ANNUAL REPORTS IN MEDICINAL CHEMISTRY
Volume 42

Sponsored by the Division of Medicinal Chemistry of the American Chemical Society

Editor-in-Chief: ***JOHN E. MACOR***

BRISTOL-MYERS SQUIBB, R&D
WALLINGFORD, CT, USA

Annual Reports in
MEDICINAL CHEMISTRY

VOLUME **42**

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84 Theobald's Road, London WC1X 8RR, UK
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands
Linacre House, Jordan Hill, Oxford OX2 8DP, UK
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA

First edition 2007

ISBN: 978-0-12-373912-4
ISSN: 0065-7743

For information on all Academic Press publications visit our website at books.elsevier.com

Printed and bound in USA

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CHAPTER 7

Case History: JANUVIA™ (Sitagliptin), a Selective Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type 2 Diabetes

Ann E. Weber* and **Nancy Thornberry****

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1. INTRODUCTION

Diabetes is a global epidemic affecting more than 240 million people worldwide. The incidence of this disease is growing at an alarming rate, with 380 million cases predicted by 2025. Each year over 3.8 million people die from complications of diabetes, including heart disease, stroke and kidney failure. The vast majority

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Annual Reports in Medicinal Chemistry, Volume 42
ISSN 0065-7743, DOI 10.1016/S0065-7743(07)42007-3

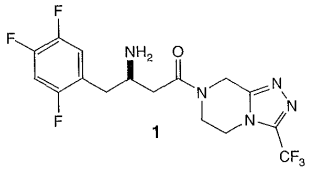

Figure 1 JANUVIA™ (sitagliptin).

(90–95%) of cases are type 2 diabetes, largely resulting from the increasing prevalence of obesity and sedentary lifestyles [1].

Despite the availability of a range of agents to treat type 2 diabetes, glucose control remains suboptimal, with less than 50% of patients achieving stated glycemic goals. In addition, current therapies have limited durability and/or are associated with significant side effects such as GI intolerance, hypoglycemia, weight gain, lactic acidosis and edema [2]. Thus, significant unmet medical needs remain. In particular, safer, better tolerated medications which provide increased efficacy and long-term durability are desired. JANUVIA™ (sitagliptin, **1**, Figure 1), a dipeptidyl peptidase IV (DPP-4) inhibitor, represents a promising new approach to the treatment of this disease.

2. PATHOGENESIS OF TYPE 2 DIABETES

The pathogenesis of type 2 diabetes involves a set of three primary defects: insulin resistance, insulin secretory dysfunction, and hepatic glucose overproduction. Insulin resistance is a common predisposing defect, and is believed to occur as a consequence of obesity in most individuals. As long as an individual maintains insulin secretion adequate to compensate for insulin resistance, plasma glucose levels remain normal; however, if β-cell function declines, and the pancreas is no longer able to produce adequate amounts of insulin to compensate for the insulin resistance, hyperglycemia – and subsequently, diabetes mellitus – results. Not only does this β-cell defect lead to hyperglycemia and the onset of diabetes, the progressive decline in β-cell function during the course of diabetes leads to the need for more and more complex treatment regimens to manage glucose control in diabetic patients, and ultimately, to the need for insulin. As expected from the pathogenesis of type 2 diabetes, therapies that increase the circulating concentrations of insulin have proven therapeutically beneficial in the treatment of type 2 diabetes [2]. Indeed, sulfonylureas and related insulin secretagogues currently represent 42% of the total worldwide oral market, with sales in excess of $1.7 billion, notwithstanding mechanism-based side effects of hypoglycemia and weight gain. In addition, current insulin secretagogues commonly fail to maintain adequate glycemic control, and may contribute to the progressive decline in β-cell function. Thus, current unmet medical needs in the treatment of type 2 diabetes include insulin secretagogues which are

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