BROLENE EYE DROPS®

(PROPAMIDINE ISETHIONATE)

AND

BROLENE EYE OINTMENT®

(DIBROMOPROPAMIDINE ISETHIONATE)

RECLASSIFICATION APPLICATION

SANOFI-AVENTIS AUSTRALIA PTY LTD
12-24 TALAVERA ROAD, MACQUARIE PARK, NSW 2113,
AUSTRALIA

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ABBREVIATIONS

ADEC	Australian Drug Evaluation Committee
ADR	Adverse Drug Reaction
ADRAC	Adverse Drug Reaction Advisory Committee
AE	Adverse Event
CARM	Centre for Adverse Reactions Monitoring
CMI	Consumer Medicine Information
MCC	Medicines Classification Committee
NDPSC	National Drugs and Poisons Scheduling Committee
PSUR	Periodic Safety Update Report
TTHWP	Trans Tasman Harmonisation Working Party

SUBMISSION FOR RECLASSIFICATION OF PROPAMIDINE ISETHIONATE AND DIBROMOPROPAMIDINE ISETHIONATE

1. Purpose of the Application

This application seeks to support the recommendation made by the Australian National Drugs and Poisons Scheduling Committee (NDPSC) at the February 2006 meeting regarding the rescheduling of propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment from 'Pharmacy Only Medicine' to 'General Sale' medicine**.**

2. Name of Company Requesting Reclassification

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park, NSW, 2113
Australia

Tel: +61 2 8666 2633
Fax: +61 2 8666 3055
e-mail: aujune.hanna@sanofi-aventis.com

3. Products Affected by Rescheduling Request

Product (1):

- International non-proprietary name: Propamidine isethionate.
- Proprietary name: Brolene Eye Drops.
- Dose form and strength: Eye drops, 0.1% w/v.
- Pack size: 10 mL bottle.
- Registration number: TT50-0717.

Product (2):

- International non-proprietary name: Dibromopropamidine isethionate.
- Proprietary name: Brolene Eye Ointment.
- Dose form and strength: Eye ointment, 1.5 mg/g.
- Pack size: 5 g tube.
- Registration number: TT50-0717/1.

4. Background

Propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment have been registered in New Zealand since 1969. Both products are indicated for the treatment of minor eye infections such as 'sticky eyes', inflammation of the eyelids and conjunctivitis in both adults and children. Currently in New Zealand both products are scheduled as 'Pharmacy Only Medicine', whilst in Australia they are scheduled as 'General Sale' medicine.

While reviewing products in anticipation of a joint agency, the discrepancy between the scheduling of these two products was raised by the Trans Tasman Harmonization Working Party (TTHWP) at a meeting held in October 2005. The subsequent recommendations from the TTHWP meeting were put forward to the NDPSC.

At the NDPSC meeting held in October 2005 it was noted that this issue had been previously discussed at a Medicines Classification Committee (MCC) meeting held in June 2005. It had been documented at that MCC meeting that the scheduling of products for ophthalmic use in New Zealand remained appropriate and that it would not be suitable for antibacterial eye products to be sold as 'General Sale' medicines. However, no specific safety issues were raised at the meeting by the MCC.

Consequently the October 2005 NDPSC meeting agreed to foreshadow a recommendation that Australia harmonise with the New Zealand scheduling for propamidine and dibromopropamidine

At the February 2006 NDPSC meeting it was noted that the safety of propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment was last reviewed by the NDPSC in 1992 where the Australian Drug Evaluation Committee (ADEC) recommended that both compounds remain unscheduled as they had been for many years, provided that the products are labelled appropriately.

It was also documented in the 'Record of Reasons' for the NDPSC February 2006 meeting, that the Centre for Adverse Reactions Monitoring (CARM) have received only three reports for propamidine isethionate and two reports for dibromopropamidine**.** Two of the reports for propamidine isethionate were associated with ophthalmic use (conjunctivitis and local site reaction/dysesthesia) while the third was associated with

topical use (contact dermatitis). Both reports received for dibromopropamidine isethionate were due to topical administration resulting in contact dermatitis.

Subsequently, at the February 2006 NDPSC meeting the Committee agreed to recommend that New Zealand consider harmonising with the 'General Sale' scheduling status of dibromopropamidine and propamidine on the basis that there were no significant safety issues noted with ophthalmic use of dibromopropamidine isethionate and propamidine isethionate.

Sanofi-aventis supports the recommendation put forward by the NDPSC that New Zealand considers harmonising with the less restrictive scheduling status of dibromopropamidine isethionate and propamidine isethionate available in Australia, due to the safety profile of the two products.

5. Present Classification of Medicine

Both propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment are classified as 'Pharmacy Only Medicine' in New Zealand. The products are indicated for the treatment of minor eye infections such as 'sticky eyes', inflammation of the eyelids and conjunctivitis in adults and children.

6. Classification Sought

This application seeks to support the recommendation from the NDPSC for the rescheduling of propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment from 'Pharmacy Only Medicine' to that of 'General Sale' medicine.

7. Classification Status in Australia

Propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment have been registered in Australia since the early 1960's and are both scheduled as 'General Sale' medicines.

8. Current Packaging

Propamidine Isethionate Eye Drops

The packaging currently consists of a bottle label and a carton, which includes a Consumer Medicine Information (CMI) leaflet. The bottle is also tamper evident.

All critical information (such as the indications, directions for use and storage conditions) as well as the required warning statements, are printed on the current packaging and on the CMI.

Warning statements currently on the carton:

- For external use only.
- If symptoms persist consult your doctor.
- Do not use when wearing hard or soft contact lenses.
- Use within 4 weeks of opening (or 7 days if used in hospitals).
- Keep out of reach and sight of children.

Dibromopropamidine Isethionate Eye Ointment

The packaging currently consists of a tube label and a carton, which contains a CMI leaflet.

All critical information (such as the indications, directions for use and storage conditions) as well as the required warning statements are printed on the current packaging and on the CMI.

Warning statements currently on the carton:

- For external use only.
- If symptoms persist consult your doctor.
- Do not use when wearing hard or soft contact lenses.
- Use within 4 weeks of opening.
- Keep out of reach and sight of children.

9. Proposed Packaging

Propamidine Isethionate Eye Drops

The proposed packaging changes are:

- Removing the 'Pharmacy Only Medicine' statement on the carton and label.
- The inclusion of a tamper evident statement, such as 'Do not use if cap seal is broken', on the carton.

Dibromopropamidine Isethionate Eye Ointment

The proposed packaging changes are:

- Removing the 'Pharmacy Only Medicine' statement on the carton and label.
- Making the packaging tamper evident by placing tape seals on the carton flaps.

- The inclusion of a tamper evident statement, such as 'Use only if carton seal is unbroken', on the carton.

10. A Statement of the Benefits to be derived from the Proposed Change

The treatment of conjunctivitis and other minor eye conditions is unlikely to require the supervision of a healthcare professional as the symptoms are often readily identifiable by the patient and, as such, self-diagnosis is common. This is demonstrated by the current classification of propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment as 'Pharmacy Only Medicine', which allows for consumer access without pharmacist supervision.

The current packaging contains all critical information and the necessary warning statements. However, sanofi-aventis proposes that the carton artwork be updated to include relevant tamper evident statements on the carton. This is in order to ensure that the quality of the product will not be compromised at any time. In addition, the availability of the CMI as a package insert provides sufficient information for consumer use of either product.

Propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment have been registered in New Zealand since 1969 and have been proven to be safe and effective forms of treatment for minor eye conditions. In the last 18 months, no Adverse Drug Reaction (ADR) reports were received by sanofi-aventis even though combined sales figures for both products in New Zealand were calculated at 108,926 units. In Australia, the combined sales figures of the products in the last 18 months are 334,686 units and only one ADR has been reported to Adverse Drug Reaction Advisory Committee (ADRAC). Furthermore, safety data gathered post-marketing did not reveal any new findings, trends or increased reporting frequency for either product.

As such, the rescheduling is unlikely to have any impact on patient selection, nor on patient safety, however it will aid in the Trans Tasman harmonisation process and as such we concur with the recommendation of a less restrictive scheduling made by the NDPSC.

11. Adverse Events

New Zealand

In the last 18 months the sales figures for propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment were 55,184 and 53,742 units respectively.

The combined quantity distributed in the last 18 months was 108,926 units. No ADR reports were forwarded to CARM by sanofi-aventis as none were received during this time.

Australia

In the last 18 months the sales figures for propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment were 177,146 and 157,540 units respectively.

The combined quantity distributed in the last 18 months was 334,686 units. Five Adverse Events (AE) were reported to sanofi-aventis in that period. From these five reports only one was considered a serious ADR report and met the criteria to be forwarded to ADRAC by sanofi-aventis.

12. Post-Marketing Experience

The Periodic Safety Update Report (PSUR) available at the moment covers the period of January 1994 to January 1999. The next PSUR is expected to be available by the end of October 2006.

The PSUR reviewed contains information on adverse events from all sources reported to sanofi-aventis in association with propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment. At the time it was complied, both products were being marketed in the following countries: Australia, Ghana, Hong Kong, Ireland, Malaysia, New Zealand, Norway, Pakistan and the United Kingdom.

During this period the combined sales figures for these products were 6,000,000 units.

Propamidine Isethionate Eye Drops
From the approximate 5,150,000 bottles that were sold during this period there were only 9 reports with 17 adverse events. All were reported by Health Professionals and considered non serious.

Dibromopropamidine Isethionate Eye Ointment
From the approximate 850,000 tubes that were sold during this period a total of 18 reports with 18 adverse effects were reported. 17 were reported by Health Professionals and one case was reported by the Health Authorities.
16 cases were considered non serious, while the remaining two cases were classified as serious.

From the PSUR it was concluded that the adverse events reported did not significantly modify the safety profile of either preparation as there was no evidence of a significant increase in frequency in the reporting rate or in the frequency of any single event. As a result no modification of the Reference Safety Information was required.

13. Conclusion

Both propamidine isethionate eye drops and dibromopropamidine isethionate eye ointment are safe, effective products that have been successfully marketed for over 30 years in both Australia and New Zealand. Therefore sanofi-aventis, in order to aid with the Trans-Tasman harmonization project, supports the recommendation made at the NDPSC February 2006 meeting to reschedule propamidine isethionate and dibromopropamidine isethionate from 'Pharmacy Only Medicine' to 'General Sale' medicine.