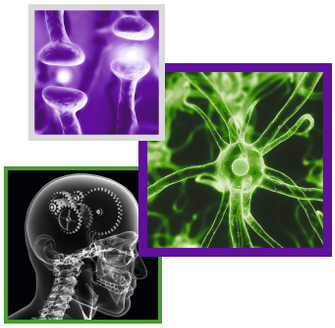
COMPANY PROFILE

Neurodegenerative Disease Management



Piramal Imaging

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Piramal Imaging, a division of Piramal Enterprises Ltd, is a global radiopharmaceutical company that is actively developing novel PET radiotracers for use in molecular imaging. The company focuses on developing innovative products that improve early detection and characterization of chronic and life-threatening diseases, leading to better therapeutic outcomes and improved quality of life.

Practice points

- Piramal Imaging is a molecular imaging company developing novel PET tracers to improve detection and characterization of chronic and life-threatening diseases, leading to better therapeutic outcomes and improved health-related quality of life.
- Piramal Imaging has assembled a product portfolio of molecular imaging tracers that address major clinical needs in neurology, oncology and cardiovascular medicine.
- Advances in molecular imaging have helped Piramal Imaging develop improved diagnostic tools that enable earlier detection and better characterization of diseases and is a major driver of precision medicine through more precise selection of patients for appropriate treatment, more specific dosing of medication and improved monitoring of therapeutic response.
- CNS disorders such as Alzheimer's disease constitute a major area of focus for Piramal Imaging, based on the hypothesis that earlier detection of β-amyloid plaque deposits can yield more timely and more accurate diagnosis, leading to better patient outcomes.
- Piramal Imaging's lead product, Neuraceq™, is a radiopharmaceutical indicated for PET imaging of the brain to detect β-amyloid in the brains of adult patients with cognitive impairment.
- Piramal Imaging supplies Neuraceq to drug companies developing disease-modifying therapies for Alzheimer's disease, and has established an extensive network to ensure continuity of supply.
- Piramal Imaging aims to replicate its proof-of-concept work in Alzheimer's disease with other radiotracers designed to detect oncologic and cardiovascular biomarkers, benefits that will help the company create value for patients, physicians, payers and society in general.

KEYWORDS:
• Alzheimer's disease • beta-amyloid • cardiology diagnostics • CNS diagnostics • molecular imaging • Neuraceq™ (florbetaben F18) • oncology diagnostics • PET imaging

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Future Medicine part of fsg

Piramal Imaging was established in April 2012 through Piramal Group's acquisition of the molecular imaging R&D portfolio of Bayer Pharma AG. The company is a division of Piramal Enterprises, one of India's largest diversified companies, with a presence in the pharmaceuticals, financial services and healthcare information management sectors. Piramal Imaging originated in Berlin, Germany, where the first imaging contrast agents were invented and the company maintains its R&D facility on the Bayer Pharma campus in Berlin, although it is independent from Bayer. Piramal Imaging has a US facility in Boston, MA; a UK subsidiary hosting Global Commercial Operations in the Langstone/Havant area; and representatives' offices in Munich, Germany and Milan, Italy.

Piramal Imaging started with a core team of approximately 20 staff members who joined the company from Bayer. At the time of the Piramal Group acquisition of the Bayer Pharma R&D portfolio, the company's lead product candidate, Neuraceq™ (florbetaben ^{18}F), was in Phase III of clinical development. While the Phase III program was still ongoing, Bayer transferred the product's dossier to Piramal Imaging, which coordinated regulatory submissions to the US FDA, the EMA and Korean and Japanese health authorities. Neuraceq obtained EU's approval in February 2014, FDA approval in March 2014 and Korean approval in December 2014. The company now comprises approximately 80 employees.

Today, Piramal Imaging is developing a product portfolio of molecular imaging probes that address major clinical needs in neurology, oncology and cardiovascular medicine. These products are designed to provide innovative diagnostic imaging solutions to reduce the burden of disease, leveraging advances in molecular imaging. Such advances aid Piramal Imaging in developing improved diagnostic tools that enable earlier detection and better characterization of diseases, as well as selection of the right therapy at the appropriate dose and monitoring of therapeutic response.

Piramal Imaging's specific focus on molecular imaging is designed to facilitate the practice and application of personalized/precision medicine. In this context, 'personalized medicine' is an approach that enables targeting of the origins of disease, leading to earlier, more accurate diagnosis, selection of appropriate therapy and ultimately, better patient outcomes. It is therefore instructive to differentiate molecular imaging from morphological imaging, which involves use of a contrast agent to detect the size and contours of body tissue, as with MRI, a modality that, for example, very accurately detects brain atrophy, shrinkage of the whole brain or particular regions of the brain affected by Alzheimer's disease (AD). Molecular imaging, by contrast, refers to detection of disease at the molecular level, allowing detection of pathological molecular events at the onset of disease, before morphological changes can be measured. β-amyloid imaging, which detects the pathological molecule that causes AD, is thus a prime example of molecular imaging technologies.

Focus on Alzheimer's disease

Indeed, the promise of molecular imaging is perhaps most vividly demonstrated in diseases of the CNS, a prime example being dementia due to AD – the most prevalent dementia, and an area of major focus for Piramal Imaging. Early identification and accurate diagnosis of cognitive and functional impairment due to AD and other etiologies are crucial for optimization of patient care and initiation of appropriate therapy.

Piramal Imaging's focus on AD is driven by the limitations of conventional diagnostic modalities. Although history-taking, neuropsychological tests and structural brain imaging are considered a mainstay of clinical diagnosis in patients with evidence of cognitive decline, these tests cannot diagnose AD with very high certainty particularly at an early stage, nor can they sufficiently rule out AD as the underlying etiology of cognitive decline [1]. In addition, not recognizing treatment options, social stigma and other factors may contribute to a substantial delay in diagnosing AD [2]. Prior to the advent of molecular imaging, autopsy was the only method to definitively diagnose AD [3,4]. However, autopsy and clinical studies show a significant rate of misdiagnosis of AD (20–30%, and even higher in very early stages of cognitive decline [4,5]), which may result in improper management decisions and excess medical costs. Underdiagnosis is another limiting factor; as many as 28 million of the world's 36 million people with dementia are thought to be undiagnosed [5]. Conversely, a false-positive diagnosis of AD can lead to unnecessary care and potentially harmful medications, placing

additional strain on the patient and caregiver. In a longitudinal analysis of 88 misdiagnosed patients, present in the National Alzheimer's Coordinating Center Uniform Data Set (2005–2010) database, estimates of the number of patients on a potentially inappropriate medication regimen ranged from 18 to 67% [6].

The focus on AD stems from the hypothesis that earlier detection of β-amyloid plaques can yield more timely and more accurate diagnosis at an earlier timepoint when therapeutic interventions have proven beneficial [7,8]. Evidence suggests that AD is a continuum ranging from a clinical asymptomatic stage to severe dementia [9]. Better detection methods are therefore needed to reduce the frequency of misdiagnosis. Fortunately, radiotracers applied with modern imaging technologies are now available to accurately detect these protein depositions. When used in conjunction with other clinical tests, *in vivo* imaging technologies and molecular imaging in particular can assist in the diagnosis of AD by detecting the presence or absence of β-amyloid plaques.

Neuraceq is a radiopharmaceutical that binds to β-amyloid protein. It is a fluorine-18 (^{18}F)-labeled radioactive agent indicated for PET imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. The Neuraceq clinical development program included 978 administrations to 872 subjects in nine clinical trials and two non-interventional image-reading studies. In the clinical studies, Neuraceq was found to be generally safe and well tolerated, with no related serious adverse events (AEs) reported. The most common AEs were erythema (1.7%), irritation (1.2%) and pain (3.9%) at the injection site; all reported AEs were mild to moderate and of short duration [10].

In a global phase III histopathology study involving 205 end-of-life individuals who consented to donate their brains after death including 74 deceased subjects whose brains were collected and assessed for the presence of neuritic β-amyloid plaques, Neuraceq detected plaques with high sensitivity and specificity. Scans from 46 of 47 subjects with β-amyloid were correctly read as positive, yielding a sensitivity of 97.9% (95% CI: 93.8–100%). Positive scans, along with other clinical tests, help determine if cognitive impairment is due to β-amyloid pathology (i.e., AD). Scans from 24 of 27 subjects without β-amyloid were correctly read as negative, resulting in 88.9% specificity (95% CI: 77.0–100%). Negative scans allow physicians to consider alternative causes of cognitive impairment not associated with β-amyloid pathology. The histopathology study demonstrated a high degree of accuracy: negative and positive predictive values for Neuraceq were 96.0 (95% CI: 88.3–100%) and 93.9% (95% CI: 87.2–100%), respectively. Assessment of the same cortical regions by PET and histopathology in autopsied patients demonstrated a direct correlation between Neuraceq uptake and pathologic β-amyloid deposition. The study showed that visual assessment was very robust compared with quantification, and both modalities were largely overlapping in their positive and negative readouts during whole brain assessment [11].

Image-reading studies confirmed the reproducibility and reliability of the visual assessment based on the electronic reader training to be used in future clinical practice [12]. Clinical trials have not only demonstrated the robustness of the tracer in terms of its negative and positive predictive value, but also demonstrated its predictive value in cognitively impaired patients with positive amyloid scans. In a prospective outcome study, a substantial proportion of patients progressed to dementia due to AD over a 2-year and 4-year time frame. At 4-year follow-up, 88% (21/24) of individuals with mild cognitive impairment (MCI) and positive Neuraceq uptake converted to clinical dementia due to AD, whereas none of 21 Neuraceq-negative individuals with MCI experienced such a conversion [13]. Although the study was not designed to determine progression, other studies have confirmed these results independently [14].

Phase III results led to approval of Neuraceq in the USA, EU and Korea in 2014. Based on the Neuraceq clinical development experience, molecular imaging of β-amyloid can result in enhanced diagnostic accuracy, increased confidence for patients and physicians and improved patient outcomes. β-amyloid imaging can change physician behavior in terms of altered diagnostic thinking, testing and management of patients undergoing evaluation for cognitive decline. Results from the Neuraceq Phase III trials demonstrated that the β-amyloid tracer has a high positive and negative predictive value

hence particularly assisting in the differential diagnosis in clinically difficult patients. After β-amyloid imaging, physicians indicated that they were most likely to treat patients with cognitive decline in a manner consistent with their knowledge of the underlying amyloid pathology [15,16].

Evidence also suggests, earlier, more accurate detection of AD may yield health-economic benefits. Budget impact models in the USA suggest that the added cost of a PET scan is largely made up for by the decrease in evaluations and increased probability of a definitive diagnosis [17]. In a retrospective analysis of New Jersey Medicaid claims data (1997–2009), earlier treatment contributed to a delay in institutionalization among AD patients, resulting in significant cost savings to Medicaid. Even a modest delay in institutionalization (91 days) reduced Medicaid costs by US$ 19,108 per institutionalized patient. Incorporating an 18.5% cost offset from increased use of other medical services, as well as drug costs associated with earlier treatment, yielded a net savings of US$ 12,687 per patient [17].

In addition to conducting clinical studies and supporting investigator sponsored studies of Neuraceq, Piramal Imaging expedites Neuraceq supply contracts with drug companies developing disease-modifying therapies for AD. Drug developers are using β-amyloid detection methods to enable optimal patient selection in clinical trials. These companies view selection of the right patients via β-amyloid imaging as a prerequisite for successful AD drug development.

In order to provide access for patients and physicians to use Neuraceq in clinical routine, Piramal recently decided to support the Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) trial, sponsored by the Alzheimer's Association and managed by American College of Radiology and the American College of Radiology Imaging Network. The 4-year IDEAS study will enroll 18,488 eligible Medicare beneficiaries of age 65 and older to more than 200 sites throughout the USA, and will assess the impact of β-amyloid PET scanning on patient benefit such as management or avoidance of costs [18]. The IDEAS investigators are reportedly confident of obtaining clinical evidence to help drive Centers for Medicare and Medicaid reimbursement of β-amyloid PET scanning to make this important tool accessible.

Piramal Imaging has also secured 20 radiopharmacy sites to manufacture and supply Neuraceq, and is currently expanding its manufacturing partner network in Europe, the USA and Asia-Pacific markets to provide world-wide access. Establishing an extensive Neuraceq supply network is important because the compound's physical half-life translates into limited shelf life (the compound must be injected within 10 h post-production), necessitating a decentralized production network. Piramal continues to conduct clinical and health outcomes studies, reaching out to referring physician audiences (neurologists, geriatricians, psychiatrists) to build a broader body of evidence on the clinical utility and benefits of β-amyloid imaging with Neuraceq.

Other CNS product candidates in development

Piramal Imaging recently initiated a Phase I trial of an ^{18}F-labeled compound targeting Tau, a potential biomarker for diagnosing non-AD dementias as well as for monitoring neurodegeneration in AD-related dementia. Tau tangles are an important measure of neuronal death and correlate strongly with cognitive decline. Detection of Tau may therefore contribute to advanced monitoring of cognitive performance in patients with dementia.

Another CNS product candidate is an ^{18}F-labeled deuterated monoamine oxidase B (MAO-B) ligand specifically targeting activated astrocytes during neuroinflammation. An early component of neuroinflammation, astrogliosis is involved in neurodegenerative disorders including AD, multiple sclerosis, amyotrophic lateral sclerosis and Parkinson's disease. PET imaging of activated astrocytes during neuroinflammation would enhance characterization and monitoring of disease progression and therapy. A Phase I study is currently planned to further investigate this ^{18}F-MAO-B ligand.

Oncology product candidates

Piramal Imaging's developmental pipeline also includes two radiotracers for potential use in cancer diagnosis. ^{68}Ga-bombesin, a peptide labeled with the radioactive isotope ^{68}Gallium, is being investigated in a Phase I/II trial as a potential diagnostic for prostate cancer. ^{68}Ga-bombesin detects the gastrin-releasing peptide receptor, which is overexpressed in

prostate cancer. Importantly, gastrin-releasing peptide receptor shows no expression in normal prostate and in benign tissue. ^{68}Ga-bombesin is thought to be potentially useful in improving the accurate detection and staging of primary prostate cancer and also has an upside potential in the recurrent setting (restaging).

The other oncology product candidate, also in Phase I, is ^{18}F-FSPG, a new tracer for imaging the x_C^- transporter, which plays a key role in cancer growth [19] and progression and glutathione-based drug resistance [20]. FSPG is an amino acid derived from glutamate. The favorable biodistribution and clearance pattern of ^{18}F-FSPG suggest its potential use as a PET tracer in patients with non-small-cell lung cancer [21] or hepatocellular carcinoma. ^{18}F-FSPG is also being investigated for follow-up of patients with intracranial malignancies after neurosurgery/radiation treatment in cases with equivocal MRI findings.

An additional focus in cardiovascular disease

Molecular imaging also has potential diagnostic applications in cardio- and cerebro-vascular diseases. Piramal Imaging is investigating ^{18}F-GP1, a small fluorine-18-labeled molecule for detection of activated platelets during thrombus formation. GP1 has a high affinity to the GPIIb/IIIa receptor, which is the key receptor involved in platelet aggregation [22]. ^{18}F-GP1 is currently in phase I of clinical development.

Future perspective

Through its exclusive focus on molecular imaging, Piramal Imaging aspires to enhance its position as an innovator and leading player in the field. The company is currently perceived as a competent specialist and reliable partner in R&D, product supply and marketing of PET tracers. Piramal Imaging will continue to provide biomarker-specific PET tracers and logistical support to pharmaceutical companies conducting clinical trials of therapeutic compounds, particularly of potential disease-modifying treatments for AD. Just as the available data on β-amyloid detection provide proof of concept in AD, the company aims to do the same for detection of other biomarkers in oncology and cardiovascular disease. Piramal Imaging compounds are currently studied in seven investigational new drug (or country-equivalent) trials that are open and actively recruiting – a large number of trials for a company of this size.

As the company moves forward, Piramal Imaging will focus on creating value for its various stakeholders. For patients and physicians, enhanced value will result from improving early detection and characterization of chronic and life-threatening diseases, leading to better therapeutic outcomes and improved quality of life. For payers and society in general, value will accrue through development and delivery of PET tracers that address unmet medical needs and make healthcare more cost effective. In so doing, Piramal Imaging will contribute to reducing the overall burden of disease.

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