MARCH 03

(8A)

ABRIDGED PRODUCT LICENCE APPLICATION

MEDICAL ASSESSMENT REPORT

LICENCE No:	PL/12295/0001-2-3
PROPRIETARY NAME:	MONOZEM 120,180 & 240 CAPSULES
ACTIVE(S):	DILTIAZEM HYDROCHLORIDE 120MG,180MG & 240MG
COMPANY NAME:	PHARMATEC INTERNATIONAL
E C ARTICLE:	4.8(a) (iii)
LEGAL STATUS:	POM

1. INTRODUCTION

This abridged application is for a new once daily sustained release capsule formulation of diltiazem in three dose strengths. The capsules, of different sizes, contain the same formulation of extended release pellets consisting of an active core prepared from sugar spheres, diltiazem hydrochloride and binders coated with a release controlling polymer membrane. The applicant claims essential similarity with Tildiem Conventional Release Tablets from Lorex, currently licensed in the UK. The applicant cites in their claim the relevant CPMP guidelines concerning hybrid applications.

2. BACKGROUND

The originator product was first licensed in France in 1979 and in the UK in 1984 (PI/04969/0005). This application was originally received with the product names being [redacted]. These code names have now been changed to the proprietary name indicated above.

3. INDICATIONS

The claimed indications are for the treatment of mild to moderate hypertension and angina pectoris. These indications are consistent with those currently approved and licensed.

4. DOSE & DOSE SCHEDULE

The recommended dose and dose schedule is based on once daily administration and the total recommended daily dose is consistent with that approved and licensed for the conventional release tablets cited as comparator. The recommended doses are therefore consistent with current accepted therapeutic practice. It is however noted that the starting dose recommended by the applicant is 240mg once daily whereas the conventional release tablet starting dose is recommended to be 60mg three times daily.

5. TOXICOLOGY

No new toxicology data was provided. A review of the toxicology of the active substance was included in the dossier.

6. CLINICAL PHARMACOLOGY

The dossier included a number of pharmacokinetic studies conducted during the early development phase of the product and what were described as three pivotal studies with the final formulation proposed for marketing.

In part two of the dossier under the heading 'Composition' abbreviated descriptions are provided of a series of four pilot studies undertaken to investigate the absorption profiles in man of developmental formulations using different pellets. On the basis of these experiments, as described, the applicant would appear to have selected the final formulation used in the 'definitive' pharmacokinetic and clinical studies. It was clearly shown that alteration in the coating thickness of the pellets did effect the pharmacokinetic profile. During the course of these studies, the applicant observed and recognised the known facts that diltiazem exhibits non-linear pharmacokinetics. In view of the known variability in diltiazem kinetics it was noted that no evidence was provided to demonstrate the individual kinetic profiles of the proposed three dose strengths when used in man.

Study 13742 was a three-way crossover study in 24 healthy subjects which compared a single 240mg dose of the test product when administered, fed and fasted with a 60mg immediate release product administered 8 hourly. It was noted that the original protocol intended to compare equivalent daily doses of 240mg but that a protocol amendment was introduced; no explanation for the revision to the original protocol was identified in the dossier. The results of this particular study indicated that there was no significant effect of food on the bioavailability of diltiazem from these sustained release pellets. The applicant claimed to have demonstrated bioequivalence between the immediate release formulation and the sustained release formulation over a period of 24 hours when the observed results were normalised to a 180mg equivalent dose. The mathematical methods for this dose adjustment were not provided. No evidence was provided in support of this questionable mathematical exercise.

Study 13988 was a steady state four-way crossover study carried out in 24 healthy subjects. The doses used and compared were:
1 sustained release 240mg capsule vs 3x60mg tablets taken 8 hourly and 2x180mg sustained release capsules taken together vs 2x60mg tablets taken 8 hourly.
Steady state was considered to have been achieved after 7 days continuous dosing. The results at steady state would appear to show that bioequivalence was demonstrated between the two formulations where equivalent daily doses of 360mg had been administered. The values determined were within the published guidelines limits of ± 20%, the power of the study was determined to have been above the nominal 80% limit. The dose normalising mathematical exercise was applied to the results from the 240 mg capsule and bioequivalence was claimed in respect of it to the conventional release total daily dose of 180mg. No evidence or detailed explanation for the normalisation exercise was provided.

A third study was described in which radio labelled pellets were administered and tracked in the gastrointestinal tract, in fasting and fed states and the plasma levels compared to that found following administration of an oral diltiazem solution. This particular experiment confirmed that gastric emptying of pellets is significantly delayed by food. Transit through the small intestine was not affected by food and the bioavailability from the extended release capsules was not affected by food.

In summary it was clear from the two key studies described above that the 240mg capsule produces considerably higher plasma levels than conventional 60mg tablets given 8 hourly. The use of mathematical normalisation techniques of an undefined nature and without reference to the non-linear kinetics of diltiazem raises questions concerning the claimed bioequivalence between these two dose forms. It did appear however from the steady state study that equivalent daily doses totalling 360mg produced comparable plasma profiles.

Additional information should be requested with regard to the methods used and the rationale for their use.

7. EFFICACY

The dossier contained a report from a single clinical study in hypertensive patients and indicated that a number of other ongoing clinical studies were not being reported in the dossier. The basic design of the single reported study appeared to be reasonably satisfactory, however, the mid-day dosing is not considered to be an ideal time for once daily anti-hypertensive therapy. The starting dose was considered to be slightly high at 240 mg with no rationale behind the selection of this particular dose strength. The control in this particular study was placebo and the study commenced with an initial 4 week washout period followed by crossover 4 weeks active and 4 weeks placebo, the total number of subjects being 24. The results of pre-dose blood pressure measurements indicated that the active produced a satisfactory reduction in blood pressure compared with the placebo and that the 24

hour ambulatory monitoring confirmed this observation throughout the monitoring period.

While this small study does confirm the activity of the dose form, it does not provide satisfactory evidence in respect of the selected starting dose. Additional information from the other ongoing studies should be obtained before a final decision on the starting dose efficacy is made.

8. SAFETY

A review of the safety of diltiazem was provided. The adverse event profiles from the volunteer and patient studies as provided in the submission were consistent with the known profile of side effects induced by diltiazem. There were no serious of unexpected adverse events reported from the volunteer studies. Two serious adverse events were reported in association with a study in patients with angina, both of these events were considered to be not drug related, the one being an acute myocardial infarct and the second being sudden death after the trial.

In terms of the overall safety of this new product there were no indicators to suggest it would introduce any new hazards to the therapeutic arena.

9. EXPERT REPORTS

The clinical expert report was basically satisfactory. However, the expert did not adequately address the selection of 240mg as the claimed starting dose, nor was there adequate attention paid to the mathematical exercises used in normalisation of the observed values recorded during the bioavailability studies.

10. DATA SHEET

The draft data sheet as provided was essentially satisfactory and consistent with the claimed indications and other provisions of the application.

11. PATIENT INFORMATION LEAFLET

A patient information draft text was not provided.

12. LABELLING

The draft labelling text as provided was essentially satisfactory.

13. MLA 201

The MLA 201 was essentially satisfactory, however modifications will be required to introduce the new proprietary name now notified by the company.

14. SUMMARY OF PRODUCT CHARACTERISTICS

The text of the proposed summary of product characteristics was consistent with that of the product licence application details.

15. DISCUSSION

This was generally a well presented and logical application. However, the proposed starting dose is higher than that currently recommended and has not been adequately justified or demonstrated by clinical evidence. The use of mathematical techniques to normalise the results from the pharmacokinetic experiments raises some questions and requires clarification by the applicant.

16. RECOMMENDATION

It is recommended that further information be obtained from the company following requests under Section 44 of the Medicines Act and that this application should not be determined until the final assessment of the new information.

[redacted]

March 1993

[redacted] PHARMATEC INTERNATIONAL

PL/12295/0001-2-3 MONOZEM 120,180 & 240MG CAPSULES

[redacted]

Section 44 Medical Points

1. Clarification is requested on the rationale behind modifying the original protocol for protocol No. 13742 so that the total daily doses administered to the subjects were different.

2. Clarification is requested as to the rationale for using different total daily doses in the study conducted under protocol No. 13988.

3. Information is requested on the methods used to 'dose normalise' the results recorded during the above two named studies.

4. Information is requested on the pharmacokinetic profiles of the three dose strengths as reassurance that the dose normalisation procedures can be properly applied in the case of these products.

5. Clinical evidence is requested in respect of the proposed recommended starting dose which is noted to be higher than that of the nominated comparator product.

6. Full reports of the clinical studies named in the dossier should be provided as evidence of efficacy and safety for these products.

[redacted]

21A

ABRIDGED PRODUCT LICENCE APPLICATION
MEDICAL ASSESSMENT REPORT
ON RESPONSES TO SECTION 44 LETTER

LICENCE No.: PL/12295/0001-2-3

PROPRIETARY NAME: Monozem (Angiozem) 120, 180, 240 mg

ACTIVE(S): Diltiazem hydrochloride

COMPANY NAME: Pharmatec International

EC ARTICLE: 4.8.a.(iii)

LEGAL STATUS: POM

1. INTRODUCTION

The clinical response to the section 44 letter was dated August 1993. [redacted]

2. BACKGROUND

There have been difficulties in respect of the proposed name for this product.

3. INDICATIONS

There were no issues raised in this area.

4. DOSE & DOSE SCHEDULE

The applicant has provided justification and evidence in support of the proposed starting dose of 240mg once daily.

5. TOXICOLOGY

There were no issues raised in this area.

6. CLINICAL PHARMACOLOGY

The applicants response included come new evidence and clarification of the methods used in dose adjustment. The intra and inter subject variability seen in the healthy and the hypertensive subjects was within the anticipated levels for this active and this type of product dose proportionality was demonstrated. Overall the pharmacokinetic profile as now recognised would appear to be satisfactory for the proposed clinical uses.

7. EFFICACY

Reports of the clinical trials which were mentioned in the original dossier were provided. It would appear that even though the numbers were small that the product as proposed for marketing is efficacious at the doses recommended.

8. SAFETY

The additional clinical data provided did not raise any new safety concerns.

9. EXPERT REPORTS

The clinical responses as addressed by a clinical expert were satisfactory.

10. DATA SHEET [UK]

There were no issues raised in this area. The January 1994 revision contains a new product name - Angiozem excel.

11. PATIENT INFORMATION LEAFLET

The draft text of a patient information leaflet, as included with the January 1994 revisions, was satisfactory. However, all references to the Medicines Control Agency should be deleted from the leaflet.

12. LABELLING

There were no issues raised in this area.

13. MLA 201

The January 1994 revised MLA201 pages cannot be used in the licence as they do not properly refer back to the original application forms (MLA201) dated 9 October 1992.

14. SUMMARY OF PRODUCT CHARACTERISTICS [EC]

There were no issues raised in this area.

15. DISCUSSION

The clinical responses were acceptable for the purposes of supporting the efficacy and safety of the product. The MLA and other documents need editing and revision prior to the grant of a licence.

16. RECOMMENDATION

A licence should be granted when the documents have been satisfactorily revised and the name of the product agreed.

17. ASSESSOR

[redacted]

April 1994

FILE NOTE:

Telephoned [redacted] on 5 April 1994 concerning the revisions needed for the MLA and patient leaflet. Discussed the name of the product and the possible resolution by the following means, to be discussed with [redacted]:

Pharmatec to change their product name to e.g. Diltiazem XL 120, 180, 240 [redacted]

[redacted]

[redacted]