

Public Assessment Report

Doxycycline 50mg Capsules

PL 13931/0027

DOXYCYCLINE 50MG CAPSULES

PL 13931/0027

UKPAR

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DOXYCYCLINE 50MG CAPSULES

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Channelle Medical a Marketing Authorisation (licence) for the medicinal product Doxycycline 50mg Capsules (PL 13931/0027). This is a prescription only medicine [POM] used to treat various infections, such as: chest, lung and nose infections; urinary tract infections; acne (a skin infection); eye infections; sexually transmitted diseases; fevers associated with louse or tick bites; and malaria (when chloroquine is not effective).

Doxycycline 50mg Capsules contain the active ingredient doxycycline hyclate which interferes with the production of proteins in certain micro-organisms.

The clinical data presented to the MHRA, before licensing, demonstrated that Doxycycline 50mg Capsules is essentially similar or equivalent to the approved product, Vibramycin 50mg Capsules, and as such can be used interchangeably.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Doxycycline 50mg Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

DOXYCYCLINE 50MG CAPSULES

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Doxycycline 50mg Capsules (PL 13931/0027) to Chanelle Medical on 23 March 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Vibramycin 50mg Capsules (PL 00057/0238), granted 18 December 1984.

Doxycycline 50mg Capsules contain the active ingredient doxycycline hyclate. The product is indicated for use in the treatment of a variety of infections including respiratory tract infections, sexually transmitted diseases, skin infections (acne vulgaris), ophthalmic infections, rickettsial infections and chloroquine-resistant falciparum malaria. Doxycycline is also indicated for prophylaxis in scrub typhus, travellers' diarrhoea (enterotoxigenic *Escherichia coli*), leptospirosis and malaria.

Doxycycline is primarily bacteriostatic and is believed to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

Please note that the assessment reports that follow were written in response to Doxycycline 50mg and 100mg Capsules. A marketing authorisation was granted for Doxycycline 100mg Capsules (PL 13931/0028) on 18 October 2004.

PHARMACEUTICAL ASSESSMENT

PL NUMBER: PL 13931/0027-8
PRODUCT: Doxycycline 50mg and 100mg Capsules
ACTIVE: Doxycycline Hyclate
COMPANY: Chanelle Medical Ltd.
LEGAL STATUS: POM

REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

The site of drug product manufacture is supported with a Manufacturer's Licence issued by the Irish Medicines Board.

INTRODUCTION

These generic applications for Doxycycline Capsules claim essential similarity to Vibramycin Capsules, PLs 00057/0238 and 00057/5059R, under Directive 2001/83/EC, as amended. The originator products were licensed in 1984 and 1990, respectively, in the UK thereby fulfilling the 10-year claim of essential similarity.

Doxycycline is a tetracycline with a wide spectrum of activity against Gram-positive and Gram-negative bacteria. The recommended posology is 200mg (single or divided doses) on the first day of treatment, then 100mg per day thereafter. Doxycycline unlike other tetracyclines is not notably influenced by the ingestion of food or milk.

The formulation consists of a dry blend of active substance and excipients encapsulated into gelatin capsules, with differing colour and size for the two different strengths of capsules.

DRUG SUBSTANCE

General information

Doxycycline Hyclate is the subject of a Ph.Eur. monograph and supplied to Chanelle Medical by a suitable drug substance manufacturer.

Nomenclature

Doxycycline Hyclate (rINN).

General properties

Doxycycline hyclate is a yellow powder and exists as the hydrochloride, hemiethanol, hemihydrate salt. It is hygroscopic and freely soluble in water, sparingly soluble in alcohol. It dissolves in solutions of alkali hydroxides and carbonates.

Manufacturers

A suitable site of production of the drug substance is named.

Control of Drug Substance

Specification

The drug substance is controlled to the specifications of the Ph.Eur.

Analytical procedures/Validation of analytical procedures

There have been no details provided for the analytical testing of the active substance. This is accepted as European Pharmacopoeial methods are used for controlling the active substance.

Batch analyses

The applicant states that drug substance received from the supplier will be subject to routine in-house confirmatory tests.

Justification of specification

The drug substance specification complies with the Ph.Eur. specification which requires no further justification.

Reference standards or materials

Satisfactory reference standards are identified.

Container closure system

The active raw material is packaged into double polyethylene bags and then packed into cardboard drums.

Stability summary and conclusions

Long term stability studies (25°C/60% RH) up to 48 months have been provided for the drug substance. Overall, there were no obvious trends in the stability studies, with respect to decrease in assay, increase in related substances, change in acidity or increase in water content. The data demonstrate that the drug substance is stable. However, as the containers used for these studies were not sufficiently representative of that used in routine storage and transport of the drug substance, the results were not considered supportive of the proposed re-test period.

Accelerated stability studies have been provided for batches of the drug substance packaged in the proposed commercial packaging. The results indicate that the drug substance is stable in the packaging used. In the absence of long term stability data in the proposed commercial packaging, the applicant has committed to testing the drug substance for compliance with the Ph.Eur. monograph immediately prior to manufacture of the finished product.

Post-approval stability protocol and stability commitment

An acceptable post-approval stability protocol was presented according to ICH guidelines.

DRUG PRODUCT

Description and composition of the drug product

Table 1: Composition of Chanelle Doxycycline Capsules 50mg and 100mg

Name of substance	Reference monograph
Doxycycline (as Doxycycline Hyclate)	Ph.Eur.
Microcrystalline cellulose (Avicel PH 101)	Ph.Eur.
Purified talc	Ph.Eur.
Sodium lauryl sulphate	Ph.Eur.
Colloidal silicon dioxide	Ph.Eur.
Magnesium stearate	Ph.Eur.
<u>Hard Gelatin Capsules</u>	
Titanium dioxide (E171)	Ph.Eur.
Water (Targeted moisture)	Ph.Eur.
Gelatin	Ph.Eur.

The active ingredient is doxycycline (as doxycycline hyclate) 50mg and 100mg.

In addition to the list in Table 1, the 50mg capsules also contain Quinoline Yellow Fr.Pharm. and Sunset Yellow Fr.Pharm. in the gelatin capsule.

In addition to the list in Table 1, the 100mg capsules also contain Indigo Carmine (E132) Swiss Pharm. and Erythrosine (E127) Fr.Pharm. in the gelatin capsule.

The quantities of excipients are representative of their function and are non-unique for capsule production. Apart from the composition of the gelatin capsule, the 50mg and 100mg formulations are identical with respect to their qualitative composition.

The clinical trial formula has been stated to be identical to that proposed for marketing. A Certificate of Analysis of the clinical trial supplies used in the bioequivalence study has been provided. The applicant has confirmed that the formulation of the product used in the bioequivalence study is the same as the final formula.

Drug substance

Doxycycline exists as a hemiethanol, hemihydrate, hydrochloride salt. It is a yellow, crystalline powder, no known polymorphs are stated in the literature. Being freely soluble in water (1 in 3), its particle size is not deemed critical to dissolution, however, doxycycline hyclate is hygroscopic, therefore adequate protection from moisture is required.

Excipients

The applicant states that the choice of excipients for the dosage form was based on the brand leader ‘Vibramycin™’, although only two (magnesium stearate and sodium lauryl sulphate)

of the excipients are qualitatively identical to the brand leader. Considering the non-unique capsule formulation, the choice of the common capsule excipients is deemed acceptable.

Formulation development

The rationale for the formulation is based on matching the performance release characteristics of this generic drug product to the brand leader. The amounts of excipients used have not been discussed or rationalised. However, considering the drug product is bioequivalent to the brand leader and adequate stability of the drug product has been demonstrated, this is accepted.

Overages

There are no declared overages in the formulation.

Physicochemical and biological properties

Adequate dissolution profiles have been provided demonstrating a very fast release of the active substance, comparable to the brand leader and demonstrates that with respect to release profiles, the generic drug product fulfils the claim of essential similarity.

Manufacturing process development

The manufacturing process is described. A flow diagram of the manufacturing process has been provided.

Container closure system

The capsules are blister packed into white PVC/PVdC and aluminium foil. Strips are packed into cartons with PIL.

Microbiological attributes

The formulation does not support microbial growth as demonstrated by the inability to recover test organisms.

Compatibility

Compatibility studies between the active substance and the excipients have not been performed. However, this absence is acceptable as stability data have been provided.

Manufacturer(s)

A suitable site of product manufacture has been named.

Batch formula

The batch formulae have been presented. The quantity of doxycycline hyclate is calculated based on the actual potency of the input raw material.

Description of manufacturing process and process controls

The manufacturing process has been described. The two strengths of Doxycycline Capsules are manufactured from the same qualitative and quantitative blend, with the only differences being the size and colour of the capsules.

In Process controls

In –process controls are presented and suitable limits have been supplied for the tests. Details have been provided on the frequency of testing and the theoretical yield of the batch has been calculated.

Control of critical steps and intermediates

Critical step(s) have been identified.

Process validation and/or Evaluation

Validation data have been provided for three separate pre-encapsulation blends. Each blend was used to manufacture the two different capsule strengths.

Pre-encapsulation blend homogeneity was satisfactory. Granules were demonstrated to have good flow characteristics supporting the good uniformity of content observed with the capsules. Satisfactory validation data have been provided. Confirmation has been provided that scale-up to full production size batches will use the same type of equipment and manufacturing conditions used in the manufacture of the validation batches.

Control of excipients

The excipients used in the pre-encapsulation blend are of Ph.Eur. Quality. The constituents of the capsule are controlled to the Ph.Eur., French Pharmacopoeia and Swiss Pharmacopoeia. The colourants are stated to comply with the Directive 78/25/EEC.

The applicant tests the excipients to a minimum of an identity test.

Specifications

Ph.Eur. or national pharmacopoeias, accepted.

Analytical procedures

Ph.Eur. or national pharmacopoeias, accepted.

Validation of analytical procedures

Ph.Eur. or national pharmacopoeias, accepted.

Excipients of human or animal origin

Gelatin. Certificates of Suitability have been provided from the suppliers.

Control of Drug Product

Specification(s)

Acceptable finished product specifications have been provided.

Analytical procedures

Satisfactory analytical procedures are described.

Validation of analytical procedures

Adequate analytical validation data have been provided for the assay and related substance method.

Batch analyses

The applicant has used the same granule blend to manufacture the different strengths of capsule. Considering the capsules differ in fill weight this is accepted. Three batches of each strength of capsule have been manufactured at the site of product manufacture. Compliance with the finished product specifications has been demonstrated.

Characterisation of impurities

Ph.Eur. Impurities.

Reference standards or materials

EPCRS

Container closure system

PVC/PVdc aluminium blisters.

Stability summary and conclusion

Data (up to 36 months at 25°C/60% RH and 6 months 40°C/75% RH) have been provided for batches manufactured at the site of product manufacture stored at real and accelerated stability conditions. The data were considered to support a shelf life of 24 months.

Post-approval stability protocol and stability commitment

An acceptable post-approval stability protocol has been provided.

ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

Satisfactory.

OTHER INFORMATION

Bioanalytical methods

The applicant has developed a suitable method for detection and quantification of doxycycline in plasma samples. Adequate validation data has been provided.

Bioavailability, bioequivalence

Data from the bioequivalence study comparing Chanelle's Doxycycline Capsules 100mg and Vibramycin 100mg Capsules have been provided. The study was 2-way, cross over study with 26 volunteers and 13 day wash-out. The reference product was the Irish Vibramycin. Bioequivalence was demonstrated within CPMP guidelines.

The applicant has also conducted a comparative, randomised, two period, two treatment, two sequence, single dose, cross-over bioequivalence study to compare plasma concentration profiles following administration of the proposed product and Vibramycin 50mg capsules (Pfizer Limited UK). Dissolution profiles for the test and reference products are similar. A Certificate of Analysis demonstrates that the test product complies with the requirements of the finished product specification.

Results

The results of the bioequivalence study for the 50mg capsules are summarised below.

Parameter	Point Estimate % (μ_T/μ_R)	Lower limit	Upper limit
Ln C _{max}	95.38	88.95	102.27
Ln AUC _{0→last}	99.38	91.78	107.61
Ln AUC _{0→inf}	101.17	93.46	109.52

90% confidence intervals for C_{max} and AUC ratios complied with acceptance criteria specified in current guidelines (80 to 125%). The products can therefore be considered as bioequivalent.

Essential similarity

Comparative dissolution profiles have been provided comparing the generic biobatch, pilot scale and UK Vibramycin. A fast dissolution is apparent for all capsules. Comparable impurity profiles have been provided for the UK Vibramycin and generic Doxycycline Capsules. Evidence of bioequivalence to the UK innovator product has been included (see above).

Comment on expert report

The pharmaceutical expert, a pharmacist with regulatory experience, has written a supportive expert report for the applications.

CONCLUSION

These immediate release generic capsules have demonstrated essential similarity to the innovator Vibramycin with respect to release and impurity profiles. Marketing authorisations may be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required.

CLINICAL ASSESSMENT

LICENCE NO: PL 13931/0027-8
PROPRIETARY NAME: Doxycycline Capsules 50mg & 100mg
ACTIVE(S): Doxycycline hyclate
COMPANY NAME: Chanelle Medical Ltd
EC ARTICLE: 10.1(a)(iii)
LEGAL STATUS: POM

INTRODUCTION

These are national standard abridged applications for marketing authorisations for Doxycycline 50 mg and 100mg capsules from Chanelle Medical. The applications claim essential similarity to the brand leader product Vibramycin 50mg capsules held by Pfizer Ltd and first licensed on 18 December 1984. This is an application made in accordance with Directive 2001/83/EC Article 10.1(a)(iii).

BACKGROUND

Doxycycline is a member of the tetracycline series of antibiotics.

INDICATIONS

Infections caused by susceptible strains of Gram positive and Gram negative bacteria and certain other micro-organisms. This includes various organisms responsible for pneumonia and other lower respiratory tract infections, urinary tract infections, sexually transmitted infections, ophthalmic infections, skin infections, rickettsial infections and an exhaustive list of conditions outlined in the Section 4.1 (Indications) of the SPC.

POSOLOGY AND METHOD OF ADMINISTRATION

Adults:

200mg initial dose for the first day (as single or divided doses) followed by a 100mg/day maintenance dose.

In severe infections, 200 mg should be given throughout.

Doxycycline capsules should be taken with adequate amounts of fluid on the sitting or standing position and well before retiring at night to reduce the risk of oesophageal irritation and ulceration. If gastric irritation occurs it is recommended that doxycycline be taken with food or milk.

Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided.

When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

TOXICOLOGY

The toxicology of doxycycline is well established and no new data are required for these applications.

CLINICAL PHARMACOLOGY

Pharmacokinetics.

Bioequivalence studies comparing doxycycline and Vibramycin were conducted.

Bioequivalence study 0101021825

A single dose cross-over study in 26 healthy males was conducted to compare the bioavailability of Doxycycline 100mg Capsules and Vibramycin 100mg capsules. Both test and reference product doses were 200mg doxycycline (2x100mg doxycycline capsules) administered under fasting conditions.

Results

The pharmaceutical parameters measured for bio-equivalence for both the test and reference products were within the requirements for bio-equivalence, i.e., for AUC_{0-inf} , the primary variable, the 90% confidence interval was 95.01 -105.71 and for C_{max} the 90% confidence interval was 98.16-112.14.T

Table 1: Pharmacokinetic Variables for Doxycycline (Study No 0101021825)

Pharmacokinetic variable		Treatment	
		Doxycycline Capsules (Test Product) (n=26)	Vibramycin Capsules (n=26)
AUC_{0-t} (mcg/h/mL)	Mean	46.338	46.699
	Range	24.098 – 74.365	31.348 – 84.607
AUC_{0-inf} (mcg/mL)	Mean	51.519	51.409
	Range	27.963 – 82.082	34.557 – 89.269
C_{max} (mcg/mL)	Mean	2.732	2.604
	Range	1.798 – 4.455	1.986 – 4.120
T_{max} (h)	Mean	2.56	2.40
	Range	1.50 – 5.00	1.0 – 5.00
Half-life (h)	Mean	17.97	17.58
	Range	13.01 – 28.28	9.76 – 23.83

Study conclusion

The 100mg capsule of the applicant formulation and the reference Vibramycin 100mg capsule are bioequivalent.

Bioequivalence study DOXY062C

This is a comparative, randomized, two-period, two-treatment, two-sequence, single dose, crossover bioequivalence study of Doxycycline 50 mg Capsules (one capsule) (Chanelle Medical - Ireland) versus Vibramycin 50 mg Capsules (one capsule) (Pfizer Ltd., UK) in healthy participants under fasting conditions.

The applicant states that the study has been performed in compliance with Good Clinical Practice (GCP).

26 healthy-male participants ages between 18 and 45 years, (body-mass index 19 to 30 kg/m² inclusive, non-smokers or moderate smokers (smokers of not more than 10 cigarettes per day), were recruited.

The study consisted of two treatment periods each lasting 96.0 hours. The two periods were separated by a washout period of 180 hours.

In each treatment period, a single dose of doxycycline 50 mg was administered orally with 240ml of water.

Results

The 26 participants completed the study and were analyzed with regards to safety in period I & II. 26 participants were evaluated for pharmacokinetic data.

Pharmacokinetic parameters

Bioequivalence assessment for $AUC_{0\rightarrow inf}$ and $AUC_{0\rightarrow last}$

The statistical procedures employed in this study were standard methods routinely used in bioavailability and bioequivalence studies, these can be summarized as follows:
Bioequivalence assessment based on the balanced design with 26 subjects.

The evaluation of extent parameters $AUC_{0\rightarrow inf}$ and $AUC_{0\rightarrow last}$ are presented in Table 2. The evaluation was based on multiplicative model using parametric procedures. The results are very similar for both parameters. The results for the ln transformed $AUC_{0\rightarrow inf}$ and $AUC_{0\rightarrow last}$ are described below:

Table 2: The Doxycycline pharmacokinetic parameters of the study products evaluated in 26 participants.

Pharmacokinetic Results Summary	Parameters (Unit)	Test DOXYCYCLINE®		Reference VIBRAMYCIN™	
As Geometric Means (ranges) for C _{max} and AUC	C _{max} (µg/mL)	0.843		0.884	
		0.526	1.581	0.463	1.776
	AUC _{0→last} (µg.h/mL)	12.242		12.318	
		7.638	20.387	5.450	21.515
	AUC _{0→inf} (µg.h/mL)	14.871		14.699	
		10.074	24.445	6.756	25.476
As medians (ranges) for t _{max} , and t _{1/2}	t _{max} (h)	2.00		1.88	
		0.50	3.50	1.00	5.00
	t _{1/2} (h)	20.27		18.96	
		10.54	41.51	9.84	35.66
Bioequivalence Results Summary	Parameter	Point Estimate % (µ _T /µ _R)		Lower limit	Upper limit
	Ln C _{max}	95.38		88.95	102.27
	Ln AUC _{0→last}	99.38		91.78	107.61
	Ln AUC _{0→inf}	101.17		93.46	109.52

The results pertaining to AUC_{0→inf}, gave a (1-2α) 100 % confidence interval for (µ_T/µ_R) that fell between **93.46** and **109.52** the |T| statistics with the corresponding P values calculated for TOST was 5.06828 (0.00002) and 4.56368 (0.00006) were both greater than t (0.05, 24) = 1.71088. Consequently, the null hypotheses H₀₁ and H₀₂ were simultaneously rejected at the 5% level of significance.

The results pertaining to AUC_{0→last}, gave a (1-2α) 100 % confidence interval for (µ_T/µ_R) that fell between **91.78** and **107.61**. The |T| statistics with the corresponding P values calculated for TOST was 4.66280 (0.00005) and 4.93064 (0.00002) were both greater than t (0.05, 24) = 1.71088. Consequently, the null hypotheses H₀₁ and H₀₂ were simultaneously rejected at the 5% level of significance.

From Doxycycline data, with regards to the ln AUC_{0→inf}, bioequivalence was concluded according to 0.80 to 1.25 acceptance criterion.

Bioequivalence Assessment for C_{max}

The results pertaining to C_{max}, gave a (1-2α) 100 % confidence interval for (µ_T/µ_R) that fell between **88.95** and **102.27**. The |T| statistics with the corresponding P values calculated for TOST was 5.85508 (0.00000) and 5.08762 (0.00000) were both greater than t (0.05, 24) = 1.71088. Consequently, the null hypotheses H₀₁ and H₀₂ were simultaneously rejected at the 5% level of significance.

From Doxycycline data, with regards to the ln C_{max} bioequivalence was concluded according to 0.80 to 1.25 acceptance criterion.

Assessment for T_{max}

The statistical evaluation of the secondary rate parameter t_{max} is given. The evaluation was performed using additive model with non-parametric procedure. The point estimate (median ratio) = **106.40%**. The lower and upper limits of confidence interval were **88.20 %** and **127.90 %**, respectively. The point estimate indicates significant difference in time to reach maximum concentration between the both products.

Adverse events (AEs)

All participants are included in the safety analysis with regards to the laboratory examination.

The tolerance of the products studied was good. However, one case of fainting attack for few seconds was observed at study period II and was considered an adverse drug reaction.

No adverse events neither serious adverse events were observed during the follow up examination for all participants.

No serious adverse event, or unexpected adverse drug reaction occurred during the study.

Bioequivalence study DOXY062C conclusions

The study proved the bioequivalence of both products with regard to the amount of the drug present in the plasma as described by $AUC_{0 \rightarrow \infty}$ parameter and with regard to bioequivalence rate given by C_{max} .

Medical Assessor's comments On Bioequivalence study DOXY062C

This assessor concurs with the study conclusions that the results demonstrate that the applicant Doxycycline 50mg capsules is bioequivalent to the reference innovator product Vibramycin 50mg Capsules.

Discussion and overall conclusions on bioequivalence of Doxycycline 50mg capsules

The aim of the study was to assess the bioequivalence of two Doxycycline formulations in healthy participants after a single oral dose of one capsule containing 50 mg of Doxycycline. The test product Doxycycline 50 mg Capsules of Chanelle Medical, Ireland was compared with the reference product Vibramycin 50 mg Capsules of Pfizer Ltd., UK.

The statistical evaluation of the primary extent bioequivalence parameter $AUC_{0 \rightarrow \infty}$ indicated its 90% confidence intervals within the bioequivalence range (80 to 125%). For the primary rate bioequivalence parameter C_{max} both lower and upper limits of 90% confidence interval were found within the bioequivalence range, too. Thus, the two investigated products were considered bioequivalent and therefore essentially similar.

The tolerance of both products was good. One case of fainting attack for few seconds was observed at study period II, and was considered an adverse drug reaction. However, no serious adverse events or unexpected adverse drug reactions have occurred in this study.

EFFICACY

The efficacy of doxycycline is well established and no new data are required for these applications.

SAFETY

The safety of doxycycline is well established and no new data are required for these applications.

EXPERT REPORTS

A Clinical Expert Report has been provided. The expert reviews the toxicology, pharmacology and therapeutics of doxycycline and concludes that doxycycline 100mg is bio-equivalent to Vibramycin 100mg and is suitable for the proposed indications. The proposed SmPC is justified on the basis of the findings of the bio-equivalence study and the findings in the literature.

SUMMARY OF PRODUCTS CHARACTERISTICS

Satisfactory.

PATIENT INFORMATION LEAFLET

Satisfactory.

LABELLING

Satisfactory.

MARKETING AUTHORISATION FORM

This is satisfactory.

CONCLUSIONS

These products can be concluded to be essentially similar.

Recommendation

Product licences should be granted.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Doxycycline 50mg 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 Doxycycline 50mg Capsules and Vibramycin 50mg Capsules (PL 00057/0238).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for Vibramycin 50mg Capsules.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with doxycycline is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

DOXYCYCLINE 50MG CAPSULES

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application for Doxycycline 50mg Capsules on 30 August 2002.
2	Following standard checks the MHRA informed the applicant that its application was considered valid on 9 October 2002.
3	The MHRA's assessment of the submitted clinical and quality data was completed on 6 December 2002.
4	Further information was requested from the company on 20 January 2003.
5	The applicant's response to further information request was received on 18 June 2003.
6	Further information was requested from the company on 25 September 2003 (quality) and 21/22 October 2003 (clinical).
7	The applicant's response to further information requests was received on 19 February 2004.
8	Further information was requested from the company on 23 March 2004 (clinical) and 28 April 2004 (quality).
9	Further information was received from the company on 7 May 2004 (clinical) and 3 June 2004 (quality).
10	Further information was requested from the company on 13 August 2004 (quality).
11	The applicant's response to further information request was received on 7 September 2004.
12	The applicant's response to outstanding information request (clinical) was received on 11 July 2005.
13	Further information was requested from the company on 12 December 2005 (quality).
14	The applicant's response to further information request (quality) was received on 19 January 2006.
15	Further information was requested from the company on 31 January 2006 (quality).
16	A telephone discussion of the application between the MHRA and applicant resolved the request of 31 January 2006. Further information was also requested on 3 February 2006 (quality).
17	The applicant responded to further information request (quality) on 14 February 2006.
18	Further clarification was sought from the company on 23 February 2006 (quality).
19	The applicant's response to the clarification was assessed on 17 March 2006.
20	The MHRA completed its assessment of the application on 21 March 2006.
21	The application was determined on 23 March 2006.

DOXYCYCLINE 50MG CAPSULES

PL 13931/0027

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxycycline 50 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg doxycycline (as doxycycline Hyclate).
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Hard gelatin capsules.
Size 3 capsules with white body and an opaque yellow cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxycycline has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

Respiratory tract infections:

Pneumonia and other lower respiratory tract infections due to susceptible strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and other organisms. *Mycoplasma pneumoniae* pneumonia. Treatment of chronic bronchitis, sinusitis.

Urinary tract infections caused by susceptible strains of *Klebsiella* species, *Enterobacter species*, *Escherichia coli*, *Streptococcus faecalis* and other organisms.

Sexually transmitted diseases:

Infections due to *Chlamydia trachomatis* including uncomplicated urethral, endocervical or rectal infections. Non-gonococcal urethritis caused by *Ureaplasma urealyticum* (T-mycoplasma). Doxycycline is also indicated in chancroid, granuloma inguinale and lymphogranuloma venereum. Doxycycline is an alternative drug in the treatment of gonorrhoea and syphilis.

Skin infections:

Acne vulgaris, when antibiotic therapy is considered necessary.

Since Doxycycline is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines, such as:

Ophthalmic infections: Due to susceptible strains of gonococci, staphylococci and *Haemophilus influenzae*. Trachoma, although the infectious agent, as judged by immunofluorescence, is not always eliminated. Inclusion conjunctivitis may be treated with oral Doxycycline alone or in combination with topical agents.

Rickettsial infections: Rocky Mountain spotted fever, typhus group, Q fever, Coxiella endocarditis and tick fevers.

Other infections: Psittacosis, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse and tick-borne relapsing fever, tularaemia glanders, melioidosis, chloroquine-resistant falciparum malaria and acute intestinal amoebiasis (as an adjunct to amoebicides).

Doxycycline is an alternative drug in the treatment of leptospirosis, gas gangrene and tetanus.

Doxycycline is indicated for prophylaxis in the following conditions: Scrub typhus, travellers' diarrhoea (enterotoxigenic *Escherichia coli*), leptospirosis and malaria. Prophylaxis of malaria should be used in accordance to current guidelines, as resistance is an ever changing problem.

4.2 Posology and method of administration

Route of Administration:

Oral

Adults:

The usual dosage of Doxycycline for the treatment of acute infections in adults is 200 mg on the first day (as a single dose or in divided doses) followed by a maintenance dose of 100 mg/day. In the management of more severe infections, 200 mg daily should be given throughout treatment.

Doxycycline capsules should be administered with adequate amounts of fluid. This should be done in the sitting or standing position and well before retiring at night to reduce the risk of oesophageal irritation and ulceration. If gastric irritation occurs, it is recommended that Doxycycline be given with food or milk. Studies indicate that the absorption of Doxycycline is not notably influenced by simultaneous ingestion of food or milk.

Exceeding the recommended dosage may result in an increased incidence of side effects. Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided.

When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Dosage recommendations in specific infections:

Acne vulgaris:

50 mg daily with food or fluid for 6 to 12 weeks.

Sexually transmitted diseases:

100 mg twice daily for 7 days is recommended in the following infections: uncomplicated gonococcal infections (except anorectal infections in men); uncomplicated urethral, endocervical or rectal infection caused by *Chlamydia trachomatis*; non-gonococcal urethritis caused by *Ureaplasma urealyticum*. Acute epididymo-orchitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoea* 100 mg twice daily for 10 days. Primary and secondary syphilis: Non-pregnant penicillin allergic patients who have primary or secondary syphilis can be treated with the following regime: doxycycline 200mg orally twice daily for two weeks as an alternative to penicillin.

Louse and tick-borne relapsing fevers:

A single dose of 100 or 200 mg according to severity.

Chloroquine-resistant falciparum malaria:

200 mg daily for at least 7 days. Due to the potential severity of the infection, a rapid-acting schizonticide such as quinine should always be given in conjunction with Doxycycline; quinine dosage recommendations vary in different areas.

Prophylaxis of malaria

100mg daily in adults and children over the age of 12 years. Prophylaxis can begin 1-2 days before travel to malarial areas. It should be continued daily during travel in the malarial areas and for 4 weeks after the traveller leaves the malarial area. For current advice on geographical resistance patterns and appropriate chemoprophylaxis, current guidelines or the Malaria Reference Laboratory should be consulted, details of which can be found in the British National Formulary (BNF).

For the prevention of scrub typhus:

200 mg as a single dose.

For the prevention of travellers' diarrhoea in adults:

200 mg on the first day of travel (administered as a single dose or as 100 mg every 12 hours) followed by 100 mg daily throughout the stay in the area. Data on the use of the drug prophylactically are not available beyond 21 days.

For the prevention of leptospirosis:

200 mg once each week throughout the stay in the area and 200 mg at the completion of the trip. Data on the use of the drug prophylactically are not available beyond 21 days.

Use for children:

See under 'contraindications'

Use in the elderly:

Doxycycline may be prescribed in the elderly in the usual dosages with no special precautions. No dosage adjustment is necessary in the presence of renal impairment.

Use in patients with impaired hepatic function:

See under "Special warnings and precautions for use".

Use in patients with renal impairment:

Studies to date have indicated that administration of Doxycycline at the usual recommended doses does not lead to accumulation of the antibiotic in patients with renal impairment, see under "Special warnings and precautions for use".

4.3 Contraindications

Persons who have hypersensitivity to doxycycline, any of its inert ingredients or to any of the tetracyclines. The use of drugs of the tetracycline class during tooth development (pregnancy, infancy and childhood to the age of 12 years) 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. Doxycycline is therefore contraindicated in these groups of patients.

Pregnancy:

Doxycycline is contraindicated in pregnancy. It appears that the risks associated with the use of tetracyclines during pregnancy are predominantly due to effects on teeth and skeletal development. (See above about use during tooth development).

Nursing mothers: Tetracyclines are excreted into milk and are therefore contraindicated in nursing mothers. (See above about use during tooth development).

Children:

Doxycycline is contraindicated in children under the age of 12 years. As with other tetracyclines, Doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracyclines in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. (See above about use during tooth development).

4.4 Special warnings and precautions for use

Use in patients with impaired hepatic function: Doxycycline should be administered with caution to patients with hepatic impairment or those receiving potentially hepatotoxic drugs.

Abnormal hepatic function has been reported rarely and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline.

Use in patients with renal impairment: Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal renal function. This percentage excretion may fall to a range as low as 1 - 5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 ml/min). Studies have shown no significant difference in the serum half-life of doxycycline in individuals with normal and severely impaired renal function. Haemodialysis does not alter the serum half-life of doxycycline. The anti-anabolic action of the tetracyclines may cause an increase in blood urea. Studies to date indicate that this does not occur with the use of Doxycycline in patients with impaired renal function.

Photosensitivity: Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients likely to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs and treatment should be discontinued at the first evidence of skin erythema.

Microbiological overgrowth: The use of antibiotics may occasionally result in the overgrowth of non-susceptible organisms including *Candida*. If a resistant organism appears, the antibiotic should be discontinued and appropriate therapy instituted.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and has ranged in severity from mild to life-threatening. It is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Oesophagitis: Instances of oesophagitis and oesophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class, including doxycycline. Most of these patients took medications immediately before going to bed or with inadequate amounts of fluid.

Bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.

Porphyria: There have been rare reports of porphyria in patients receiving tetracyclines.

Venereal disease: When treating venereal disease, where co-existent syphilis is suspected, proper diagnostic procedures including dark-field examinations should be utilised. In all such cases monthly serological tests should be made for at least four months.

Beta-haemolytic streptococci Infections: Infections due to group A beta-haemolytic streptococci should be treated for at least 10 days.

Myasthenia gravis: Due to a potential for weak neuromuscular blockade, care should be taken in administering tetracyclines to patients with myasthenia gravis.

Systemic lupus erythematosus: Tetracyclines can cause exacerbation of SLE.

Methoxyflurane: Caution is advised in administering tetracyclines with methoxyflurane. See section 4.5.

Doxycycline 50 mg Capsules contain the colouring sunset yellow, E110. E110 can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

4.5 Interaction with other medicinal products and other forms of interaction

The absorption of doxycycline may be impaired by concurrently administered antacids containing aluminium, calcium or magnesium or other drugs containing these cations; oral zinc, iron salts or bismuth preparations. Dosages should be maximally separated.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving Doxycycline in conjunction with penicillin.

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Tetracyclines depress plasma prothrombin activity and reduced doses of concomitant anticoagulants may be necessary.

The serum half-life of doxycycline may be shortened when patients are concurrently receiving barbiturates, carbamazepine or phenytoin. An increase in the daily dosage of Doxycycline should be considered.

Alcohol may decrease the half-life of doxycycline.

A few cases of pregnancy or breakthrough bleeding have been attributed to the concurrent use of tetracycline antibiotics with oral contraceptives.

Doxycycline may increase the plasma concentration of ciclosporin. Co-administration should only be undertaken with appropriate monitoring.

The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity. Section 4.4.

Laboratory test interactions: False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

4.6 Pregnancy and lactation

See 'Contraindications'

4.7 Effects on ability to drive and use machines

The effect on the ability to drive and operate machinery has not been studied.

4.8 Undesirable effects

The following adverse reactions have been observed in patients receiving tetracyclines, including doxycycline:

Autonomic nervous system: Flushing.

Body as a whole or hypersensitivity reactions, including anaphylactic shock, anaphylaxis, anaphylactoid reaction, anaphylactoid purpura, hypotension, pericarditis, angioneurotic oedema, exacerbation of systemic lupus erythematosus, dyspnoea, serum sickness, peripheral oedema, tachycardia and urticaria.

Central and Peripheral nervous system: Headache. Bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported in individuals receiving full therapeutic dosages of tetracyclines. In relation to benign intracranial hypertension, symptoms included blurring of vision, scotoma and diplopia. Permanent visual loss has been reported.

Gastro-intestinal: Gastro-intestinal symptoms are usually mild and seldom necessitate discontinuation of treatment. Abdominal pain, anorexia, nausea, vomiting, diarrhoea, dyspepsia and rarely dysphagia. Oesophagitis and oesophageal ulceration have been reported in patients receiving doxycycline. A significant proportion of these occurred with the hyclate salt in the capsule form. (See 'Special warnings and precautions for use' section).

Hearing/Vestibular: Tinnitus.

Blood: Porphyria

Haemopoietic: Haemolytic anaemia, thrombocytopenia, neutropenia, porphyria, and eosinophilia have been reported with tetracyclines.

Liver/Biliary: Transient increases in liver function tests, hepatitis, jaundice, hepatic failure and pancreatitis have been reported rarely.

Musculo-Skeletal: Arthralgia and myalgia.

Skin: Rashes including maculopapular and erythematous rashes, exfoliative dermatitis, erythema multiforme, Steven-Johnson syndrome and toxic epidermal necrolysis. Photosensitivity skin reactions (see 'Special warnings and precautions for use' section).

Superinfection - there have been reports for products in the tetracycline class of stomatitis and vaginitis. As with all antibiotics, overgrowth of non-susceptible organisms may cause candidiasis, glossitis, staphylococcal enterocolitis, pseudomembranous colitis (with *Clostridium difficile* overgrowth) and inflammatory lesions (with candidal overgrowth) in the anogenital region. Similarly there have been reports for products in the tetracycline class of stomatitis and vaginitis.

Urinary system - increased blood urea. (See 'Special warnings and precautions for use' section 4.4)

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discolouration of thyroid tissue. No abnormalities of thyroid function are known to occur.

Tetracyclines may cause discoloration of teeth and enamel hypoplasia, but usually only after long-term use.

4.9 Overdose

Acute overdosage with antibiotics is rare. In the event of overdosage discontinue medication. Gastric lavage plus appropriate supportive treatment is indicated.

Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxycycline is primarily bacteriostatic and is believed to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

5.2 Pharmacokinetic properties

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They are concentrated by the liver in the bile and excreted in the urine and faeces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration. Studies reported to date indicate that the absorption of doxycycline, unlike certain other tetracyclines, is not notably influenced by the ingestion of food or milk. Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 micrograms/ml of doxycycline at 2 hours decreasing to 1.45 micrograms/ml at 24 hours. Doxycycline has a high degree of lipid solubility and a low affinity for calcium. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Doxycycline 50 mg Capsules:

Microcrystalline Cellulose

Purified Talc

Magnesium Stearate

Colloidal Silicon Dioxide

Sodium Lauryl Sulphate

Titanium Dioxide (E171)
Quinoline Yellow (E104)
Sunset Yellow (E110)
Gelatin

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Doxycycline 50 mg Capsules are packed into blister strips of white PVC/PVdC sealed with aluminium lidding foil. The blisters are then packed into a carton.
Pack sizes; 8, 16, 28. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Chanelle Medical
Loughrea
Co. Galway
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 13931/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/03/2006

10 DATE OF REVISION OF THE TEXT

23/03/2006

Patient Information Leaflet

DOXYCYCLINE 50MG CAPSULES

PL 13931/0027



DOXYCYCLINE 50 MG CAPSULES PATIENT INFORMATION LEAFLET

Please read this leaflet. This leaflet tells you about Doxycycline Capsules. Please read it before you start to take the medicine. It will help you. If you do not understand or you want to know more, ask your doctor or pharmacist (chemist). Keep this leaflet, you may want to read it again.

**The name of this medicine is Doxycycline 50 mg Capsules.
The active ingredient in the capsules is doxycycline hydrochloride.**

What is in your medicine?

Each white/yellow capsule contains 50mg doxycycline as doxycycline hydrochloride. Inactive ingredients are: microcrystalline cellulose, talc, magnesium stearate, colloidal hydrated silica, sodium lauryl sulphate, gelatin, and the colours titanium dioxide (E171), Quinoline yellow (E104) and sunset yellow (E110).

Doxycycline 50 mg Capsules are available in cartons containing 28 capsules.

Product Licence Holder and Manufacturer
Chenelle Medical, Loughrea, Co. Galway, Ireland.
UK Distributor
Chenelle Medical UK Ltd, Chobden Barn, Smeardon, Kent, TN27 8FR, UK.

What type of medicine is Doxycycline?

Doxycycline is one of a group of medicines called tetracycline antibiotics. It is used to treat many different types of infections.

What is your medicine for?

You may be given Doxycycline by your doctor to treat infections such as:

- Chest, lung or nasal infections e.g. bronchitis, pneumonia, sinusitis.
- Urinary tract infections e.g. cystitis, urethritis.
- Acne which is a skin infection.
- Eye infections.
- Sexually transmitted diseases e.g. gonorrhoea, syphilis, chlamydia.
- Fevers associated with louse or tick bites.
- Malaria, when chloroquine is not effective.

Doxycycline is also used to prevent certain infections developing, these are scrub typhus, travellers' diarrhoea, malaria and leptospirosis.

Your doctor may want you to take Doxycycline to treat another infection not listed above. You may also be prescribed an additional medicine to take with Doxycycline to treat your infection. If in doubt talk to your doctor.

Before you take your medicine

If the answer is **YES** to any of the questions below **DO NOT TAKE DOXYCYCLINE**.

- Have you been told you are allergic to Doxycycline or any other tetracycline antibiotic?
- Are you allergic to any of the other ingredients in Doxycycline Capsules listed above?
- Are you pregnant or trying to become pregnant?
- Are you breast feeding?
- Is this medicine prescribed for a child under the age of 12 years?

Tetracyclines should not be used during tooth development (during pregnancy, infancy and children below 12 years old) as such use may lead to permanent discolouration or underdevelopment of the teeth (yellow-grey-brown).

Avoid exposure to strong sunlight while taking this medicine. Your skin may be more sensitive to sunburn than normal. If you get a skin rash, itching, redness or severe sunburn when out in strong sunlight or under ultraviolet light (e.g. on a sun bed) stop taking the medicine and check with your doctor.

If the answer is **YES** to any of the following questions tell your doctor before you start Doxycycline.

- Are you likely to be exposed to strong sunlight or ultraviolet light (e.g. on a sun bed)?
- Do you have liver problems?
- Do you have myasthenia gravis (a disease which causes unusual tiredness and weakness of certain muscles, particularly in the eyelids)?
- If you are suspected as having syphilis, your doctor will continue to monitor you after your treatment has stopped.

Doxycycline 50 mg Capsules contain the colouring sunset yellow, E110. E110 can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

Can Doxycycline be taken with other medicines?

Some medicines may interfere with Doxycycline. You should tell your doctor if you are taking any of the medicines listed below. Also check with your doctor if you are taking any other medicines:

- Antacids (indigestion remedies), iron preparations, oral zinc or bismuth. If you take these at the same time of day as Doxycycline it may stop this medicine from working properly.
- Warfarin or coumarins (used to prevent blood clots). Tetracyclines may increase the action of these drugs.
- Oral contraceptives (birth control pills). Use of birth control pills with tetracyclines may impair the effect of the birth control pill and increase the chance of unwanted pregnancy.
- Penicillin antibiotics (used to treat infections). Doxycycline may reduce the effect of these antibiotics.
- Alcohol. Alcohol may reduce the effect of Doxycycline.
- Carbamazepine, phenytoin (medicines used to control epilepsy) and barbiturates (used to control epilepsy or as a sedative).
- Cyclosporin (used to affect the body's immune response).
- Methoxyflurane (an anaesthetic).

Can you drive whilst taking this medicine?

The effect of doxycycline on the ability to drive and operate machinery has not been studied.

DOXYCYCLINE 50MG CAPSULES

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How to take your medicine

Doxycycline should only be taken by mouth.

Usual Dose (Respiratory, Urinary tract, Chliferitic and other infections):	200mg on the first day then 100mg daily. The duration of treatment is dependent on the infection being treated.
Acne:	200mg daily for 8-12 weeks, with food or fruit.
Sexually Transmitted Diseases:	100mg twice daily for 7-10 days.
Primary and Secondary Syphilis:	200mg twice daily for 2 weeks.
Fever associated with loose or tick bites:	Single dose of 100mg or 200mg depending on severity.
Treatment of malaria, when chloroquine is not effective:	200mg daily for at least 7 days.
Prevention of malaria:	100mg daily from 1-2 days before travelling until 4 weeks after returning.
Prevention of scrub typhus:	Single dose of 200mg.
Prevention of travelers' diarrhoea:	100mg twice daily on the first day of travel, followed by 100mg daily throughout the stay in the area. If you are planning to take these capsules for more than 21 days, please consult your doctor.
Prevention of leptospirosis:	200mg once each week during the stay in the area; 200mg on completion of the trip. If you are planning to take these capsules for more than 21 days, please consult your doctor.

Doctors may prescribe different doses to those depending on the infection being treated. Check with your doctor if you are not sure why you have been prescribed the medicine.

The label on the pack will tell you what dose YOU should take, how often and for how long to take it. If you are still not sure, ask your doctor or pharmacist.

- Take Doxycycline capsules with a glass of water.
- It is best to take your capsules at the same time each day when standing or while sitting.
- Doxycycline capsules should be taken well before retiring at night in order to decrease the risk of irritation or ulceration of the throat or oesophagus.
- If your stomach is upset, Doxycycline capsules can be taken with milk or a glass of juice.
- Take the capsules for the full time of treatment, even when you begin to feel better. If you stop taking the capsules too soon, the infection may return.

What if you take too many capsules?

An occasional extra dose taken by accident is unlikely to be a problem, but if a large overdose has been taken contact your doctor or your nearest hospital Casualty Department immediately.

What if you miss a dose?

Do not worry. If you forget to take a capsule take it as soon as you can. Take your next capsule at the right time.

How quickly will the treatment start to work?

You should start to feel better within a few days. If you have been given Doxycycline for acne it may be a few weeks before you start to see an improvement.

What if you do not feel better?

If your infection gets worse or you do not start to feel better within a few days (even for sore), or a new infection develops, go back and see your doctor.

Does this medicine cause undesirable effects?

Doxycycline may cause some undesirable effects. The undesirable effects listed below are infrequent:

- Upset stomach
- Feeling or being sick
- Diarrhoea
- Difficulty in swallowing
- Sore or painful tongue or mouth
- Loss of appetite
- Soreness and itching of the rectal and/or genital area.

These undesirable effects are usually mild. If they are troublesome, severe, or do not wear off as treatment goes on tell your doctor.

Other undesirable effects which may occur include:

- Skin rash.
- Faking or peeling of the skin.
- Your skin may be more sensitive to sunlight than it is normally when taking this medicine.
- Very severe headache which may be associated with visual disturbances such as blurred vision.
- Inflammation and/or ulcers of the toilet. These are very unlikely if you take the capsules with water while standing or when sitting (See "How to take your medicine").
- Blood disorders. These are due to an imbalance in numbers of different types of cells in the blood. Symptoms may include tiredness, easy bruising or bleeding into infection.
- Worsening of a disease called systemic lupus erythematosus (SLE). This is a disease affecting a number of organs. If any of these undesirable effects occur, consult with your doctor.

All medicines can cause allergic reactions. Serious allergic reactions are very rare. Any sudden wheeziness, difficulty in breathing, chest pain, fever, swollen lips, tongue or itching especially affecting the whole body should be reported to a doctor immediately. The following have also been reported:

- Discolouration of thyroid tissue when given for long periods. But the medicine does not impair thyroid function.
- Inflammation of the bowel.
- Bulging fontanelles (soft spot on head) or intars.
- Abnormal liver function tests, inflammation of the liver, jaundice and inflammation of the pancreas.
- Pericarditis (inflammation of the membrane surrounding the heart).
- Discolouration and underdevelopment of teeth.

It is important to tell your doctor or pharmacist if you suffer any other undesirable effects which are not listed above.

Look after your medicine

This treatment is for YOU. Do not give it to others. Do not take this medicine after the date stamped on the pack.

Where to keep your medicine

Keep out of the reach and sight of children.

Further information

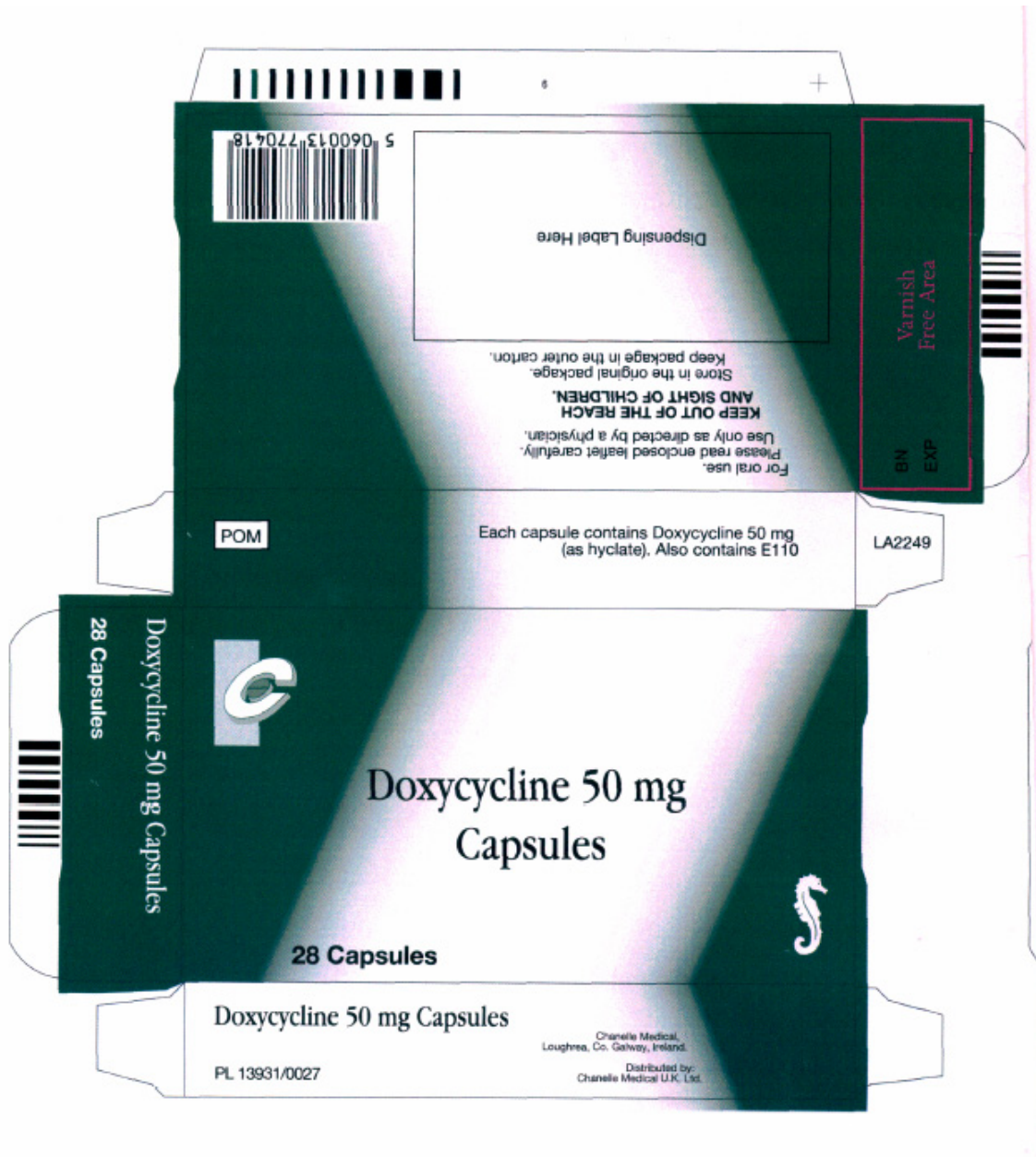
This leaflet does not contain all the information about this medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist. The information in this leaflet is about Doxycycline Capsules.



Labels/Packaging

DOXYCYCLINE 50MG CAPSULES

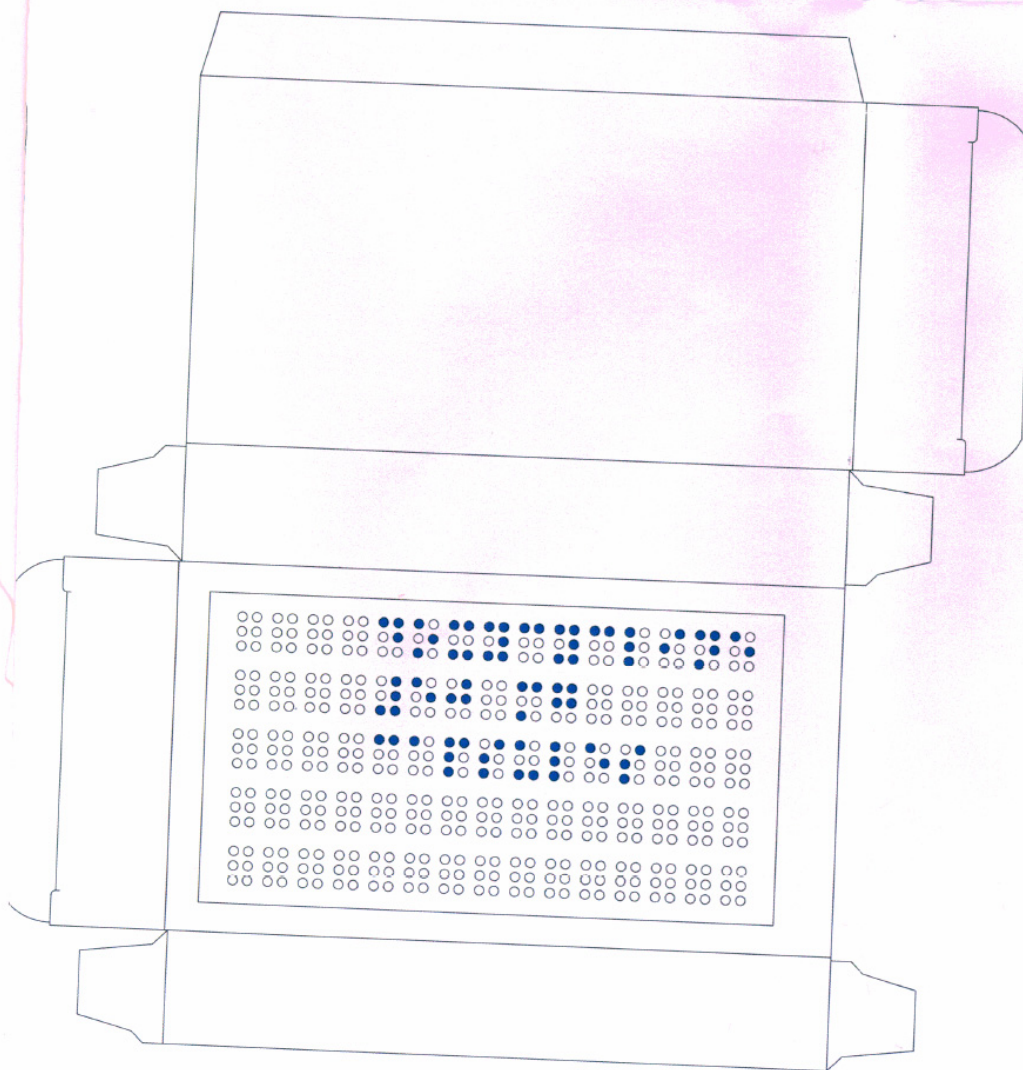
PL 13931/0027



DOXYCYCLINE 50MG CAPSULES

PL 13931/0027

Braille on packaging



DOXYCYCLINE 50MG CAPSULES

PL 13931/0027
Blister packaging

