pharmaxis

# Building a healthy future

2009 Annual Review

# This Annual Review

Pharmaxis' Annual Review is designed to provide shareholders with a snapshot of the company's activities for the year. For more detail, the 2009 Statutory Annual Report can be accessed on the Pharmaxis website www.pharmaxis.com.au



## Company overview

Pharmaxis is a specialty pharmaceutical company involved in the research, development and commercialisation of new therapies for undertreated respiratory diseases.

Our therapeutic interests include lung diseases such as bronchiectasis, cystic fibrosis, and asthma; as well as chronic obstructive pulmonary diseases including chronic bronchitis and pulmonary fibrosis.

The company's first product, Aridol, is approved for sale in Australia, major European countries and Korea. It is designed to identify lung inflammation and assist in diagnosing and managing asthma. The second product, Bronchitol has completed the first regulatory Phase 3 clinical trials in both cystic fibrosis and bronchiectasis.

Behind these products we have a growing pipeline of early stage opportunities that will serve us well for the future. Pharmaxis operates in the highly competitive and highly regulated environment of human healthcare and takes its social and ethical responsibilities seriously.

### Notice of Meeting

The 2009 Annual General Meeting of Pharmaxis Ltd will be held at the Intercontinental Sydney, Corner of Bridge and Phillip Streets, Sydney on Wednesday, 21 October, at 2.30pm.

*Cover: Bronchitol clinical trial participant Georgia Jones.*

We have now laid the foundations for a profitable business, a business that is built for a sustainable future and a business that has the capacity to bring new medicines to people with difficult health problems.

Our major product Bronchitol is tackling one of the more difficult genetic diseases of the world's population. It is a disease from birth, is life limiting and requires daily treatments with many different agents. This disease, cystic fibrosis, can be tackled and there have been dramatic improvements in the health and quality of life of people affected by it.

The development of a new drug for cystic fibrosis has a unique set of challenges, not least of which is understanding the number and type of existing drugs that are taken regularly and the daily physiotherapy that patients undergo. For any drug to be successful it has to show a clinical benefit over and above the best current clinical practice. It has to do so over many months, in patients with different severities of disease, who are undergoing different treatment regimens. This is a high bar for any drug development program.

We know that lung function declines rapidly for people with cystic fibrosis, however, things are improving. In the last 20 years life expectancy has improved by more than 20 percent and at the same time the associated deterioration in lung function has slowed.

The purpose of Bronchitol is to help improve this situation even further. The results of our Phase 3 clinical trial which were reported during the year, showed that Bronchitol improved lung function irrespective of the patient's age and disease severity, holding out the promise of slowing down lung function decline. Furthermore Bronchitol is precision formulated for delivery to the lungs through an easy-to-use, pocket-size inhaler, a feature which we hope will ease the daily lives of patients burdened with time consuming and complex treatment regimes.

On this product and indication alone, we can build a successful business. The treatment of cystic fibrosis is concentrated in a small number of centres worldwide making it relatively straight forward to introduce a new product.

However, our efforts go beyond cystic fibrosis and we continue to reach into patient groups with other congested lung diseases including bronchiectasis.

Equipment testing and certification of the new factory should be complete in the early part of 2010, which puts us in control of all aspects of the business – from manufacture to marketplace. This has always been our stated objective.

Successful pharmaceutical companies cannot afford to rely on only one product to sustain them through the future. Currently, major pharmaceutical companies have healthy cash positions but are under pressure with inadequate pipelines to replace the older products that are either being superseded or subject to price cuts due to generic competition. The seeds of a successful product are often sown as much as ten years before it reaches the market. The drug discovery team at Pharmaxis has been working to long term objectives and now some of their earliest discoveries have reached the clinic. In addition, we are building out the Bronchitol and Aridol franchise with product innovation and clinical expansion.

In the past year Pharmaxis laid out a number of challenging goals, prioritised the key components of the business and completed laying important foundations for the future. Ahead is the task of garnering marketing approval for Bronchitol as efficiently as we can and making it available to patients with congestive lung diseases such as cystic fibrosis and bronchiectasis.

It is my pleasure to present our 2009 Annual Review. We thank you for your support and look forward to completing the next stage of building Pharmaxis into a globally competitive pharmaceutical company.

**Alan Robertson**
Chief Executive Officer

## 2008/9 Highlights

- Short term Phase 2 cystic fibrosis dosing trial with Bronchitol returns positive results
- Long term Phase 3 bronchiectasis trial demonstrates Bronchitol safe after 12 months treatment
- Marketing application filed for Bronchitol in Australia
- First patient receives Bronchitol in Europe through the compassionate use scheme
- PXS4159 enters formal preclinical safety studies
- Aridol pricing application in Europe approved
- Submission of New Drug Application for Aridol to the FDA
- Commencement of a second Phase 3 trial with Bronchitol in patients with cystic fibrosis
- Pivotal Phase 3 trial in patients with cystic fibrosis demonstrates that Bronchitol is safe and effective
- European marketing application review timetable agreed with E.U. regulators
- Numerous data presentations at scientific meetings covering Aridol, Bronchitol and PXS25
- Completion of $54 million capital raising to new and existing investors


## Aridol

Aridol[1] was conceived by a team of research scientists at the Royal Prince Alfred Hospital in Sydney in response to the difficulties and unpredictability associated with existing lung function challenge tests. It can often be hard to confirm an accurate diagnosis of asthma, and it was this recognition that drove the innovation that led to Aridol. Aridol was designed to detect 'twitchy', or hyperresponsive airways, which is a common feature of asthma, however, it is particularly useful for detecting airway inflammation. A positive Aridol test may be used to confirm a diagnosis of asthma, and furthermore, to support a decision to start regular anti-inflammatory treatment – such as an inhaled steroid.

Aridol is the first lung function test of its kind, and has required a significant effort in education and clinical trial work for it now to be positioned as one of the few worldwide standards for the detection of sensitive airways.

During the year, Aridol has been presented at a number of high profile scientific congresses in Europe and the United States, and has been the subject of much discussion amongst the scientific community. As further clinical experience is gained with Aridol, we believe that it will become established as the preferred lung function test, not only because of the extensive body of scientific data supporting it but because of its convenience and ease of use.

The major markets for Aridol are the U.S., Germany and South Korea, and during the year Pharmaxis filed a marketing application with the U.S. FDA. We are optimistic about a positive review and are planning for a launch into the U.S. for the first part of 2010. The launch will be driven out of our office in Pennsylvania and initially will concentrate on the larger population centres in the U.S., and those hospitals undertaking large numbers of lung function challenge tests. In Europe, Aridol is now registered for sale in most major markets and is available through a network of distributors. Sales in Europe over the year increased by 96%, albeit from a low base, and first sales were made in Korea, although reimbursement has not yet been finalised in that jurisdiction.

**Aridol is the first lung function test of its kind…**

Aridol is now included as a recommended test by the World Anti-Doping Agency.

Aridol is now included as a recommended test by the World Anti-Doping Agency (WADA). Exercise-induced asthma is a relatively common condition, which affects tens of thousands of athletes worldwide. On 1 January 2009, a new set of WADA guidelines came into force. They apply to the 20% of elite athletes that have exercise-induced asthma, and signal a change to the way the athlete can seek approval to use their asthma medications. Aridol is helping to ensure that elite athletes around the world are properly diagnosed with asthma and correctly use their asthma drugs during competition.

Asthma is a chronic disease that affects about 20 million people in America and its primary cause is inflammation in the lungs, which reduces the size of the airways, making it more difficult to breathe. We expect Aridol will have an important role to play in asthma in the future. Last year, in addition to presentations at scientific forum, there were seven new publications in scientific journals, including the results from the second Phase 3 clinical trial forming the basis of the U.S. marketing application.

## Bronchitol

Bronchitol[2] is a drug designed to improve the lives of people living with obstructive airway disease. Bronchitol is precision formulated for delivery to the lungs through an easy-to-use, pocket-sized portable inhaler. Its principal mode of action is to restore normal lung hydration, improve mucus clearance and lung hygiene.
A normal healthy lung is surrounded by a surface liquid that is kept intact by a thin film of mucus. Normal homeostatic mechanisms keep the fluid layer suitably hydrated so that the cilia can beat properly, set up currents within the airway surface liquid and clean the lungs of excessive mucus and other secretions. Where the airway surface liquid is impaired or dehydrated, the cilia can't fulfil their normal function and the lungs can become clogged with mucus, leading eventually to irreversible damage and loss of lung function. This loss of lung function is the principal reason for reduced life expectancy. A clinical condition where this is most manifested is cystic fibrosis. The progressive decline in lung function associated with cystic fibrosis is a key symptom of the disease and seems to be inevitable. However, recent studies conducted by Pharmaxis and others have suggested for the first time, that this decline in lung function may not be inexorable. The main obstructive lung diseases are: chronic bronchitis, emphysema and asthma and those affecting fewer people include cystic fibrosis, bronchiectasis, bronchiolitis and allergic bronchopulmonary aspergillosis.

**Cystic Fibrosis**

Cystic fibrosis is a genetic disease affecting over 75,000 people in the world. It is often diagnosed soon after birth and is very difficult to treat. The main clinical goal is to keep the patients lungs in good condition and to prevent lung function loss – which, on average, can amount to 2% every year. In consultation with various cystic fibrosis organisations and clinicians, and with the assistance of the regulatory agents in the U.S. and Europe, Pharmaxis designed a

*1 Aridol (mannitol bronchial challenge test).*
*2 Brochintol has not yet been approved for any indication in any market.*


**The drugs of the future are being researched by our discovery team of medicinal chemists and biologists and their focus is on new approaches to respiratory medicine.**

- → **PXS25** inhibits the function of a protein that is heavily involved in scar formation and wound repair. While important for normal repair of the body, excessive production of this protein can cause fibrosis in a variety of conditions and it is believed to be important in the development of kidney fibrosis in people with diabetes. In the lung, it leads to a condition called pulmonary fibrosis and it is in this clinical condition that PXS25 has been most extensively studied. The first data was presented at a major scientific congress in the U.S. in 2009 and human trials are about to get underway.
- → **PXS4159** is a new anti-inflammatory agent that Pharmaxis is investigating for the treatment of asthma and other inflammatory conditions. PXS4159 has proven to be effective in preclinical models and is undergoing additional evaluation before being considered for studies in humans.

**Bronchitol is a drug designed to improve the lives of people living with obstructive airway disease...**


Dr Alan Robertson announces results of Phase 3 Bronchitol trial.

comprehensive clinical trial programme that, if successfully executed, will allow us to seek a marketing application for the use of Bronchitol in treating cystic fibrosis worldwide. During the year we reported the results of two important aspects of this programme; namely, a Phase 3 trial in 325 subjects designed to show Bronchitol was safe and effective, and a multidose trial designed to demonstrate the most appropriate dose of Bronchitol for treating cystic fibrosis.

The Phase 3 trial reported in May 2009 and its main clinical endpoint was to determine if Bronchitol, when delivered twice a day for six months, improved lung function when measured against a placebo. The trial took place across 40 centres around the world and enrolled patients aged 6 years and older who were variously affected by the disease from mild through to severe. The trial asked the very hardest question: could Bronchitol be added to treatment regimes of patients who were receiving the very best current medications and clinical practice and would it provide an additional benefit? The answer to the question was a clear yes. After six months treatment, patients receiving Bronchitol experienced no further loss of lung function and, in fact, saw their lung function improve by 6.5% on average. In addition to lung function improvements, lung capacity improved, the time in which patients were free from an infection was lengthened and the frequency of infectious episodes was also reduced. The initial results from the trial were presented at the 2009 European CF meeting and will also be presented at the 2009 North American CF meeting. Presentation of the scientific data is important for raising awareness of the product and allowing scientific scrutiny of the data.

A second Phase 3 clinical trial is required for the U.S. marketing application. This trial is targeting the recruitment of 300 patients with cystic fibrosis and is due to report the results in the first half of 2010. The trial is being conducted under the Food and Drug Administration's Special Protocol Assessment (SPA) scheme and is taking place at hospitals in Argentina, the U.S., Canada, Belgium, Germany, France and the Netherlands. The trial is essentially a confirmatory study for the first trial and is expected to reinforce the positive outcomes from many clinical trials conducted with Bronchitol to date. Bronchitol has been awarded development fast-track status in the U.S. and orphan drug designation in both the U.S. and the E.U.

### Bronchiectasis

Bronchiectasis is a chronic, progressive condition of the lung that is very difficult to treat. For the patient it means breathlessness, persistent coughing, excessive mucus production and poor quality of life. In spite of the fact that there are over half a million people in the world with bronchiectasis, no drugs have been specifically approved to treat the condition and the patient has to rely on physiotherapy and antibiotics to help clear the chest. Pharmaxis has conducted a number of clinical trials in people with bronchiectasis and is embarking on a final Phase 3 trial following discussions last year with both the European regulator and the U.S. regulator. The work in bronchiectasis is designed to complement the work we are doing in cystic fibrosis and eventually lead to a market expansion for Bronchitol.

# Operations Overview

**The new manufacturing facility was completed in May 2009.**

In addition to our operations in Sydney, Pharmaxis has offices in the United States, China and the United Kingdom.

The new manufacturing facility was completed in May 2009 according to schedule and budget. When the manufacturing equipment is installed and validated, it will have the capacity to produce sufficient Bronchitol to treat 40,000 patients each year. The building was completed with expansion in mind and, when it is required, the building can accommodate additional manufacturing equipment to bring capacity up to 80,000 patients per year. The equipment installation and validation is proceeding as planned and we expect to have the facility fully operational by the second quarter of 2010.

In addition to our operations in Sydney, Pharmaxis has offices in the United States, China and the United Kingdom. These offices are principally concerned with regulatory and marketing matters.

After 4 years as a NASDAQ listed company, it was decided that we should move from our NASDAQ listing to a Level 1 ADR programme. This means that while our ADRs can still be traded in the U.S. on the over-the-counter market, we are no longer subject to the reporting requirements of the U.S. Securities and Exchange Commission. This decision was taken following a review of trading on NASDAQ and an understanding that investors who wished to own Pharmaxis shares prefer to own Australian ordinary shares. While the accounting standards gap between Australia and the U.S. has now essentially closed, the increasing costs (both peripheral and direct) associated with maintaining a NASDAQ listing could not be justified. Pharmaxis shares continue to trade on the Australian exchange as they always have and our voluntary delisting from NASDAQ should not have any impact on our shareholder base.

# Governance

During 2009, Richard van den Broek joined the Pharmaxis Board of Directors. Richard has been Managing Partner of HSMR Advisors, LLC, an investment fund focused on the biotechnology industry and from 2000 through 2003 was a Partner at Cooper Hill Partners, LLC, an investment fund focused on the healthcare sector. Previously, Richard had a ten year career as a biotech analyst, starting at Oppenheimer & Co., then Merrill Lynch, and finally at Hambrecht & Quist.

Denis Hanley is chairperson of the Remuneration and Nomination Committee and Malcolm McComas is chairperson of the Audit committee.

Our Board of Directors is:

**Denis Hanley**
*Chairman*

**Alan Robertson**
*Chief Executive Officer*

**Will Delaat**
*Independent Director*

**Peter Farrell**
*Independent Director*

**Malcolm McComas**
*Independent Director*

**Richard van den Broek**
*Independent Director*

**John Villiger**
*Independent Director*

Peter Farrell has indicated that he will not seek re-election when he retires by rotation at this year's annual meeting due to increasing work commitments. We thank Peter for his valuable contribution over the past 3½ years.

Detailed Director biographies can be found on our website www.pharmaxis.com.au and in the 2009 Statutory Annual Report.

Pharmaxis has a Corporate Governance Framework which is reviewed and updated as necessary each year. Details can also be found on our website www.pharmaxis.com.au and in the 2009 Statutory Annual Report.

# Financial History

Pharmaxis completed 2009 with a cash position of A$125 million.

Research & development continues as our major expense. In 2009 this was $29 million, compared to $20 million in 2008. Of this total expenditure the drug discovery group which is working on drug discovery for respiratory and immune disorders made up seven per cent; the preclinical group which has been conducting toxicology studies in PXS4159 and PXS25 and additional efficacy data in PXS25 made up six per cent; the clinical group which designs and manages the global clinical trial programs made up 64 per cent; and the manufacturing operations which produce material for clinical trials and stability studies and develop production processes made up 21 per cent. The increase in R&D expenses in 2009 is primarily attributable to an increase in the number and size of clinical trials in the dosing stage during 2009.

Commercial expenses of A$6.2 million include the costs of developing our sales and marketing infrastructure and supporting the development and awareness of Pharmaxis products with key respiratory clinicians around the world. Commercial expenses increased in 2009 as we launched Aridol in several European countries and prepared for its launch in the U.S., and as preparation commenced for the commercial launch of Bronchitol in the EU and the US. Administration expenses of A$5.8 million include finance, administrative, IT, office, public company and professional service costs. Administration expenses increased in 2009 as we supported our expanded clinical program, our growing international presence and as we completed the larger facility at Frenchs Forest. Finance costs represent the ongoing finance charge associated with the capitalised finance lease of the new building which commenced in May 2009.

Aridol sales for 2009 were A$0.6 million. Australian sales grew by 7.5%, European sales grew by 95.5% as new individual marketing authorisations were received, sales to pharmaceutical companies decreased by 64% and we made our first sales to Korea. Other income is predominantly amounts paid by pharmaceutical companies for promotion of their products by our sales representatives.

In 2009 we invested A$11.4 million in property, plant and equipment, the majority of which related to the fit-out and installation of manufacturing equipment in the new facility. We have approximately A$2.8 million remaining to spend on the facility.

(prepared in accordance with Australian equivalents to International Financial Reporting Standards)

| Year ended 30 June<br>(in thousands, except per share data) | 2009<br>A$ | 2008<br>A$ | 2007<br>A$ | 2006<br>A$ | 2005<br>A$ |
|---|---|---|---|---|---|
| **Income Statements** | | | | | |
| Revenue from sale of goods | 595 | 527 | 205 | 8 | – |
| Gross profit | 442 | 398 | 156 | 6 | – |
| Interest | 5,347 | 7,402 | 5,278 | 4,282 | 1,702 |
| Other income | 523 | 1,576 | 2,152 | 1,299 | 1,219 |
| Expenses | | | | | |
| Research & development | (29,308) | (19,996) | (23,840) | (16,978) | (9,269) |
| Commercial | (6.202) | (4,557) | (3,240) | (1,946) | (963) |
| Administration | (5,800) | (5,231) | (4,666) | (4,391) | (3,134) |
| Finance expenses | (122) | – | – | – | – |
| Loss before income tax | (35,120) | (20,408) | (24,160) | (17,728) | (10,445) |
| Income tax expense | (51) | (32) | (19) | (5) | – |
| Loss for the year | (35,171) | (20,440) | (24,179) | (17,733) | (10,445) |
| | Cents | Cents | Cents | Cents | Cents |
| Earnings per share | (18.0) | (10.8) | (13.6) | (11.1) | (8.4) |

| As at 30 June | 2009<br>A$ | 2008<br>A$ | 2007<br>A$ | 2006<br>A$ | 2005<br>A$ |
|---|---|---|---|---|---|
| **Balance Sheets** | | | | | |
| Cash and cash equivalents | 124,993 | 111,842 | 76,182 | 97,840 | 33,390 |
| Plant & equipment | 32,698 | 3,668 | 3,521 | 3,205 | 2,477 |
| Total Assets | 163,997 | 125,049 | 82,648 | 104,267 | 37,937 |
| Total liabilities | 26,306 | 5,928 | 6,089 | 5,379 | 2,470 |
| Total shareholders' equity | 137,691 | 119,121 | 76,559 | 98,888 | 35,467 |
| **Share Data** | | | | | |
| Ordinary shares on issue | 217,659 | 194,515 | 177,949 | 176,904 | 134,770 |
| Options over ordinary shares on issue | 15,075 | 1,536 | 9,836 | 9,692 | 10,914 |

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**Pharmaxis Ltd**

20 Rodborough Rd
Frenchs Forest NSW 2086
AUSTRALIA
Phone: +61 2 9454 7200
Fax: +61 2 9451 3622
Email: info@pharmaxis.com.au
Web: www.pharmaxis.com.au