CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-350

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	July 31, 2009
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 22-350
Applicant Name	Bristol-Myers Squibb
Proprietary / Established (USAN) Names	Onglyza saxagliptin
Dosage Forms / Strength	Tablets 2.5 mg and 5 mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Action:	*Approval*

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding saxagliptin and the reader should refer to the reviews in the action package for a more detailed discussion. Saxagliptin is an inhibitor of the serine protease enzyme - dipeptidyl peptidase IV (DPP-4) which is responsible for the rapid degradation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are short-lived intestinal peptides released in response to food ingestion that have an inhibitory effect on glucagon (which would result on inhibiting hepatic glucose synthesis) and an enhancing effect on insulin secretion when serum glucose is elevated. DPP-4 inhibitors therefore enhance the effect of the incretins by increasing their circulating half-life. Of note is that incretins have minimal, if any, effect on insulin secretion when glucose is normal or low and therefore would likely have less hypoglycemia as compared to some of the other agents used to treat diabetes.

The Agency has recently approved two agents that manifest their activity through the incretin pathway. The first is sitagliptin, a DPP-4 inhibitor like saxagliptin that is also administered orally, and the other is exenatide, a 34-amino acid GLP-1 analogue that has agonistic activity at the GLP-1 receptor and is given by twice-daily subcutaneous injection.

Over the last two to three years, concerns over the cardiovascular safety of certain diabetic drugs have led to debate regarding the adequacy of development programs to assure that these agents don't increase the cardiovascular risk in diabetic populations, which already have a 2-4 fold increase risk for cardiovascular events compared to matched non-diabetic populations. This issue was discussed at an Advisory Committee meeting in July of 2008, where the panel recommended that glycemic control agents for type 2 diabetes coming before the agency for approval should have pre-approval cardiovascular assessment screening, with further post-approval definitive testing to determine that increased cardiovascular risks associated with the medication are not noted. After much internal deliberation, we issued a final guidance

incorporating recommendations from the advisory committee. This guidance allows for a two-step, 'step-wise' assessment of potential cardiovascular risk during drug development. The first step, 'step-one', is to make a determination that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than 1.8 compared to a control group (with a point estimate near unity). Assuring that there is not an eighty percent increase in risk would allow marketing while a longer and larger outcome study, which would assure even less risk, is conducted. The boundary of 1.8 was chosen because a more conservative 'goal-post' to pre-approval testing would be too burdensome/prohibitive to drug develop, but this level of assurance (1.8) would be feasible and would provide some assurances while further testing was underway. The 'step-two' testing would be accomplished by a larger outcome study that must demonstrate that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than 1.3 compared to a control group in order for marketing to continue. Although one could question whether ruling out an 80% increase for initial marketing and ultimately ruling out a 30% increase is enough assurance, the reality is that these goals are what is practical to actual test in a randomized trial and the practicality of the situation was instrumental in dictating the risk ratios described above. It should also be noted that these risk ratios should be viewed in the context of the necessity that the point estimate is near unity.

These principles incorporate recommendations from the advisory committee. The details of this approach are outlined in the guidance[1], but of relevance is that at the time of issuance of the guidance, three NDA's were in review. We concluded that recommendations should apply to all ongoing programs including those with applications pending with the agency at the time of guidance issuance. Although not totally in alignment with the guidance, two of the three seemed to, in spirit, fulfill 'step-one' which would allow for marketing while awaiting the results of a 'step-two' definitive study. These two applications, one being this one, were presented at an Advisory Committee meeting (April 1 and 2, 2009), where the majority of the panel members concurred that 'step-one' had been fulfilled for saxagliptin that would allow marketing from a cardiovascular evaluation standpoint. Please see reviews of Drs. Parks, Joffe and Lowy for further details.

As another point for consideration, there has been concern with the DPP-4 inhibitors in regard to their potential adverse event profile based on their promiscuity toward other DPP enzymes, in particular DPP-8/9. During phase 3 development of a different DPP-4 agent, it was noted that monkeys developed dose and duration dependent cutaneous lesions that ranged from some flaking and blistering to frank ulceration and necrosis requiring euthanasia of the animals. Therefore, 13-week monkey studies (the most sensitive species) have been required of all DPP-4 agents in development. Sitagliptin, the currently marketed agent, did not cause these lesions in monkeys, and it was felt that this was because it was highly selective for DPP-4 with little activity for other DPP enzymes. Saxagliptin is also fairly selective for DPP-4, but it has been noted to cause these lesions. However, this happens only at doses 20-fold (mild) to 60-fold (necrotizing) above clinical exposure, so a large safety margin exists.

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[1] Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008, Clinical/Medical.

Another concern is that there are now postmarketing reports of pancreatitis in association with Byetta and Januvia that call into question if drugs working through the incretin system may have adverse effects on the pancreas. This is actively under review, but needs to be considered for any evaluation, and perhaps, labeling for saxagliptin.

Finally, a non-clinical finding for saxagliptin that will require further exploration was unexpected teratorgenicity in a rat embryofetal development study during co-administration of saxagliptin/metformin in a fixed dose tablet. This finding has been thoroughly reviewed and discussed by the division and upper pharmacology/toxicology management, all of which concur that this would not prohibit marketing, but should be more thoroughly explored as part of a post-marketing requirement to inform labeling and perhaps our concepts of what is needed for other combination tablets. I will discuss this issue more below.

The Division and I agree that saxagliptin may be approved for marketing as long as appropriate labeling can be agreed upon.

Efficacy

Efficacy has been thoroughly discussed in Ms. Mele's and Drs. Lowy and Joffe's reviews. I agree with their conclusions and I will not repeat the specifics here. The following table from Dr. Joffe's review (Page 13) demonstrates the efficacy results for the randomized trials.

Table 2. HbA1c (%) results for the phase 2 and 3 clinical trials (intent-to-treat population)

Study	N	Baseline mean ± SE[1]	Change from baseline Adj. mean ± SE[2]	Difference in adjusted mean change 95% CI	p-value
Study CV181008 (dose-ranging) – 12-weeks for cohort 1; 6 weeks for cohort 2					
Saxa 2.5 mg (cohort 1)	55	7.6±0.8	-0.7±0.1	-0.5 (-0.8, -0.1)	<0.01
Saxa 5 mg (cohort 1)	47	8.1±1.1	-0.9±0.1	-0.6 (-1.0, -0.3)	<0.001
Saxa 10 mg (cohort 1)	63	7.8±1.0	-0.8±0.1	-0.5 (-0.9, -0.2)	<0.001
Saxa 20 mg (cohort 1)	54	7.9±1.0	-0.7±0.1	-0.5 (-0.8, -0.1)	<0.01
Saxa 40 mg (cohort 1)	52	7.8±1.0	-0.8±0.1	-0.5 (-0.9, -0.2)	<0.01
Placebo (cohort 1)	67	7.9±1.0	-0.3±0.1		
Saxa 100 mg (cohort 2)	44	7.8±1.0	-1.1±0.1	-0.7 (-1.0,-0.5)	Not provided
Placebo (cohort 2)	41	7.6±1.1	-0.4±0.1		
Study CV181011 (monotherapy)					
Saxa 2.5 mg	100	7.9±0.9	-0.4±1.0	-0.6 (-0.9, -0.3)	<0.0001
Saxa 5 mg	103	8.0±1.1	-0.5±1.0	-0.6 (-0.9, -0.4)	<0.0001
Saxa 10 mg	95	7.8±0.9	-0.5±0.8	-0.7 (-1.0, -0.4)	<0.0001
Placebo	92	7.9±0.9	0.2±1.2		
Study CV181038 (monotherapy)					
Saxa 2.5 mg (AM)	67	8.0±0.1	-0.7±0.1	-0.5 (-0.7, -0.2)	<0.01
Saxa 2.5 mg→5 mg (AM)	69	8.0±0.1	-0.6±0.1	-0.4 (-0.7, -0.1)	0.01
Saxa 5 mg (AM)	69	7.9±0.1	-0.7±0.1	-0.4 (-0.7, -0.1)	<0.01
Saxa 5 mg (PM)	70	7.9±0.1	-0.6±0.1	-0.4 (-0.6, -0.1)	0.02
Placebo	68	7.8±0.1	-0.3±0.1		

Study CV181013 (add-on to thiazolidinedione)					
Saxa 2.5 mg	192	8.2±0.1	-0.7±0.1	-0.4 (-0.6, -0.2)	<0.001
Saxa 5 mg	183	8.4±0.1	-0.9±0.1	-0.6 (-0.8, -0.4)	<0.001
Placebo	180	8.2±0.1	-0.3±0.1		
Study CV181014 (add-on to metformin)					
Saxa 2.5 mg	186	8.1±0.1	-0.6±0.1	-0.7 (-0.9, -0.5)	<0.001
Saxa 5 mg	186	8.1±0.1	-0.7±0.1	-0.8 (-1.0, -0.6)	<0.001
Saxa 10 mg	180	8.0±0.1	-0.6±0.1	-0.7 (-0.9, -0.5)	<0.001
Placebo	175	8.1±0.1	+0.1±0.1		
Study CV181040 (add-on to sulfonylurea)					
Saxa 2.5 mg	246	8.4±0.1	-0.5±0.1	-0.6 (-0.8, -0.5)	<0.001
Saxa 5 mg	250	8.5±0.1	-0.7±0.1	-0.7 (-0.9, -0.6)	<0.001
Placebo + glyburide	264	8.4±0.1	+0.1±0.1		
Study CV181039 (initial combination with metformin)					
Saxa 5 mg + met	306	9.4±0.1	-2.5±0.1	-	-
Saxa 10 mg + met	315	9.5±0.1	-2.5±0.1	-	-
Saxa 10 mg	317	9.6±0.1	-1.7±0.1	-	-
Met	313	9.4±0.1	-2.0±0.1	-	-

[1]±SD for -008 and -011; [2]±SD for -011; SE=standard error; CI=confidence interval

The table above demonstrates that the sponsor has conducted multiple monotherapy and combination studies that do demonstrate that saxagliptin has a modest but clinically important hypoglycemic effect as measured by change in HbA1c. I agree with Dr. Joffe's conclusions that there is little difference between the 2.5 mg and 5 mg dose, but there is enough evidence based on the totality of the data (presented in the other reviews) to suggest that the 5 mg dose may provide additional efficacy for some patients not adequately responding to the 2.5 mg dose, while not increasing clinical important safety issues.

I do note that the amount of DPP-4 inhibition at 24-hours with the 2.5 mg dose is 37% while that with the 5 mg dose is 65%. This is interesting because it was original theorized by other sponsors that these agents would need to have 80% inhibition at 24-hours to be clinically effective. However, we now have saxagliptin and alogliptin which have had less inhibition than 80% at 24-hours, but seem to have a plateau in their clinical dose response well below the 80% DPP-4 inhibition level.

Safety

The available safety data and conclusions are outlined in Drs. Lowy, Joffe and Parks reviews and I agree with there conclusions and would refer the reader to their excellent reviews for an overview of the safety issues. I will only comment on selected issues.

In regards to the cardiovascular safety evaluation, the filing of this application predated Agency guidance. As such, this program did not have pre-specified definitions or prospective adjudication of major cardiovascular endpoints and any evaluation was retrospective in nature. Therefore the cardiovascular event data were evaluated in many different ways. I believe the

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