may usually be continued following restoration of effective blood volume and blood pressure. The appearance of hypotension after the initial dose does not preclude subsequent careful dose titration with drug after effective management.

Surgery/Anaesthesia

In patients undergoing surgery or during anaesthesia ACE inhibitors may cause hypotension or even hypotensive shock due to enhancement of agents producing hypotension. Trandolapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment. If it is not possible to withhold the ACE inhibitor, volume management should be handled with care.

Agranulocytosis and Bone Marrow Depression

In patients on angiotensin converting enzyme inhibitors, agranulocytosis and bone marrow depression have been seen rarely. They are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Therefore, regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (eg lupus erythematosus and scleroderma), especially associated with

impaired renal function and concomitant therapy particularly with corticosteroids and antimetabolites.

Aortic stenosis/hypertrophic cardiomyopathy
ACE inhibitors should be used with caution in patients with an obstruction in the outflow tract of the left ventricle.

Proteinuria
It may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Hyperkalaemia
Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics, the concomitant use of agents to treat hypokalaemia, diabetes mellitus and/or left ventricular dysfunction after myocardial infarction. Potassium supplements or potassium sparing diuretics are generally not recommended, since they may lead to significant increases in plasma potassium. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with frequent monitoring of serum potassium.

Angioneurotic Oedema
Rarely, ACE inhibitors (such as trandolapril) may cause angioneurotic oedema that includes swelling of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx especially during the first week of treatment. However in rare cases severe angiodema may develop after long term treatment with an ACE inhibitor. Patients experiencing angioneurotic oedema must immediately discontinue Trandolapril therapy and given an agent belonging to another class of drugs and be monitored until oedema resolution.

Angioneurotic oedema to the face will usually resolve spontaneously. Oedema involving not only the face but also the tongue, glottis or larynx may be life-threatening because of the risk of airway obstruction.

Angioneurotic oedema involving the tongue, glottis or larynx requires immediate sub-cutaneous administration of 0.3-0.5 ml of adrenaline solution (1:1000) or slow intravenous adrenalin (1mg/ml), with control of ECG and blood pressure. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

Caution must be exercised in patients with a history of idiopathic angioneurotic oedema and Trandolapril is contraindicated if angioneurotic oedema was an adverse reaction to an ACE inhibitor (see Contraindications, section 4.3).

Cough
During treatment with an ACE inhibitor, a dry and non-productive cough may occur which disappears after discontinuation.

Elderly
Some elderly patients may be more responsive to an ACE inhibitor than younger patients. Administration of low initial doses and evaluation of renal function at the beginning of the treatment is recommended.

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Children

ACE inhibitors should not be administered to children unless safety and efficacy have been established.

This product contains 31 mg lactose.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Contains sunset yellow (E110) which may cause allergic reactions.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Drug Interactions

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to Trandolapril. Adrenergic-blocking drugs should only be combined with trandolapril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia particularly in renal failure. Trandolapril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

Antidiabetic Agents

As with all ACE-inhibitors, concomitant use of antidiabetic medicines (insulin or oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycaemia. Therefore, blood glucose should be closely monitored in diabetics treated with a hypoglycaemic agent and trandolapril, particularly when starting or increasing the dose of ACE-inhibitor, or in patients with impaired renal function.

Non-steroid anti-inflammatory medicinal products:

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (ie acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Combinations Necessitating a Warning

In some patients already receiving diuretic treatment or are volume and/or salt depleted particularly if this treatment has been recently instituted, the fall in blood pressure on initiation of treatment with Trandolapril may be excessive. The risk of symptomatic hypotension may be reduced by stopping the diuretic a few days before starting treatment with Trandolapril. If it is necessary to continue the diuretic treatment, the patient should be monitored, at least after the initial administration of Trandolapril. As with all antihypertensives, combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension. Trandolapril may reduce the elimination of lithium and serum levels of lithium should be monitored.

Anaphylactoid reactions to high-flux polyacrylonitrile membranes used in haemodialysis have been reported in patients treated with ACE inhibitors. As with other antihypertensives of this chemical class this combination should be avoided when prescribing ACE inhibitors to renal dialysis patients.

The effects of certain anaesthetics may be enhanced by ACE inhibitors.

Allopurinol, cytostatic or immunosuppresive agents, systemic corticosteroids or procainamide may increase the risk of leucopenia, if used concomitantly with ACE inhibitors.

The antihypertensive effect of ACE inhibitors may be reduced by the administration of NSAIDs. An additive effect on serum potassium increase has been described when NSAIDs and ACE inhibitors have been used concomitantly, while renal function may be reduced.

Antacids cause reduced bioavailability of ACE inhibitors.

The antihypertensive effects of ACE inhibitors may be reduced by sympathomimetics, patients should be carefully monitored.

No clinical interaction has been observed in patients with left ventricular dysfunction after myocardial infarction when Trandolapril has been concomitantly administered with thrombolytics, aspirin, beta blockers, calcium channel blockers, nitrates, anticoagulants, diuretics or digoxin.

Alcohol enhances the hypotensive effect.

4.6 PREGNANCY AND LACTATION

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation

Due to insufficient experience trandolapril is contra-indicated during lactation.

It is not known whether trandolapril is excreted in mother’s milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Given the pharmacological properties of Trandolapril, no particular effect is expected. However, in some individuals, ACE inhibitors may affect the ability to drive or operate machinery particularly at the start of treatment, when changing over from other medication or during concomitant use of alcohol. Therefore, after the first dose, or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 UNDESIRABLE EFFECTS

The following adverse reactions have been reported in long-term hypertension clinical trials with trandolapril. Within each system organ class, the reactions are ranked under headings of frequency, using the following convention: common (>1/100 to 1/10), uncommon (>1/1000 to 1/100).

Adverse Reactions Reported In Long Term Hypertension Trials With Trandolapril (n = 1049) That Occurred At A Frequency Greater Than Or Equal To 0.5%

Body System	Preferred Term	Frequency
Nervous system disorders	Headache Dizziness	Common (2.3%) Common (1.7%)
Cardiac disorders	Palpitations	Uncommon (0.7%)

Body System	Preferred Term	Frequency
Vascular disorders	Hypotension	Uncommon (0.5%)
Respiratory, thoracic and mediastinal disorders	Cough	Common (3.9%)
Gastrointestinal disorders	Nausea	Uncommon (0.5%)
Skin and subcutaneous tissue disorders	Pruritus	Uncommon (0.5%)
General disorders and administration site conditions	Asthenia Malaise	Common (2.1%) Uncommon (0.5%)

The following adverse reactions have been reported in the post myocardial infarction clinical trial with trandolapril. Within each system organ class, the reactions are ranked under headings of frequency, using the following convention: common (>1/100, ≤ 1/10), uncommon (>1/1000, ≤ 1/100).

Adverse Reactions Reported With Trandolapril In Post Myocardial Infarction Patients In The TRACE Study (n = 876) That Occurred At A Frequency Greater Than Or Equal To 0.5%

Body System	Preferred Term	Frequency
Nervous system disorders	Dizziness	Common (1.9%)
Cardiac disorders	Heart failure	Uncommon (0.8%)
Vascular disorders	Hypotension	Common (2.1%)
Respiratory, thoracic and mediastinal disorders	Cough	Common (3.9%)
Investigations	Creatinine Increased	Uncommon (0.6%)

In addition, other significant adverse events seen in clinical trials and postmarketing surveillance seen with trandolapril and those reported with other ACE inhibitors are listed below:

Nervous system disorders:
Transient ischaemic attacks have been reported with the use of ACE inhibitors.

Cardiac disorders:
Tachycardia, arrhythmias, angina pectoris, and myocardial infarction have been reported in association with hypotension during ACE inhibitor treatment.

Vascular disorders:
Cerebral haemorrhage has been reported with the use of ACE inhibitors.

Respiratory, thoracic and mediastinal disorders:
Sinusitis, rhinitis, glossitis, and bronchospasm have been reported, but rarely in association with ACE inhibitor treatment. Dyspnoea and bronchitis have been observed with ACE inhibitors, including trandolapril.

Gastrointestinal disorders:
Vomiting, abdominal pain, diarrhoea, constipation and dry mouth have been reported with ACE inhibitors, including trandolapril. Indigestion and ileus have been occasionally reported with ACE inhibitor treatment. Pancreatitis has also been observed in postmarketing reports with trandolapril.

Hepatobiliary disorders:
There have been reports of individual incidents of cholestatic jaundice and hepatitis connected with the use of ACE inhibitors.

Skin and subcutaneous tissue disorders:
Allergic hypersensitivity reactions such as pruritus and rash have been reported. Urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis-like efflorescences, and alopecia, which may be accompanied by fever, myalgia, arthralgia,

eosinophilia and/or increased ANA (anti-nuclear antibody) -titres have been occasionally reported with ACE inhibitor treatment. Alopecia and sweating have also been observed in postmarketing reports with trandolapril.
In very rare cases, angioneurotic oedema has occurred. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with trandolapril must be discontinued and appropriate therapy instituted immediately.

Renal and urinary disorders:
Deterioration of renal function and acute renal failure have been reported with the use of ACE inhibitors.

Investigations:
Reversible (on stopping treatment) increases in blood urea and plasma creatinine may result, particularly if renal insufficiency, severe heart failure or renovascular hypertension are present. Decreased haemoglobin, haematocrit, platelets and white cell count, and individual cases of agranulocytosis or pancytopenia and serum bilirubin have been reported with ACE inhibitor treatment. Haemolytic anaemia has been reported in some patients with a congenital deficiency concerning G-6 PDH (glucose-6-phosphate dehydrogenase) during treatment with ACE inhibitors. Leucopoenia and elevated liver enzymes (including SGOT and SGPT) have also been observed in postmarketing reports with trandolapril.
There have been reports of individual incidents of cholestatic jaundice, hepatitis, pancreatitis and ileus connected with the use of ACE inhibitors.

4.9 OVERDOSE

Symptoms expected with ACE inhibitors are severe hypotension, shock, stupor, bradycardia, electrolyte disturbance and renal failure.

After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently.

Therapeutic measures depend on the nature and severity of the symptoms. Measurements to prevent absorption such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake and hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered, ACE inhibitors may be removed from the circulation by hemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: cardiovascular system – agents acting on the renin-angiotensin system – ACE inhibitors, plain, ATC code: C09A A 10.

Trandolapril capsules contain the prodrug trandolapril, a non-peptide angiotensin converting enzyme (ACE) inhibitor with a carboxyl group but without a sulphydryl group. Trandolapril is rapidly absorbed and then non-specifically hydrolysed to its potent, long-acting active metabolite, trandolaprilat.

Trandolaprilat binds tightly and in a saturable manner to ACE.

The beneficial effects of ACE inhibitors in hypertension and in heart failure appear to result primarily from the suppression of the plasma angiotensin aldosterone system.

The administration of trandolapril causes decreases in the concentrations of angiotensin II, aldosterone and atrial natriuretic factor and increases in plasma renin activity and concentrations of angiotensin I. Renin is an endogenous enzyme synthesised by the kidneys and released into the circulation where it converts angiotensinogen to angiotensin I. Angiotensin I is then converted by angiotensin converting enzyme to angiotensin II which is a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure,

as well as for stimulation of the adrenal gland to secrete aldosterone. Inhibition of ACE results in a decreased plasma angiotensin II leading to decreased vasopressor activity and to reduced aldosterone secretion. The cessation of the negative feedback of angiotensin II on the renin secretion results in an increase of the plasma renin activity. ACE also degrades the potent vasodepressive kinin peptide bradykinin to inactive metabolites. Therefore inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin-system which contributes to peripheral vasodilation by activating the prostaglandin system. Trandolapril thus modulates the renin-angiotensin-aldosterone system which plays a major part in regulating blood volume and blood pressure and consequently has a beneficial antihypertensive effect.

The administration of usual therapeutic doses of Trandolapril to hypertensive patients produces a marked reduction of both supine and erect blood pressure. The antihypertensive effect is evident after 1 hour, with a peak effect between 8 and 12 hours, persisting for at least 24 hours.

The properties of trandolapril might explain the results obtained in the regression of cardiac hypertrophy with improvement of diastolic function, and improvement of arterial compliance in humans. In addition a decrease in vascular hypertrophy has been shown in animals.

Achievement of optimal blood pressure reduction may require several weeks of therapy in some patients. The antihypertensive effects are maintained during long term therapy.

The haemodynamic effects of ACE therapy in patients with heart failure result from both arteriolar and venodilatation. Systemic vascular resistance is decreased and venous capacity increased. Thus, pre - and after - load are reduced. Consequences are a decrease in left ventricular filling pressure/capillary wedge pressure and an increase in cardiac output; heart rate remains unchanged or may even decrease. Clinically, signs and symptoms of the heart failure will improve and exercise capacity will increase. These effects are maintained during long term treatment.

5.2 PHARMACOKINETIC PROPERTIES

Trandolapril is very rapidly absorbed after oral administration. The amount absorbed is equivalent to 40 to 60% of the administered dose and is not affected by food consumption.

The peak plasma concentration of trandolapril is observed 30 minutes after administration. Trandolapril disappears rapidly from the plasma with a half-life of less than one hour.

Trandolapril is hydrolysed to trandolaprilat, a specific angiotensin converting enzyme inhibitor. The amount of trandolaprilat formed is not modified by food consumption. The peak plasma concentration of trandolaprilat is reached after 4 to 6 hours.

In the plasma trandolaprilat is more than 80% protein-bound. It binds saturably, with a high affinity, to angiotensin converting enzyme. The major proportion of circulating trandolaprilat is also non-saturably bound to albumin.

After repeated administration of Trandolapril in a single daily dose, steady state is reached on average in four days, both in healthy volunteers and in young or elderly hypertensives. The effective half-life of trandolaprilat is between 16 and 24 hours. The terminal half life of elimination is between 47 and 98 hours, depending on dose. This terminal phase probably represents binding/dissociation kinetics of the trandolaprilat/ACE complex.

Trandolaprilat eliminated in the urine in the unchanged form accounts for 10 to 15% of the dose of trandolapril administered. After oral administration of the labelled product in man, 33% of the radioactivity is found in the urine and 66% in the faeces.

The renal clearance of trandolaprilat is proportional to the creatinine clearance. The plasma concentrations of trandolaprilat are significantly higher in patients with a creatinine clearance less than or equal to 30 ml/min. However, after repeated dosing in patients with chronic renal

failure steady state is also reached on average in four days, whatever the degree of renal failure.

5.3 PRECLINICAL SAFETY DATA

Acute oral toxicity studies of trandolapril and its active metabolite, trandolaprilat, in rats and mice showed both compounds to be non-toxic with respective LD_{50} values of > 4000 mg/kg and > 5000 mg/kg.

Repeat dose oral toxicity was evaluated in the rat and dog with studies of up to 18 and 12 months duration respectively. The principal observations in these studies were of anaemia (doses of 20 mg/kg/day and above in the rat 30 day study and 25 mg/kg/day and above in the dog 6 month study), gastric irritation and ulceration (doses of 20 mg/kg/day and above in the rat 30 day study and 125 mg/kg/day in the dog 6 month study) and renal lesions (20 mg/kg/day and above in the rat 30 day study and 10 mg/kg/day in the dog 30 day study): renal lesions were also seen in the 6 month studies in the rat and dog (from doses of 0.25 and 25 mg/kg/day respectively) - these were reversible on cessation of treatment.

Reproduction toxicity studies showed effects on renal development in offspring with increased incidence of renal pelvic dilation; this was seen at doses of 10 mg/kg/day and above in the rat but these changes did not affect the normal development of the offspring.
Trandolapril was not mutagenic or carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule contents:
Povidone PVP K-30
Lactose anhydrous
Pregelatinised starch
Sodium stearyl fumarate

Capsule shell:
Erythrosin (E127)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Gelatin
Sunset yellow FCF-FD&C Yellow 6 (E110)

Printing ink:
Shellac
Iron oxide black (E172)
Propylene glycol

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Store in the original package

6.5 NATURE AND CONTENTS OF CONTAINER

Aluminium-aluminium blisters.
Blister packs of 14, 20, 28, 30, 50, 60, 98 & 100 capsules.
Calendar packs of 28 capsules.
Hospital packs of 40, 50 & 200 (5x40) capsules.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0801
PL 00289/0805

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/01/2008

10 DATE OF REVISION OF THE TEXT
30/01/2008

1 NAME OF THE MEDICINAL PRODUCT
Trandolapril 2 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 2 mg trandolapril.

Excipient: 30.0 mg lactose/capsule

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard.

Body : Medium orange, Imprinting: TD2
Cap: Medium orange, Imprinting: TD2

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Mild or moderate hypertension.

Left ventricular dysfunction after myocardial infarction.

It has been demonstrated that Trandolapril improves survival following myocardial infarction in patients with left ventricular dysfunction (ejection fraction $\leq$ 35 percent), with or without symptoms of heart failure, and/or, with or without residual ischaemia. Long-term treatment with Trandolapril significantly reduces overall cardiovascular mortality. It significantly decreases the risk of sudden death and the occurrence of severe or resistant heart failure.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Adults

Mild or moderate hypertension
For adults not taking diuretics, without congestive heart failure and without renal or hepatic insufficiency; the recommended initial dosage is 0.5 mg as a single daily dose. A 0.5 mg dose will only achieve a therapeutic response in a minority of patients. Dosage should be doubled incrementally at intervals of 2 to 4 weeks, based on patient response, up to a maximum of 4 mg as a single daily dose. The usual maintenance dose range is 1 to 2 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 4 mg Trandolapril, combination therapy should be considered.

Left ventricular dysfunction after myocardial infarction
Following a myocardial infarction, therapy may be initiated as early as on the third day. Treatment should be initiated at a daily dose of 0.5 mg. The dose should be progressively increased to a maximum of 4 mg as a single daily dose. Depending upon the tolerability such as symptomatic hypotension, this forced titration can be temporarily suspended.

In the event of hypotension, all concomitant hypotensive therapies such as vasodilators including nitrates, diuretics, must be carefully checked and if possible their dose reduced.

The dose of Trandolapril should be lowered only if the previous measures are not effective or not feasible.

Elderly
The dose in elderly patients is the same as in adults. There is no need to reduce the dose in elderly patients with normal renal and hepatic function. Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to the need for the control of blood pressure.

Prior Diuretic Treatment
In patients who are at risk from a stimulated renin-angiotensin system (eg patients with water and sodium depletion) the diuretic should be discontinued 2-3 days before beginning therapy with 0.5 mg trandolapril to reduce the likelihood of symptomatic hypotension. The diuretic may be resumed later if required.

Cardiac Failure
In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 0.5 mg Trandolapril once daily under close medical supervision in hospital.

Dosage Adjustment in Renal Impairment
For patients with mild or moderate renal impairment (creatinine clearance of 10-70 ml/min) the usual adult and elderly doses are recommended.

For patients with severe renal impairment (creatinine clearance of <10 ml/min) the usual adult and elderly starting doses are also recommended but the maximum daily dose should not exceed 2 mg. In these patients therapy should be under close medical supervision.

Dialysis
It is not known for certain if trandolapril or trandolaprilat are removed by dialysis. However, it would be expected that dialysis could remove the active moiety, trandolaprilat, from the circulation, resulting in a possible loss of control of blood pressure. Therefore careful monitoring of the patient's blood pressure during dialysis is required, and the dosage of trandolapril adjusted if needed.

Dosage Adjustment in Hepatic Impairment
In patients with severely impaired liver function a decrease in the metabolic clearance of the parent compound trandolapril and the active metabolite trandolaprilat results in a large increase in plasma trandolapril levels and to a lesser extent an increase in trandolaprilat levels. Treatment with Trandolapril should therefore be initiated at a dose of 0.5 mg once daily under close medical supervision.

Children
Trandolapril has not been studied in children and therefore use in this age group is not recommended.

4.3 CONTRAINDICATIONS
Known hypersensitivity to trandolapril or any other ACE inhibitor or to any of the excipients.

History of angioneurotic oedema associated with administration of an ACE inhibitor.

Hereditary/idiopathic angioneurotic oedema.

Second and third trimester of pregnancy (see section 4.4 and 4.6).

Lactation.

Use in children.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Trandolapril should not be used in patients with aortic stenosis or outflow obstruction.

Assessment of Renal Function

Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment. Proteinuria may occur if renal impairment is present prior to therapy or relatively high doses are used.

Impaired Renal Function

Patients with severe renal insufficiency may require reduced doses of trandolapril; their renal function should be closely monitored. In the majority, renal function will not alter. In patients with renal insufficiency, congestive heart failure or unilateral or bilateral renal artery stenosis, in the single kidney as well as after renal transplantation, there is a risk of impairment of renal function and severe hypotension. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy. In these patients treatment should be started in hospital under close medical supervision with low doses and careful dose titration.

Renal failure in association with ACE inhibitors has mainly been reported in patients with severe heart failure or underlying renal disease, including renal artery stenosis.

Some hypertensive patients with no apparent pre-existing renal disease may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when trandolapril is given concomitantly with a diuretic. Dosage reduction of trandolapril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency the risk of hyperkalaemia should be considered and the patient's electrolyte status checked regularly.

Patients who are dialysed using high flux polyacrylonitrile membranes and treated with ACE inhibitors are likely to experience anaphylactoid reactions such as facial swelling, flushing, hypotension and dyspnoea within a few minutes of commencing haemodialysis. It is recommended to use an alternative membrane or an alternative anti hypertensive drug.

Patients with renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a solitary kidney are treated with ACE inhibitors. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis. In these patients treatment should be started in hospital under close medical supervision with low doses and careful dose titration. Diuretic treatment should be discontinued and renal function should be monitored during the first weeks of therapy.

Impaired Liver Function

Trandolapril is a prodrug metabolised to its active moiety in the liver. Thus particular caution and close monitoring should be applied to patients with impaired liver function as it may lead to elevated plasma levels, therefore dose adaptation may be required.

Symptomatic Hypotension

In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of Trandolapril as well as after increasing the dose of Trandolapril. ACE inhibitors may cause a profound fall in blood pressure. It has been reported mainly in

patients with severe heart failure with or without renal insufficiency. It is also more likely to occur in patients who have been volume-and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. This is more likely to occur in patients on high dose loop diuretics, or those with hyponatraemia or functional renal impairment. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with Trandolapril. These patients should also be kept under very close medical supervision when starting treatment preferably in hospital with low doses and careful titration. These considerations also apply to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with Trandolapril may usually be continued following restoration of effective blood volume and blood pressure. The appearance of hypotension after the initial dose does not preclude subsequent careful dose titration with drug after effective management.

Surgery/Anaesthesia
In patients undergoing surgery or during anaesthesia ACE inhibitors may cause hypotension or even hypotensive shock due to enhancement of agents producing hypotension. Trandolapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment. If it is not possible to withhold the ACE inhibitor, volume management should be handled with care.

Agranulocytosis and Bone Marrow Depression
In patients on angiotensin converting enzyme inhibitors, agranulocytosis and bone marrow depression have been seen rarely. They are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Therefore, regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (eg lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and antimetabolites.

Aortic stenosis/hypertrophic cardiomyopathy
ACE inhibitors should be used with caution in patients with an obstruction in the outflow tract of the left ventricle.

Proteinuria
It may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Hyperkalaemia
Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics, the concomitant use of agents to treat hypokalaemia, diabetes mellitus and/or left ventricular dysfunction after myocardial infarction. Potassium supplements or potassium sparing diuretics are generally not recommended, since they may lead to significant increases in plasma potassium. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with frequent monitoring of serum potassium.

Angioneurotic Oedema
Rarely, ACE inhibitors (such as trandolapril) may cause angioneurotic oedema that includes swelling of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx especially during the first week of treatment. However in rare cases severe angiodema may develop after long term treatment with an ACE inhibitor. Patients experiencing angioneurotic oedema must immediately discontinue Trandolapril therapy and given an agent belonging to another class of drugs and be monitored until oedema resolution.

Angioneurotic oedema to the face will usually resolve spontaneously. Oedema involving not only the face but also the tongue, glottis or larynx may be life-threatening because of the risk of airway obstruction.

Angioneurotic oedema involving the tongue, glottis or larynx requires immediate sub-cutaneous administration of 0.3-0.5 ml of adrenaline solution (1:1000) or slow intravenous adrenalin (1mg/ml), with control of ECG and blood pressure. The patient should be hospitalised and observed for at least 12 to 24 hours and should not be discharged until complete resolution of symptoms has occurred.

Caution must be exercised in patients with a history of idiopathic angioneurotic oedema and Trandolapril is contraindicated if angioneurotic oedema was an adverse reaction to an ACE inhibitor (see Contraindications, section 4.3).

Cough
During treatment with an ACE inhibitor, a dry and non-productive cough may occur which disappears after discontinuation.

Elderly
Some elderly patients may be more responsive to an ACE inhibitor than younger patients. Administration of low initial doses and evaluation of renal function at the beginning of the treatment is recommended.

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Children
ACE inhibitors should not be administered to children unless safety and efficacy have been established.

This product contains 30 mg lactose.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Drug Interactions
Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to Trandolapril. Adrenergic-blocking drugs should only be combined with trandolapril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia particularly in renal failure. Trandolapril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

Antidiabetic Agents
As with all ACE-inhibitors, concomitant use of antidiabetic medicines (insulin or oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with greater risk of hypoglycaemia. Therefore, blood glucose should be closely monitored in diabetics treated with a hypoglycaemic agent and trandolapril, particularly when starting or increasing the dose of ACE-inhibitor, or in patients with impaired renal function.

Non-steroid anti-inflammatory medicinal products:

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (ie acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Combinations Necessitating a Warning

In some patients already receiving diuretic treatment or are volume and/or salt depleted particularly if this treatment has been recently instituted, the fall in blood pressure on initiation of treatment with Trandolapril may be excessive. The risk of symptomatic hypotension may be reduced by stopping the diuretic a few days before starting treatment with Trandolapril. If it is necessary to continue the diuretic treatment, the patient should be monitored, at least after the initial administration of Trandolapril. As with all antihypertensives, combination with a neuroleptic or tricyclic antidepressant increases the risk of orthostatic hypotension. Trandolapril may reduce the elimination of lithium and serum levels of lithium should be monitored.

Anaphylactoid reactions to high-flux polyacrylonitrile membranes used in haemodialysis have been reported in patients treated with ACE inhibitors. As with other antihypertensives of this chemical class this combination should be avoided when prescribing ACE inhibitors to renal dialysis patients.

The effects of certain anaesthetics may be enhanced by ACE inhibitors.

Allopurinol, cytostatic or immunosuppresive agents, systemic corticosteroids or procainamide may increase the risk of leucopenia, if used concomitantly with ACE inhibitors.

The antihypertensive effect of ACE inhibitors may be reduced by the administration of NSAIDs. An additive effect on serum potassium increase has been described when NSAIDs and ACE inhibitors have been used concomitantly, while renal function may be reduced.

Antacids cause reduced bioavailability of ACE inhibitors.

The antihypertensive effects of ACE inhibitors may be reduced by sympathomimetics, patients should be carefully monitored.

No clinical interaction has been observed in patients with left ventricular dysfunction after myocardial infarction when Trandolapril has been concomitantly administered with thrombolytics, aspirin, beta blockers, calcium channel blockers, nitrates, anticoagulants, diuretics or digoxin.

Alcohol enhances the hypotensive effect.

4.6 PREGNANCY AND LACTATION

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation
Due to insufficient experience trandolapril is contra-indicated during lactation.
It is not known whether trandolapril is excreted in mother's milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Given the pharmacological properties of Trandolapril, no particular effect is expected. However, in some individuals, ACE inhibitors may affect the ability to drive or operate machinery particularly at the start of treatment, when changing over from other medication or during concomitant use of alcohol. Therefore, after the first dose, or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 UNDESIRABLE EFFECTS

The following adverse reactions have been reported in long-term hypertension clinical trials with trandolapril. Within each system organ class, the reactions are ranked under headings of frequency, using the following convention: common (>1/100 to 1/10), uncommon (>1/1000 to 1/100).

Adverse Reactions Reported In Long Term Hypertension Trials With Trandolapril (n = 1049) That Occurred At A Frequency Greater Than Or Equal To 0.5%

Body System	Preferred Term	Frequency
Nervous system disorders	Headache Dizziness	Common (2.3%) Common (1.7%)
Cardiac disorders	Palpitations	Uncommon (0.7%)
Vascular disorders	Hypotension	Uncommon (0.5%)
Respiratory, thoracic and mediastinal disorders	Cough	Common (3.9%)
Gastrointestinal disorders	Nausea	Uncommon (0.5%)
Skin and subcutaneous tissue disorders	Pruritus	Uncommon (0.5%)
General disorders and administration site conditions	Asthenia Malaise	Common (2.1%) Uncommon (0.5%)

The following adverse reactions have been reported in the post myocardial infarction clinical trial with trandolapril. Within each system organ class, the reactions are ranked under headings of frequency, using the following convention: common (>1/100, ≤ 1/10), uncommon (>1/1000, ≤ 1/100).

Adverse Reactions Reported With Trandolapril In Post Myocardial Infarction Patients In The TRACE Study (n = 876) That Occurred At A Frequency Greater Than Or Equal To 0.5%

Body System	Preferred Term	Frequency
Nervous system disorders	Dizziness	Common (1.9%)
Cardiac disorders	Heart failure	Uncommon (0.8%)
Vascular disorders	Hypotension	Common (2.1%)
Respiratory, thoracic and mediastinal disorders	Cough	Common (3.9%)
Investigations	Creatinine Increased	Uncommon (0.6%)

In addition, other significant adverse events seen in clinical trials and postmarketing surveillance seen with trandolapril and those reported with other ACE inhibitors are listed below:

Nervous system disorders:
Transient ischaemic attacks have been reported with the use of ACE inhibitors.

Cardiac disorders:
Tachycardia, arrhythmias, angina pectoris, and myocardial infarction have been reported in association with hypotension during ACE inhibitor treatment.

Vascular disorders:
Cerebral haemorrhage has been reported with the use of ACE inhibitors.

Respiratory, thoracic and mediastinal disorders:
Sinusitis, rhinitis, glossitis, and bronchospasm have been reported, but rarely in association with ACE inhibitor treatment. Dyspnoea and bronchitis have been observed with ACE inhibitors, including trandolapril.

Gastrointestinal disorders:
Vomiting, abdominal pain, diarrhoea, constipation and dry mouth have been reported with ACE inhibitors, including trandolapril. Indigestion and ileus have been occasionally reported with ACE inhibitor treatment. Pancreatitis has also been observed in postmarketing reports with trandolapril.

Hepatobiliary disorders:
There have been reports of individual incidents of cholestatic jaundice and hepatitis connected with the use of ACE inhibitors.

Skin and subcutaneous tissue disorders:
Allergic hypersensitivity reactions such as pruritus and rash have been reported. Urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, psoriasis-like efflorescences, and alopecia, which may be accompanied by fever, myalgia, arthralgia, eosinophilia and/or increased ANA (anti-nuclear antibody) -titres have been occasionally reported with ACE inhibitor treatment. Alopecia and sweating have also been observed in postmarketing reports with trandolapril.
In very rare cases, angioneurotic oedema has occurred. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with trandolapril must be discontinued and appropriate therapy instituted immediately.

Renal and urinary disorders:
Deterioration of renal function and acute renal failure have been reported with the use of ACE inhibitors.

Investigations:
Reversible (on stopping treatment) increases in blood urea and plasma creatinine may result, particularly if renal insufficiency, severe heart failure or renovascular hypertension are present. Decreased haemoglobin, haematocrit, platelets and white cell count, and individual cases of agranulocytosis or pancytopenia and serum bilirubin have been reported with ACE inhibitor treatment. Haemolytic anaemia has been reported in some patients with a congenital deficiency concerning G-6 PDH (glucose-6-phosphate dehydrogenase) during treatment with ACE inhibitors. Leucopoenia and elevated liver enzymes (including SGOT and SGPT) have also been observed in postmarketing reports with trandolapril.
There have been reports of individual incidents of cholestatic jaundice, hepatitis, pancreatitis and ileus connected with the use of ACE inhibitors.

4.9 OVERDOSE

Symptoms expected with ACE inhibitors are severe hypotension, shock, stupor, bradycardia, electrolyte disturbance and renal failure.

After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently.

Therapeutic measures depend on the nature and severity of the symptoms. Measurements to prevent absorption such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake and hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered, ACE inhibitors may be removed from the circulation by hemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: cardiovascular system – agents acting on the renin-angiotensin system – ACE inhibitors, plain, ATC code: C09A A 10.

Trandolapril capsules contain the prodrug trandolapril, a non-peptide angiotensin converting enzyme (ACE) inhibitor with a carboxyl group but without a sulphydryl group. Trandolapril is rapidly absorbed and then non-specifically hydrolysed to its potent, long-acting active metabolite, trandolaprilat.

Trandolaprilat binds tightly and in a saturable manner to ACE.

The beneficial effects of ACE inhibitors in hypertension and in heart failure appear to result primarily from the suppression of the plasma angiotensin aldosterone system.

The administration of trandolapril causes decreases in the concentrations of angiotensin II, aldosterone and atrial natriuretic factor and increases in plasma renin activity and concentrations of angiotensin I. Renin is an endogenous enzyme synthesised by the kidneys and released into the circulation where it converts angiotensinogen to angiotensin I. Angiotensin I is then converted by angiotensin converting enzyme to angiotensin II which is a potent vasoconstrictor responsible for arterial vasoconstriction and increased blood pressure, as well as for stimulation of the adrenal gland to secrete aldosterone. Inhibition of ACE results in a decreased plasma angiotensin II leading to decreased vasopressor activity and to reduced aldosterone secretion. The cessation of the negative feedback of angiotensin II on the renin secretion results in an increase of the plasma renin activity. ACE also degrades the potent vasodepressive kinin peptide bradykinin to inactive metabolites. Therefore inhibition of ACE results in an increased activity of circulating and local kallikrein-kinin-system which contributes to peripheral vasodilation by activating the prostaglandin system. Trandolapril thus modulates the renin-angiotensin-aldosterone system which plays a major part in regulating blood volume and blood pressure and consequently has a beneficial antihypertensive effect.

The administration of usual therapeutic doses of Trandolapril to hypertensive patients produces a marked reduction of both supine and erect blood pressure. The antihypertensive effect is evident after 1 hour, with a peak effect between 8 and 12 hours, persisting for at least 24 hours.

The properties of trandolapril might explain the results obtained in the regression of cardiac hypertrophy with improvement of diastolic function, and improvement of arterial compliance in humans. In addition a decrease in vascular hypertrophy has been shown in animals.

Achievement of optimal blood pressure reduction may require several weeks of therapy in some patients. The antihypertensive effects are maintained during long term therapy.

The haemodynamic effects of ACE therapy in patients with heart failure result from both arteriolar and venodilatation. Systemic vascular resistance is decreased and venous capacity increased. Thus, pre - and after - load are reduced. Consequences are a decrease in left ventricular filling pressure/capillary wedge pressure and an increase in cardiac output; heart

rate remains unchanged or may even decrease. Clinically, signs and symptoms of the heart failure will improve and exercise capacity will increase. These effects are maintained during long term treatment.

5.2 PHARMACOKINETIC PROPERTIES

Trandolapril is very rapidly absorbed after oral administration. The amount absorbed is equivalent to 40 to 60% of the administered dose and is not affected by food consumption.

The peak plasma concentration of trandolapril is observed 30 minutes after administration. Trandolapril disappears rapidly from the plasma with a half-life of less than one hour.

Trandolapril is hydrolysed to trandolaprilat, a specific angiotensin converting enzyme inhibitor. The amount of trandolaprilat formed is not modified by food consumption. The peak plasma concentration of trandolaprilat is reached after 4 to 6 hours.

In the plasma trandolaprilat is more than 80% protein-bound. It binds saturably, with a high affinity, to angiotensin converting enzyme. The major proportion of circulating trandolaprilat is also non-saturably bound to albumin.

After repeated administration of Trandolapril in a single daily dose, steady state is reached on average in four days, both in healthy volunteers and in young or elderly hypertensives. The effective half-life of trandolaprilat is between 16 and 24 hours. The terminal half life of elimination is between 47 and 98 hours, depending on dose. This terminal phase probably represents binding/dissociation kinetics of the trandolaprilat/ACE complex.

Trandolaprilat eliminated in the urine in the unchanged form accounts for 10 to 15% of the dose of trandolapril administered. After oral administration of the labelled product in man, 33% of the radioactivity is found in the urine and 66% in the faeces.

The renal clearance of trandolaprilat is proportional to the creatinine clearance. The plasma concentrations of trandolaprilat are significantly higher in patients with a creatinine clearance less than or equal to 30 ml/min. However, after repeated dosing in patients with chronic renal failure steady state is also reached on average in four days, whatever the degree of renal failure.

5.3 PRECLINICAL SAFETY DATA

Acute oral toxicity studies of trandolapril and its active metabolite, trandolaprilat, in rats and mice showed both compounds to be non-toxic with respective LD_{50} values of > 4000 mg/kg and > 5000 mg/kg.

Repeat dose oral toxicity was evaluated in the rat and dog with studies of up to 18 and 12 months duration respectively. The principal observations in these studies were of anaemia (doses of 20 mg/kg/day and above in the rat 30 day study and 25 mg/kg/day and above in the dog 6 month study), gastric irritation and ulceration (doses of 20 mg/kg/day and above in the rat 30 day study and 125 mg/kg/day in the dog 6 month study) and renal lesions (20 mg/kg/day and above in the rat 30 day study and 10 mg/kg/day in the dog 30 day study): renal lesions were also seen in the 6 month studies in the rat and dog (from doses of 0.25 and 25 mg/kg/day respectively) - these were reversible on cessation of treatment.

Reproduction toxicity studies showed effects on renal development in offspring with increased incidence of renal pelvic dilation; this was seen at doses of 10 mg/kg/day and above in the rat but these changes did not affect the normal development of the offspring.
Trandolapril was not mutagenic or carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule contents:
Povidone PVP K-30
Lactose anhydrous
Pregelatinised starch

Sodium stearyl fumarate

Capsule shell:
Erythrosin (E127)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Gelatin

Printing ink:
Shellac
Iron oxide black (E172)
Propylene glycol

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Aluminium-aluminium blisters.
Blister packs of 7, 14, 20, 28, 30, 56, 60, 98 capsules.
Calendar packs of 28, 98 capsules.
Hospital packs of 28, 50 & 280 (10x28) capsules.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0802
PL 00289/0806

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/01/2008

10 DATE OF REVISION OF THE TEXT
30/01/2008

PATIENT INFORMATION LEAFLET

TRANDOLAPRIL 0.5, 1 and 2 mg CAPSULES

PACKAGE LEAFLET: INFORMATION FOR THE USER

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 TRANDOLAPRIL IS AND WHAT IT IS USED FOR

- Trandolapril belongs to a group of drugs called angiotensin-converting enzyme inhibitors (ACE inhibitors). It works by relaxing the blood vessels making it easier for the heart to pump blood around the body. This helps to reduce blood pressure and relieve the strain on the heart muscle.
- Trandolapril is used:
  - In the treatment of high blood pressure
  - To protect the heart after a heart attack.

2 BEFORE YOU TAKE TRANDOLAPRIL

Do NOT take Trandolapril if you:
- are allergic (hypersensitive) to trandolapril or any of the other ingredients of this medicine
- are allergic (hypersensitive) to any other ACE inhibitors (e.g. lisinopril, ramipril)
- have suffered from angioedema or Quinke's oedema (these are severe allergic reactions, including swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing)
- are pregnant (second or third trimester) or are breast-feeding.

Trandolapril is not suitable for children.

Take special care with Trandolapril
Tell your doctor before you start to take this medicine if you:
- have a condition known as aortic stenosis (the narrowing of one of the valves of the heart) or any other obstruction that slows the flow of blood in the heart
- have been taking diuretics (water tablets) for a long time or have been on a low salt diet
- have recently had severe or prolonged sickness or diarrhoea
- have kidney problems
- are on dialysis (as some types of dialysis membrane remove trandolapril from the blood)
- have liver problems
- have diabetes mellitus
- have suffered from a condition known as heart failure
- have a condition known as connective tissue disease (lupus or scleroderma)
- need an operation or an anaesthetic. Tell your doctor or dentist that you are taking Trandolapril.

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:
- Any other medication for high blood pressure (e.g. captopril, enalapril, propranolol)
- Diuretics (water tablets, e.g. bendroflumethiazide, amiloride, spironolactone) or potassium supplements
- Antacids (e.g. calcium carbonate)
- Antidiabetic medicines (e.g. glibenclamide, insulin, metformin)
- Lithium or tricyclic antidepressants (e.g. dosulepin, amitriptyline)
- Any of the group of medicines known as tranquilisers (e.g. chlorpromazine, thioridazine, flupentixol)
- Anti-inflammatory pain killers (e.g. ibuprofen, diclofenac, indometacin)
- Sympathomimetics which may be found in decongestants or cough/cold remedies or asthma remedies (e.g. ephedrine, pseudoephedrine, salbutamol)
- Allopurinol (for gout) or procainamide (for abnormal heart rhythm)
- Immunosuppressants (e.g. ciclosporin), steroid medication (e.g. prednisolone) or anticancer agents.

If you are due to have an operation, it is important that you tell the surgeon, dentist or nursing staff that you are taking Trandolapril. It may affect the anaesthetic or other treatments used.

Using Trandolapril with food and drink
You may take Trandolapril with or after food and with drink.
Drinking alcohol increases the blood pressure lowering effect of Trandolapril.
Alcohol can also reduce your reactions, see "Driving and using machines".

Pregnancy and breast-feeding
Do not take Trandolapril if you are pregnant and in your second or third trimester. It is not recommended to take Trandolapril if you are planning to become pregnant or are pregnant and in your first trimester.
Do not take Trandolapril if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Trandolapril can make some people feel dizzy or faint, especially when they first start to take the capsules. This can be made worse by alcohol, even in small amounts. Do not drive, operate machinery or do anything that requires you to be alert for several hours after your first dose or any increase in the dose of Trandolapril. Wait and see how the capsules affect you.

Important information about some of the ingredients of Trandolapril
Patients who are intolerant to **lactose** should note that Trandolapril capsules contain a small amount of lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Trandolapril 1mg Capsules also contain sunset yellow (E110), which may cause allergic reactions.

3 HOW TO TAKE TRANDOLAPRIL

Always take Trandolapril exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is as follows:

Hypertension:
The usual starting dose is one 0.5 mg capsule, once a day. Your doctor will probably increase this dose to one 1 mg or one 2 mg capsule, once a day. The maximum dose of trandolapril is 4 mg a day.

Following a heart attack:
Treatment will normally be started quite as early as the third day after a heart attack, usually at a low dose of 0.5 mg each day. Your doctor will probably increase this dose gradually to a maximum of 4 mg each day.

Dose for adults treated earlier with diuretics (water tablets):
The diuretic treatment (water tablets) should be discontinued at least 72 hours (3 days) before beginning treatment with Trandolapril, and/or treatment may be started with 0.5 mg once daily. Afterwards the dose will be adjusted when your doctor sees the effect of the treatment.

Patients that are older than 70 years of age:
It is not necessary to reduce the dose if you have normal kidney function. You must start with a low dose, and your doctor will watch your blood pressure and measure your kidney function during treatment.
However, caution is needed if at the same time you are being treated with diuretics (water tablets) or you have reduced heart, liver or kidney function.

Patients with kidney problems:
If you have kidney problems, the maximum dose of trandolapril should not exceed 2 mg a day.

Patients with liver problems:
The initial dose is 0.5 mg daily. Afterwards your doctor may adjust your dose as needed.

Children:
This medicinal product is not recommended for children.

If you take more Trandolapril than you should
If you (or someone else) swallow a lot of the capsules all together, or if you think a child has swallowed any of the capsules, contact your nearest hospital casualty department or your doctor immediately. An overdose is likely to cause very low blood pressure (dizziness

and fainting), shock, unconsciousness, slow heart rate or kidney failure. Treatment should include emptying the stomach contents and if the blood pressure should fall too low, volume expansion should be considered. Please take this leaflet, any remaining capsules and the container with you to the hospital or doctor so that they know which capsules were consumed.

If you forget to take Trandolapril
If you forget to take a capsule, take one as soon as you remember, unless it is nearly time to take the next one. Never take two doses together. Take the remaining doses at the correct time.

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

4 POSSIBLE SIDE EFFECTS

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

If you develop any of the following symptoms, contact a doctor immediately:
- you get a swollen face, tongue and/or throat, severe reddening of the skin (hives) and/or have difficulty in swallowing and/or breathing (angioedema).
- you feel ill after your first dose (a few people react to their first dose and feel very dizzy, weak, faint and are sick)
- you get a lot of infections with sore throats or mouth ulcers or if you bruise more easily while you are on this medicine.

The following side effects have been reported at the approximate frequencies shown:

Common (affecting fewer than one person in 10 but more than one person in 100):
- Cough
- Headaches
- Weakness
- Dizziness.

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):
- Low blood pressure
- Irregular heartbeat (palpitations)
- Itching
- Feeling sick (nausea)
- General feeling of being unwell (malaise)
- The condition known as heart failure
- Chest pain
- Increases in creatinine (used to test your kidney function).

Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):
- Inflamed sinuses
- Runny and itchy nose
- Inflammation of the tongue
- Difficulty in breathing
- Wheezing
- Shortness of breath.

Very rare (affecting fewer than one person in 10,000):
- serious allergic reactions causing swelling of the face, fingers/toes, tongue or throat (angioneurotic oedema).

Side effects with unknown frequency:
- Transient ischaemic attack (mini-stroke)
- faster heart beat
- irregular heart beat
- chest pain (angina)
- heart attack
- cerebral haemorrhage (bleeding in the brain)
- vomiting
- abdominal pain
- diarrhoea
- constipation
- dry mouth
- indigestion
- ileus (blockage of the intestine)
- pancreatitis (inflammation of the pancreas)
- hepatitis (inflammation of the liver)
- jaundice (yellowing of the skin and whites of the eyes)
- deterioration of kidney function
- kidney failure
- hair loss
- sweating
- bronchitis
- allergic reactions with an itchy rash
- serious illnesses with blistering of the skin (toxic epidermal necrosis) or skin, mouth, eyes and genitals (Stevens-Johnson syndrome) which may include fever and muscle pain
- psoriasis (thickened and sore skin patches)
- abnormal liver function tests
- blood disorders may occur, which may be characterised by pallor, fever or chills, sore throat, ulcers in your mouth or throat
- unusual bleeding or unexplained bruising due to low blood platelets.

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 TRANDOLAPRIL

Keep out of the reach and sight of children. Do not store above 25°C. Store in the original package. Do not use Trandolapril after the expiry date that is stated on the outer packaging.

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 Trandolapril contains:
- The active ingredient is trandolapril
- Each capsule contains 0.5, 1 or 2 mg of trandolapril
- The other ingredients are:
  - 0.5 mg capsules: povidone, lactose, pregelatinised starch, sodium stearyl fumarate. The capsule shell contains erythrosine (E127), titanium dioxide (E171), yellow iron oxide (E172), gelatin and quinoline yellow (E104). The printing ink contains shellac, iron oxide black (E172), propylene glycol
  - 1 mg capsules: povidone, lactose, pregelatinised starch, sodium stearyl fumarate. The capsule shell contains erythrosine (E127), titanium dioxide (E171), yellow iron oxide (E172), gelatin and sunset yellow (E110). The printing ink contains shellac, iron oxide black (E172), propylene glycol
  - 2 mg capsules: povidone, lactose, pregelatinised starch, sodium stearyl fumarate. The capsule shell contains erythrosine (E127), titanium dioxide (E171), yellow iron oxide (E172), gelatin. The printing ink contains shellac, iron oxide black (E172), propylene glycol.

What Trandolapril looks like and contents of the pack:
- Trandolapril 0.5 mg Capsules are rich yellow and medium orange coloured, hard capsules. The capsules are imprinted with TD0.5
- Trandolapril 1 mg Capsules are light orange and medium orange coloured, hard capsules. The capsules are imprinted with TD1
- Trandolapril 2 mg Capsules are medium orange coloured, hard capsules. The capsules are imprinted with TD2
- The product is available in the following pack sizes: 0.5 and 1 mg capsules: 14, 20, 28, 30, 40, 50, 60, 98, 100 and 200 capsules.
  2 mg capsules: 7, 14, 20, 28, 30, 50, 56, 60, 98 and 280 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation holder and company responsible for manufacture: TEVA UK Limited, Eastbourne, BN22 9AG.

PL 00289/0800
PL 00289/0801
PL 00289/0802

This leaflet was last revised: December 2007.

TEVA UK Limited

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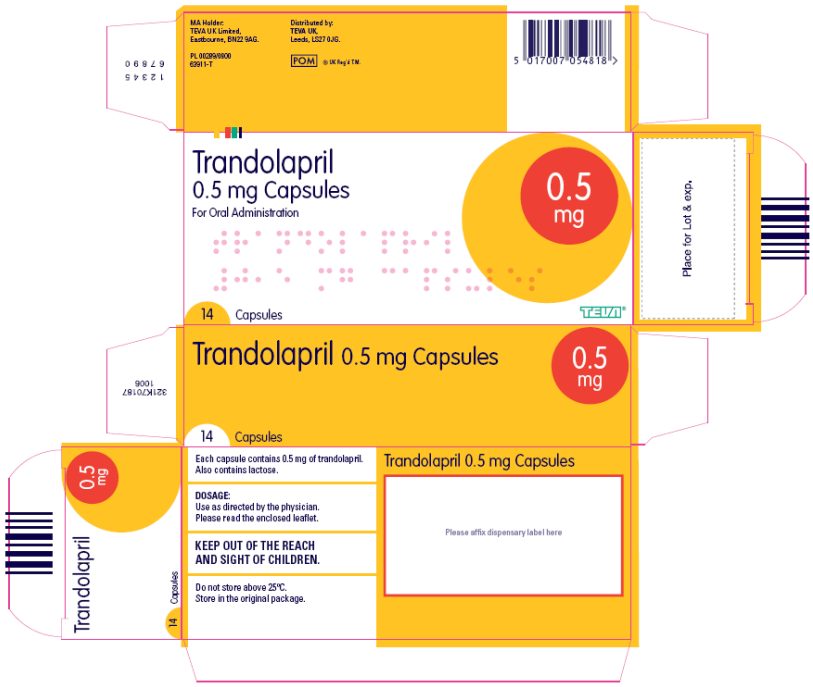
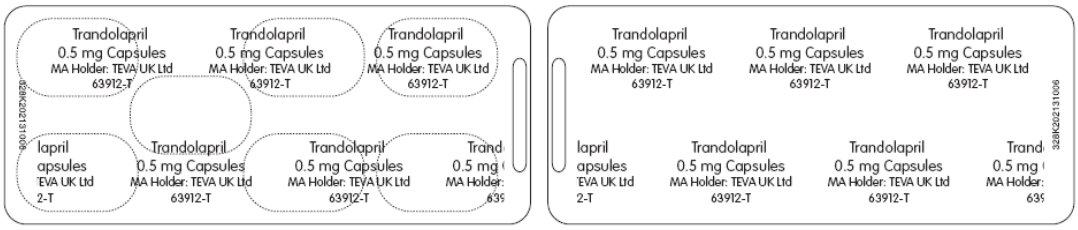
322K101950108

LABELLING

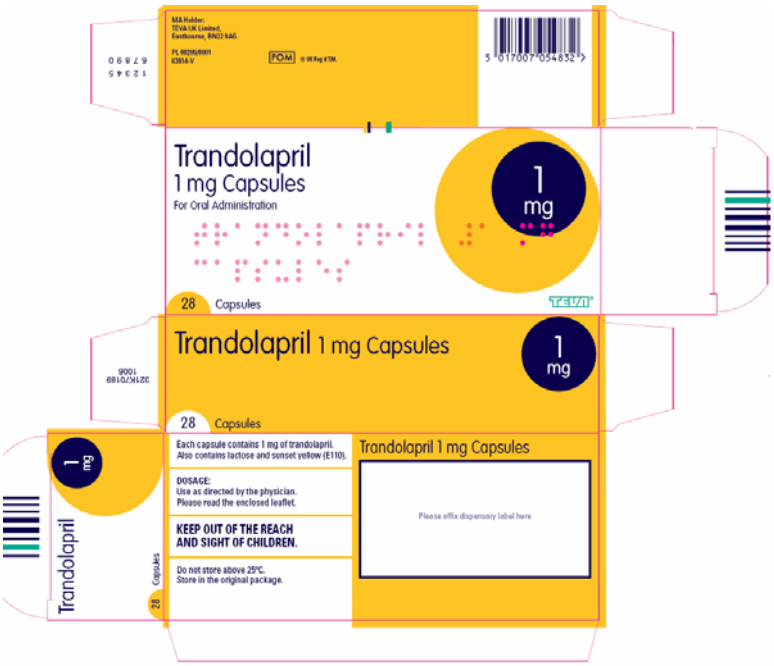
Trandolapril 0.5mg Capsules
Carton



Trandolapril 0.5mg Capsules
Blister foil



Trandolapril 1mg Capsules
Carton



Trandolapril 1mg Capsules
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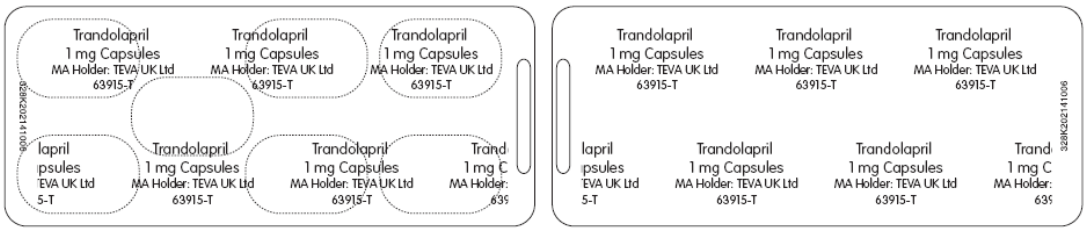
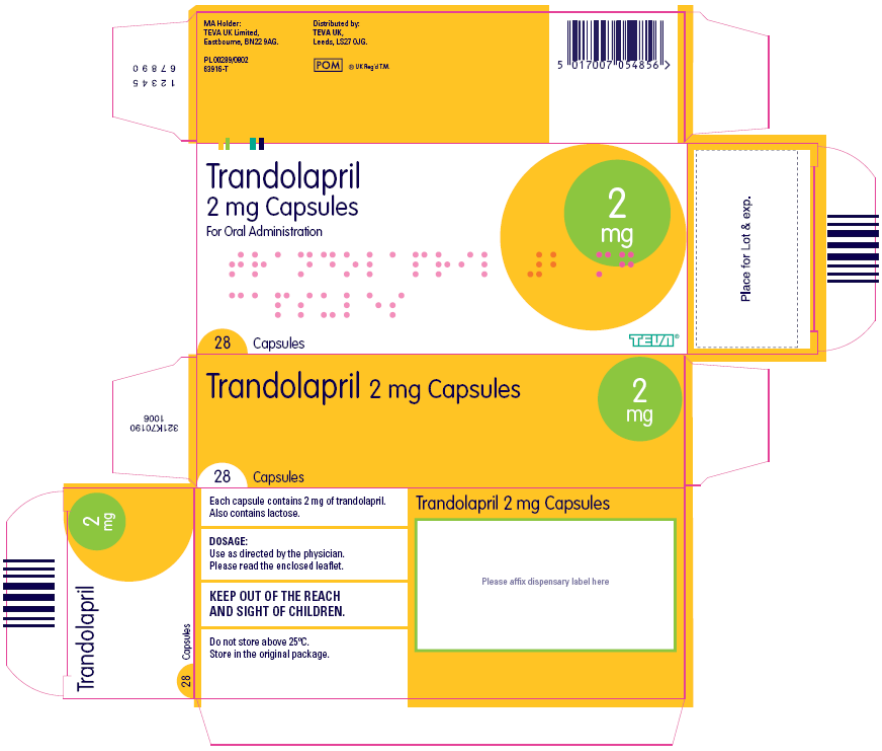


Trandolapril 2mg Capsules
Carton



Trandolapril 2mg Capsules
Blister foil