Minozran MR 100mg Prolonged release capsules, hard

Ranmino MR 100mg Prolonged release capsules, hard

PL 14894/0425-6

UKPAR

TABLE OF CONTENTS

Lay summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 9
Summary of product characteristics Page 10
Patient information leaflet Page 24
Labelling Page 27
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard (product licence numbers: PL 14894/0425-6). These medicines are available only by prescription.

Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard contain minocycline, which is an antibiotic used in the treatment of acne.

Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
MINOZRAN MR 100MG PROLONGED RELEASE CAPSULES, HARD
RANMINO MR 100MG PROLONGED RELEASE CAPSULES, HARD
PL 14894/0425-6

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Preclinical assessment Page 6
Clinical assessment Page 7
Overall conclusions and risk benefit assessment Page 8
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard on 20 January 2010. These medicines are only available on prescription.

The applicant claims that Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard are generic versions of Minocin MR capsules 100mg (PL 15142/0101), first authorised to Cyanamid of Great Britain Ltd on 20 November 1991, currently authorised to Meda Pharmaceuticals Ltd. The ten year rule is, therefore, complied with and the legal basis of these applications is acceptable.

Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard are indicated for the treatment of acne.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
All aspects of the manufacture and control of minocycline are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of minocycline for inclusion in these medicinal products.

Appropriate stability data have been generated, supporting the shelf life.

DRUG PRODUCT

Composition of the finished product
The finished product contains the excipients microcrystalline cellulose, povidone (K-30), opadry OY-S-58910 white (hypromellose (E464), titanium dioxide (E171), macrogol, talc) hypromellose phthalate (HP 50), castor oil, purified talc, gelatin, water, red iron oxide (E172), yellow iron oxide (E172), azorubine (E122), patent blue V (E131), quinoline yellow (E104), acetone, opacode S-1-7305HV (contains shellac glaze), purified water, N-butyl alcohol, lecithin (soya) (E322) and Antifoam DC1510 (food grade). Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective Ph. Eur. Monographs, where relevant monographs exist. All excipients are controlled by suitable specifications.

Satisfactory certificates of analysis have been provided for all excipients.

Certification confirms that none of the excipients contain material of animal or human origin apart from the gelatin. Satisfactory TSE Certificates of Suitability have been provided as evidence of compliance of the gelatine with current requirements.

There were no novel excipients used and no overages.

Dissolution and impurity profiles
Dissolution and impurity profiles for the drug product were found to be similar to those for the reference product.

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

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

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately
validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**
The capsules are available in blister strips comprised of white opaque PVC film coated uniformly with PVdC on the inner side with a backing of aluminium foil coated with heat seal lacquer on the inner side. The capsules are available in pack sizes of 50 or 56 capsules. Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set for this product. This is satisfactory.

**Product literature**
All product literature (SPCs, PILs and labelling) is satisfactory. The package leaflets were submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflets are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

**Other information**
Three separate studies have been conducted by the applicant:

- Randomised, open label, two treatment, two period, two sequence, single dose, cross-over bioequivalence study vs Minocin MR under fasting conditions.
- Randomised, open label, two treatment, two period, two sequence, single dose, cross-over bioequivalence study vs Minocin MR under fed conditions.
- Randomised, open label, two period, two sequence, multiple dose, crossover bioequivalence study at steady state vs Minocin MR under fasting conditions.

**Bioavailability, bioequivalence**
Bioequivalence study results are summarised below:

**Fasted:**

Results for main pharmacokinetic parameters:

<table>
<thead>
<tr>
<th></th>
<th>Test (mean ± SD)</th>
<th>Reference (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (ng/mL)</td>
<td>1184.79 ± 249.563</td>
<td>1081.46 ± 259.213</td>
</tr>
<tr>
<td>AUC\text{t} (ng.h/mL)</td>
<td>22371.02 ± 6450.524</td>
<td>23060.50 ± 6333.640</td>
</tr>
<tr>
<td>AUC\infty (ng.h/mL)</td>
<td>24444.61 ± 6742.518</td>
<td>24534.45 ± 6816.845</td>
</tr>
<tr>
<td>T\text{max} (h)*</td>
<td>2.625 ± 1.13</td>
<td>3.455 ± 1.24</td>
</tr>
</tbody>
</table>
Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

### Minocycline test vs. reference

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>110.06 (102.49-118.20)</td>
<td>96.56 (91.61-101.78)</td>
</tr>
<tr>
<td>$AUC_t$ (ng.h/mL)</td>
<td>96.56 (91.61-101.78)</td>
<td>98.40 (93.97-103.03)</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>98.40 (93.97-103.03)</td>
<td></td>
</tr>
</tbody>
</table>

**Fed:**

Results for main pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1127.43 ± 214.529</td>
<td>1072.53 ± 229.620</td>
</tr>
<tr>
<td>$AUC_t$ (ng.h/mL)</td>
<td>23997.02 ± 4477.266</td>
<td>24340.96 ± 5559.199</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>25798.85 ± 4329.816</td>
<td>26129.26 ± 5823.384</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)*</td>
<td>5.334 ± 2.1684</td>
<td>5.522 ± 1.5037</td>
</tr>
</tbody>
</table>

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

### Minocycline test vs. reference

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point estimate (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>105.53 (99.96-111.42)</td>
</tr>
<tr>
<td>$AUC_t$ (ng.h/mL)</td>
<td>99.41 (94.02-105.110)</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>99.21 (93.37-105.40)</td>
</tr>
</tbody>
</table>

**Steady state:**

Results for main pharmacokinetic parameters:

### Minocycline test vs. reference

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1520.05 ± 367.634</td>
<td>1465.21 ± 419.755</td>
</tr>
<tr>
<td>$AUC_t$ (ng.h/mL)</td>
<td>19884.40 ± 4779.758</td>
<td>19711 ± 5403.98</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)*</td>
<td>2.946 ± 1.3909</td>
<td>2.878 ± 0.8263</td>
</tr>
</tbody>
</table>

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>104.91 % (99.90-110.18%)</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (ng/mL)</td>
<td>101.66 % (98.38-105.04%)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/mL)</td>
<td>98.15 % (94.22-102.25 %)</td>
</tr>
</tbody>
</table>

90% confidence intervals for key pharmacokinetic parameter ratios comply with current requirements. \( T_{\text{max}} \) was also comparable for test and reference products. Based on the results provided, the products can be considered bioequivalent.

The proposed products are delivered via the same route using the same pharmaceutical form as the UK reference product. Evidence of bioequivalence has also been provided. Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard are generics of Minocin MR capsules 100mg (PL 15142/0101).

**Comment on Expert report**
A summary of the application has been prepared by an appropriately qualified expert.

**ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE**
Marketing Authorisations may be granted.
PRECLINICAL ASSESSMENT

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

Clinical Background
Minocycline in a modified release formulation is currently approved in the UK for the treatment of acne. Systemic antibacterial treatment is useful in inflammatory acne that does not respond adequately to topical treatment. Tetracyclines are broad-spectrum antibiotics whose value has decreased because of increasing bacterial resistance. They remain, however, the treatment of choice for certain infections (those caused by Chlamydia, Rickettsia, Brucella and Spirochaete), and are also used in other types of infections such as acne. As such, minocycline is an alternative to tetracycline which offers less likelihood of bacterial resistance but may sometimes cause irreversible pigmentation.

Indications
Treatment of acne

Dose and Dose Regimen
Adults and children over the age of 12: 100 mg every 24h

GCP Aspects
The clinical trials are conducted in accordance with GCP.

Orphan Medicinal Products
Not applicable

Paediatric Development Programme
Minocycline is not indicated in children less than 12 years of age.

Scientific Advice
Not applicable

Legal Status
POM

CLINICAL PHARMACOLOGY

Pharmacokinetics

Introduction and overview
Minocycline is rapidly absorbed after oral administration, approximately 95% of the maximum serum concentration is achieved by the first hour post dosing. After an oral administration of 100mg, the following PK parameters have been reported: $C_{\text{max}} = 1.76 \mu g/ml$, $AUC = 22.4\mu g/ml/h$ and $T_{\text{max}} = 1.87h$. The upper GI tract is the site where most active absorption occurs.
At steady state maximum and minimum concentrations of minocycline were 3.5 μg/ml and 2.3 μg/ml, respectively. Drug serum levels after administering a modified release formulation (MR) ranged from 0.16-3.77 μg/ml. This MR formulation contained a double pulse delivery system in which a portion of each dose was absorbed from the stomach and a second dose was available for absorption in the upper GI tract. These levels were very similar to those obtained with a 50 mg twice a day dose using an immediate release formulation.

Minocycline has wide tissue distribution and penetration in body fluids and tissues after oral administration, the highest levels being found in bile, liver, duodenum, thyroid and lung. Concentrations well above the therapeutic serum levels have been demonstrated in the various portions of the skin (dermis, epidermis and scrapings). The high lipophilicity of Minocycline at physiological pH may be responsible for the more favourable tissue penetration properties when compared with other tetracyclines. The average protein binding in plasma lies between 75 and 85% and the serum half life is approximately 16 h.

Minocycline is partially metabolised to inactive substances, with hydroxylation and N-demethylation as the major pathways. It has low average renal clearance compared with other tetracyclines. The urinary recovery at 24h is about 5%, while the amount of drug recovered in faeces is about 20-34%.

Minocycline may have different kinetics in debilitated elderly, in whom the dose should be adjusted by body weight, but are not modified in renal impairment or liver disease.

The pharmacokinetic characteristics of minocycline have been well studied in the past. There are no particular regulatory concerns for a generic version provided that bioequivalence can be established.

Bioequivalence
The applicant presents the result of three clinical trials in support of this application: a bioequivalence study in the fasted state, in the fed state and in the steady state. These are assessed separately.

Bioequivalence in the fasting state
A randomised, open label, 2-treatment, 2-period, 2-sequence, single dose, crossover, bioequivalence study in healthy human adult male subjects, under fasting conditions
Washout: 12 days

Test Product
Minocycline HCL MR capsules 100 mg

Reference Product
Minocin MR (Minocycline capsules 100 mg)

Study design
This is an open label, randomised, two-way, two-period, single dose crossover study in 40 healthy overnight fasted healthy male volunteers who were given a single dose
of each drug with 240 ml of water. Drugs were administered in subsequent periods after 12 days of washout. Blood samples were obtained at pre-dose and at intervals up to 96 hours post-dosing.

A total of 40 subjects were planned, recruited and dosed. Only 39 subjects were included in the final analysis. One subject was withdrawn because he developed chickenpox.

Plasma drug concentrations were determined using a validated HPLC-MS method with a LOQ of 30.3 ng/ml. Basic pharmacokinetic (PK) parameters were calculated for both drugs and included $T_{\text{max}}$, $C_{\text{max}}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $T_{\frac{1}{2}}$ and $K_e$. ANOVA test was performed on PK parameters for log-transformed data using linear models procedures. The protocol defined acceptance criteria of 0.8 – 1.25 for both AUC and $C_{\text{max}}$.

**Results**

Results for main pharmacokinetic parameters:

### Minocycline test vs. reference

<table>
<thead>
<tr>
<th></th>
<th>Test (mean ± SD)</th>
<th>Reference (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1184.79 ± 249.563</td>
<td>1081.46 ± 259.213</td>
</tr>
<tr>
<td>$AUC_t$ (ng.h/mL)</td>
<td>22371.02 ± 6450.524</td>
<td>23060.50 ± 6333.640</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>24444.61 ± 6742.518</td>
<td>24534.45 ± 6816.845</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)*</td>
<td>2.635 ± 1.13</td>
<td>3.455 ± 1.24</td>
</tr>
</tbody>
</table>

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

### Minocycline test vs. reference

<table>
<thead>
<tr>
<th></th>
<th>Point estimate (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>110.06 (102.49-118.20)</td>
</tr>
<tr>
<td>$AUC_t$ (ng.h/mL)</td>
<td>96.56 (91.61-101.78)</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>98.40 (93.97-103.03)</td>
</tr>
</tbody>
</table>

The design of the bioequivalence trial in the fasting state followed the recommended guidelines. The results of this study meet the criteria.

**Bioequivalence in the fed state**

A randomised, open label, 2 treatment, 2 period, 2 sequence, single dose, crossover, bioequivalence study of in healthy adult male subjects, under fed conditions.

Washout period: 10 days

**Test Product**

Minocycline HCL MR capsules 100 mg

**Reference Product**

Minocin MR (Minocycline capsules 100 mg)
**Study design**

This is an open label, randomised, two-way, two-period, single dose crossover study in 40 healthy male volunteers who were given a single dose of each drug with 240 ml of water 30 minutes after a high-calorie, high-fat breakfast. Drugs were administered in subsequent periods after 10 days of washout. Blood samples were obtained at pre-dose and at intervals up to 96 hours post-dosing.

A total of 40 subjects were planned, recruited and dosed. Only 39 subjects were included in the final analysis as one subject was absent.

Plasma drug concentrations were determined using a validated LC/MS/MS method with a LOQ of 30.3 ng/ml. Basic pharmacokinetic (PK) parameters were calculated for both drugs and included $T_{\text{max}}$, $C_{\text{max}}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, $T_{1/2}$ and $K_{el}$. ANOVA test was performed on PK parameters for log-transformed data using linear models procedures. The protocol defined acceptance criteria of 0.8 – 1.25 for both AUC and $C_{\text{max}}$.

**Results**

Results for main pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Parent drug</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>$1127.43 \pm 214.529$</td>
</tr>
<tr>
<td></td>
<td>$AUC_t$ (ng.h/mL)</td>
<td>$23997.02 \pm 4477.266$</td>
</tr>
<tr>
<td></td>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>$25798.85 \pm 4329.816$</td>
</tr>
<tr>
<td></td>
<td>$T_{\text{max}}$ (h)*</td>
<td>$5.334 \pm 2.1684$</td>
</tr>
</tbody>
</table>

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

**Minocycline test vs. reference**

<table>
<thead>
<tr>
<th></th>
<th>Point estimate (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>105.53 (99.96-111.42)</td>
</tr>
<tr>
<td>$AUC_t$ (ng.h/mL)</td>
<td>99.41 (94.02-105.11)</td>
</tr>
<tr>
<td>$AUC_{\infty}$ (ng.h/mL)</td>
<td>99.21 (93.37-105.40)</td>
</tr>
</tbody>
</table>

The design of the bioequivalence trial in the fasting state followed the recommended guidelines. The results of this study meet the criteria.

**Bioequivalence in steady state**

A randomised, open label, 2 treatment, 2 period, 2 sequence, single dose, crossover, bioequivalence study at steady state of Minocycline Hydrochloride MR 100 mg capsules and Minocin MR 100 mg capsules, in healthy adult male subjects, under fasting conditions.

Washout: 17 days

**Test Product**

Minocycline HCL MR capsules 100 mg

MHRA PAR; MINOZRAN MR 100MG PROLONGED RELEASE CAPSULES, HARD, AND RANMINO MR 100MG PROLONGED RELEASE CAPSULES, HARD THR 14894/0425-6
Reference Product
Minocin MR (Minocycline capsules 100 mg)

Study design
This was a randomised, open label, 2-treatment, 2-sequence, multiple dose, crossover, bioequivalence study. A total of 40 subjects were recruited but only 37 completed both periods. Subjects were to receive seven consecutive doses (once a day) of both test and reference drug sequentially in a randomised order. The doses were administered after overnight fasting with 240 ml of water. Post dosing meals and fluid intake were standardised for all subjects.

Blood samples were taken at pre-dose on days 1, 4, 5, 6, and 7 and post-dose at intervals up to 24h on day 7 in each period.

Plasma drug concentrations were determined using a validated LC/MS/MS method with a LOQ of 30.3 ng/ml. Basic pharmacokinetic (PK) parameters were calculated for both drugs and included T\text{max} and C\text{max} at steady state, AUC\text{t}, and % fluctuation (percentage fluctuation during steady state). ANOVA test was performed on PK parameters for log-transformed data using linear models procedures. The protocol defined acceptance criteria of 0.8 – 1.25 for AUC and C\text{max}.

Results

Results for main pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Minocycline test vs. reference</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (ng/mL)</td>
<td>1520.05 ± 367.634</td>
<td>1465.21 ± 419.755</td>
</tr>
<tr>
<td>AUC\text{t} (ng.h/mL)</td>
<td>19884.40 ± 4779.758</td>
<td>19711 ± 5403.98</td>
</tr>
<tr>
<td>AUC\text{∞} (ng.h/mL)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>T\text{max} (h)*</td>
<td>2.946 ± 1.3909</td>
<td>2.878 ± 0.8263</td>
</tr>
</tbody>
</table>

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th>Minocycline test vs. reference</th>
<th>Parent drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (ng/mL)</td>
<td>104.91 % (99.90-110.18%)</td>
</tr>
<tr>
<td>C\text{min} (ng/mL)</td>
<td>101.66 % (98.38-105.04%)</td>
</tr>
<tr>
<td>AUC\text{o-t} (ng.h/mL)</td>
<td>98.15 % (94.22-102.25 %)</td>
</tr>
<tr>
<td>AUC\text{∞} (ng.h/mL)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Three subjects were withdrawn in period II due to intercurrent illnesses (which were deemed unrelated to the study medication and resolved without sequelae). In one subject, eosinophilia was detected at the end of the study. Since eosinophilia is reported in the SPC of this product, the event was thought to be probably related to the drug study and a report will be given when results of the follow-up are available.
The design of the steady state bioequivalence trial is adequate for the purpose of this application. The results of this study meet the criteria.

**Conclusion on Bioequivalence**

The applicant has submitted three bioequivalence studies in support of this Marketing Authorisation application. These trials were designed following the CHMP guidelines on this topic. The results yielded support the claim of bioequivalence between the applicant’s proposed formulation and the reference drug.

**Pharmacodynamics**

**Introduction**

Minocycline is a bacteriostatic drug that acts by inhibiting the synthesis of proteins in the bacterial ribosomes (specifically the 30S sub group). This link prevents the formation of the ribosomal complex by inhibiting the binding of the amino-acyl-t-RNA to the mRNA ribosome complex and, hence, protein synthesis.

Clinical studies have shown that serum minocycline concentrations above the modal MIC of the drug for sensitive strains of Propionibacterium acnes were achieved in patients regardless of sex, dosage, drug formulation or frequency of administrations using the oral route.

In general, bacteria develop antibiotic resistance by acquiring mobile genetic elements such as plasmids. Mobile plasmids and transposons encode for pump proteins that efflux tetracyclines away from ribosomes. In the case of clinically relevant resistant strains of P. acnes, mobile elements have not been found. Rather, point mutations have been identified.

Additional studies have shown that minocycline may increase IL-1 levels and decrease T lymphocyte proliferation and IL-2, interferon-gamma and TNF-alpha production.

The pharmacodynamics characteristics of minocycline have been well studied in the past. There are no particular regulatory concerns for a generic version.

**CLINICAL EFFICACY**

**Overview**

The efficacy of minocycline in the treatment of acne has been demonstrated in non-comparative and comparative trials with topical and systemic treatments. Due to its lipophilic nature, it may concentrate in sebaceous follicles and exert a more profound effect on P. acnes than other tetracyclines.

The clinical efficacy of minocycline in the treatment of acne has been well studied in the past. There are no particular regulatory concerns for a generic formulation.
CLINICAL SAFETY

Overview
The safety aspects of minocycline have been described in the past. The clinical trials presented by the applicant did not disclose any new possible adverse drug reactions.

The safety information currently contained in the SPC is adequate. There are no regulatory concerns for a generic formulation.

EXPERT REPORTS
The clinical expert is suitably qualified.

PRODUCT LITERATURE
All product literature is medically satisfactory.

OVERALL CONCLUSION
Marketing Authorisations may be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
The efficacy of Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard is well established. The SPCs, PILs and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Minozran MR 100mg Prolonged release capsules, hard and Ranmino MR 100mg Prolonged release capsules, hard. The risk benefit ratio is therefore considered to be acceptable.
### STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>STEPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 12 September 2005</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 21 October 2005</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the clinical dossier on 16 December 2005 and the quality dossier on 27 January 2006</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical and quality dossier on 23 August 2006</td>
</tr>
<tr>
<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier 20 March 2007</td>
</tr>
<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the dossier on 23 March 2007</td>
</tr>
<tr>
<td>7</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 17 April 2007</td>
</tr>
<tr>
<td>8</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the dossier on 5 June 2007</td>
</tr>
<tr>
<td>9</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 16 July 2007</td>
</tr>
<tr>
<td>10</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the dossier on 6 November 2007</td>
</tr>
<tr>
<td>11</td>
<td>The MHRA requested further information relating to the quality dossier on 15 April 2008</td>
</tr>
<tr>
<td>12</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the dossier on 30 October 2008</td>
</tr>
<tr>
<td>13</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 12 December 2008</td>
</tr>
<tr>
<td>14</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the dossier on 6 February 2009</td>
</tr>
<tr>
<td>15</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 7 April 2009</td>
</tr>
<tr>
<td>16</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the dossier on 14 April 2009</td>
</tr>
<tr>
<td>17</td>
<td>The application was determined on 20 January 2010</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Minozran MR 100mg Prolonged release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 100mg of the active ingredient minocycline (as the hydrochloride).

For excipients, see 6.1

3 PHARMACEUTICAL FORM
Prolonged release capsule, hard

Minozran MR 100mg Prolonged release capsules, hard comprise of chocolate brown cap/light brown body of size ‘1’ imprinted with ‘R/MCNMR’ on cap and ‘100’ on body in white edible ink containing a mixture of off-white to light yellow and yellow coloured granules to a mixture of yellowish grey to brown coloured granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Minozran MR 100mg Prolonged release capsules, hard are indicated for the treatment of acne.

4.2 Posology and method of administration
Dosage:
Adults: One 100mg capsule every 24 hours.
Children over 12 years: One 100mg capsule every 24 hours.
Children under 12 years: Minozran MR 100mg Prolonged release capsules, hard is not recommended.
Elderly: No special dosing requirements.

Administration:
To reduce the risk of oesophageal irritation and ulceration, the capsules should be swallowed whole with plenty of fluid, while sitting or standing. Unlike earlier tetracyclines, absorption of Minozran MR 100mg Prolonged release capsules, hard is not significantly impaired by food or moderate amounts of milk.

Treatment of acne should be continued for a minimum of 6 weeks. If, after six months, there is no satisfactory response Minozran MR 100mg Prolonged release capsules, hard should be discontinued and other therapies considered. If Minozran MR 100mg Prolonged release capsules, hard is to be continued...
for longer than six months, patients should be monitored at least three monthly thereafter for signs and symptoms of hepatitis or SLE or unusual pigmentation (see Special warnings and precautions).

4.3 Contraindications
Known hypersensitivity to tetracyclines, or to any of the components of Minozran MR 100mg Prolonged release capsules, hard. Use in pregnancy, lactation, children under the age of 12 years, complete renal failure.

4.4 Special warnings and precautions for use
Minozran MR 100mg Prolonged release capsules, hard should be used with caution in patients with hepatic dysfunction and in conjunction with alcohol and other hepatotoxic drugs. It is recommended that alcohol consumption should remain within the Government's recommended limits.

Rare cases of auto-immune hepatotoxicity and isolated cases of systemic lupus erythematosus (SLE) and also exacerbation of pre-existing SLE have been reported. If patients develop signs or symptoms of SLE or hepatotoxicity, or suffer exacerbation of pre-existing SLE, minocycline should be discontinued.

Clinical studies have shown that there is no significant drug accumulation in patients with renal impairment when they are treated with Minozran MR 100mg Prolonged release capsules, hard in the recommended doses. In cases of severe renal insufficiency, reduction of dosage and monitoring of renal function may be required. The anti-anabolic action of the tetracyclines may cause an increase in serum urea. In patients with significantly impaired renal function, higher serum levels of tetracyclines may lead to uraemia, hyperphosphataemia and acidosis. If renal impairment exists, even usual oral and parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity.

Caution is advised in patients with myasthenia gravis as tetracyclines can cause weak neuromuscular blockade.

Cross-resistance between tetracyclines may develop in micro-organisms and cross-sensitisation in patients. Minozran MR 100mg Prolonged release capsules, hard should be discontinued if there are signs/symptoms of overgrowth of resistant organisms, e.g. enteritis, glossitis, stomatitis, vaginitis, pruritus ani or Staphylococcal enteritis.

Patients taking oral contraceptives should be warned that if diarrhoea or breakthrough bleeding occur there is a possibility of contraceptive failure.

Minocycline may cause hyperpigmentation at various body sites (see Administration and 4.8 Undesirable Effects). Hyperpigmentation may present regardless of dose or duration of therapy but develops more commonly during long term treatment. Patients should be advised to report any unusual pigmentation without delay and Minozran MR 100mg Prolonged release capsules, hard should be discontinued.
If a photosensitivity reaction occurs, patients should be warned to avoid direct exposure to natural or artificial light and to discontinue therapy at the first signs of skin discomfort.

As with other tetracyclines, bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported. Presenting features were headache and visual disturbances including blurring of vision, scotoma and diplopia. Permanent vision loss has been reported. Treatment should cease if evidence of raised intracranial pressure develops.

**Use in the elderly:**
Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Use in children:**
The use of tetracyclines during tooth development in children under the age of 12 years may cause permanent discolouration. Enamel hypoplasia has also been reported.

**Laboratory monitoring:**
Periodic laboratory evaluations of organ system function, including haematopoietic, renal and hepatic should be conducted.

Minozran MR 100mg Prolonged release capsules, hard contain azorubine which may cause allergic reaction

**4.5 Interaction with other medicinal products and other forms of interaction**
Tetracyclines depress plasma prothrombin activity and reduced doses of concomitant anticoagulants may be necessary.

Diuretics may aggravate nephrotoxicity by volume depletion.

Bacteriostatic drugs may interfere with the bactericidal action of penicillin. Avoid giving tetracycline-class drugs in conjunction with penicillin. Absorption of Minozran MR 100mg Prolonged release capsules, hard is impaired by the concomitant administration of antacids, iron, calcium, magnesium, aluminium bismuth and zinc salts (interactions with specific salts, antacids, bismuth containing ulcer – healing drugs, quinapril which contains a magnesium carbonate excipient). It is recommended that any indigestion remedies, vitamins, or other supplements containing these salts are taken at least 3 hours before or after a dose of Minozran MR 100mg Prolonged release capsules, hard. Unlike earlier tetracyclines, absorption of Minozran MR 100mg Prolonged release capsules, hard is not significantly impaired by food or moderate amounts of milk.

The concomitant use of tetracyclines may reduce the efficacy of oral contraceptives.
Administration of isotretinoin should be avoided shortly before, during and shortly after minocycline therapy. Each drug alone has been associated with pseudotumor cerebri (benign intracranial hypertension) (see 4.4 Special warnings and precautions).

Interference with laboratory and other diagnostic tests:
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

4.6 Pregnancy and lactation

Use in pregnancy:
Minozran MR 100mg Prolonged release capsules, hard should not be used in pregnancy unless considered essential.

Results of animal studies indicate that tetracyclines cross the placenta, are found in foetal tissues and can have toxic effects on the developing foetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. Minozran MR 100mg Prolonged release capsules, hard therefore, should not be used in pregnancy unless considered essential.

In humans, Minozran MR 100mg Prolonged release capsules, hard, like other tetracycline-class antibiotics, crosses the placenta and may cause foetal harm when administered to a pregnant woman. In addition, there have been post marketing reports of congenital abnormalities including limb reduction. If Minozran MR 100mg Prolonged release capsules, hard is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the foetus.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long term use of the drugs but has been observed following repeated short term courses. Enamel hypoplasia has also been reported.

Tetracyclines administered during the last trimester form a stable calcium complex throughout the human skeleton. A decrease in fibula growth rate has been observed in premature human infants given oral tetracyclines in doses up to 25 mg/kg every 6 hours. Changes in fibula growth rate were shown to be reversible when the drug was discontinued.

Use in lactation:
Tetracyclines have been found in the milk of lactating women who are taking a drug in this class. Permanent tooth discolouration may occur in the developing infant and enamel hypoplasia has been reported.
4.7 Effects on ability to drive and use machines
Headache, light-headedness, dizziness, tinnitus and vertigo (more common in women) and, rarely, impaired hearing have occurred with Minozran MR 100mg Prolonged release capsules, hard. Patients should be warned about the possible hazards of driving or operating machinery during treatment. These symptoms may disappear during therapy and usually disappear when the drug is discontinued.

4.8 Undesirable effects
Adverse reactions are shown below under the MedDRA system organ classification:
Common: ≥1%
Uncommon: ≥0.1% and < 1%
Rare: ≥0.01% and < 0.1%
Very Rare: < 0.01%

Infections and Infestations
Very Rare: Oral and anogenital candidiasis, vulvovaginitis.

Blood and Lymphatic System Disorders
Rare: Eosinophilia, leucopenia, neutropenia, thrombocytopenia.
Very Rare: Haemolytic anaemia, pancytopenia.
There are also reports of: Agranulocytosis

Immune System Disorders
Rare: Anaphylaxis /anaphylactoid reaction (including shock), including fatalities.
There are also reports of: Hypersensitivity, pulmonary infiltrates, anaphylactoid purpura.

Endocrine Disorders
Very Rare: Abnormal thyroid function, brown-black discolouration of the thyroid.

Metabolism and Nutrition Disorders
Rare: Anorexia.

Nervous System Disorders
Common: Dizziness (lightheadedness).
Rare: Headache, hypoesthesia, paraesthesia, intracranial hypertension, vertigo.
Very Rare: Bulging fontanelle.
There are also reports of: convulsions, sedation.

Ear and Labyrinth Disorders
Rare: Impaired hearing, tinnitus.

Cardiac Disorders
Rare: Myocarditis, pericarditis.
Respiratory, Thoracic and Mediastinal Disorders
Rare: Cough, dyspnoea.
Very Rare: Bronchospasm, exacerbation of asthma, pulmonary eosinophilia.
There are also reports of: Pneumonitis.

Gastrointestinal Disorders
Rare: Diarrhoea, nausea, stomatitis, discolouration of teeth, vomiting.
Very Rare: Dyspepsia, dysphagia, enamel hypoplasia, enterocolitis, oesophagitis, oesophageal ulceration, glossitis, pancreatitis, pseudomembranous colitis.

Hepatobiliary Disorders
Rare: Increased liver enzymes, hepatitis, autoimmune hepatotoxicity. (See Section 4.4 Special warnings and precautions for use).
Very Rare: Hepatic cholestatis, hepatic failure (including fatalities), hyperbilirubinaemia, jaundice.

Skin and Subcutaneous Tissue Disorders
Rare: Alopecia, erythema multiforme, erythema nodosum, fixed drug eruption, hyperpigmentation of skin, photosensitivity, pruritus, rash, urticaria, vasculitis.
Very Rare: Angioedema, exfoliative dermatitis, hyperpigmentation of nails, Stevens-Johnson Syndrome, toxic epidermal necrolysis.

Musculoskeletal, Connective Tissue and Bone Disorders
Rare: Arthralgia, lupus-like syndrome, myalgia.
Very Rare: Arthritis, bone discolouration, cases of or exacerbation of systemic lupus erythematosus (SLE) (See Section 4.4 Special warnings and Special precautions for use), joint stiffness, joint swelling.

Renal and Urinary Disorders
Rare: Increased serum urea, acute renal failure, interstitial nephritis.

Reproductive System and Breast Disorders
Very Rare: Balanitis.

General Disorders and Administration Site Conditions
Uncommon: Fever.
Very Rare: Discolouration of secretions.

The following syndromes have been reported. In some cases involving these syndromes, death has been reported. As with other serious adverse reactions, if any of these syndromes are recognised, the drug should be discontinued immediately:

- Hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, pericarditis. Fever and lymphadenopathy may be present.
- Lupus-like syndrome consisting of positive antinuclear antibody, arthralgia, arthritis, joint stiffness or joint swelling, and one or more of the following: fever, myalgia, hepatitis, rash, vasculitis.
- Serum sickness-like syndrome consisting of fever, urticaria or rash, and arthralgia, arthritis, joint stiffness or joint swelling. Eosinophilia may be present.

Hyperpigmentation of various body sites including the skin, nails, teeth, oral mucosa, bones, thyroid, eyes (including sclera and conjunctiva), breast milk, lacrimal secretions and perspiration has been reported. This blue/black/grey or muddy-brown discolouration may be localised or diffuse. The most frequently reported site is in the skin. Pigmentation is often reversible on discontinuation of the drug, although it may take several months or may persist in some cases. The generalised muddy-brown skin pigmentation may persist, particularly in areas exposed to the sun.

4.9 **Overdose**

Dizziness, nausea and vomiting are the adverse effects most commonly seen with overdose. There is no specific antidote. In cases of overdose, discontinue medication; treat symptomatically with gastric lavage and appropriate supportive measures. Minocycline is not removed in significant quantities by haemodialysis or peritoneal dialysis.

5 **PHARMAKOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Antiinfectives for systemic use – tetracyclines; ATC code: J01AA08

Minozran MR 100mg Prolonged release capsules, hard contains the active ingredient minocycline as minocycline hydrochloride, a semi-synthetic derivative of tetracycline.

5.2 **Pharmacokinetic properties**

Minozran MR 100mg Prolonged release capsules, hard have been formulated as a "double pulse" delivery system in which a portion of the minocycline dose is delivered in the stomach, and a second portion of the dose is available for absorption in the duodenum and upper GI tract.

5.3 **Preclinical safety data**

None stated.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Minocycline hydrochloride uncoated granules

Microcrystalline cellulose
Povidone (K-30)

**Immediate release coated granules**

Minocycline hydrochloride uncoated granules
Opadry OY-S-58910 White
Hypermellose (E464)
Titanium dioxide (E171)
Macrogol
Talc

**Prolonged release coated granules**

Hypermellose phthalate
Castor oil
Purified talc

**Lubrication**

Purified talc

**Capsule Shell**

**Body Composition**

Gelatin
Water
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

**Cap composition**

Gelatin
Water
Azorubine (E122)
Patent blue V (E131)
Quinoline yellow (E104)
Titanium dioxide (E171)

**Printing ink**

Opacode S-1-7305HV (contains Shellac glaze)
Titanium dioxide (E171)
Purified water
Lecithin (soya) (E322)
Simeticone

6.2 **Incompatibilities**

Not applicable

6.3 **Shelf life**

2 years
6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
Blister strips comprises of white opaque PVC film coated uniformly with PVdC on inner side with a backing of aluminium foil coated with heat seal lacquer on inner side.

Available in pack sizes of 50 or 56 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirement.

7 MARKETING AUTHOURISATION HOLDER
Ranbaxy UK Limited
20 Balderton Street,
London
W1K 6TL, UK.

8 MARKETING AUTHOURISATION NUMBER(S)
PL 14894 / 0425

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION
20/01/2010

10 DATE OF REVISION OF THE TEXT
20/01/2010

1 NAME OF THE MEDICINAL PRODUCT
Ranmino MR 100mg Prolonged release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 100mg of the active ingredient minocycline (as the hydrochloride).

For excipients, see 6.1

3 PHARMACEUTICAL FORM
Prolonged release capsule, hard
Ranmino MR 100mg Prolonged release capsules, hard comprise of chocolate brown cap/light brown body of size ‘1’ imprinted with ‘R/MCNMR’ on cap and ‘100’ on body in white edible ink containing a mixture of off-white to light yellow and yellow coloured granules to a mixture of yellowish grey to brown coloured granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ranmino MR 100mg Prolonged release capsules, hard are indicated for the treatment of acne.

4.2 Posology and method of administration
Dosage:
Adults: One 100mg capsule every 24 hours.
Children over 12 years: One 100mg capsule every 24 hours.
Children under 12 years: Ranmino MR 100mg Prolonged release capsules, hard is not recommended.
Elderly: No special dosing requirements.

Administration:
To reduce the risk of oesophageal irritation and ulceration, the capsules should be swallowed whole with plenty of fluid, while sitting or standing. Unlike earlier tetracyclines, absorption of Ranmino MR 100mg Prolonged release capsules, hard is not significantly impaired by food or moderate amounts of milk.

Treatment of acne should be continued for a minimum of 6 weeks. If, after six months, there is no satisfactory response Ranmino MR 100mg Prolonged release capsules, hard should be discontinued and other therapies considered. If Ranmino MR 100mg Prolonged release capsules, hard is to be continued for longer than six months, patients should be monitored at least three monthly thereafter for signs and symptoms of hepatitis or SLE or unusual pigmentation (see Special warnings and precautions).

4.3 Contraindications
Known hypersensitivity to tetracyclines, or to any of the components of Ranmino MR 100mg Prolonged release capsules, hard. Use in pregnancy, lactation, children under the age of 12 years, complete renal failure.

4.4 Special warnings and precautions for use
Ranmino MR 100mg Prolonged release capsules, hard should be used with caution in patients with hepatic dysfunction and in conjunction with alcohol and other hepatotoxic drugs. It is recommended that alcohol consumption should remain within the Government's recommended limits.
Rare cases of auto-immune hepatotoxicity and isolated cases of systemic lupus erythematosus (SLE) and also exacerbation of pre-existing SLE have been reported. If patients develop signs or symptoms of SLE or hepatotoxicity, or suffer exacerbation of pre-existing SLE, minocycline should be discontinued.

Clinical studies have shown that there is no significant drug accumulation in patients with renal impairment when they are treated with Ranmino MR 100mg Prolonged release capsules, hard in the recommended doses. In cases of severe renal insufficiency, reduction of dosage and monitoring of renal function may be required. The anti-anabolic action of the tetracyclines may cause an increase in serum urea. In patients with significantly impaired renal function, higher serum levels of tetracyclines may lead to uraemia, hyperphosphataemia and acidosis. If renal impairment exists, even usual oral and parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity.

Caution is advised in patients with myasthenia gravis as tetracyclines can cause weak neuromuscular blockade.

Cross-resistance between tetracyclines may develop in micro-organisms and cross-sensitisation in patients. Ranmino MR 100mg Prolonged release capsules, hard should be discontinued if there are signs/symptoms of overgrowth of resistant organisms, e.g. enteritis, glossitis, stomatitis, vaginitis, pruritus ani or Staphylococcal enteritis.

Patients taking oral contraceptives should be warned that if diarrhoea or breakthrough bleeding occur there is a possibility of contraceptive failure.

Minocycline may cause hyperpigmentation at various body sites (see Administration and 4.8 Undesirable Effects). Hyperpigmentation may present regardless of dose or duration of therapy but develops more commonly during long term treatment. Patients should be advised to report any unusual pigmentation without delay and Ranmino MR 100mg Prolonged release capsules, hard should be discontinued.

If a photosensitivity reaction occurs, patients should be warned to avoid direct exposure to natural or artificial light and to discontinue therapy at the first signs of skin discomfort.

As with other tetracyclines, bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported. Presenting features were headache and visual disturbances including blurring of vision, scotoma and diplopia. Permanent vision loss has been reported. Treatment should cease if evidence of raised intracranial pressure develops.

**Use in the elderly:**
Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

MHRA PAR; MINOZRAN MR 100MG PROLONGED RELEASE CAPSULES, HARD, AND RANMINO MR 100MG PROLONGED RELEASE CAPSULES, HARD THR 14894/0425-6
**Use in children:**
The use of tetracyclines during tooth development in children under the age of 12 years may cause permanent discolouration. Enamel hypoplasia has also been reported.

**Laboratory monitoring:**
Periodic laboratory evaluations of organ system function, including haematopoietic, renal and hepatic should be conducted.

Ranmino MR 100mg Prolonged release capsules, hard contain azorubine which may cause allergic reaction

**4.5 Interaction with other medicinal products and other forms of interaction**
Tetracyclines depress plasma prothrombin activity and reduced doses of concomitant anticoagulants may be necessary.

Diuretics may aggravate nephrotoxicity by volume depletion.

Bacteriostatic drugs may interfere with the bactericidal action of penicillin. Avoid giving tetracycline-class drugs in conjunction with penicillin.

Absorption of Ranmino MR 100mg Prolonged release capsules, hard is impaired by the concomitant administration of antacids, iron, calcium, magnesium, aluminium bismuth and zinc salts (interactions with specific salts, antacids, bismuth containing ulcer – healing drugs, quinapril which contains a magnesium carbonate excipient). It is recommended that any indigestion remedies, vitamins, or other supplements containing these salts are taken at least 3 hours before or after a dose of Ranmino MR 100mg Prolonged release capsules, hard. Unlike earlier tetracyclines, absorption of Ranmino MR 100mg Prolonged release capsules, hard is not significantly impaired by food or moderate amounts of milk.

The concomitant use of tetracyclines may reduce the efficacy of oral contraceptives.

Administration of isotretinoin should be avoided shortly before, during and shortly after minocycline therapy. Each drug alone has been associated with pseudotumor cerebri (benign intracranial hypertension) (see 4.4 Special warnings and precautions).

Interference with laboratory and other diagnostic tests:
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

**4.6 Pregnancy and lactation**
**Use in pregnancy:**
Ranmino MR 100mg Prolonged release capsules, hard should not be used in pregnancy unless considered essential.
Results of animal studies indicate that tetracyclines cross the placenta, are found in foetal tissues and can have toxic effects on the developing foetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. Ranmino MR 100mg Prolonged release capsules, hard therefore, should not be used in pregnancy unless considered essential.

In humans, Ranmino MR 100mg Prolonged release capsules, hard, like other tetracycline-class antibiotics, crosses the placenta and may cause foetal harm when administered to a pregnant woman. In addition, there have been post marketing reports of congenital abnormalities including limb reduction. If Ranmino MR 100mg Prolonged release capsules, hard is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the foetus.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long term use of the drugs but has been observed following repeated short term courses. Enamel hypoplasia has also been reported.

Tetracyclines administered during the last trimester form a stable calcium complex throughout the human skeleton. A decrease in fibula growth rate has been observed in premature human infants given oral tetracyclines in doses up to 25mg/kg every 6 hours. Changes in fibula growth rate were shown to be reversible when the drug was discontinued.

**Use in lactation:**
Tetracyclines have been found in the milk of lactating women who are taking a drug in this class. Permanent tooth discolouration may occur in the developing infant and enamel hypoplasia has been reported.

**4.7 Effects on ability to drive and use machines**
Headache, light-headedness, dizziness, tinnitus and vertigo (more common in women) and, rarely, impaired hearing have occurred with Ranmino MR 100mg Prolonged release capsules, hard. Patients should be warned about the possible hazards of driving or operating machinery during treatment. These symptoms may disappear during therapy and usually disappear when the drug is discontinued.

**4.8 Undesirable effects**
Adverse reactions are shown below under the MedDRA system organ classification:

Common: 1%

Uncommon: ≥0.1% and < 1%

Rare: ≥0.01% and < 0.1%

Very Rare: < 0.01%

**Infections and Infestations**
Very Rare: Oral and anogenital candidiasis, vulvovaginitis.

**Blood and Lymphatic System Disorders**
Rare: Eosinophilia, leucopenia, neutropenia, thrombocytopenia.
Very Rare: Haemolytic anaemia, pancytopenia.
There are also reports of: Agranulocytosis

**Immune System Disorders**
Rare: Anaphylaxis /anaphylactoid reaction (including shock), including fatalities.
There are also reports of: Hypersensitivity, pulmonary infiltrates, anaphylactoid purpura.

**Endocrine Disorders**
Very Rare: Abnormal thyroid function, brown-black discolouration of the thyroid.

**Metabolism and Nutrition Disorders**
Rare: Anorexia.

**Nervous System Disorders**
Common: Dizziness (lightheadedness).
Rare: Headache, hypoesthesia, paraesthesia, intracranial hypertension, vertigo.
Very Rare: Bulging fontanelle.
There are also reports of: convulsions, sedation.

**Ear and Labyrinth Disorders**
Rare: Impaired hearing, tinnitus.

**Cardiac Disorders**
Rare: Myocarditis, pericarditis.

**Respiratory, Thoracic and Mediastinal Disorders**
Rare: Cough, dyspnoea.
Very Rare: Bronchospasm, exacerbation of asthma, pulmonary eosinophilia.
There are also reports of: Pneumonitis.

**Gastrointestinal Disorders**
Rare: Diarrhoea, nausea, stomatitis, discolouration of teeth, vomiting.
Very Rare: Dyspepsia, dysphagia, enamel hypoplasia, enterocolitis, oesophagitis, oesophageal ulceration, glossitis, pancreatitis, pseudomembranous colitis.

**Hepatobiliary Disorders**
Rare: Increased liver enzymes, hepatitis, autoimmune hepatotoxicity. (See Section 4.4 Special warnings and precautions for use).
Very Rare: Hepatic cholestatis, hepatic failure (including fatalities), hyperbilirubinaemia, jaundice.
Skin and Subcutaneous Tissue Disorders
Rare: Alopecia, erythema multiforme, erythema nodosum, fixed drug eruption, hyperpigmentation of skin, photosensitivity, pruritis, rash, urticaria, vasculitis.
Very Rare: Angioedema, exfoliative dermatitis, hyperpigmentation of nails, Stevens-Johnson Syndrome, toxic epidermal necrolysis.

Musculoskeletal, Connective Tissue and Bone Disorders
Rare: Arthralgia, lupus-like syndrome, myalgia.
Very Rare: Arthritis, bone discolouration, cases of or exacerbation of systemic lupus erythematosus (SLE) (See Section 4.4 Special warnings and Special precautions for use), joint stiffness, joint swelling.

Renal and Urinary Disorders
Rare: Increased serum urea, acute renal failure, interstitial nephritis.

Reproductive System and Breast Disorders
Very Rare: Balanitis.

General Disorders and Administration Site Conditions
Uncommon: Fever.
Very Rare: Discolouration of secretions.

The following syndromes have been reported. In some cases involving these syndromes, death has been reported. As with other serious adverse reactions, if any of these syndromes are recognised, the drug should be discontinued immediately:

- Hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, pericarditis. Fever and lymphadenopathy may be present.
- Lupus-like syndrome consisting of positive antinuclear antibody, arthralgia, arthritis, joint stiffness or joint swelling, and one or more of the following: fever, myalgia, hepatitis, rash, vasculitis.
- Serum sickness-like syndrome consisting of fever, urticaria or rash, and arthralgia, arthritis, joint stiffness or joint swelling. Eosinophilia may be present.

Hyperpigmentation of various body sites including the skin, nails, teeth, oral mucosa, bones, thyroid, eyes (including sclera and conjunctiva), breast milk, lacrimal secretions and perspiration has been reported. This blue/black.grey or muddy-brown discolouration may be localised or diffuse. The most frequently reported site is in the skin. Pigmentation is often reversible on discontinuation of the drug, although it may take several months or may persist in some cases. The generalised muddy-brown skin pigmentation may persist, particularly in areas exposed to the sun.
4.9 **Overdose**
Dizziness, nausea and vomiting are the adverse effects most commonly seen with overdose. There is no specific antidote. In cases of overdose, discontinue medication, treat symptomatically with gastric lavage and appropriate supportive measures. Minocycline is not removed in significant quantities by haemodialysis or peritoneal dialysis.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
Pharmacotherapeutic group: Antiinfectives for systemic use – tetracyclines; 
**ATC code: J01AA08**

Ranmino MR 100mg Prolonged release capsules, hard contains the active ingredient minocycline as minocycline hydrochloride, a semi-synthetic derivative of tetracycline.

5.2 **Pharmacokinetic properties**
Ranmino MR 100mg Prolonged release capsules, hard have been formulated as a "double pulse" delivery system in which a portion of the minocycline dose is delivered in the stomach, and a second portion of the dose is available for absorption in the duodenum and upper GI tract.

5.3 **Preclinical safety data**
None stated.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

**Minocycline hydrochloride uncoated granules**
Microcrystalline cellulose
Povidone (K-30)

**Immediate release coated granules**
Opadry OY-S-58910 White
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol
Talc

**Prolonged release coated granules**
Hypermellose phthalate
Castor oil
Purified talc
Lubrication
Purified talc

**Capsule Shell**

**Body Composition**
Gelatin
Water
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

**Cap composition**
Gelatin
Water
Azorubine (E122)
Patent blue V (E131)
Quinoline yellow (E104)
Titanium dioxide (E171)

**Printing ink**
Opacode S-1-7305HV (contains Shellac glaze)
Titanium dioxide (E171)
Purified water
Lecithin (soya) (E322)
Simeticone

6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
2 years

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

6.5 **Nature and contents of container**
Blister strips comprises of white opaque PVC film coated uniformly with PVdC on inner side with a backing of aluminium foil coated with heat seal lacquer on inner side.

Available in pack sizes of 50 or 56 capsules.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirement.
7 MARKETING AUTHORISATION HOLDER
Ranbaxy UK Limited
20 Balderton Street,
London
W1K 6TL, UK.

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894 / 0426

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/01/2010

10 DATE OF REVISION OF THE TEXT
20/01/2010
PACkAGE LEAFLET: INFORMATION FOR THE USER

Minozran MR 100mg
Prolonged release capsules, hard

Minocycline hydrochloride

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

In this leaflet:
1. What Minozran is and what it is used for
2. Before you take Minozran
3. How to take Minozran
4. Possible side effects
5. Storing Minozran
6. Further information

1. What Minozran is and what it is used for

Minozran contains minocycline, which is a tetracycline antibiotic, used in the treatment of acne.

Minozran treat the infection and help the spots to heal.

2. Before you take Minozran

Do not take Minozran, if any of the following apply to you unless you have told your doctor or pharmacist:

- if you have had an allergic reaction to any tetracycline antibiotics (e.g. doxycycline, tetracycline, oxytetracycline or minocycline) or any of the other ingredients in the capsule (see section 6 for a list of the ingredients)
- if you are pregnant, planning to become pregnant, or are breast-feeding
- if you have kidney disease
- if the person this has been prescribed to is under the age of 15;

Take special care with Minozran and tell your doctor or pharmacist if:

- you have liver disease
- you have kidney disease
- you suffer from a disease called myasthenia gravis (muscle weakness);

Minozran may affect some medical tests.

If you visit a hospital or medical practice for any medical tests you should tell the doctor that you are taking this medicine.

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:

- anticoagulants (e.g. warfarin, used to thin the blood)
- penicillins, antibiotics (e.g. amoxicillin, isometamid) (or other penicillins or cephalosporins);
- quinapril used in the treatment of heart problems
- ergotamine or methysergide used in the treatment of migraine
- diuretics (water tablets)
- antacids used for indigestion
- ulcer healing medicine containing bismuth
- medicines containing zinc salts, calcium, aluminium or magnesium
- oral contraceptives: minocycline may reduce the effectiveness of the combined oral contraceptive pill. Additional contraceptive precautions should be taken as advised by your doctor;

Taking Minozran with food and drink

Do not drink alcohol during treatment. The absorption of minocycline can be reduced by food, milk or milk products.

Pregnancy and breast-feeding

Do not take Minozran if you are pregnant or plan to become pregnant, as it can affect the development of your unborn baby.

Do not breast-feed if you are taking Minozran as it can pass into breast milk. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive or use machines if you suffer from dizziness, a headache, light-headedness and in rare cases hearing loss, while taking this medicine.

3. How to take Minozran

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

Adults:

The usual dose is one capsule a day. This should be taken at the same time each day.

Elderly

Your doctor will advise if any dosage reduction is needed.

- Do not slack or chew Minozran
- Swallow the capsule whole with a glass of water while sitting or standing.
- Avoid taking at the same time as food, milk or milk products as these can reduce the absorption of Minozran

Patients being treated for certain diseases may need monthly blood tests to check that the infection is clearing up.

If you take more Minozran than you should

Consult your doctor or go to the nearest hospital casualty department immediatedly.

Take this leaflet or some capsules with you so your doctor will know what you have taken.

If you forget to take Minozran

If you miss a dose you should take it as soon as you are able. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for a forgotten dose.

4. Possible Side Effects

Like all medicines, Minozran can cause side effects, although not everybody gets them. Most people do not get side effects with this medicine.

The following effects are very rare, but you should stop taking your medicine and contact your doctor immediately if you go to the casualty department at your nearest hospital if any of them happen to you:

- Severe allergic reaction resulting in wheezing, shortness of breath, rash, swelling and a drop in blood pressure,
- Headache, with blurred or double vision or loss of vision,
- Swelling, stiff or painful joints or muscle
5. Storing Minoxiran
Keep out of the reach and sight of children. Keep in the original packaging until use.

6. Further Information
What Minoxiran contains
The active substance is minocycline (as the hydrochloride salt). Other ingredients of the granules are microcrystalline cellulose, povidone (K-30) and purified talc.

The capsule coating contains hydroxypropylmethyl cellulose (E464), titanium dioxide (E171), macrogol, talc, hydroxypropyl methylcellulose and caser ole.

The capsule shell contains gelatin, water, red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172), azorubine (E122), sodium laurate (E123) and quinoline yellow (E104).

The printing ink contains: shellac glaze, titanium dioxide (E171) and ethylamino ethanol and amylsorbe.

What Minoxiran looks like and contents of the pack
Minoxiran MR prolonged release capsules, hard, have a light brown body with a chocolate brown cap, printed with "R/MC" on the cap and "100" on the body in white ink. The capsules contain a mixture of off-white yellow granules and yellowish grey to brown coloured granules.

The capsules are supplied in packages of 50 and 90 prolonged release capsules, hard in blister packs. Not all pack sizes are marketed.

Marketing Authorisation Holder
Ranbaxy UK Limited
20 Balderton Street
London W1K 6TL
United Kingdom
Tel: 020 8280 1600
Fax: 003492031617

Manufacturer responsible for batch release:
Ranbaxy Lanka Ltd., Splanfield, Cork Road, Cashel, Co.Tipperary, Republic of Ireland and Basics GmbH, Herrnhuter Weg 201, 45159, Leverkusen, Germany

For any information about this medicine, please contact the Marketing Authorisation Holder:
Ranbaxy (UK) Limited, 20 Balderton Street, London W1K 6TL

Version 2 of leaflet 03-May-2008
This leaflet was last approved in 12-2008.

RANBAXY
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, please ask your doctor or your 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.
- ulcers, healing medicine containing bismuth
- medicine containing zinc salts, iron, calcium, aluminium or magnesium
- oral contraceptives: Minocycline may reduce the effectiveness of the combined oral contraceptive pill. Additional contraceptive precautions should be taken as advised by your doctor.

Taking Ranmimo with food and drink
do not drink alcohol during treatment. The absorption of Ranmimo can be reduced by food, milk, or milk products.

Pregnancy and breast feeding:
Do not take Ranmimo if you are pregnant or plan to become pregnant, as it can affect the development of your unborn baby.

Do not breast-feed if you are taking Ranmimo as it can pass into breast milk. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Do not drive or use machines if you suffer from dizziness, a headache, light-headedness and in rare cases hearing loss, while taking this medicine.

1. What Ranmimo are and what they are used for
Ranmimo contain minocycline, which is a tetracycline antibiotic, used in the treatment of acne.
Ranmimo treat the infection and help the spots to heal.

2. Before you take Ranmimo
Do not take Ranmimo, if any of the following apply to you unless you have told your doctor or pharmacist:
- if you have had an allergic reaction to any tetracycline antibiotics in the past (e.g. doxycycline, tetracycline, minocycline) or any of the other ingredients in the capsule; (See section 6 for a list of the ingredients)
- if you are pregnant planning to become pregnant or breast feeding;
- if you have kidney disease;
- if the person this has been prescribed for is under the age of 12;

Take special care with Ranmimo and tell your doctor or pharmacist if:
- you have liver disease
- you have kidney disease
- you suffer from a disease called myasthenia gravis (muscle weakness).
Ranmimo may affect some medical tests, if you visit a hospital or medical practice for any medical tests you should tell the doctor that you are taking this medicine.

3. How to take Ranmimo
Always take Ranmimo exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults:
The usual dose is one capsule a day. This should be taken at the same time each day.

Elders:
Your doctor will advise if any dosage reduction is needed.
- Do not exceed the maximum dose.
- Swallow the capsule whole with a glass of water while sitting or standing.
- Avoid taking at the same time as food, milk or milk products as these can reduce the absorption of Ranmimo.

Patients being treated for certain diseases may need monthly blood tests to check that the infection is clearing up.

If you take more Ranmimo than you should
Consult your doctor or go to the nearest hospital casualty department immediately. Take the leaflet or some capsules with you so your doctor will know what you have taken.

If you forget to take Ranmimo
If you miss a dose you should take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for a forgotten dose.

4. Possible Side Effects
Like all medicines, Ranmimo can cause side effects, although not everybody gets them. Most people do not get side effects with this medicine.

The following effects are very rare, but you should stop taking this medicine and contact your doctor immediately if you:
- get a severe skin reaction (e.g. rash, swelling of the face, lips or tongue, breathing difficulty, change in blood)</td>
nearest hospital if any of them happen to you:

- Severe allergic reaction resulting in wheezing, shortness of breath, rash, swelling and a drop in blood pressure;
- Headache, with blurred or double vision;
- Swelling, stiffness or painful joints or muscle pain; Tender, bruise like swellings of the skin;
- Pain in the abdomen, pale stools or difficulty passing urine;
- Yellowing of the skin or whites of the eyes;
- Sudden unexplained fever or sore throat, extreme tiredness, confusion;
- Unexplained bruising or bleeding;
- Pain in the upper abdomen or back;
- Swelling and redness of the tongue, inside of the mouth, around the eyes;
- Heartburn or difficulty in swallowing, lower abdominal pain or blood and mucus in stools;
- Difficulty breathing or chest pain;
- Inflammation of the blood vessels;
- A worsening or development of symptoms of SLE (systemic lupus erythematosis) or a worsening of the symptoms of myasthenia gravis (muscle weaknesses);
- Numbness, tingling feelings (like pins and needles) in the hands and feet;
- Blistering skin rash or skin peeling off;
- Unusual bleeding or increased tendency to bleed; persistent sore throat; frequent infections; extreme tiredness. These may be due to decrease in the number of certain blood cells. Very rarely all these symptoms may present together.

Other side effects which may occur are:

Common (less than 1 in 10 but more than 1 in 100 patients treated):

- Dizziness (light headedness);

Uncommon (less than 1 in 100 but more than 1 in 10000):

- fever;

Rare (less than 1 in 10000 but more than 1 in 100000):

- blood disorders;
- loss of appetite;
- headache;
- vertigo;
- impaired hearing;
- ringing in the ears;
- cough;
- diarrhoea, nausea, vomiting;
- inflamed mouth or tongue;
- hair loss;
- itchy skin, rash, sensitivity of the skin to sunlight;

Very Rare (less than 1 in 10000 patients):

- Redness, swelling, itching and soreness of gums;
- vaginal thrush (candida infection of the vagina);
- discolouration of teeth;
- dark discoloration of nails;
- poorly developed or disfigured teeth;
- thrush in the mouth;

There are also reports of fits and sensations.

Contact your doctor if you notice any staining of your skin, teeth (including adult teeth), tongue, lips, gums or nails so that your treatment can be reviewed. Slight blue-black/grey colour staining of the skin, teeth, nails, inside of the mouth, eyes, ears, breast milk or sweat has been reported. Staining may appear at any time during treatment.

Staining usually goes away on stopping treatment with Ranmin, although it may take several months or may not go away at all in some cases. The generalised muddy-brown colour of skin may not go away, particularly in areas that are exposed to the sun. Inform your doctor without delay if you notice any staining so that your treatment can be reviewed.

5. Storing Ranmin

Keep out of the reach and sight of children. Keep in the original packaging until use. Do not use Ranmin after the expiry date which is stated on the label after (EXP). The expiry date refers to the last day of the month.

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 Ranmin contains

The active substance is minocycline (as the hydrochloride salt). The other ingredients of the granules are microcrystalline cellulose, povidone (K-30) and purified talc.

The tablet coating contains:

- HPMC (E464), titanium dioxide (E171), macroglide 325 (E401), talc, hypromellose phthalate and carnauba wax.

The capsule shell contains gelatin, water, red iron oxide (E172), titanium dioxide (E171) yellow iron oxide (E172), azo-cremine (E122), patent blue V (E131), quinoline yellow (E104).

The printing ink contains: shellac glaze, titanium dioxide (E171), lecithin, spearmint.

What Ranmin looks like and contents of the pack

Ranmin MR prolonged release capsules, hard have a light brown body with a chocolate brown cap, printed with "RANMINAR" on the cap and "100" on the body in white edible ink. The capsules contain a mixture of off-white yellow granules and yellowish grey to brown coloured granules.

The capsules are supplied in packages of 50 and 56 prolonged release capsules, hard in blister packs.

Not all pack sizes are marketed.

Marketing Authorisation Holder

Ranbaxy UK Limited
20 Balderton Street
London W1K 5TL
United Kingdom
Tel: 0207 260 1600
Fax: 020 7260 1617

Manufacturer responsible for batch release:

Ranbaxy Ireland Ltd., Spallan, Cork Road, Cashel, Co Tipperary, Republic of Ireland, and Basics GmbH, Memminger Straße 201, Gebäude G 2, 93307 Lichtenau, Germany.

For any information about this medicine, please contact the Marketing Authorisation Holder.
Ranbaxy (UK) Limited, 20 Balderton Street, London W1K 5TL.

Version 2 of leaflet 05 May 2008
This leaflet was last approved 12/2006.

MHRA PAR; MINOZRAN MR 100MG PROLONGED RELEASE CAPSULES, HARD, AND RANMINO MR 100MG PROLONGED RELEASE CAPSULES, HARD THR 14894/0425-6
LABELLING

Label:

PRESS CAPSULE THROUGH THE FOIL FROM THE OTHER SIDE.

RANBAXY     RANBAXY
Minozran MR Minozran MR
100 mg      100 mg
Prolonged Release Prolonged Release
Capsules, Hard Capsules, Hard
Minocycline    Minocycline
Hydrochloride   Hydrochloride
Ranbaxy (UK) Limited Ranbaxy (UK) Limited

PRESS CAPSULE THROUGH THE FOIL FROM THE OTHER SIDE.

RANBAXY     RANBAXY
Minozran MR Minozran MR
100 mg      100 mg
Prolonged Release Prolonged Release
Capsules, Hard Capsules, Hard
Minocycline    Minocycline
Hydrochloride   Hydrochloride
Ranbaxy (UK) Limited Ranbaxy (UK) Limited

PRESS CAPSULE THROUGH THE FOIL FROM THE OTHER SIDE.

RANBAXY     RANBAXY
Minozran MR Minozran MR
100 mg      100 mg
Prolonged Release Prolonged Release
Capsules, Hard Capsules, Hard
Minocycline    Minocycline
Hydrochloride   Hydrochloride
Ranbaxy (UK) Limited Ranbaxy (UK) Limited
Carton:

Minozran MR 100mg
Prolonged release capsule, hard

Each capsule contains, as the active ingredient:
Minocycline hydrochloride 100 mg.
Prolonged release capsule.
Also contains azorubine (E122). Please refer to enclosed patient information leaflet for further information.
For oral use only.
Use as directed by a physician.
This medicinal product does not require any special storage conditions.
Store in the original package.
DO NOT EXCEED THE STATED DOSE.

MA Holder:
Ranbaxy (UK) Limited
20 Balderton Street,
London W1K 8TL, UK
PL No. 14894/0425

RANBAXY
Minozran MR 100mg
Prolonged release capsule, hard

Minocycline Hydrochloride

Please read the enclosed leaflet before taking this medicine

MHRA PAR; MINOZRAN MR 100MG PROLONGED RELEASE CAPSULES, HARD, AND RANMINO MR 100MG PROLONGED RELEASE CAPSULES, HARD THR 14894/0425-6
Ranmimo MR 100mg
Prolonged release capsule, hard

Each capsule contains, as the active ingredient:
Minocycline hydrochloride 100 mg

Prolonged release capsule.
Also contains azorubine (E122). Please refer to enclosed patient information leaflet for further information.

For oral use only.
Use as directed by a physician.
This medicinal product does not require any special storage conditions.
Store in the original package.
DO NOT EXCEED THE STATED DOSE.

MA Holder:
Ranbaxy (UK) Limited
20 Balderston Street,
London W1K 6TL, UK
PL No. 14894/0426

RANBAXY
Ranmimo MR 100mg
Prolonged release capsule, hard

CODE No.: MPOCRUG529193

RANBAXY
Ranmimo MR 100mg
Prolonged release capsule, hard

Minocycline Hydrochloride