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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:	<i>Approval</i>

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 guidance¹, 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.

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 teratogenicity 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 ± SE¹	Change from baseline Adj. mean ± SE²	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 their 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

most pertinent aspect of this is that, no matter how the data is 'sliced and diced', the criteria of being less than the 1.8 goal-post was met with a point estimate near unity (bearing in mind all the caveats inherent in any type of unplanned, retrospective analysis on an endpoint that was not originally identified as something of interest and where only a small number of events occurred). This does give us some reassurance that saxagliptin will not have a negative cardiovascular impact and while not a perfect analysis, does fulfill the spirit of our guidance and the Advisory Committee voting reflected this view point as well. I believe that due to this being an unplanned analysis, retrospective in nature, and with limited events, labeling should not include this analysis and should only have the standard labeling that we use for diabetic agents noting no conclusive evidence of cardiovascular benefit with any anti-diabetic drug. I believe to do otherwise would be misleading, would misrepresent our degree of comfort with the data, and would create an unfair playing field for other agents.

Hypersensitivity was noted in subjects exposed to saxagliptin (using a collection of 65 preferred terms related to anaphylactic reaction, angioedema, hypersensitivity, edema and urticaria) 2.4% (50 events/2043 subjects) compared to 0.6% (5 events/799 subjects) receiving placebo. However, these rates were similar when a saxagliptin/ metformin group (0.9%:9 events/978 subjects) was compared to metformin alone (0.9%-3 events/328 subjects). For the term 'hypersensitivity' there were 18 events (18/2043, 0.9%) compared to none for placebo. I reviewed the case summaries supplied by the sponsor and all of these were minor, most associated with seasonal rhinitis, and did not cause interruption of therapy. It is difficult to interpret these results since there are small numbers involved, but there are reports of hypersensitivity/anaphylaxis/angioedema/Stevens-Johnson syndrome with Januvia that has resulted in labeling changes, so this will need to close monitoring.

As noted by Dr. Joffe, there appears to be minor dose-dependent reductions in lymphocyte counts without evidence of clinical repercussions. I agree with him that this could be further evaluated in the outcome study.

Dr. Joffe also notes that the incidence of fracture is 1.0 per 100 patient-years for saxagliptin (n=35/3021 subjects) compared to 0.6 per 100 patient-years for comparator (n=7/1127 subjects). The sponsor has been asked to clarify how many of these fractures were the result of major trauma and this is pending at this time, but as with the lymphocyte findings, this can also be an analysis incorporated into the outcome study.

Saxagliptin and comparator groups had similar incidence of ALT >3x and >5x elevations, but had four cases >10x ULN (Sax group included all doses, N=3376; Comparator n=1232). Two of these cases had viral hepatitis. The other cases did not demonstrate Hy's Law criteria and there was approximately a 3:1 randomization for saxagliptin compared to placebo. As such, I do not believe that a liver signal has been demonstrated, but this can continue to be evaluated in the outcome study. The review team, to further evaluate for hepatic toxicity, requested additional cases of severe transaminitis that have occurred since the 120-day safety update. This search revealed one case that fulfilled criteria for Hy's law. However, upon unblinding this case it was revealed that the subject was taking a comparator medication (glipizide).

As mentioned above, drugs that work through the incretin system may have adverse effects on the pancreas, and this is actively being explored by the agency. As noted in Dr. Joffe's review, there were very few events and those that occurred were similar between saxagliptin-treated and comparator-treated subjects. However, for the other two drugs we are concerned about (Januvia and Byetta), there did not appear to be a pre-clinical or clinical signal in their application, yet we have post-marketing reports that are concerning. Therefore, this will need to be carefully monitored.

Regarding the teratogenicity finding mentioned above, two fetus rats from a single dam and litter were noted to have neural tube malformations (craniorachischisis) in the treatment group of saxagliptin/metformin combination at 114x and 4x the clinical dose respectively. Craniorachischisis is apparently a rather rare finding in control rats and is therefore a cause of concern. There were not any such findings in a group receiving a lower saxagliptin but identical metformin dose (21x and 4x clinical dose). The sponsor put forth what they felt was a plausible mechanism that related to reduced folate and homocysteine levels due to metformin use, but since the exposure to metformin did not change between the two groups, and saxagliptin does not have any effect on metformin levels or metabolism, we felt this explanation was inadequate. It should also be noted that these findings have not been demonstrated with metformin given as a single agent or with saxagliptin given as a single agent (saxagliptin given at doses greater than 1500x clinical exposure).

These findings were discussed with the Reproductive and Developmental Toxicological Subcommittee (RDTS) as well as with the Director and Associate Director of Pharmacology/Toxicology where it was decided that the findings may be drug related and would require further exploration. However, it was also felt that since these findings had not been demonstrated with either drug given as monotherapy increased likelihood that these findings were spurious and that, combined with a several-fold safety margin, would allow marketing of saxagliptin while further investigation was being done post-approval. As such, the pharmacology/toxicology review staff members are recommending two required non-clinical postmarketing studies to further explore this finding. Until these studies are completed and reviewed, labeling should advise of these findings of co-administration of metformin and saxagliptin in animals to inform clinicians who may be taking care of women that are pregnant or are planning on becoming pregnant.

Advisory Committee Meeting

An advisory committee meeting was held on April 1, 2009 to discuss the cardiovascular safety data included in this application. Regarding whether the sponsor had provided evidence to rule out an unacceptable excess of cardiovascular risk, 10 panel members voted yes and 2 panel member voted no. All panel members voted that an appropriate outcome trial should be conducted post-marketing.

Conclusions and Recommendations

Saxagliptin has demonstrated efficacy for the 2.5 mg and 5 mg doses in reduction of HbA1c levels. This application does have adequate cardiovascular evaluation data to allow initial

marketing, but will require a formal outcome study. There are other clinical concerns as noted above (decreased lymphocyte counts, fractures, skin reactions and hepatotoxicity), but for some of these they didn't occur more often than in placebo/comparator treated subjects or for those that did occur more frequently the concern would not be serious enough to rise to the level of not allowing marketing. However, the planned outcome trial will allow an excellent opportunity to collect further data to define these concerns. I recommend approval of this application.

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/s/

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