CONCORDIA PHARMACEUTICALS, INC., Plaintiff, v. METHOD PHARMACEUTICALS, LLC, et al., Defendants.

Civil Action No. 3:14CV00016

UNITED STATES DISTRICT COURT FOR THE WESTERN DISTRICT OF VIRGINIA, CHARLOTTESVILLE DIVISION

2016 U.S. Dist. LEXIS 50221

April 13, 2016, Decided
April 13, 2016, Filed

PRIOR HISTORY: *Concordia Pharms., Inc. v. Method Pharms., LLC, 2015 U.S. Dist. LEXIS 151505 (W.D. Va., Nov. 4, 2015)*

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For Winder Laboratories, LLC, Defendant: Joshua Counts Cumby, LEAD ATTORNEY, Venable LLP, Washington, [*2] DC.

For Matthew Scott Tucker, Defendant: Edward Kyle McNew, Michie, Hamlett, Lowry, Rasmussen & Tweel, PLLC, Charlottesville, VA.

For Steven Pressman, Defendant: Joshua Counts Cumby, LEAD ATTORNEY, Venable LLP, Washington, DC; Roger Anthony Colaizzi, LEAD ATTORNEY, Venable LLP, Washington, DC.

JUDGES: Hon. Glen E. Conrad, Chief United States District Judge.

OPINION BY: Glen E. Conrad

OPINION

MEMORANDUM OPINION

In this action under the Lanham Act, the plaintiff, Concordia Pharmaceuticals, Inc. ("Concordia"), and the defendants, Method Pharmaceuticals, Inc. and Matthew Scott Tucker (collectively, "Method"), have moved to

exclude certain opinions offered by the opposing side's expert witnesses. The court held a hearing on the motions on March 3, 2016.[1] This memorandum opinion sets forth the court's rulings on the parties' motions.

1 During the March 3, 2016 hearing, the court also heard oral argument on the parties' cross-motions for summary judgment. On March 29, 2016, Concordia's motion for summary judgment was denied, and Method's motion for summary judgment was granted in part and denied in part. The case is proceeding to trial solely on Concordia's claim under the Lanham Act.

Background

The facts of this case are outlined [*3] in detail in the court's memorandum opinion on the parties' cross-motions for summary judgment. Thus, only a brief summary follows here.

In May of 2014, Concordia acquired the Donnatal® line of products ("Donnatal") from PBM Pharmaceuticals, Inc. ("PBM"). Donnatal is a line of combination phenobarbital and belladonna alkaloid ("PBA") products that is used as adjunctive therapy in the treatment of irritable bowel syndrome **("IBS")** and acute enterocolitis. Donnatal is available by prescription in either tablet or elixir form.

Donnatal was first introduced in the 1930s, before drug manufacturers were required to prove that drugs were both safe and effective in order to obtain approval by the Food and Drug Administration ("FDA"). Although Donnatal products have been approved for safety, the FDA has yet to determine their effectiveness.

For over thirty years, Donnatal faced competition from generic PBA products that were pharmaceutically equivalent to Donnatal. Beginning in August of 2011, manufacturers of the generic versions began to take their products off the market. Once the inventories of previously manufactured generic products were eliminated, Donnatal was the only line of PBA products [*4] available for prescription.

In 2013, Method began making plans to develop and market a new product that would be pharmaceutically equivalent to Donnatal. The new product was eventually named Me-PB-Hyos. Method reached out to Winder Laboratories, LLC ("Winder"), which had previously developed another product for Method, and expressed an interest in having Winder manufacture its Me-PBHyos products. Winder and Method agreed on the price that Winder would charge for supplying the products, and Method issued purchase orders for initial stability tests.

In March of 2014, Method used publicly-available copies of the Donnatal product labels and package inserts as templates to create labels and inserts for the Me-PB-Hyos products. Method then proceeded to list the Me-PB-Hyos products with two pharmaceutical databases, Medi-Span and First Databank, which are used by members of the pharmaceutical industry to determine whether generic substitutes are available for brand name products. Method advised the databases that it intended to start marketing the Me-PB-Hyos products on June 1, 2014. Based on the information provided by Method, which included the product labels and package inserts, the Me-PB-Hyos [*5] products were assigned the same Generic Product Identifier ("GPI") as Donnatal. The listings also indicated that the Me-PB-Hyos products would be available at a lower price.

Ultimately, after this litigation ensued, Method halted its plans to market the Me-PBHyos products, and the products were never manufactured by Winder or any other company. In mid-October 2014, Medi-Span removed the listings for the Me-PB-Hyos products. Around the same time, First Databank moved its listings for the Me-PB-Hyos products from active listings to archived listings.

After Method's Me-PB-Hyos products were listed with Medi-Span and First Databank, Donnatal prescriptions and unit sales declined. The parties dispute, however, whether the decline in prescriptions and unit sales was caused by the listings for the Me-PB-Hyos products.

From January of 2012 to June 2014, the prices of Donnatal products increased by over 1,400%. This included a 100% increase that Concordia implemented after acquiring the rights to Donnatal from PBM. It is undisputed that Concordia's profits and profit margin for Donnatal tablets and elixir increased after Method's Me-PB-Hyos products were listed with the databases. However, Concordia [*6] claims that its profits would have been even higher if Method had not listed the Me-PB-Hyos products and, thus, that it experienced lost profits as a result of the listings.

Procedural History

PBM commenced this action against Method on April 29, 2014, asserting claims of false advertising and unfair competition under the Lanham Act and related claims under state law. Following a series of amendments, the case is now being pursued against Method and Tucker, Method's founder and president, by. Concordia.

Following the completion of discovery, the parties filed cross-motions for summary judgment. On March 29, 2016, Concordia's motion for summary judgment was denied and Method's motion for summary judgment was granted in part and denied in part. A jury trial on the remaining claims under the Lanham Act is scheduled to begin on April 18, 2016.

The case is now before the court on the parties' motions to exclude opinions proffered by the opposing side's expert witnesses. Method seeks to exclude certain opinions of Dr. Brian Reisetter and Ivan Hofmann. Concordia seeks to exclude certain opinions of Dr. William Fassett and John Wills. Dr. Reisetter and Dr. Fassett are pharmacists who were retained [*7] to offer opinions regarding the database listings for Method's Me-PB-Hyos products. Hofmann and Wills are certified public accountants who were retained to offer opinions pertaining to damages.

Standard of Review

The admissibility of expert witness testimony is governed by *Rule 702 of the Federal Rules of Evidence.* The rule provides as follows:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
>
> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
>
> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evid. 702.

Under this rule, the district court acts as a gatekeeper to ensure that an expert's testimony "is not only relevant, but reliable." *Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 589, 113 S. Ct. 2786, 125 L. Ed. 2d 469 (1993).* "The rule 'requires that the [expert] testimony must be the product of reliable principles and methods that are reliably applied to the facts of the case.'" *United States v. Wilson, 484 F.3d 267, 274 (4th Cir. 2007)* (quoting *Fed. R. Evid. 702* advisory committee's note). In conducting its gatekeeping function, the [*8] court's primary goal is "to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael, 526 U.S. 137, 152, 119 S. Ct. 1167, 143 L. Ed. 2d 238 (1999).* The scope of the court's gatekeeping inquiry ultimately "depend[s] upon the particular expert testimony and facts of the case." *EEOC v. Freeman, 778 F.3d 463, 466 (4th Cir. 2015)* (citing *Kumho, 526 U.S. at 150*).

The party proffering the expert testimony has the burden of establishing its admissibility by a preponderance of the evidence. *Daubert, 509 U.S. at 593 n.10*; see also *Cooper v. Smith & Nephew, Inc., 259 F.3d 194, 199 (4th Cir. 2001).* In deciding whether a party has sustained its burden, the court must focus on the principles and methodology employed by the expert rather than the expert's ultimate conclusions. *Daubert, 509 U.S. at 595.* As the Supreme Court has recognized, however, "conclusions and methodology are not entirely distinct from one another." *General Elec. Co. v. Joiner, 522 U.S. 136, 146, 118 S. Ct. 512, 139 L. Ed. 2d 508 (1997).* Neither Daubert nor *Rule 702* requires the court "to admit opinion evidence that is connected to existing data only by the ipse dixit of the expert." Id. Instead, the

court "may conclude that there is simply too great an analytical gap between the data and the opinion proffered," and accordingly choose to exclude the opinion. Id.

Of course, "the court need not determine [*9] that expert testimony a litigant seeks to offer into evidence is irrefutable or certainly correct." *United States v. Moreland, 437 F.3d 424, 431 (4th Cir. 2006)*. "As with all other admissible evidence, expert testimony is subject to being tested by `[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof.' Id. (quoting *Daubert, 509 U.S. at 596*). However, because "expert witnesses have the potential to be both powerful and quite misleading," the court must ensure that any all expert testimony is both relevant and reliable. *Cooper, 259 F.3d at 199* (internal citations and quotation marks omitted).

Discussion

I. Dr. Reisetter

Concordia retained Dr. Brian Reisetter to offer opinions on the market impact and industry consequences of Method's submissions to Medi-Span and First Databank. Dr. Reisetter is a licensed pharmacist with a doctorate in pharmacy administration, who also works as a consultant for the pharmaceutical and medical industries. He has performed extensive research concerning the effects of pharmaceutical database listings on the perceptions and behavior of pharmacists and doctors. In the instant action, Dr. Reisetter has offered the opinion that Method's efforts to list its Me-PB-Hyos products with Medi-Span and First Databank "caused [*10] the marketplace to believe that there was an actual 'generic' or pharmaceutical equivalent for Donnatal appropriate for substitution," and that this "set off a series of inevitable downstream events in the marketplace that adversely affected the number of prescriptions for Donnatal filled and units sold, despite no such product being available." Reisetter Rep. ¶ 1.

In moving to exclude Dr. Reisetter's opinions on the market impact and industry consequences of Method's submissions to the pharmaceutical databases, Method questions the reliability and relevance of his opinions. Specifically, Method argues that Dr. Reisetter was not provided with full information regarding "availability issues" that were experienced with Donnatal products; that Dr. Reisetter improperly utilized Prozac as an example to explain how generic substitution occurs when a generic drug is linked to a brand drug in a pharmacy software system based on the products' GPI code; and that Dr. Reisetter improperly relied upon surveys conducted in other cases in forming his opinions in the instant case.

Having considered the parties' arguments, the court concludes that none of the issues identified by Method warrants the [*11] exclusion of Dr. Reisetter's testimony. To the extent Method faults Dr. Reisetter for not considering certain discrete "availability issues" that it identified during discovery, such as emails indicating that some pharmacies had incorrect or outdated National Drug Code ("NDC") numbers for Donnatal products, there is no indication that these issues were raised during Dr. Reisetter's deposition or considered by Method's own experts in rendering their opinions. While the availability issues identified by Method could arguably affect the weight accorded to Dr. Reisetter's testimony, the court is unable to conclude that they render his testimony inadmissible. Instead, these issues, and any effect that they may have on Dr. Reisetter's opinions, can be adequately addressed on cross-examination.

The court also declines to preclude Dr. Reisetter from using Prozac to illustrate how generic substitution commonly occurs in the pharmaceutical industry. In his report, Dr. Reisetter did not suggest that Prozac and Donnatal are similarly situated drugs. Instead, he merely used Prozac as an example to explain how generic substitution occurs when a generic drug is linked to a brand drug in a pharmacy [*12] software system based on the information contained in the pharmaceutical database listings. Method correctly points out that Prozac and the generic versions of fluoxetine are distinguishable from the products at issue in this case on a number of grounds. However, the court ultimately agrees with Concordia that these distinctions go to the weight of Dr. Reisetter's testimony regarding generic substitution rather than its admissibility.

Finally, the fact that Dr. Reisetter based his opinions, at least in part, on surveys performed in connection with other cases or research projects does not justify excluding Dr. Reisetter's testimony. While the court may ultimately limit the extent to which Dr. Reisetter is permitted to reference specific responses to survey questions, the court will permit him to offer opinion testimony based on the results of the prior surveys. See *Fed. R. Evid. 703* ("If

experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted."). The defendants remain free to cross-examine Dr. Reisetter about the particular questions posed in his prior surveys, the specific [*13] populations of pharmacists surveyed, and the conclusions that he ultimately reached. The defendants are also free to point out that Dr. Reisetter's opinions are not based on quantitative or qualitative research employed to determine actual market behavior in response to the particular database listings at issue in this case. However, the court will not preclude Dr. Reisetter from offering opinions informed by surveys conducted in previous cases.[2]

> 2 Because the prior surveys conducted by Dr. Reisetter did not account for the actual allegations in this case, Method correctly points out that the survey results would not support a false advertising claim based on a theory of implied falsity. See *PBM Prods., LLC v. Mead Johnson & Co., 639 F.3d 111, 122 (4th Cir. 2011)* ("Because the surveys failed to account for the actual allegations in the case, they failed to provide the required evidence of [implied] falsity."). Nonetheless, this does not render Dr. Reisetter's opinions inadmissible. Concordia's false advertising claim does not turn on proof of implied falsity. Instead, Concordia maintains that Method made literally false statements regarding its Me-PB-Hyos products. Moreover, as other courts have previously recognized, an expert's "data and testimony need not [*14] prove the plaintiffs' case by themselves; they must merely constitute one piece of the puzzle that the plaintiffs endeavor to assemble before the jury." *City of Tuscaloosa v. Harcros Chems.,Inc., 158 F.3d 548, 564-65 (11th Cir. 1998).*

For these reasons, Method's motion to exclude the opinions and testimony of Dr. Reisetter will be denied.

II. Dr. Fassett

Method retained Dr. William Fassett to review the reports from Concordia's experts, and to offer his own opinions regarding market conditions applicable to the sale of Donnatal products and the effect of the database listings for Method's Me-PB-Hyos products. Dr. Fassett has been a licensed pharmacist for over 45 years and is a professor emeritus of pharmacotheraphy at Washington State University. His career has involved the traditional practice of pharmacy, as well as pharmaceutical sales and marketing, pharmacy management, and advising formulary committees with respect to drug coverage decisions. Dr. Fassett also sits on the editorial board of several peer-reviewed publications related to pharmacy and the pharmaceutical industry, and has authored peer-reviewed publications relating to drug use review, product selection, and computer applications in the pharmaceutical industry.

Concordia seeks to exclude three opinions [*15] expressed in Dr. Fassett's expert report. The first opinion challenged by Concordia pertains to drug price increases. In his report, Dr. Fassett opined that price increases are not uncommon in the pharmaceutical industry; that the ultimate reactions of pharmacists and prescribers to price increases are generally consistent; and that he would expect formularies to eventually exclude Donnatal, and prescriptions for Donnatal to ultimately decrease, in response to increased prices. Dr. Fassett cited the prescription pain reliever Vivomo as an example of this principle in operation. Vivomo, like Donnatal, currently has no generic equivalent. According to Dr. Fassett's report, the manufacturer increased the price of Vivomo by over 600%, beginning on January 1, 2014. Subsequent to the price increases, Vivomo experienced increased sales dollars, fewer prescriptions and unit sales, exclusion from formularies, and substitution, "all of which," according to Dr. Fassett, "would be expected with Donnatal." Fassett Rep. ¶ 91.

The second opinion challenged by Concordia is Dr. Fassett's opinion that a class review may have affected the formulary status of Donnatal. In his report, Dr. Fassett explained [*16] that "low-claim-volume products like Donnatal (with an average of between 7,000 and 12,000 prescriptions per month) may 'fly below the radar' for a period of time until the level of expenditure becomes significant enough to warrant analysis, or until the formulary committee conducts a review of the entire therapeutic class." Fassett Rep. ¶ 45. During his deposition, Dr. Fassett further noted that the entry of new drug products into the therapeutic class could trigger a class review that potentially affects the formulary status of any or all drugs within the class.

The final opinion challenged by Concordia is Dr. Fassett's opinion that he "would not expect a significant

degree of loyalty to Donnatal among prescribers or pharmacists." Fassett Rep. ¶ 84. Because generic versions of Donnatal were commercially available for over 30 years, Dr. Fassett reasoned that "pharmacists and other participants in the market for prescription drugs would have stopped thinking of Donnatal as a brand drug and instead considered it a generic or multi-source product." Id. ¶ 84.

Concordia seeks to exclude all three of these opinions offered by Dr. Fassett on the ground that they are based on mere speculation. [*17] Having thoroughly reviewed Dr. Fassett's report and the applicable portions of his deposition, the court is unpersauded. It is clear from the record that Dr. Fassett's opinions are derived from his decades of experience as a pharmacist, during which he dispensed Donnatal and its generic competitors; his extensive experience working with formulary committees; and his specialized knowledge of how formulary committees make coverage determinations.

The fact that the opinions at issue are based, in large measure, on Dr. Fassett's personal experience does not preclude him from offering the opinions. "[T]he test of *Rule 702* expressly contemplates that an expert may be qualified on the basis of experience." *Wilson, 484 F.3d at 274* (quoting *Fed. R. Evid. 702* advisory committee's note). When an expert relies primarily on his own experience to render an expert opinion, the court must require the witness to "explain how [his] experience leads to the conclusion reached, why [his] experience is a sufficient basis for the opinion, and how [his] experience is reliably applied to the facts." Id.

Based on the current record, there is substantial reason to believe that Dr. Fassett will be able to establish a sufficient basis for each of the opinions challenged [*18] by Concordia. Any perceived weaknesses in the evidentiary support for Dr. Fassett's opinions can be appropriately addressed on cross-examination. Accordingly, Concordia's motion to exclude Dr. Fassett's opinions will be denied.

III. Hofmann

Concordia retained Ivan Hofmann to analyze and quantify the financial damages Concordia experienced as a result of the pharmaceutical database listings for Method's Me-PBHyos products. Hofmann concluded that Donnatal prescriptions and sales would have been higher "but for" the listings. Hofmann Rep. ¶ 79. He calculated lost profit damages based on lost Donnatal prescriptions and lost unit sales of Donnatal products. Hofmann ultimately opined that Concordia experienced "no less than $29.4 million" in lost profits from June 2014 to June 2015 "due to the listing of Me-PB-Hyos" in the pharmaceutical databases. Hofmann Rep. ¶ 81.

After carefully considering Hofmann's report and the portions of his deposition testimony provided by the parties, the court concludes that Hofmann's opinion regarding the amount of lost profit damages incurred by Concordia must be excluded. Specifically, the court finds that Concordia has failed to establish that Hofmann's lost [*19] profit calculations were "the product of reliable principles and methods" that were "reliably applied" to the particular facts of this case. *Wilson, 484 F.3d at 274.* The methodology employed by Hofmann in reaching his conclusions failed to take into account numerous market factors that could have affected Donnatal sales and prescriptions, and was based on selectively chosen data and unsupported assumptions.

For instance, Hofmann concluded that the listings for Method's Me-PB-Hyos products, which were never manufactured or sold, were the sole cause of the reduction in Donnatal prescriptions and sales from June 2014 to June 2015, and that the significant increases in the prices of Donnatal products played no role in the decline. In determining that Donnatal prescription volume is "generally unaffected by price increases," Hofmann purportedly considered whether "historical price increases" resulted in decreased Donnatal prescriptions. Hofmann Rep. ¶¶ 48-55. However, he limited his analysis to two price increases in 2012, which were implemented at a time when existing inventories of competing generic products were being eliminated from the market. Hofmann completely disregarded a price increase that was implemented [*20] in December of 2013, which was followed by a reduction in prescription volume and unit sales. The timing of this particular price increase is particularly relevant, since it occurred after generic PBA products had been removed from the market, but before Method's products were listed with the pharmaceutical databases. Nonetheless, it was not addressed in Hoffman's analysis of historical price increases. Concordia has failed to prove that the selective analysis employed by Hofmann in evaluating the effect of increased prices was predicated on a scientifically sound or reliable methodology.

Additionally, in calculating lost profits, Hofmann failed to consider numerous other market factors that could have contributed to the decline in Donnatal sales and prescriptions. For instance, in 2013 and 2014, after the price of Donnatal was significantly increased and generic versions were no longer available, Donnatal was removed from certain health plan formularies. These formulary changes were not addressed in Hofmann's report. Nor was the impact of newer drugs available for the treatment of IBS, which, unlike Donnatal, have been approved for effectiveness by the FDA. Likewise, Hofmann did not [*21] consider whether sales of Donnatal were affected by marketing initiatives or pricing strategies utilized by competitors in the IBS market. Instead, aside from discussing select price increases, Hofmann's report is devoid of any discussion of other factors that could have contributed to the lost profits that Concordia allegedly experienced during the time period at issue.

The court is convinced that this methodological flaw also renders Hofmann's lost profit calculations unreliable. See, e.g., *MyGallons LLC v. U.S. Bancorp, 521 F. App'x 297, 307 (4th Cir. 2013)* (holding that the district court abused its discretion in allowing testimony by a damages expert that did not rest on "the requisite 'reliable foundation' that was required for such testimony," and emphasizing that the expert's projections "ignored business realities and relied on sheer speculation"); *Pharmanetics, Inc. v. Aventis Pharms., Inc., 182 F. App'x 267, 271 (4th Cir. 2006)* (affirming the district court's decision to exclude expert testimony on lost sales, where the expert assumed that only the defendant's actions caused the plaintiff's losses and failed to consider other factors that would have caused lost sales); *MicroStrategy Inc. v. Business Objects, S.A., 429 F.3d 1344, 1355 (Fed. Cir. 2005)* (emphasizing that district courts have "the responsibility to exclude an expert opinion that overlooks factors that render the testimony unreliable and/or [*22] speculative"). Even if these other market factors "may not have made a difference in the ultimate outcome of his analysis," Hofmann's failure to consider them, or to offer an explanation for his failure, creates "enough of a doubt as to the overall reliability of [his] opinions as to render them inadmissible." *Smithers v. C&G Custom Module Hauling, 172 F. Supp. 2d 765, 771 (E.D. Va. 2000).*

The reliability of Hofmann's lost profits calculations is further undermined by the fact that they were based on assumptions unsupported by the record. For instance, Hofmann assumed that the database listings for Method's products had the same effect on the sales of Donnatal tablets and elixir. However, this assumption is contrary to the very evidence on which Hofmann relied. In his report, Hofmann cited extensively to a declaration executed by Aaron Hullett, a sales director for Concordia, in which Hullett noted that unit sales of Donnatal tablets decreased dramatically after Me-PB-Hyos was listed with Medi-Span and First Databank. While Hullett went on to note that Donnatal is also available as an elixir, he did not attempt to attribute the decline in elixir sales to the presence of Me-PB-Hyos in the pharmaceutical databases. Instead, Hullett acknowledged that "the majority [*23] of [elixir] sales are to hospitals, which generally do not rely on drug databases for purchasing in the same manner as pharmacists." Hullett Dec. 11, 2014 Decl. ¶ 9 (emphasis added).

Even though Hullett expressly recognized that the database listings for Me-PB-Hyos would have had a lesser impact on the sales of Donnatal elixir, Hofmann nonetheless included 100% of the decline in sales of sixteen ounce bottles of Donnatal elixir in his damages calculation. See Hofmann Rep. 31-32 (attributing 17,190 lost unit sales of elixir to Method). The court agrees with Method that Hofmann's failure to account for the distinction recognized by Hullett further undermines the reliability of Hofmann's lost profit calculations, as does his failure to address the fact that sales of Donnatal tablets and elixir followed the same trajectory during the period of alleged harm. See *Tyger Constr. Co. v. Pensacola Constr. Co., 29 F.3d 137, 142 (4th Cir. 1994)* (emphasizing that "[a]n expert's opinion as to damages must be causally related to the alleged harm" and "should be excluded when it is based on assumptions which are speculative and are not supported by the record").

For these and other reasons cited by Method, the court will exclude Hofmann's opinion that Concordia suffered "no less [*24] than $29.4 million" in lost profits from June 2014 through June 2015 "due to the listing of Me-PB-Hyos" in the pharmaceutical databases. Hofmann Rep. ¶ 81. To the extent Concordia argues that Method's criticisms of Hofmann's report go more to the weight of his expert testimony than its admissibility, the court disagrees. Concordia has simply not met its burden of showing that Hofmann's lost profits calculations rest upon a sufficient factual basis and a reliable application of established principles and methods. Accordingly, his opinion as to the total amount of lost profit damages

incurred by Concordia must be excluded under *Rule 702*, Daubert, and its progeny.[3]

> 3 As the court noted in ruling on the parties' cross-motions for summary judgment, the court's decision to limit the opinions offered by Hofmann does not necessarily preclude him from testifying altogether. His specialized knowledge could still assist the jury in other ways, and Concordia may present objective data and elicit other factual testimony from Hofmann to support its claim for damages.

IV. Wills

Method retained John Wills as a rebuttal damages expert. Wills did not attempt to offer his own opinion regarding the amount of damages [*25] suffered by Concordia. Instead, he evaluated Hofmann's report and ultimately opined that the lost profit damages compiled by Mr. Hofmann "are speculative and inconsistent with the facts in this case." Wills Rep. 2.

In light of the court's decision to exclude Hofmann's opinion on the amount of lost profit damages incurred by Concordia, it appears that Wills' rebuttal opinions are no longer relevant and that his attendance at trial may be unnecessary. Accordingly, the motion to exclude Wills' rebuttal opinions will be dismissed without prejudice. Should Method ultimately elect to call Wills as a witness and elicit expert opinions from him, the court will revisit the admissibility of his opinions.

Conclusion

For the foregoing reasons, Method's motion to exclude certain opinions of Dr. Reisetter will be denied; Concordia's motion to exclude certain opinions of Dr. Fassett will be denied; Method's motion to exclude Hofmann's opinion on the amount of lost profit damages incurred by Concordia will be granted; and Concordia's motion to exclude Wills' rebuttal opinions will be dismissed without prejudice.

The Clerk is directed to send copies of this memorandum opinion and the accompanying order [*26] to all counsel of record.

DATED: This 13th day of April, 2016.

/s/ Glen E. Conrad

Chief United States District Judge

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner

v.

JANSSEN ONCOLOGY, INC.,

Patent Owner

U.S. Patent No. 8,822,438 to Auerbach *et al.*
Issue Date: September 2, 2014
Title: Methods and Compositions for Treating Cancer

Inter Partes Review No. IPR2016-01332

DECLARATION OF IVAN T. HOFMANN, CPA/CFF, CLP

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I, Ivan T. Hofmann, hereby declare as follows.

I. Introduction

1. I am over the age of eighteen and otherwise competent to make this declaration.

2. I have been retained as an independent expert on behalf of MYLAN PHARMACEUTICALS INCORPORATED ("Mylan" or "Petitioner") for the above-captioned *inter partes* review ("IPR").

3. I understand that this IPR involves U.S. Patent No. 8,822,438 (the "'438 Patent" or the "Patent-at-Issue").[1] MYL Ex. 1001. I understand that Alan H. Auerbach and Arie S. Belldegrun are the named inventors and that, according to the United States Patent and Trademark Office ("USPTO") records, the '438 Patent is currently assigned to JANSSEN ONCOLOGY, INC. ("Janssen" or "Patent Owner"). MYL Ex. 1001.

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[1] I understand that the Patent Trial and Appeal Board instituted trial in IPR2016-00286, captioned *Amerigen Pharms. Ltd. (Petitioner) v. Janssen Oncology, Inc. (Patent Owner)*, on May 31, 2016. I also understand that in conjunction with the petition, Amerigen filed the declaration of DeForest McDuff dated December 4, 2015 (the "McDuff Declaration"). I reviewed the McDuff Declaration in forming my opinions.

4. My company, Gleason IP, a division of Gleason & Associates, P.C. ("Gleason"), has been retained by Perkins Coie LLP on behalf of Mylan to evaluate aspects of commercial success, from an economic perspective, as it pertains to Zytiga (abiraterone acetate) and the '438 Patent. Gleason is being compensated for the work performed on this engagement based on the time incurred by me at a rate of $435 per hour and by other Gleason personnel, working at my direction and under my supervision, at rates ranging from $95 to $275 per hour. Our compensation is not affected by the outcome of this case.

5. In formulating my opinions, I have considered all documents cited in this declaration. I have included a list of these documents in **Attachment A-1** to this declaration. This declaration summarizes my current opinions, which are subject to change depending upon additional information and/or analysis. I reserve the right to supplement this declaration in response to any opinions of experts on behalf of the Patent Owner and/or as additional information becomes available.

II. Qualifications

6. I am a Managing Director at Gleason, which is an economic, accounting, and financial consulting firm that provides services primarily in the areas of Valuation, Litigation Support, Intellectual Property, Forensic Accounting and Financial

Reorganization. I am the leader of the Intellectual Property Practice. Prior to joining Gleason, I worked for the global firm of Deloitte & Touche, LLP.

7. I graduated *magna cum laude* from the University of Notre Dame in 1994 with a Bachelor of Business Administration degree and a double major in Economics and Accounting. I am a Certified Public Accountant ("CPA"). I am also Certified in Financial Forensics ("CFF"). I am a member of the Licensing Executives Society ("LES") and have received my Certified Licensing Professional ("CLP") designation, which is granted by the LES to professionals with demonstrated knowledge and experience in the areas of intellectual property and licensing. I have attended and instructed numerous continuing education seminars since the completion of my formal education and have been a speaker on numerous occasions on a variety of financial, economic, accounting, and valuation topics. I have presented to various bar associations and organizations on the issues of intellectual property, financial damages, valuation, financial statement analysis, and other topics.

8. I have extensive knowledge and experience in the areas of economic and market analysis as it relates to litigation matters. My experience in intellectual property matters includes the valuation of intellectual property, analysis of objective indicia of nonobviousness, market analysis involving product performance, the determination of damages associated with patent infringement and other intellectual property (including

lost profits, disgorgement, and reasonable royalty, as applicable), consideration of irreparable harm, analysis of *Panduit* Factors related to demand for patented features, and market analysis of non-infringing alternatives. I have analyzed damages claims in trademark infringement, false advertising, and other cases involving the Lanham Act. I have experience in a broad range of industries, including pharmaceuticals, manufacturing, technology, healthcare, communications, construction, extractive, and other industries.

9. My work experience includes litigation support and consulting engagements with a variety of pharmaceutical and biologics companies. In my work in the pharmaceutical industry, I have performed financial and economic analysis for over one hundred prescription pharmaceutical products, including virtually every major therapeutic class of drugs. I have been asked to study and analyze objective indicia of nonobviousness (including commercial success and nexus), consider claims of irreparable harm, determine and quantify damages, perform product pipeline consulting, and assist with licensing and settlement discussions.

10. In the course of my work in providing consulting and expert services, I regularly analyze and review data for the pharmaceutical industry, including IMS Health Services, Inc. ("IMS"), Symphony Health Solutions, and other information service providers. I am knowledgeable regarding the role of pharmaceutical databases

such as First Databank, Medispan, Gold Standard, and other information sources in the fulfillment of prescriptions. I am also knowledgeable regarding the process of prescription writing, fulfillment, and generic substitution in the pharmaceutical industry. I have analyzed data and information and testified as an expert witness numerous times in matters involving the pharmaceutical industry and the role of brand versus generic competition. I have been qualified as an expert witness in pharmaceutical economics and specifically to address the issues of commercial success and nexus on numerous occasions by various federal courts and institutions.

11. I have been engaged by the USPTO and Office of the Solicitor as an expert to analyze and testify on issues involving objective indicia of nonobviousness, including commercial success and nexus related to proceedings in which both the Honorable David Kappos, Under Secretary of Commerce for Intellectual Property and former Director of the USPTO, and the Honorable Michelle Lee, in her official capacity as Under Secretary of Commerce for Intellectual Property and Director of the USPTO, were defending the USPTO's denial of certain patent applications.

12. I also have extensive experience in analyzing, calculating, and determining damages and other financial and economic issues in various dispute settings. I have been designated as a testifying expert in federal and state courts, Delaware Chancery Court, the United States International Trade Commission, and on

matters before various domestic and international arbitration panels. I have analyzed damages involving intellectual property disputes, breach of contract claims, shareholder disputes, insurance recovery, class actions, and others. I also have experience assessing claims of irreparable harm in connection with temporary restraining order and preliminary injunction hearings, and determining whether financial damages are calculable. My full *curriculum vitae* is included as **Attachment A-2**.

III. Case Background

A. Prostate Cancer

13. I understand that prostate cancer occurs in the male prostate, a small gland "that produces the seminal fluid that nourishes and transports sperm."[2] "Prostate cancer is one of the most common types of cancer in men,"[3] with a one-in-seven lifetime risk

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[2] I am not an oncologist or urologist. I cite my understandings to technical issues and various sources for those technical understandings as identified throughout this declaration. MYL Ex. 1051, Mayo Clinic Website, Prostate cancer, http://www.mayoclinic.org/diseases-conditions/prostate-cancer/basics/definition/con-20029597?p=1 ("Mayo Clinic") (accessed 6/28/2016).

[3] MYL Ex. 1051 (Mayo Clinic).

of being diagnosed.[4] In recent years, estimates for prostate cancer indicate nearly 181,000 new cases and more than 26,000 deaths annually in the U.S. alone.[5]

14. I understand that patients diagnosed with prostate cancer may undergo a variety of treatment options, including: (1) active surveillance (i.e., no action taken until disease progresses); (2) radiation therapy (i.e., using "high-powered energy to kill cancer cells") and surgical removal of the prostate; (3) chemotherapy (i.e., using drugs to kill cancer cells); (4) hormone therapy (e.g., interrupting production of testosterone to kill or slow growth of cancer cells); and (5) other treatments such as cryosurgery (e.g., freezing tissue to kill cancer cells) and immunotherapy (e.g., genetically engineering immune cells to kill cancer cells).[6]

15. Castrate-resistant prostate cancer ("CRPC") refers to prostate cancer that is able to grow despite usage of treatments lowering androgen production.[7] Metastatic castrate-resistant prostate cancer ("mCRPC") refers to CRPC that has metastasized

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[4] MYL Ex. 1041, Cancer.org (ACS), "What are the key statistics about prostate cancer?" http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics ("ACS") (accessed 6/28/2016).

[5] MYL Ex. 1041 (ACS).

[6] MYL Ex. 1051 (Mayo Clinic).

[7] MYL Ex. 1040, Cancer.net (ASCO Patient Website), Treatment of Metastatic Castration-Resistant Prostate Cancer, http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer ("ASCO") (accessed 6/28/2016).

beyond the prostate into other parts of the body.[8] Studies have found that approximately 10 percent to 20 percent of patients with prostate cancer develop CRPC within five years of follow-up.[9] Among these patients, at the time of CRPC diagnosis, at least 84 percent would already have mCRPC, and of the remaining non-metastatic patients at the time of diagnosis, 33 percent would develop mCRPC within two years.[10]

B. Zytiga (abiraterone acetate)

16. Zytiga (abiraterone acetate) is a CYP17 inhibitor indicated in combination with prednisone for the treatment of mCRPC.[11] Zytiga works by interrupting androgen production (including, for example, testosterone) in the testes, adrenal glands, and tumor.[12] Zytiga is a type of hormone therapy.[13]

17. Zytiga's label indicates a recommended dose of 1,000 mg (via four 250-mg tablets) administered orally once-daily in combination with 5 mg prednisone

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[8] MYL Ex. 1040 (ASCO).

[9] MYL Ex. 1050, Kirby, M., C. Hirst, and E.D. Crawford (2011), "Characterising the Castration-Resistant Prostate Cancer Population: A Systematic Review," Int'l J. Clinical Practice 65(11):1180–1192, at 1180 ("Kirby").

[10] MYL Ex. 1050 (Kirby) at 1180.

[11] MYL Ex. 1065, Zytiga Label, 5/20/2015, at 1.

[12] MYL Ex. 1066, Zytiga Website, How Zytiga® (abiraterone acetate) Works, https://www.zytiga.com/print/about-zytiga/how-zytiga-works ("Zytiga Website") (accessed 6/28/2016).

[13] MYL Ex. 1051 (Mayo Clinic).
MYL Ex. 1066 (Zytiga Website).

administered orally twice daily.[14] The FDA initially approved Zytiga in April 2011 with an indication limited to patients whose prostate cancer progressed after treatment with docetaxel, a chemotherapy drug.[15] In December 2012, the FDA approved Zytiga for treatment of patients with or without prior chemotherapy treatment.[16]

C. The '438 Patent

18. The '438 Patent, entitled "Methods and Compositions for Treating Cancer," was filed on February 24, 2011, and issued on September 2, 2014.[17] The abstract reads as follows:[18]

> Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17α-hydroxylase/C17,20-lyase inhibitor, such as abiraterone acetate (i.e., 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene), in combination with at least one additional therapeutic agent such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17α-hydroxylase/C17,20-lyase inhibitor, and at least one additional therapeutic agent, such as an anti-cancer agent or a steroid.

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[14] MYL Ex. 1065 (Zytiga Label) at 1.

[15] MYL Ex. 1046, FDA Website, Drugs@FDA – Zytiga, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails (accessed 6/28/2016); MYL Ex. 1045, FDA News Release, "FDA expands Zytiga's use for late-stage prostate cancer," 12/10/2012, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm331492.htm (accessed 6/30/2016) ("FDA News Release").

[16] MYL Ex. 1065 (Zytiga Label) at 1; MYL Ex. 1045 (FDA News Release).

[17] MYL Ex. 1001 ('438 patent).

[18] MYL Ex. 1001 ('438 patent).

19. Independent claim 1, the only independent claim, reads as follows: "A method for the treatment of prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone."[19]

D. Prosecution of the '438 Patent

20. I understand that the application from which the '438 Patent issued was filed on February 24, 2011, and the '438 Patent issued on September 2, 2014.[20] During that period, I understand that Johnson & Johnson ("J&J") and related parties corresponded with the USPTO regarding the patentability of the presented claims.[21] In particular, I understand that the USPTO rejected the presented claims several times on the grounds of obviousness and double patenting, but ultimately allowed 20 claims based on "unexpected commercial success of the launch of the drug" and withdrawal of a co-pending patent application.[22]

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[19] MYL Ex. 1001 ('438 patent).
[20] MYL Ex. 1001 ('438 patent).
[21] For brevity, I typically refer to these related entities, collectively, as J&J.
[22] MYL Ex. 1013 ('438 Patent Prosecution History July 3, 2013 Notice of Allowance) at 2–3; MYL Ex. 1039 ('438 Patent Prosecution History September 11, 2012 Office Action) at 1–6.

IV. The Definitions of Commercial Success and Nexus Relative to Objective Indicia of Nonobviousness

21. It is my understanding that "commercial success" is a legal construct that has been established through case law. Analysis of commercial success is premised on the concept that if a product is economically successful, it may provide objective evidence of nonobviousness.

22. I also understand that courts have found that commercial success may not provide objective indicia of nonobviousness for asserted claims of patents where the underlying product (or in the case of pharmaceuticals, the underlying compound) is protected by a patent and/or regulatory exclusivity that prevents competition in the market. Similarly, I understand that the existence of blocking patents disincentivizes others from pursuing a solution to a market demand if the solution would infringe a blocking patent.

23. I further understand that the commercial success of the product must be attributable to the alleged novel features of the claimed invention. I understand this to mean that, to support a finding of nonobviousness, any alleged commercial success requires that the success of the claimed product must have resulted from the merits of the claimed invention as opposed to the prior art or other extrinsic factors. In other words, there must be a causal correlation, or "nexus," between the unique merit of the claimed invention and the success of the product. I also understand that if purported

commercial success is due to an element in the prior art, no nexus exists. In essence, I understand that if the feature that drives the purported commercial success was known in the prior art, such success is not pertinent.

V. The Performance of Zytiga Does Not Provide Objective Indicia of Nonobviousness of the '438 Patent Due to the Existence of a Blocking Patent

24. The performance of Zytiga fails to provide objective indicia of nonobviousness of the claims of the '438 Patent because no other company had an ability to commercialize a pharmaceutical product containing the compounds both before and after the filing date of the '438 Patent because of patent exclusivities, as discussed below. A blocking patent is one that effectively blocks others from making, selling, or using a product without use of that patent.[23]

25. U.S. Patent No. 5,604,213 (the "'213 Patent"), entitled "17-Substituted Steroids Useful in Cancer Treatment," describes the abiraterone compound and methods for treating an androgen-dependent or estrogen-dependent disorder using that

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[23] *See, e.g.*, MYL Ex. 1054, Murphy et al. (2012), Patent Valuation: Improving Decision Making through Analysis, Wiley, at 102. ("A blocking patent is a patent that blocks a rights holder on a different patent from exploiting the different patented invention without a license to the blocking patent.").

compound.[24] According to the FDA's Orange Book, a publication where companies list patents that are asserted to cover pharmaceutical products, the '213 Patent has been alleged to cover Zytiga.[25] The application from which the '213 Patent issued was filed in 1994 and the '213 Patent issued in 1997, long before the earliest filing date to which '438 Patent claims priority: the date of its provisional patent application filed in 2006.[26] According to the FDA, the '213 Patent is expected to expire in December 2016.[27]

26. The '213 Patent is a blocking patent covering Zytiga and thus creates economic and legal barriers to commercially launching products containing abiraterone. This, in turn, creates a disincentive for potential competitors to research and develop abiraterone and the claimed '438 Patent subject matter due to the inability to commercialize an abiraterone-containing product. From an economic perspective, the existence of a blocking patent that prevents others from making, selling, or using an abiraterone product would provide companies limited economic incentives to develop the invention claimed in the '438 Patent.

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[24] MYL Ex. 1005 ('213 patent); MYL Ex. 1036 ('438 Patent Prosecution History February 24, 2011 Initial Application) at 7, 10.

[25] MYL Ex. 1047, FDA Website, Orange Book, Zytiga (NDA 202379), http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&Product_No=001&table1=OB_Rx ("Orange Book") (accessed 6/30/2016).

[26] MYL Ex. 1001 ('438 patent).

[27] MYL Ex. 1047 (Orange Book).

27. I understand that courts have found that, in the presence of blocking rights, existence of commercial success provides little probative value on whether a claimed technology is obvious.[28]

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[28] MYL Ex. 1053, *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376–77 (Fed. Cir. 2005) ("Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art....In this case Merck had a right to exclude others from practicing the weekly-dosing of alendronate specified in claims 23 and 37, given (1) another patent covering the administration of alendronate sodium to treat osteoporosis, U.S. Pat. No. 4,621,077 (issued Nov. 4, 1986); and (2) its exclusive statutory right, in conjunction with FDA marketing approvals, to offer Fosamax at any dosage for the next five years. Because market entry by others was precluded on those bases, the inference of non-obviousness of weekly-dosing, from evidence of commercial success, is weak."); MYL Ex. 1057, *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1383 (Fed. Cir. 2005) ("[A] high degree of commercial success permits the inference that others have tried and failed to reach a solution. In *Merck*, we held that evidence of commercial success resulted in a particularly weak inference because prior art patents prevented others from competing to reach the solution embodied in the claims at issue."); MYL Ex. 1048, *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740–41 (Fed. Cir. 2013) ("Where 'market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak.' This principle applies forcefully to the present case. The now expired Shroot patents blocked the market entry of 0.3% adapalene products until their expiration in 2010, long after Galderma invented 0.3% adapalene compositions of the asserted claims. As such, no entity other than Galderma could have successfully brought to 0.3% to market prior to 2010. Like the commercial success described in *Merck & Co.*, the commercial success of Differin® Gel, 0.3% is of 'minimal probative value.'").

28. Based on my analysis from an economic perspective, the existence of the '213 Patent prevents the performance of Zytiga from providing objective evidence of nonobviousness of the '438 Patent.

VI. The Performance of Zytiga Does Not Provide Objective Indicia of Nonobviousness of the '438 Patent because There is No Nexus between the Performance of Zytiga and the Claims of the '438 Patent

29. As explained above, commercial success is only informative on nonobviousness of a particular invention if there is a demonstrated nexus between that purported success and the alleged invention. However, I am not aware of any evidence provided during patent prosecution regarding nexus to the '438 Patent and the performance of Zytiga. By contrast, several factors indicate a lack of nexus between the alleged invention claimed in the '438 Patent and the performance of Zytiga.

30. As explained below, the performance of Zytiga can be attributed to factors that I understand are not claimed by the '438 Patent and were previously known. Specifically, I understand the claims of the '438 Patent do not cover (1) the individual compounds abiraterone acetate or prednisone or (2) the method using combinations of drugs for the treatment of patients with prostate cancer. As a result, there is no evidence that Zytiga sales are due to the benefits of the combination of abiraterone and prednisone, rather than the sum of the benefits of each component individually. Furthermore, I understand that the use of the specific glucocorticoid prednisone has not

been shown to have incremental benefit over other glucocorticoid steroids, which I understand are not covered by the '438 Patent.[29]

31. As discussed above, I understand that the compound that is the active ingredient in Zytiga, abiraterone acetate, is alleged to be covered by the '213 Patent, not the '438 Patent.[30] I understand that during patent prosecution, J&J provided no evidence or meaningful analysis indicating that any alleged success was due to contribution of the technology claimed in the '438 Patent versus the '213 Patent.

32. Furthermore, I understand from Dr. Garnick's Declaration that the methods of treating patients with combinations of drugs are known and common in the marketplace for cancer treatment. For example, I understand that other CYP17 inhibitors, such as ketoconazole, were previously used to treat prostate cancer before abiraterone acetate and that it was standard practice to co-administer hydrocortisone or prednisone with ketoconazole to address common side effects like hypertension, hypokalemia, and fluid retention.[31] Similarly, dosing information for Jevtana (cabazitaxel; approved before J&J filed the NDA for Zytiga), a chemotherapy drug

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[29] MYL Ex. 1002 (Declaration of Marc B. Garnick, M.D. ("Garnick Decl.")) ¶ 79.
[30] MYL Ex. 1047 (Orange Book).
[31] MYL Ex. 1002 (Garnick Decl.) ¶¶ 33, 42; MYL Ex. 1064 (Zytiga Brochure, Putting Prednisone in Perspective, 3/2015).

administered to cancer patients, is indicated with concurrent administration of prednisone.[32]

33. Given the '438 Patent does not claim the compounds or the general methods of treating patients with combinations of drugs, there is no evidence that the performance of Zytiga is due to the benefits of the combination of abiraterone and prednisone. For example, the USPTO examiner indicated that abiraterone and prednisone were known to be individually effective for the treatment of prostate cancer.[33] Yet J&J did not assert during patent prosecution that the performance of Zytiga was attributable to purported benefits of the combination beyond the known benefits of each treatment. I understand that Dr. Garnick is of the opinion that there are "no unexpected anti-cancer synergies resulting from co-administering abiraterone and prednisone" and that the sales of Zytiga are not the result of any unexpected synergies.[34]

34. Furthermore, I understand that the use of the specific glucocorticoid prednisone has not been shown to have incremental benefit over other glucocorticoid steroids. I understand from Dr. Garnick's declaration that, from a clinical perspective,

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[32] MYL Ex. 1049, Jevtana Website, Dosing and Administration, http://www.jevtana.com/hcp/dosing/default.aspx (accessed 6/28/2016).
[33] MYL Ex. 1011('438 Patent Prosecution History, March 4, 2013 Office Action) at 1–6.
[34] MYL Ex. 1002 (Garnick Decl.) ¶¶ 92-93.

the use of another glucocorticoid such as hydrocortisone, rather than prednisone, would be expected to be just as effective as prednisone in enhancing the tolerability of abiraterone administration.[35] I further understand that, from a medical perspective, treatments combining prednisone with other drugs have been known to be effective, and that the additional benefit from the combination has not been tested, but is not expected to result in any significant enhancement of anti-cancer effects.[36] Since no studies have compared the administration of abiraterone acetate plus prednisone with the administration of abiraterone acetate alone, the addition of prednisone (i.e., the alleged incremental contribution of the '438 Patent over the '213 Patent) has not been shown to have any additional benefit beyond increasing the tolerability of the treatment, which was already a known benefit of prednisone.[37] Similarly, during prosecution of the '438 Patent, the USPTO examiner determined that the alleged presence of "unexpected results because abiraterone plus prednisone being more effective than prednisone alone" was fully considered and found unpersuasive in originally denying J&J's patent application.[38]

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[35] MYL Ex. 1002 (Garnick Decl.) ¶¶ 79-80.
[36] MYL Ex. 1002 (Garnick Decl.) ¶¶ 78-79, 83, and 92.
[37] MYL Ex. 1002 (Garnick Decl.) ¶¶ 78-79, 83, and 92.
[38] MYL Ex. 1011 ('438 Patent Prosecution History, March 4, 2013 Office Action) at 1–6.

VII. The Performance Metrics for Zytiga Presented During the Prosecution of the '438 Patent are Misleading and Incomplete

35. As explained above, the USPTO cited "unexpected commercial success of the launch of the drug" as a basis for nonobviousness in granting the '438 Patent. Based upon documents at the time of the prosecution, the USPTO was presented with information about the commercial performance of Zytiga on a patient-share basis and relative to other oral cancer drugs. The information provided to the USPTO was misleading and incomplete for the reasons I describe below.

36. I am not aware of J&J providing the USPTO with any expectations or perceptions of expected commercial success of Zytiga by the broader market prior to launch. Instead, J&J relied exclusively on measures of actual Zytiga sales, including arguments based on early sales as of 2012 that were rejected by the USPTO[39] and arguments based on sales to date through April 2013.[40] Without a baseline for expectations, the term "unexpected" is misplaced.

37. An example of the misleading and incomplete performance metrics presented during patent prosecution is the information regarding Zytiga's "almost 70%

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[39] MYL Ex. 1008 ('438 Patent Prosecution History, July 3, 2012 Response) at 1–4; MYL Ex. 1039 ('438 Patent Prosecution History, September 11, 2012 Office Action) at 1–6.

[40] MYL Ex. 1012 ('438 Patent Prosecution History June 4, 2013 Response) at 7–8.

market share," and Zytiga's "market lead[ing]" position for post-chemo patients.[41] Indeed, Zytiga is approved for both pre- and post-chemo patient populations. As such, these statements are misleading by improperly focusing on the significantly smaller post-chemo patient population rather than providing Zytiga's share of the broader relevant markets. Because the pre-chemo patient population is roughly three times the size of the post-chemo population,[42] J&J's references to each individual patient population masks Zytiga's overall patient share among all mCRPC patients. Based on the ratio of post-chemo to pre-chemo patients, J&J's reported shares of 57 percent within post-chemo and 20 percent within pre-chemo as of April 2013[43] provide an overall patient share of 29 percent within all mCRPC patients.[44] Furthermore, since only about 10 percent to 20 percent of all prostate cancer patients develop CRPC (and many of these patients will have or will develop mCRPC),[45] a reasonable estimate of Zytiga's share amongst prostate cancer patients is approximately 3 percent to 6 percent.[46] In other words, accurately placing Zytiga use within its proper market context

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[41] MYL Ex. 1012 ('438 Patent Prosecution History June 4, 2013 Response) at 7–8.
[42] MYL Ex. 1012 ('438 Patent Prosecution History June 4, 2013 Response) at "Zytiga®: Most Successful Oral Oncology Launch in History," in Pharmaceuticals Commercial Overview PowerPoint, 11.
[43] MYL Ex. 1012 ('438 Patent Prosecution History June 4, 2013 Response) at 7–8.
[44] 57% × (1/4) + 20% × (3/4) = 29.25%.
[45] MYL Ex. 1050 (Kirby) at 1180.
[46] 29% × 10% = 2.9% and 29% × 20% = 5.8%.

indicates a significantly lower patient share than the ones proffered by J&J to the USPTO.

38. Another example of the incomplete performance metrics presented during the '438 Patent prosecution is the claim that Zytiga is the "the most successful oral oncology launch in history."[47] This is incomplete in light of non-oral cancer drugs with even greater sales. For example, there are at least nine non-oral cancer drugs with annual worldwide sales substantially exceeding Zytiga (abiraterone, $2.2 billion), such as Rituxan (rituximab, $7.4 billion), Avastin (bevacizumab, $6.8 billion), and Herceptin (trastuzumab, $6.7 billion). *See* **Attachment B-1**.

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[47] MYL Ex. 1012 ('438 Patent Prosecution History June 4, 2013 Response) at 7.

39. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Respectfully submitted,

Ivan T. Hofmann, CPA/CFF, CLP

Dated: June 30, 2016

Attachment A-1
Materials Reviewed

Declarations

MYL Ex. 1002: Declaration of Marc B. Garnick, M.D.

Patents

MYL Ex. 1005: U.S. Patent No. 5,604,213, 17-Substituted Steroids Useful in Cancer Treatment (filed 9/30/1994, issued 2/18/1997).

MYL Ex. 1001: U.S. Patent No. 8,822,438, Methods and Compositions for Treating Cancer (filed 2/24/2011, issued 9/2/2014).

'438 Patent Prosecution Documents

MYL Ex. 1008: File history, Applicant Response, 7/3/2012

MYL Ex. 1036: Initial Application, 2/24/2011.

MYL Ex. 1039: USPTO Action, 9/11/2012.

MYL Ex. 1011: USPTO Action, 3/4/2013.

MYL Ex. 1012: Applicant Response, 6/4/2013.

MYL Ex. 1013: USPTO Action, 7/3/2013.

Research materials

MYL Ex. 1040: Cancer.net (ASCO Patient Website), Treatment of Metastatic Castration-Resistant Prostate Cancer, http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer (accessed 6/28/2016).

MYL Ex. 1041: Cancer.org (ACS), "What are the key statistics about prostate cancer?" http://www.cancer.org/cancer/prostatecancer/detailedguide/prostatecancerkeystatistics (accessed 6/28/2016).

MYL Ex. 1045: FDA News Release, "FDA expands Zytiga's use for late-stage prostate cancer," 12/10/2012, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm331492.htm.

MYL Ex. 1046: FDA Website, Drugs@FDA – Zytiga, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails (accessed 6/28/2016).

MYL Ex. 1047: FDA Website, Orange Book, Zytiga (NDA 202379), http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202379&Product_No=001&table1=OB_Rx (accessed 6/30/2016).

MYL Ex. 1048: *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740–41 (Fed. Cir. 2013).

MYL Ex. 1049: Jevtana Website, Dosing and Administration, http://www.jevtana.com/hcp/dosing/default.aspx (accessed 6/28/2016).

MYL Ex. 1050: Kirby, M., C. Hirst, and E.D. Crawford (2011), "Characterising the Castration-Resistant Prostate Cancer Population: A Systematic Review," Int'l J. Clinical Practice 65(11):1180-1192.

MYL Ex. 1051: Mayo Clinic Website, Prostate cancer, http://www.mayoclinic.org/diseases-conditions/prostate-cancer/basics/definition/con-20029597?p=1 (accessed 6/28/2016).

MYL Ex. 1053: *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376–77 (Fed. Cir. 2005).

MYL Ex. 1054: Murphy, W.J., J.L. Orcutt, and P.C. Remus (2012), Patent Valuation: Improving Decision Making through Analysis, Hoboken, NJ: Wiley.

MYL Ex. 1055, PMLiVE Website, "Top 50 Pharmaceutical Products by Global Sales," http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales (accessed 6/30/2016)

MYL Ex. 1057: *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1383 (Fed. Cir. 2005).

MYL Ex. 1064: Zytiga Brochure, Putting Prednisone in Perspective, 3/2015.

MYL Ex. 1065: Zytiga Label, 5/20/2015.

MYL Ex. 1066: Zytiga Website, How Zytiga® (abiraterone acetate) Works, https://www.zytiga.com/print/about-zytiga/how-zytiga-works (accessed 6/28/2016).

Ivan T. Hofmann, C.P.A., C.F.F., C.L.P.

Attachment A-2

Curriculum Vitae

Professional History

Gleason IP, a division of Gleason & Associates, P.C. – Managing Director/Shareholder ***2006 to Present***

Ivan Hofmann is a managing director and shareholder at Gleason IP. He has years of professional experience with a deep specialization in complex intellectual property matters. Mr. Hofmann's IP expertise includes extensive litigation support and testifying experience in quantifying financial damages related to patent infringement and other intellectual property issues, as well as breach of contract claims, class action law suits and other litigation-related matters. His experience includes using statistical, financial, and economic analysis and models related to various technical issues. He provides value-added services in all phases of litigation in various capacities, including assistance with discovery, depositions, expert opinions, and testimony during trial.

Mr. Hofmann's experience with intellectual property matters includes false advertising cases, theft of trade secrets, and trademark infringement matters. He has performed analysis of irreparable harm in preliminary injunction hearings and regularly performs analysis of commercial success in connection with secondary considerations of nonobviousness. Mr. Hofmann has experience with intellectual property issues in numerous industries, including extensive experience in the pharmaceutical industry.

As a Certified Licensing Professional (CLP), Mr. Hofmann has demonstrated knowledge and experience in analyzing license agreements and royalty terms. He assists companies in licensing negotiations with economic analysis in licensing agreements. He also has performed royalty audits on behalf of universities and corporations. Mr. Hofmann's extensive knowledge of licensing is useful in his analysis of reasonable royalties in patent infringement cases.

Also, Mr. Hofmann has experience in the areas of accounting, auditing, forensic accounting, fraud investigations and due diligence work. He has been involved in matters in state and federal courts, as well as domestic and international arbitration and other forums for dispute resolution. His experience includes matters with public and private companies in a broad range of industries including pharmaceuticals, communications, health care, manufacturing, retail, oil and gas, coal, utilities, land development, hospitality, and others.

Deloitte & Touche LLP – Senior Manager ***1994 -2006***

Mr. Hofmann was a senior manager with the global firm of Deloitte & Touche LLP in the Forensic and Dispute Services and Assurance and Advisory services departments. He served numerous clients in various industries ranging in size from small, privately held companies to large, multi-national Fortune 500 companies.

Education and Certification

Bachelor of Business Administration, double major in Accounting and Economics, *Magna Cum Laude*, University of Notre Dame, 1994
Certified Public Accountant, Pennsylvania 1996
Certified in Financial Forensics, 2008
Certified Licensing Professional 2010

Professional and Business Affiliations

American Institute of Certified Public Accountants, Member
Pennsylvania Institute of Certified Public Accountants, Member
Licensing Executives Society, Member

Civic Affiliations

Notre Dame Club of Pittsburgh

Ivan T. Hofmann CPA/CFF, CLP
Cases in which Mr. Hofmann has testified at deposition or at trial in the past four years.

LIST OF CASES PURSUANT TO 26(a)(2)(B)

Endo Pharmaceuticals Inc. and Mallinckrodt LLC v. Teva Pharmaceuticals USA, Inc. and Barr Laboratories, Inc. – United States District Court for the District of Delaware, 2016 (Deposition)

Endo Pharmaceuticals Inc. and Mallinckrodt LLC v. Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals of New York LLC – United States District Court for the District of Delaware, 2016 (Deposition)

AstraZeneca AB v. Aurobindo Pharma Ltd., Aurobindo Pharma USA, Inc., Actavis FL Laboratories, Inc., Watson Laboratories, Inc., Wockhardt Bio AG, Wockhardt USA LLC, Sun Pharma Global FZE, Sun Pharmaceuticals Industries Ltd., Mylan Pharmaceuticals, Inc., and Amneal Pharmaceuticals, LLC – United States District Court for the District of Delaware, 2016 (Deposition)

Novartis Pharmaceuticals Corporation and Novartis AG, v. Breckenridge Pharmaceutical, Inc., Novartis Pharmaceuticals Corporation and Novartis AG, v. Roxane Laboratories, Inc., and Novartis Pharmaceuticals Corporation and Novartis AG, v. Par Pharmaceutical, Inc. – United States District Court for the District of Delaware, 2016 (Deposition)

Coalition for Affordable Drugs II LLC v. NPS Pharmaceuticals, Inc. – United States Patent Trial and Appeal Board, 2016 (Declaration, Deposition)

Lupin LTD and Lupin Pharmaceuticals, Inc. v. Senju Pharmaceutical Co., LTD., Bausch & Lomb Inc. and Bausch & Lomb Pharma Holdings Corp. – United States Patent Trial and Appeal Board, 2016 (Declaration, Deposition)

Concordia Pharmaceuticals, Inc. v. Method Pharmaceuticals, LLC and Matthew Scott Tucker – United States District Court for the Western District of Virginia, 2016 (Trial)

The Easy Life, LLC v. Go Daddy Operating Company, LLC – United States District Court for the District of Central Illinois, 2016 (Deposition)

Innopharma Licensing, Inc., Innopharma Licensing, LLC, Innopharma, Inc. and Innopharma, LLC, Mylan Pharmaceuticals, Inc., and Mylan, Inc. v. Senju Pharmaceutical Co., LTD., Bausch & Lomb Incorporated and Bausch & Lomb Pharma Holdings Corp. – United States Patent Trial and Appeal Board, 2016 (Declarations, Deposition)

Hospira, Inc. and Orion Corporation vs. Eurohealth International SARL and West-Ward Pharmaceutical Corporation – United States District Court of Delaware, 2016 (Deposition)

Senju Pharmaceutical Co., LTD., Bausch & Lomb Incorporated and Bausch & Lomb Pharma Holdings Corp. v. Lupin LTD and Lupin Pharmaceuticals, Inc. – United States District Court for the District of New Jersey, 2016 (Deposition)

Ivan T. Hofmann CPA/CFF, CLP
Cases in which Mr. Hofmann has testified at deposition or at trial in the past four years.

LIST OF CASES PURSUANT TO 26(a)(2)(B)

Senju Pharmaceutical Co., LTD., Bausch & Lomb Incorporated and Bausch & Lomb Pharma Holdings Corp. v. Innopharma Licensing, Inc., Innopharma Licensing, LLC, Innopharma, Inc. and Innopharma, LLC – United States District Court for the District of New Jersey, 2016 (Deposition)

In Re: Bendamustine Consolidated Cases – United States District Court for the District of Delaware, 2015 (Trial)

Janssen Pharmaceuticals, Inc., Grünenthal GmBH, and Depomed, Inc. v. Actavis Elizabeth LLC and Alkem Laboratories Limited, Janssen Pharmaceuticals, Inc., Grünenthal GmBH, and Depomed, Inc. v. Roxane Laboratories, Inc., Janssen Pharmaceuticals, Inc., Grünenthal GmBH, and Depomed, Inc. v. Alkem Laboratories Limited, Janssen Pharmaceuticals, Inc., Grünenthal GmBH, and Depomed, Inc. v. Actavis Laboratories UT, Inc. – United States District Court for the District of New Jersey, 2015 (Deposition)

In Re: Certain Consolidated Zoledronic Acid Cases – United States District Court for the District of New Jersey, 2015 (Deposition)

Helsinn Healthcare S.A. and Roche Palo Alto LLC v. Cipla LTD., Cipla USA, Inc. Eurohealth International Sarl, West-Ward Pharmaceutical Corp., and Mylan Institutional LLC – United States District Court for the District of Delaware, 2015 (Deposition)

In Re: Bendamustine Consolidated Cases – United States District Court for the District of Delaware, 2015 (Deposition)

Concordia Pharmaceuticals, Inc. v. Method Pharmaceuticals, LLC and Matthew Scott Tucker – United States District Court for the Western District of Virginia, 2015 (Deposition)

Zhongshan Broad Ocean Motor Co., LTD., Broad Ocean Motor LLC, and Broad Ocean Technologies, LLC v. Nidec Motor Corporation – United States Patent Trial and Appeal Board, 2015 (Declaration, Deposition)

Jazz Pharmaceuticals, Inc. v. Roxane Laboratories, Inc. – United States District Court for the District of New Jersey, 2015 (Deposition)

Apotex Corp. v. ViiV Healthcare Co. and ViiV Healthcare UK LTD. – United States Patent Trial and Appeal Board, 2015 (Deposition, Declaration)

Endo Pharmaceuticals, Inc. v. Roxane Laboratories, Inc. (13-cv-03288), Endo Pharmaceuticals Inc. v. Ranbaxy Laboratories LTD., Ranbaxy Inc. and Ranbaxy Pharmaceuticals Inc. (13-cv-04343), Endo Pharmaceuticals Inc. v. Ranbaxy Laboratories LTD., Ranbaxy Inc., and Ranbaxy Pharmaceuticals, Inc. (13-cv-08597), Endo Pharmaceuticals Inc. and Grunenthal GmBH v. Teva Pharmaceuticals USA, Inc. and Barr Laboratories, Inc. (13-cv-08060), Endo Pharmaceuticals Inc. and Grunenthal GmBH v. Impax Laboratories, Inc. and Thorx Laboratories, Inc. (12-cv-8317), Endo

Ivan T. Hofmann CPA/CFF, CLP
Cases in which Mr. Hofmann has testified at deposition or at trial in the past four years.

LIST OF CASES PURSUANT TO 26(a)(2)(B)

Pharmaceuticals Inc. and Grunenthal GmBH v. Impax Laboratories, Inc. (13-cv-435), Endo Pharmaceuticals, Inc. v. Actavis Inc. and Actavis South Atlantic LLC (12-cv-8985), Endo Pharmaceuticals Inc. and Grunenthal GmBH v. Actavis Inc., Actavis South Atlantic, LLC and Watson Pharmaceuticals, Inc. (13-cv-0436), and Endo Pharmaceuticals Inc. and Grunenthal GmBH v. Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals of New York, LLC (12-cv-8115) – United States District Court for the Southern District of New York, 2015 (Trial)

Otsuka Pharmaceutical Co., Ltd. v. Alembic Pharmaceuticals Limited, Alembic Limited, Alembic Global Holdings SA, and Alembic Pharmaceuticals Inc. – United States District Court for the District of New Jersey, 2015 (Temporary Restraining Order Hearing)

Kangaroo Media, Inc. and Immersion Entertainment, LLC v. YinzCam, Inc. – United States District Court for the Western District of Pennsylvania, 2015 (Deposition)

Endo Pharmaceuticals, Inc. v. Roxane Laboratories, Inc. (13-cv-03288), Endo Pharmaceuticals Inc. v. Ranbaxy Laboratories LTD., Ranbaxy Inc. and Ranbaxy Pharmaceuticals Inc. (13-cv-04343), Endo Pharmaceuticals Inc. v. Ranbaxy Laboratories LTD., Ranbaxy Inc., and Ranbaxy Pharmaceuticals, Inc. (13-cv-08597), Endo Pharmaceuticals Inc. and Grunenthal GmBH v. Teva Pharmaceuticals USA, Inc. and Barr Laboratories, Inc. (13-cv-08060), Endo Pharmaceuticals Inc. and Grunenthal GmBH v. Impax Laboratories, Inc. and Thorx Laboratories, Inc. (12-cv-8317), Endo Pharmaceuticals Inc. and Grunenthal GmBH v. Impax Laboratories, Inc. (13-cv-435), and Endo Pharmaceuticals Inc. and Grunenthal GmBH v. Sandoz Inc. (12-cv-8318) – United States District Court for the Southern District of New York, 2015 (Deposition)

Intendis GmBH, Intraserv GmBH & Co. KG, and Bayer Healthcare Pharmaceuticals, Inc. v. Glenmark Generics Limited and Glenmark Generics, Inc. USA – United States District Court for the District of Delaware, 2015 (Trial)

Shire Development LLC, Shire Pharmaceutical Development Inc., Cosmo Technologies Limited, and Nogra Pharma Limited, v. Cadila Healthcare Limited (d/b/a Zydus Cadila) and Zydus Pharmaceuticals (USA) Inc. – United States District Court for the District of Delaware, 2014 (Deposition)

Millenium Pharmaceuticals, Inc. v. Accord Healthcare, Inc., Actavis LLC f/k/a Actavis Inc., and Sandoz, Inc. – United States District Court for the District of Delaware, 2014 (Trial)

Merck Eprova AG v. Gnosis S.P.A. and Gnosis Bioresearch S.A. – United States District Court for the Southern District of New York, 2014 (Declaration)

Intendis GmBH, Intraserv GmBH & Co. KG, and Bayer Healthcare Pharmaceuticals, Inc. v. Glenmark Generics Limited and Glenmark Generics, Inc. USA – United States District Court for the District of Delaware, 2014 (Deposition)

Ivan T. Hofmann CPA/CFF, CLP
Cases in which Mr. Hofmann has testified at deposition or at trial in the past four years.

LIST OF CASES PURSUANT TO 26(a)(2)(B)

Laboratorios Silanes, S.A. De C.V., Instituto Bioclon, S.A. De C.V. and Rare Disease Therapeutics, Inc. v. BTG International, Inc. – United States Patent Trial and Appeal Board, 2014 (Declaration)

Millenium Pharmaceuticals, Inc. v. Accord Healthcare, Inc., Actavis LLC f/k/a Actavis Inc., and Sandoz, Inc. – United States District Court for the District of Delaware, 2014 (Deposition)

Pfizer, Inc., Wyeth, LLC, Wyeth Pharmaceuticals, Inc., PF Prism, CV v. Apotex, Inc., Apotex Corp., Breckenridge Pharmaceuticals, Inc., Alembic Pharmaceuticals Ltd., Lupin LTD, Lupin Pharmaceuticals, Inc., Mylan Pharmaceuticals, Inc., Mylan, Inc., Roxane Laboratories, Inc., Sandoz, Inc., Watson Laboratories, Inc. Florida, Wockhardt LTD., Wockhardt USA, LLC, Zydus Pharmaceuticals (USA), LLC, and Cadila Healthcare Limited – United States District Court for the District of Delaware, 2014 (Deposition)

Apotex, Inc. and Apotex Corp. vs. Acorda Therapeutics, Inc. – United States District Court for the Southern District of New York, 2014 (Deposition)

Drawbridge Special Opportunities Fund LP and Fortress Value Recovery Fund I LLC f/k/a D.B. Zwirn Special Opportunities Fund, L.P. v. PRC Williston LLC – In the Court of Chancery of the State of Delaware, 2014 (Preliminary Injunction Hearing, Deposition)

Shire LLC, Shire Development, Inc., and Shire Development, LLC v. Amneal Pharmaceuticals, LLC, Roxane Laboratories, Inc., Sandoz, Inc., Mylan, Inc., Mylan Pharmaceuticals, Inc., Actavis, Inc., Actavis, LLC, Actavis Elizabeth LLC, Johnson Matthey, Inc., and Johnson Matthey Pharmaceuticals Materials – United States District Court for the District of New Jersey, 2014 (Deposition)

Gnosis S.P.A., Gnosis Bioresearch S.A., and Gnosis U.S.A., Inc. v. South Alabama Medical Science Foundation and Gnosis S.P.A., Gnosis Bioresearch S.A., and Gnosis U.S.A., Inc. v. Merck & Cie – United States Patent Trial and Appeal Board, 2013 (Deposition)

Warner Chilcott Company, LLC v. Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Limited (d/b/a Cadila Healthcare) – United States District Court for the District of Delaware, 2013 (Deposition)

Genentech, Inc. and Roche Palo Alto, LLC v. Sandoz, Inc. – United States District Court for the Northern District of California, San Francisco, 2013 (Deposition)

Genentech, Inc. and Roche Palo Alto, LLC v. Apotex, Inc. – United States District Court for the Northern District of California, San Francisco, 2013 (Deposition)

Grant Street Group, Inc. v. RealAuction.com, LLC – United States District Court for the Western District of Pennsylvania, 2013 (Trial)

Ivan T. Hofmann CPA/CFF, CLP
Cases in which Mr. Hofmann has testified at deposition or at trial in the past four years.

LIST OF CASES PURSUANT TO 26(a)(2)(B)

The Medicines Company v. Mylan, Inc., Mylan Pharmaceuticals, Inc., and Bioniche Pharma USA, LLC, United States District Court for the Northern District of Illinois, 2013 (Deposition)

Sloan Valve Company v. Zurn Industries, Inc. and Zurn Industries, LLC – United States District Court for the Northern District of Illinois, Eastern Division, 2013 (Deposition)

Medicis Pharmaceutical Corporation and Dow Pharmaceutical Sciences, Inc. v. Actavis Mid Atlantic, LLC – United States District Court for the District of Delaware, 2013 (Deposition)

Medicis Pharmaceutical Corporation v. Actavis Mid Atlantic, LLC and Actavis, Inc. – Superior Court of Arizona, County of Maricopa, 2012 (Deposition)

Shire Development Inc., Shire Pharmaceutical Development Inc., Cosmo Technologies Limited, and Giuliani International Limited, v. Cadila Healthcare Limited (d/b/a Zydus Cadila) and Zydus Pharmaceuticals (USA) Inc. – United States District Court for the District of Delaware, 2012 (Deposition)

Medicis Pharmaceutical Corporation v. Actavis Mid Atlantic, LLC and Actavis, Inc. – Superior Court of Arizona, County of Maricopa, 2012 (Temporary Restraining Order Hearing)

Attachment B-1
IMS Health U.S. Sales Data for Select mCRPC Drugs

Drug	Company	2013	2014
Rituxan/MabThera (Rituximab)	Roche	$ 7.41	$ 7.36
Avastin (Bevacizumab)	Roche	$ 6.67	$ 6.84
Herceptin (Trastuzumab)	Roche	$ 6.48	$ 6.69
Revlimid (Lenalidomide)	Celgene	$ 4.28	$ 4.98
Gleevec (Imatinib)	Novartis	$ 4.69	$ 4.75
Neulasta (Pegfilgrastim)	Amgen	$ 4.39	$ 4.60
Velcade (Bortezomib)	Takeda and Johnson & Johnson	$ 2.85	$ 2.88
Alimta (Pemetrexed)	Eli Lilly	$ 2.70	$ 2.79
Erbitux (Cetuximab)	ImClone and Merck	$ 2.20	$ 2.26
Zytiga (Abiraterone)	Johnson & Johnson	$ 1.70	$ 2.24

Notes and sources:
Figures are in billions of $U.S.
Data are from: MYL Ex. 1055, PMLiVE Website, "Top 50 Pharmaceutical Products by Global Sales," http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales (accessed 6/30/2016)

I hereby certify that this correspondence is being transmitted via The Office Electronic Filing System (EFS) in accordance with 37 CFR 1.6(a)(4).

Date of Electronic (EFS) Transmission: June 4, 2013

Signature: /Laurie A. Phillips/ Name: Laurie A. Phillips

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Applicant(s):	Alan H. Auerbach	Conf. No.:	1597
Application No.:	13/034,340	Group Art:	1628
Filing Date:	February 24, 2011	Examiner:	San Ming R. Hui
Title:	Methods and Compositions for Treating Cancer		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE

Dear Sir:

In response to the final Office Action mailed March 4, 2013, Applicant submits the following amendments and remarks.

A list of the Claims are reflected in the listing of claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Listing of Claims:

1-36. (Canceled).

37. (Previously presented) A method for the treatment of a prostate cancer in a human comprising administering to said human a therapeutically effective amount of abiraterone acetate or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of prednisone.

38. (Previously presented) The method of claim 37, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 50 mg/day to about 2000 mg/day.

39. (Previously presented) The method of claim 38, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is from about 500 mg/day to about 1500 mg/day.

40. (Previously presented) The method of claim 39, wherein the therapeutically effective amount of the abiraterone acetate or pharmaceutically acceptable salt thereof is about 1000 mg/day.

41. (Previously presented) The method of claim 37, wherein the therapeutically effective amount of the abiraterone acetate or a pharmaceutically acceptable salt thereof is administered in at least one dosage form comprising about 250 mg of abiraterone acetate or a pharmaceutically acceptable salt thereof.

42. (Previously presented) The method of claim 37, wherein the therapeutically effective amount of the prednisone is from about 0.01 mg/day to about 500 mg/day.

43. (Previously presented) The method of claim 42, wherein the therapeutically effective amount of the prednisone is from about 10 mg/day to about 250 mg/day.

44. (Previously presented) The method of claim 44, wherein the therapeutically effective amount of the prednisone is about 10 mg/day.

45. (Previously presented) The method of claim 37, wherein the therapeutically effective amount of the prednisone is administered in at least one dosage form comprising about 5 mg of prednisone.

46. (Previously presented) The method of claim 37, comprising administering to said human about 500 mg/day to about 1500 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 0.01 mg/day to about 500 mg/day of prednisone.

47. (Previously presented) The method of claim 46, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

48. (Previously presented) The method of claim 37, wherein said prostate cancer is refractory prostate cancer.

49. (Previously presented) The method of claim 48, wherein the refractory prostate cancer is not responding to at least one anti-cancer agent.

50. (Previously presented) The method of claim 49, wherein the at least one anti-cancer agent comprises a hormonal ablation agent, an anti-androgen agent, or an anti-neoplastic agent.

51. (Previously presented) The method of claim 50, wherein the hormonal ablation agent comprises deslorelin, leuprolide, goserelin, or triptorelin.

52. (Previously presented) The method of claim 50, wherein the anti-androgen agent comprises bicalutamide, flutamide, or nilutamide.

53. (Previously presented) The method of claim 50, wherein the anti-neoplastic agent comprises docetaxel.

54. (Previously presented) The method of claim 48, comprising administering to said human about 500 mg/day to about 1500 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 0.01 mg/day to about 500 mg/day of prednisone.

55. (Previously presented) The method of claim 54, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

56. (Previously presented) The method of claim 53, comprising administering to said human about 1000 mg/day of abiraterone acetate or a pharmaceutically acceptable salt thereof and about 10 mg/day of prednisone.

Remarks

Claims 37-56 are pending.

Rejections Under 35 U.S.C. § 103

The rejection of claims 37-56 under 35 USC §103(a) as allegedly being unpatentable over O'Donell *et al.* (*British Journal of Cancer 90*:2317-2325 (2004)) ("O'Donell"), in view of Tannock et al. (*Journal of Clinical Oncology 14*:1756-1764 (1996)) (Tannock") was maintained. Applicant respectfully traverses this rejection.

In Applicant's previous reply, submitted January 11, 2013 (the "January Reply"), Applicant submitted the Ryan article. Ryan showed, *inter alia*, that the "median radiographic progression-free survival was 16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone . . . Radiographic progression-free survival was positively correlated with overall survival." According to the Office, "the superior results of using abiraterone and prednisone together is expected because abiraterone and prednisone are known to be individually effective in treating prostate cancer. At least additive effective [sic] is expected." However, the Office failed to provide any reasoning to support the expectation of at least an additive effect. In fact, the Office's own cited art is in opposition to the Office's statement that at least an additive effect is expected.

Based on Tannock, the art cited by the Office, one of ordinary skill in the art would not expect at least an additive effect for overall survival of abiraterone and acetate and progesterone. Tannock teaches that "[t]here was no significant difference in overall survival [between prednisone alone and prednisone plus the anticancer agent mitoxantrone.]" One of ordinary skill in the art, reading Tannock, would expect there to be no difference in survival between one cancer agent alone, and that same cancer agent in combination with prednisone. Thus, the present invention possesses unexpected results and is non-obvious over the cited art.

Further, the present invention has displayed commercial success. Applicant submits herewith the currently United States Food & Drug Administration approved label

for ZYTIGA™ (the "ZYTIGA label"). The ZYTIGA label indicates that "[abiraterone acetate] is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer." Taking ZYTIGA in accordance with the approved label represents a commercial embodiment of the presently claimed invention.

Applicant also submits herewith a news release from the U.S. Food and Drug Administration dated December 10, 2012 and titled "FDA expands Zytiga's use for late-stage prostate cancer." As can be seen from this 2012 news release, ZYTIGA was initially approved in April 2011 for use in patients whose prostate cancer progressed after treatment with docetaxel, a chemotherapy drug. ZYTIGA was further approved in December 2012 for use in prostate cancer patients prior to receiving chemotherapy.

Applicant also submits two further news releases from the U.S. Food and Drug Administration, one dated June 17, 2010, announcing approval of Jevtana for use in prostate cancer; and the other dated August 31, 2012, announcing the approval of Xtandi for use in patients whose prostate cancer progressed after treatment with docetaxel.

Applicant also submits herewith "Pharmaceuticals Commericial Overview", a slideshow presented by Joaquin Duato on May 23, 2013 and currently available at http://files.shareholder.com/downloads/JNJ/2514173625x0x666408/bb2972ea-2099-4ab4-b2a3-afc39e710594/Pharmaceutical_Commercial_Overview_JNJ2013.pdf (the "2013 slideshow"). According to the 2013 slideshow, at slide 11, ZYTIGA is the most successful oral oncology launch in history.

The 2013 slideshow, at slide 12, further shows the July 2012 to April 2013 ZYTIGA market share of chemo refractory prostate cancer patients, i.e., patients who have previously received chemotherapy treatment and the December 2012 to April 2013 market share of chemo naïve prostate cancer patients, i.e., patients who have not previously received chemotherapy treatment. As can be seen from the figure on the left of slide 12, ZYTIGA had almost 70% market share in July of 2012 for chemo refractory prostate cancer patients, just slightly over a year after ZYTIGA's initial approval, and despite the fact that a JEVTANA had been approved two years earlier. Despite another product, XTANDI, being introduced in August of 2012, by April of 2013, ZYTIGA was

still the market leader as of April 2013 with 57% market share in chemo refractory prostate cancer patients.

As can be seen from the figure on the right of slide 12, shortly after its approval for chemo-naïve patients in December 2012, ZYTIGA had a market share of 15%. As of April 2013, ZYTIGA's market share was 20%, higher than two other available therapies, docetaxel and XTANDI, and approaching the market share of bicalutamide, a drug first approved in 2001 for prostate cancer.

Thus, not only is ZYTIGA the most successful oral oncology launch in history, two years after its initial approval it is still the market leader for chemo refractory patients despite an earlier-introduced therapy and a later-introduced therapy. ZYTIGA also holds a strong market share in the chemo naïve prostate cancer population, despite the presence of other marketed products. This commercial success demonstrates the non-obviousness of the presently claimed invention.

Even assuming, *arguendo*, the cited art suggests the claimed combination, the present invention has shown surprising results, and commercial success. Thus, the claims are non-obvious over the cited art. Accordingly, Applicant requests reconsideration and withdrawal of the rejection under 35 USC §103(a).

III. CONCLUSION

Early consideration and prompt allowance of the claims are respectfully requested. Should the office require anything further, it is invited to contact Applicant's representative at the telephone number below.

Applicant respectfully requests that a timely Notice of Allowance be issued in the present application. Should the office require anything further, it is invited to contact Applicant's representative at the telephone number below.

Respectfully submitted,

JOHNSON & JOHNSON
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-3957
Dated: June 4, 2013
Customer No.: 27777

By: /Andrea Jo Kamage/
Andrea Jo Kamage
Reg. No. 43,703

I hereby certify that this correspondence is being transmitted via The Office Electronic Filing System (EFS) in accordance with 37 CFR 1.6(a)(4).

Date of Electronic (EFS) Transmission: June 4, 2013

Signature: /Laurie A. Phillips/ Name: Laurie A. Phillips

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Applicant(s):	Alan H. Auerbach	Conf. No.:	1597
Application No.:	13/034,340	Group Art:	1628
Filing Date:	February 24, 2011	Examiner:	San Ming R. Hui
Title:	Methods and Compositions for Treating Cancer		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NOTICE OF APPEAL

Applicant hereby appeals to the Board of Patent Appeals and Interferences from the decision of the Examiner dated March 4, 2013 finally rejecting Claims 37-56 of the above-identified application.

The item(s) checked below are appropriate:

1. ☐ An extension of time to respond to the final rejection was granted on for month(s).
2. ☐ A Petition For Extension Of Time under 37 CFR 1.136 is attached hereto in triplicate.
3. ☒ A timely response to the final rejection has been filed.
4. ☒ Fee $500.00: for filing of Notice of Appeal
   ☐ Not required (fee paid in prior appeal)
   ☒ Charge to Deposit Account No. 10-0750/AJK/CGR5001.
   ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment in connection herewith to Deposit Account No. 10-0750/AJK/CGR5001.

Respectfully submitted,

JOHNSON & JOHNSON
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-3957
Dated: June 4, 2013
Customer No.: 27777

By: /Andrea Jo Kamage/
Andrea Jo Kamage
Reg. No. 43,703

FDA NEWS RELEASE

For Immediate Release: Aug. 31, 2012
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves new treatment for a type of late stage prostate cancer

The U.S. Food and Drug Administration today approved Xtandi (enzalutamide) to treat men with late-stage (metastatic) castration-resistant prostate cancer that has spread or recurred, even with medical or surgica therapy to minimize testosterone.

Approved for prostate cancer patients previously treated with docetaxel, another anti-cancer treatment, Xtandi was reviewed under the FDA's priority review program. The program provides for an expedited six-month review for drugs that may offer major advances in treatment or that provide a treatment when no adequate therapy exists. Xtandi received FDA approval three months ahead of the product's prescription drug user fee goal date of Nov. 22, 2012.

"The need for additional treatment options for advanced prostate cancer continues to be important for patients," said Richard Pazdur, M.D., director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research. "Xtandi is the latest treatment for this disease to demonstrate its ability to extend a patient's life."

Prostate cancer forms in a gland in the male reproductive system found below the bladder and in front of the rectum. The male sex hormone testosterone stimulates the prostate tumors to grow. According to the National Cancer Institute, an estimated 241,740 men will be diagnosed with prostate cancer and 28,170 wil die from the disease in 2012.

The safety and effectiveness of Xtandi was evaluated in a study of 1,199 patients with metastatic castration-resistant prostate cancer who had received prior treatment with docetaxel. The study was designed to measure overall survival (the length of time before death) in men receiving Xtandi compared with men receiving a placebo (sugar pill). The median overall survival for patients receiving Xtandi was 18.4 months, compared with 13.6 months for the patients who received placebo.

The most common side effects observed in study participants taking Xtandi were weakness or fatigue, bacl pain, diarrhea, joint pain, hot flush, tissue swelling, musculoskeletal pain, headache, upper respiratory infections, dizziness, spinal cord compression and cauda equina syndrome, muscular weakness, difficulty sleeping, lower respiratory infections, blood in urine, tingling sensation, anxiety, and high blood pressure.

Seizures occurred in approximately 1 percent of those receiving Xtandi. Patients in the study who had a seizure stopped Xtandi therapy. The clinical study excluded patients with a history of seizure, an underlying brain injury with loss of consciousness, a temporary decrease in blood to the brain within the past 12 months, a stroke, brain metastases, an abnormal connection of the arteries and veins in the brain, or patients taking medications that may lower the seizure threshold. The safety of Xtandi is unknown in patients with these conditions.

Xtandi will be co-marketed by Astellas Pharma U.S., Inc. of Northbrook, IL and Medivation, Inc. of San Francisco, CA.

For more information:

FDA: Office of Hematology and Oncology Products[1]

FDA: Approved Drugs: Questions and Answers[2]

FDA: Drug Innovation[3]

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FDA NEWS RELEASE

For Immediate Release: June 17, 2010
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA Approves New Treatment for Advanced Prostate Cancer

The U.S. Food and Drug Administration today approved Jevtana (cabazitaxel), a chemotherapy drug used in combination with the steroid prednisone to treat men with prostate cancer. Jevtana is the first treatment for advanced, hormone-refractory, prostate cancer that has worsened during or after treatment with docetaxel, a commonly used drug for advanced prostate cancer.

In prostate cancer, the male sex hormone testosterone can cause prostate tumors to grow. Drugs, surgery or other hormones are used to reduce testosterone production or to block it. Some men have hormone refractory prostate cancer, meaning the prostate cancer cells continue to grow, despite testosterone suppression. Different treatments are needed for men with this type of cancer.

Jevtana was reviewed under the FDA's priority review program, which provides for an expedited six-month review for drugs that may offer major advances in treatment, or provide a treatment when no adequate therapy exists. Jevtana received approval ahead of the product's Sept. 30, 2010, goal date.

"Patients have few therapeutic options in this disease setting," said Richard Pazdur, M.D., director of the Office of Oncology Drug Products, part of the FDA's Center for Drug Evaluation and Research. "FDA was able to review and approve the application for Jevtana in 11 weeks, expediting the availability of this drug to men with prostate cancer."

Jevtana's safety and effectiveness was established in a single, 755-patient study. All study participants had previously received docetaxel. The study was designed to measure overall survival (the length of time before death) in men who received Jevtana in combination with prednisone compared with those who received the chemotherapy drug, mitoxantrone, in combination with prednisone. The median overall survival for patients receiving the Jevtana regimen was 15.1 months compared with 12.7 months for those who received the mitoxantrone regimen.

Side effects in those treated with Jevtana included decrease in infection-fighting white blood cells (neutropenia), anemia, decrease in the number of white blood cells (leukopenia), low level of platelets in the blood (thrombocytopenia), diarrhea, fatigue, nausea, vomiting, constipation, weakness (asthenia), and renal failure.

Prostate cancer, which usually occurs in older men, is the second most common cancer among men in the United States, behind skin cancer. In 2006, the most recent year for which numbers were available, 203,415 men developed prostate cancer and 28,372 men died from the disease, according to the Centers for Disease Control and Prevention.

Jevtana is marketed by Bridgewater, N.J.-based Sanofi-Aventis.

For more information:

- FDA: Office of Oncology Drug Products[1]
- CDC: Informed Decision Making About Prostate Cancer[2]
- NCI: Prostate Cancer[3]

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News & Events

FDA NEWS RELEASE

For Immediate Release: Dec. 10, 2012
Media Inquiries: Stephanie Yao, 301-796-0394, stephanie.yao@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA expands Zytiga's use for late-stage prostate cancer

Drug can now be used before treatment with chemotherapy

The U.S. Food and Drug Administration today expanded the approved use of Zytiga (abiraterone acetate) to treat men with late-stage (metastatic) castration-resistant prostate cancer prior to receiving chemotherapy.

The FDA initially approved Zytiga in April 2011 for use in patients whose prostate cancer progressed after treatment with docetaxel, a chemotherapy drug. Zytiga is a pill that decreases the production of male sex hormone testosterone.

In prostate cancer, testosterone stimulates prostate tumors to grow. Drugs or surgery are used to reduce testosterone production or to block testosterone's effects. Some men have castration-resistant prostate cancer, meaning the prostate cancer cells continue to grow even with low levels of testosterone.

"Today's approval demonstrates the benefit of further evaluating a drug in an earlier disease setting and provides patients and health care providers the option of using Zytiga earlier in the course of treatment," said Richard Pazdur, M.D., director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research.

The FDA reviewed Zytiga's application for this new indication under the agency's priority review program. The program provides for an expedited six-month review for drugs that may offer major advances in treatment or provide a treatment when no adequate therapy exists.

Zytiga's safety and effectiveness for its expanded use were established in a clinical study of 1,088 men with late-stage, castration-resistant prostate cancer who had not previously received chemotherapy. Participants received either Zytiga or a placebo (sugar pill) in combination with prednisone.

The study was designed to measure the length of time a patient lived before death (overall survival) and the length of time a patient lived without further tumor growth as assessed by imaging studies (radiographi progression-free survival, or rPFS).

Patients who received Zytiga had a median overall survival of 35.3 months compared with 30.1 months for those receiving the placebo. Study results also showed Zytiga improved rPFS. The median rPFS was 8.3 months in the placebo group and had not yet been reached for patients treated with Zytiga at the time of analysis.

The most common side effects reported in those receiving Zytiga include fatigue, joint swelling or discomfort, swelling caused by fluid retention, hot flush, diarrhea, vomiting, cough, high blood pressure, shortness of breath, urinary tract infection, and bruising.

The most common laboratory abnormalities included low red blood cell count; high levels of the enzyme alkaline phosphatase, which can be a sign of other serious medical problems; high levels of fatty acids, sugar, and liver enzymes in the blood; and low levels of lymphocytes, phosphorous and potassium in the blood.

Zytiga is marketed by Horsham, Pa.-based Janssen Biotech Inc.

For more information:

FDA approves Zytiga for late-stage prostate cancer (April 2011)[1]

FDA: Office of Hematology and Oncology Products[2]

FDA: Approved Drugs: Questions and Answers[3]

NCI: Prostate Cancer[4]

This press release was updated on Dec. 10, 2012 at 2:30 p.m. to correct the date when Zytiga was

originally approved to April 2011.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYTIGA safely and effectively. See full prescribing information for ZYTIGA.

ZYTIGA®

(abiraterone acetate) Tablets

For Oral Administration

Initial U.S. Approval – 2011

RECENT MAJOR CHANGES

Indications and usage (1)	12/2012
Contraindications, Pregnancy (4.1)	12/2012
Warnings and Precautions, Mineralocorticoid excess (5.1)	12/2012
Warnings and Precautions, Adrenocortical Insufficiency (5.2)	12/2012
Warnings and Precautions, Hepatotoxicity (5.3)	12/2012

INDICATIONS AND USAGE

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer. (1)

DOSAGE AND ADMINISTRATION

Recommended dose: ZYTIGA 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water. Do not crush or chew tablets. (2.1)

- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA starting dose to 250 mg once daily. (2.2)
- For patients who develop hepatotoxicity during treatment, hold ZYTIGA until recovery. Retreatment may be initiated at a reduced dose. ZYTIGA should be discontinued if patients develop severe hepatotoxicity. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablet 250 mg (3)

CONTRAINDICATIONS

- ZYTIGA is contraindicated in women who are or may become pregnant. (4.1, 8.1)

ZYTIGA® (abiraterone acetate) Tablets

WARNINGS AND PRECAUTIONS

- Mineralocorticoid excess: Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with LVEF < 50% or NYHA Class III or IV heart failure in Study 1 or LVEF < 50 % or NYHA Class II to IV heart failure in Study 2 was not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly. (5.1)
- Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. (5.2)
- Hepatotoxicity: Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue ZYTIGA dosing as recommended. (5.3)
- Food effect: ZYTIGA must be taken on an empty stomach. Exposure (area under the curve) of abiraterone increases up to 10 fold when abiraterone acetate is taken with meals. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (≥ 10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (> 20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of ZYTIGA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate. (7)

USE IN SPECIFIC POPULATIONS

- Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). (8.6)

See 17 for Patient Counseling Information and FDA-approved patient labeling.

Revised: [12/2012]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ZYTIGA is 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole with water. Do not crush or chew tablets.

2.2 Dose Modification Guidelines

Hepatic Impairment

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA and do not re-treat patients with ZYTIGA *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Avoid ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C), as ZYTIGA has not been studied in this population, and no dose adjustment can be predicted.

Hepatotoxicity

For patients who develop hepatotoxicity during treatment with ZYTIGA (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with ZYTIGA *[see Warnings and Precautions (5.3)]*. Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA. The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

3 DOSAGE FORMS AND STRENGTHS

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval-shaped tablets debossed with AA250 on one side.

4 CONTRAINDICATIONS

4.1 Pregnancy

ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Clinical Pharmacology (12.1)]*. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA *[see Adverse Reactions (6)]*.

Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14)]*. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

5.2 Adrenocortical Insufficiency

Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions (5.1)]*.

5.3 Hepatotoxicity

In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2)]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

5.4 Increased ZYTIGA Exposures with Food

ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess *[see Warnings and Precautions (5.1)]*.
- Adrenocortical Insufficiency *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Increased ZYTIGA Exposures with Food *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

Study 1: Metastatic CRPC Following Chemotherapy

Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥ 2.5X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT > 5X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=791) All Grades[1] %	ZYTIGA with Prednisone (N=791) Grade 3-4 %	Placebo with Prednisone (N=394) All Grades %	Placebo with Prednisone (N=394) Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0
Cardiac failure[8]	2.3	1.9	1.0	0.3

[1]Adverse events graded according to CTCAE version 3.0
[2]Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3]Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4]Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5]Includes all fractures with the exception of pathological fracture
[6]Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7]Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively)
[8]Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

ZYTIGA® (abiraterone acetate) Tablets

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in Study 1

Laboratory Abnormality	Abiraterone (N=791) All Grades (%)	Abiraterone (N=791) Grade 3-4 (%)	Placebo (N=394) All Grades (%)	Placebo (N=394) Grade 3-4 (%)
Hypertriglyceridemia	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Hypokalemia	28.3	5.3	19.8	1.0
Hypophosphatemia	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

Study 2: Metastatic CRPC Prior to Chemotherapy

Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥ 2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥ 2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

System/Organ Class Adverse reaction	ZYTIGA with Prednisone (N=542) All Grades[1] %	ZYTIGA with Prednisone (N=542) Grade 3-4 %	Placebo with Prednisone (N=540) All Grades %	Placebo with Prednisone (N=540) Grade 3-4 %
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema[2]	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[3]	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23.1	0.4	19.1	0.6
Diarrhea	21.6	0.9	17.8	0.9
Dyspepsia	11.1	0.0	5.0	0.2
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

[1]Adverse events graded according to CTCAE version 3.0
[2]Includes terms Edema peripheral, Pitting edema, and Generalized edema
[3]Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

Table 4: Laboratory Abnormalities in > 15% of Patients in the ZYTIGA Arm of Study 2

Laboratory Abnormality	Abiraterone (N = 542)		Placebo (N = 540)	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia[1]	56.6	6.5	50.9	5.2
High ALT	41.9	6.1	29.1	0.7
High AST	37.3	3.1	28.7	1.1
Hypernatremia	32.8	0.4	25.0	0.2
Hypokalemia	17.2	2.8	10.2	1.7

[1]Based on non-fasting blood draws

Cardiovascular Adverse Reactions:
In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

7 DRUG INTERACTIONS

7.1 Effects of Abiraterone on Drug Metabolizing Enzymes

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3)]*

In vitro, ZYTIGA inhibits CYP2C8. There are no clinical data on the use of ZYTIGA with drugs that are substrates of CYP2C8. However, patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

7.2 Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.1)]*.

ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

8.3 Nursing Mothers

ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of ZYTIGA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients receiving ZYTIGA in phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

The pharmacokinetics of abiraterone were examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

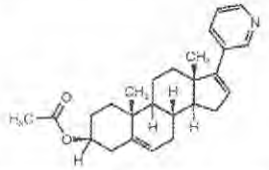
10 OVERDOSAGE

There have been no reports of overdose of ZYTIGA during clinical studies.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

11 DESCRIPTION

Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate and its structure is:



Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abiraterone acetate (ZYTIGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals *[see Warnings and Precautions (5.1)]*.

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

ZYTIGA decreased serum testosterone and other androgens in patients in the placebo-controlled phase 3 clinical trial. It is not necessary to monitor the effect of ZYTIGA on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

12.3 Pharmacokinetics

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic castration-resistant prostate cancer (CRPC). *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Absorption

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate.

At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of C_{max} were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and $AUC_{0-\infty}$ were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water *[see Dosage and Administration (2.1)]*.

Distribution and Protein Binding

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 19,669 ± 13,358 L. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

Metabolism

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate.

Excretion

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours. Following oral administration of ^{14}C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

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Patients with Hepatic Impairment

The pharmacokinetics of abiraterone was examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. Systemic exposure to abiraterone after a single oral 1,000 mg dose given under fasting conditions increased approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. ZYTIGA has not been studied in patients with baseline severe hepatic impairment (Child-Pugh Class C) *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Patients with Renal Impairment

The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). In the ESRD cohort of the trial, a single 1,000 mg ZYTIGA dose was given under fasting conditions 1 hour after dialysis, and samples for pharmacokinetic analysis were collected up to 96 hours post dose. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function *[see Use in Specific Populations (8.7)]*.

Drug Interactions

In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2, CYP2D6 and CYP2C8, a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5.

In an *in vivo* drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold *[see Drug Interactions (7.1)]*.

In a clinical study to determine the effects of abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) on a single 100 mg dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

Abiraterone is a substrate of CYP3A4, *in vitro*. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution *[see Drug Interactions (7.2)]*.

12.6 QT Prolongation

In a multi-center, open-label, single-arm trial, 33 patients with metastatic CRPC received ZYTIGA orally at a dose of 1,000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily. Assessments up to Cycle 2 Day 2 showed no large changes in the QTc interval (i.e., >20 ms) from baseline. However, small increases in the QTc interval (i.e., <10 ms) due to abiraterone acetate cannot be excluded due to study design limitations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of abiraterone acetate.

Abiraterone acetate and abiraterone did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using primary human lymphocytes and in the *in vivo* rat micronucleus assay.

ZYTIGA has the potential to impair reproductive function and fertility in humans based on findings in animals. In repeat-dose toxicity studies in male rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥ 50 mg/kg/day in rats and ≥ 250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone *[see Nonclinical Toxicology (13.2)]*. These effects were observed in rats at systemic exposures similar to humans and in monkeys at exposures approximately 0.6 times the AUC in humans.

In fertility studies in rats, reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility were observed in males dosed for 4 weeks at ≥ 30 mg/kg/day. Mating of untreated females with males that received 30 mg/kg/day abiraterone acetate resulted in a reduced number of corpora lutea, implantations and live embryos and an increased incidence of pre-implantation loss. Effects on male rats were reversible after 16 weeks from the last abiraterone acetate administration. Female rats dosed for 2 weeks until day 7 of pregnancy at ≥ 30 mg/kg/day had an increased incidence of irregular or extended estrous cycles and pre-implantation loss (300 mg/kg/day). There were no differences in mating, fertility, and litter parameters in female rats that received abiraterone acetate. Effects on female rats were reversible after 4 weeks from the last abiraterone acetate administration. The dose of 30 mg/kg/day in rats is approximately 0.3 times the recommended dose of 1000 mg/day based on body surface area.

13.2 Animal Toxicology and/or Pharmacology

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate. A dose-dependent increase in cataracts was observed in rats at 26 weeks starting at ≥ 50 mg/kg/day (similar to the human clinical exposure based on AUC). In the 39-week monkey study, no cataracts were observed at higher doses (2 times greater than the clinical exposure based on AUC). All other toxicities associated with abiraterone acetate reversed or were partially resolved after a 4-week recovery period.

14 CLINICAL STUDIES

The efficacy and safety of ZYTIGA in patients with metastatic castration-resistant prostate cancer (CRPC) that has progressed on androgen deprivation therapy was demonstrated in two randomized, placebo-controlled, multicenter phase 3 clinical trials. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded from these trials.

Study 1

Patients with metastatic CRPC who had received prior docetaxel chemotherapy:
A total of 1195 patients were randomized 2:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo once daily plus prednisone 5 mg orally twice daily (N=398). Patients randomized to either arm were to continue treatment until disease progression (defined as a 25% increase in PSA over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 39-95) and the racial distribution was 93.3% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine percent of patients enrolled had an ECOG performance status score of 0-1 and 45% had a Brief Pain Inventory-Short Form score of ≥ 4 (patient's reported worst pain over the previous 24 hours). Ninety percent of patients had metastases in bone and 30% had visceral involvement. Seventy percent of patients had radiographic evidence of disease progression and 30% had PSA-only progression. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens.

The protocol pre-specified interim analysis was conducted after 552 deaths and showed a statistically significant improvement in overall survival in patients treated with ZYTIGA compared to patients in the placebo arm (Table 5 and Figure 1). An updated survival analysis was conducted when 775 deaths (97% of the planned number of deaths for final analysis) were observed. Results from this analysis were consistent with those from the interim analysis (Table 5).

Table 5: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 1 (Intent-to-Treat Analysis)

	ZYTIGA (N=797)	Placebo (N=398)
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p-value [a]	< 0.0001	
Hazard ratio (95% CI) [b]	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio (95% CI) [b]	0.740 (0.638, 0.859)	

[a] P-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).
[b] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

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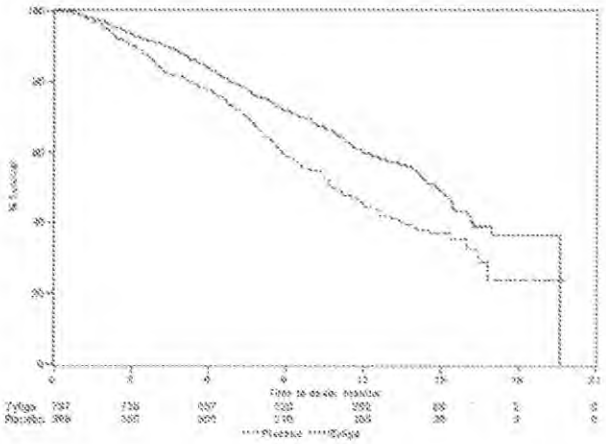
Figure 1: Kaplan-Meier Overall Survival Curves in Study 1 (Intent-to-Treat Analysis)



Study 2

Patients with metastatic CRPC who had not received prior cytotoxic chemotherapy
In Study 2, 1088 patients were randomized 1:1 to receive either ZYTIGA at a dose of 1,000 mg once daily (N=546) or Placebo once daily (N=542). Both arms were given concomitant prednisone 5 mg twice daily. Patients continued treatment until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to 3 or more) disease progression, unacceptable toxicity or withdrawal. Patients with moderate or severe pain, opiate use for cancer pain, or visceral organ metastases were excluded.

Patient demographics were balanced between the treatment arms. The median age was 70 years. The racial distribution of patients treated with ZYTIGA was 95.4% Caucasian, 2.8% Black, 0.7% Asian and 1.1% Other. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

Radiographic progression-free survival was assessed with the use of sequential imaging studies and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Working Group 2 criteria) and/or modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria for progression of soft tissue lesions. Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

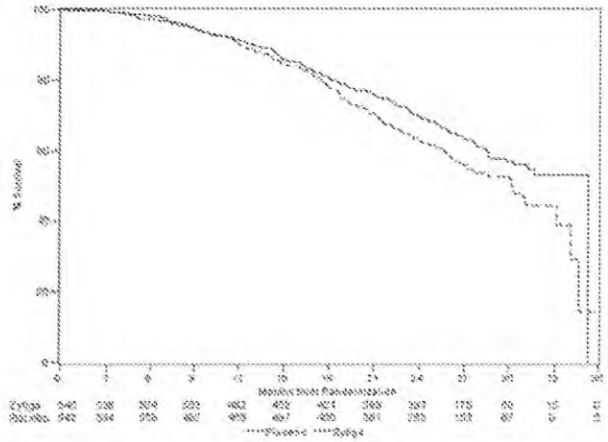
At the protocol pre-specified third interim analysis for overall survival, 37% (200 of 546) of patients treated with ZYTIGA, compared with 43% (234 of 542) of patients treated with placebo, had died. Overall survival was longer for ZYTIGA than placebo with a hazard ratio of 0.792 (95% CI: 0.655 - 0.956). The p- value was 0.0151 which did not meet the pre-specified value for statistical significance (Table 6 and Figure 2).

Table 6: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)

Overall Survival	ZYTIGA (N=546)	Placebo (N=542)
Deaths	200 (37%)	234 (43%)
Median survival (months) (95% CI)	35.3 (31.24, 35.29)	30.1 (27.30, 34.10)
p-value[a]	0.0151	
Hazard ratio[b] (95% CI)	0.792 (0.655, 0.956)	

[a] P-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).
[b] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

Figure 2: Kaplan Meier Overall Survival Curves in Study 2 (Intent-to-Treat analysis)



At the pre-specified rPFS analysis, 150 (28%) patients treated with ZYTIGA and 251 (46%) patients treated with placebo had radiographic progression. A significant difference in rPFS between treatment groups was observed (Table 7 and Figure 3).

Table 7: Radiographic Progression-free Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)

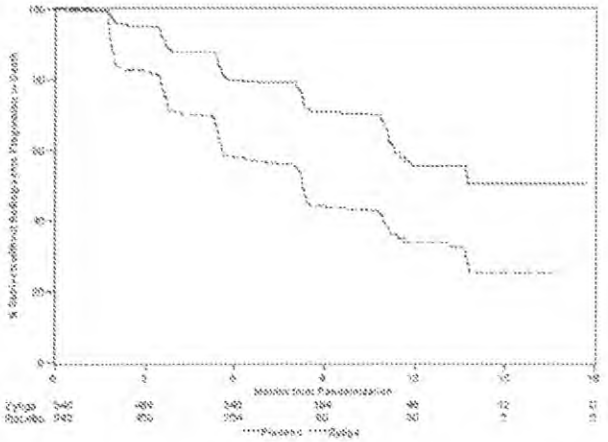
Radiographic Progression-free Survival	ZYTIGA (N=546)	Placebo (N=542)
Progression or death	150 (28%)	251 (46%)
Median rPFS (months) (95% CI)	NR (11.66, NR)	8.28 (8.12, 8.54)
p-value[a]	<0.0001	
Hazard ratio[b] (95% CI)	0.425 (0.347, 0.522)	

NR= Not reached

[a] P-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).

[b] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

Figure 3: Kaplan Meier Curves of Radiographic Progression-free Survival in Study 2 (Intent-to-Treat Analysis)



The primary efficacy analyses are supported by the following prospectively defined endpoints. The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving ZYTIGA and 16.8 months for patients receiving placebo (HR=0.580; 95% CI: [0.487, 0.691], p<0.0001).

ZYTIGA® (abiraterone acetate) Tablets

The median time to opiate use for prostate cancer pain was not reached for patients receiving ZYTIGA and was 23.7 months for patients receiving placebo (HR=0.686, 95% CI: [0.566, 0.833], p=0.0001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the ZYTIGA arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. ZYTIGA 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

NDC Number 57894-150-12

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*.

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves *[see Use in Specific Populations (8.1)]*.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA must not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

Manufactured by:
Patheon Inc.
Mississauga, Canada

Manufactured for:
Janssen Biotech, Inc.
Horsham, PA 19044

Revised: December 2012

janssen

PATIENT INFORMATION
ZYTIGA® (Zye-tee-ga)
(abiraterone acetate)
Tablets

Read this Patient Information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ZYTIGA?

ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

ZYTIGA is not for use in women.

It is not known if ZYTIGA is safe or effective in children.

Who should not take ZYTIGA?

Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

What should I tell my healthcare provider before taking ZYTIGA?

Before you take ZYTIGA, tell your healthcare provider if you:

- have heart problems
- have liver problems
- have a history of adrenal problems
- have a history of pituitary problems
- have any other medical conditions
- plan to become pregnant. See "Who should not take ZYTIGA?"
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See "Who should not take ZYTIGA?"

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ZYTIGA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ZYTIGA?

- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA one time a day.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food.** Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.

ZYTIGA® (abiraterone acetate) Tablets

- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole. Do not crush or chew tablets.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant woman must use a condom during and for one week after treatment with ZYTIGA. If their sexual partner may become pregnant, a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

What are the possible side effects of ZYTIGA?

ZYTIGA may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema).** Tell your healthcare provider if you get any of the following symptoms:
  - o dizziness
  - o fast heartbeats
  - o feel faint or lightheaded
  - o headache
  - o confusion
  - o muscle weakness
  - o pain in your legs
  - o swelling in your legs or feet
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.

The most common side effects of ZYTIGA include:

- o weakness
- o joint swelling or pain
- o swelling in your legs or feet
- o hot flushes
- o diarrhea
- o vomiting
- o cough
- o high blood pressure
- o shortness of breath
- o urinary tract infection
- o bruising
- o low red blood cells (anemia) and low blood potassium levels
- o high blood sugar levels, high blood cholesterol and triglycerides
- o certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZYTIGA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZYTIGA?

- Store ZYTIGA at 59°F to 86°F (15°C to 30°C).

Keep ZYTIGA and all medicines out of the reach of children.

General information about ZYTIGA.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ZYTIGA for a condition for which it was not prescribed. Do not give your ZYTIGA to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZYTIGA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for healthcare professionals.

For more information contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or www.Zytiga.com.

What are the ingredients of ZYTIGA?

Active ingredient: abiraterone acetate

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Patheon Inc.
Mississauga, Canada

Manufactured for:
Janssen Biotech, Inc.
Horsham, PA 19044

Revised: December 2012

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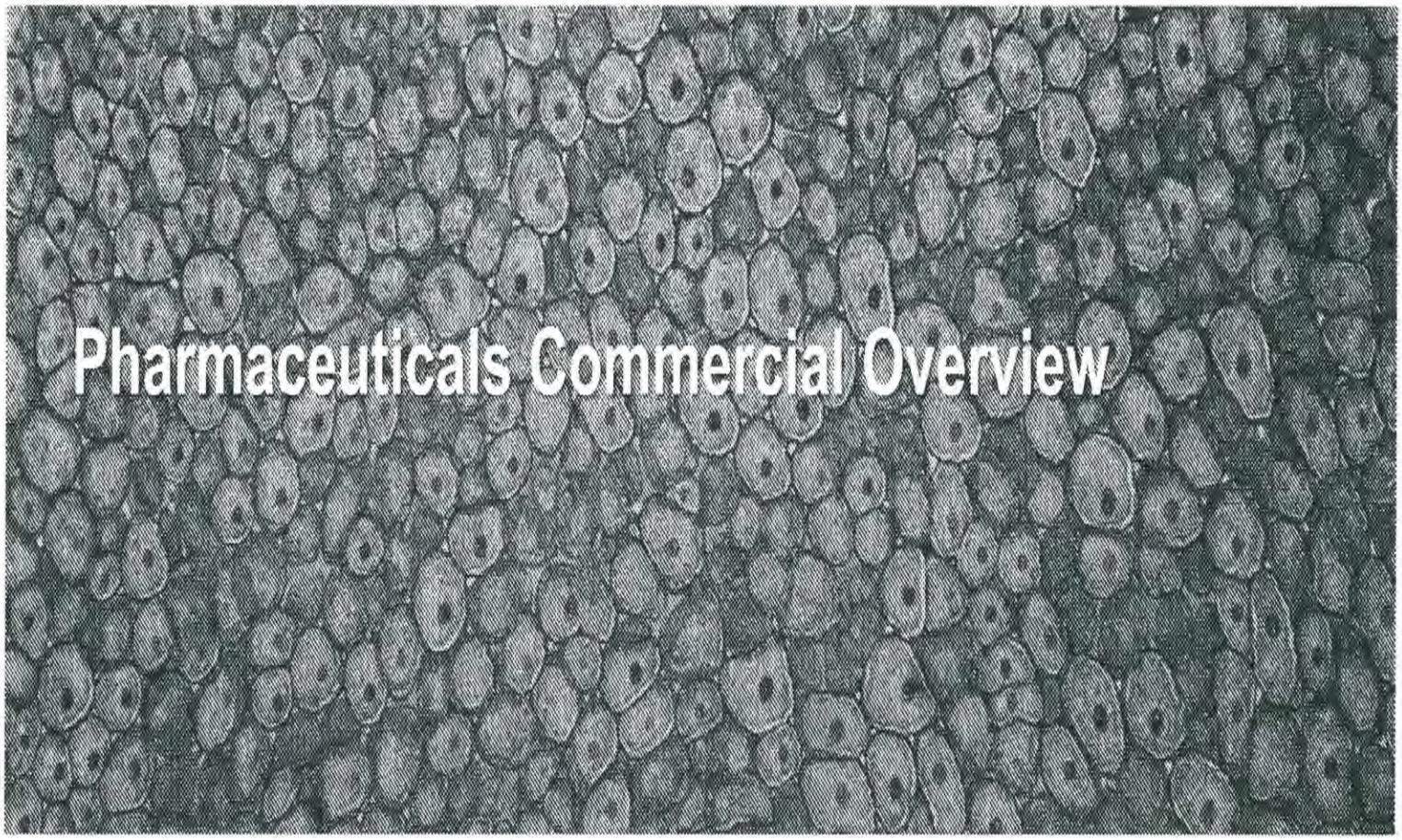

Joaquin Duato

Worldwide Chairman, Pharmaceuticals

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These presentations contain "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995. The viewer is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of the Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to, general industry conditions and competition; economic factors, such as interest rate and currency exchange rate fluctuations; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approvals; challenges to patents; significant adverse litigation or government action; impact of business combinations; financial distress and bankruptcies experienced by significant customers and suppliers; changes to governmental laws and regulations and domestic and foreign health care reforms; trends toward health care cost containment; increased scrutiny of the health care industry by government agencies; changes in behavior and spending patterns of purchasers of health care products and services; financial instability of international economies and sovereign risk; disruptions due to natural disasters; manufacturing difficulties or delays; complex global supply chains with increasing regulatory requirements; and product efficacy or safety concerns resulting in product recalls or regulatory action. A further list and description of these risks, uncertainties and other factors can be found in Exhibit 99 of Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 30, 2012. Copies of this Form 10-K, as well as subsequent filings, are available online at www.sec.gov, www.investor.jnj.com or on request from Johnson & Johnson. Neither the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statements as a result of new information or future events or developments.

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Note: Operational sales growth excludes currency impact and is a non-GAAP financial measure.

New Molecular Entities

These presentations contain statements about new molecular entities ("NMEs") and other medicines or line extensions in various stages of development. These statements are based on the Company's current knowledge of the status of development of these NMEs, medicines and line extensions and are subject to the challenges and difficulties inherent in product development. The Company assumes no obligation to update any statements regarding these NMEs, medicines or line extensions as a result of new information or future events or developments.

In addition, in biopharmaceuticals, there are higher possibilities of encountering infringement claims by competitors with respect to patents or other intellectual property rights.

Strategic Partnerships, Collaborations and Licensing Arrangements

During the course of this morning's presentations, we will discuss a number of products and compounds developed in collaboration with strategic partners or licensed from other companies. Following is an acknowledgement of those relationships that are not otherwise referenced in today's presentations.

Immunology REMICADE® and SIMPONI® marketing partners are Schering-Plough (Ireland) Company, a subsidiary of Merck & Co., Inc. and Mitsubishi Tanabe Pharma Corporation. ASP015K-JAK Inhibitor licensed from Astellas Pharma Inc., Sirukumab developed in collaboration with GlaxoSmithKline.

Neuroscience INVEGA® SUSTENNA®/XEPLION® includes technology licensed from Alkermes, Inc., NUCYNTA® co-developed with Grunenthal GmbH, RISPERDAL® CONSTA® developed in collaboration with Alkermes, Fulranumab licensed from Amgen, Inc., Bapineuzumab is being developed through a collaboration between Janssen Alzheimer Immunotherapy and Pfizer Inc., Bace Inhibitor–Prodormal Alzheimer's disease licensed from Shionogi & Co., MGluR2 PAM developed in collaboration with Addex Therapeutics, NR2B licensed from Evotec, MGluR5 PAM developed in collaboration with Vanderbilt University, AAB-003 and AAC-001 developed in collaboration with Pfizer, ULTRAM® ER licensed from Grunenthal GmbH, TRAMACET® developed in collaboration with Grunenthal GmbH, AXERT® licensed from Almirall Prodesfarma, REMINYL® is licensed from Shire PLC., LEXAPRO® co-marketed and license agreement between Xian-Janssen and Lundbeck A/S,

Infectious Diseases & Virology INCIVO® developed in collaboration with Vertex Pharmaceuticals, Simeprevir (TMC435) developed in collaboration with Medivir AB, Darunavir/cobicistat fixed-dose combination developed in collaboration with Gilead Sciences, Inc., LEVAQUIN® licensed from Daiichi Sankyo Co., Ltd., QUINVAXEM® developed in collaboration with Novartis Vaccines and Diagnostics, HIV Vaccine developed in collaboration with Beth Israel Deaconess Medical Center and National Institutues of Health, (NIH), Rabies mAb co-promoted with Sanofi Pasteur, FlumAb partially funded by NIH.

Cardiovascular/ Metabolism INVOKANA™ licensed from Mitsubishi Tanabe Pharma Corporation, XARELTO® co-developed with Bayer HealthCare.

Oncology Ibrutinib (PCI-32765) developed in collaboration and upon approval will be co-marketed with Pharmacyclics, Inc., ZYTIGA® licensed from BTG International Ltd., VELCADE® developed in collaboration with Millennium: The Takeda Oncology Company, DACOGEN® developed in collaboration with Eisai Corporation of North America, Daratumumab licensed from Genmab A/S, YONDELIS® developed in collaboration with Pharma Mar S.A., Intetumumab licensed to and co-developed with BeiGene, Ltd., PROCRIT®/EPREX® licensed from Amgen Inc., FGFR Inhibitor is licensed from Astex Pharmaceuticals, Inc.

The Pharmaceuticals Market Is Attractive and Growing

- Global market $963B in 2012
- Compound annual growth ~4.5% to $1.2T in 2017
- Market drivers
  - Aging demographics
  - Growing middle class in emerging markets
  - Rising incidence of chronic disease
  - Significant unmet medical needs

Tremendous Opportunity to Improve the Lives of Patients

Source: IMS Market Prognosis Reports, March 2013.

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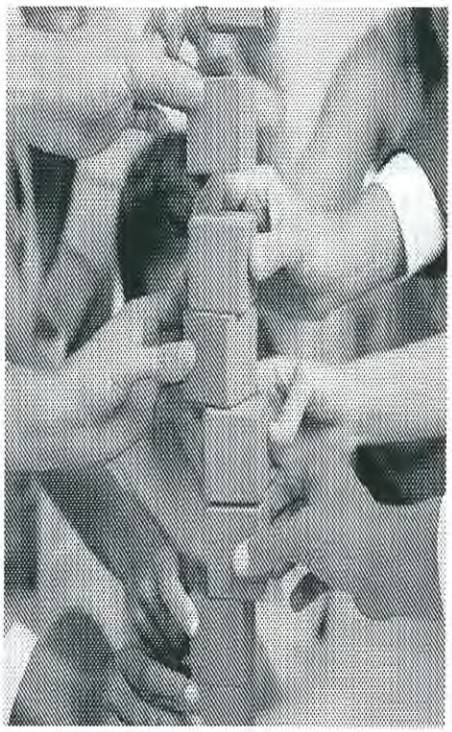
Building on the Strong Momentum in Pharmaceuticals

Focus on Transformational Medical Innovation

- Revitalizing our portfolio:
  11 new product launches in the last 4 years
- Combining superior science with best-in-class commercial capabilities
- Delivering robust growth and outpacing our peers in markets where we compete
- Next wave of growth:
  Potential for >10 NMEs & >25 LEs by 2017



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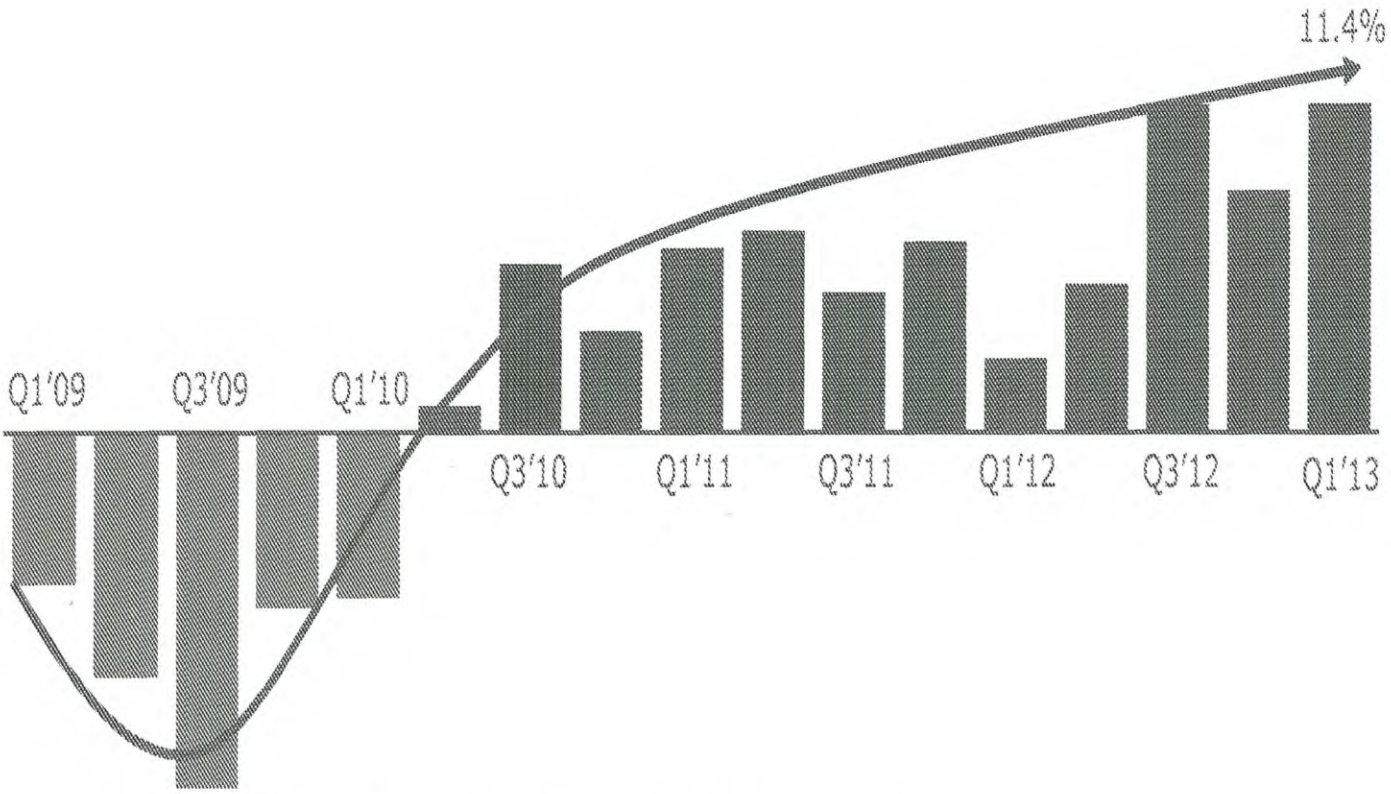
Fastest Growing Top 10 Pharmaceutical Company[1]

WW Pharmaceuticals: Operational Sales Change vs. Prior Year Respective Quarter*



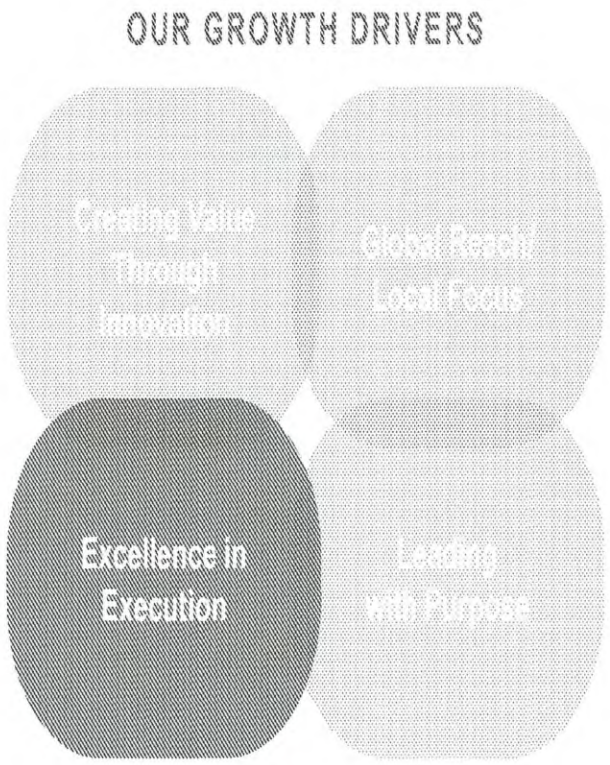
Source: 1. IMS MIDAS as of 1Q 2013 vs. prior year respective quarter (based on available data May 20, 2013).
* Q4 2009 and Q4 2010 operational sales change adjusted for the dynamics of the 53rd week in Q4 2009.

Johnson & Johnson

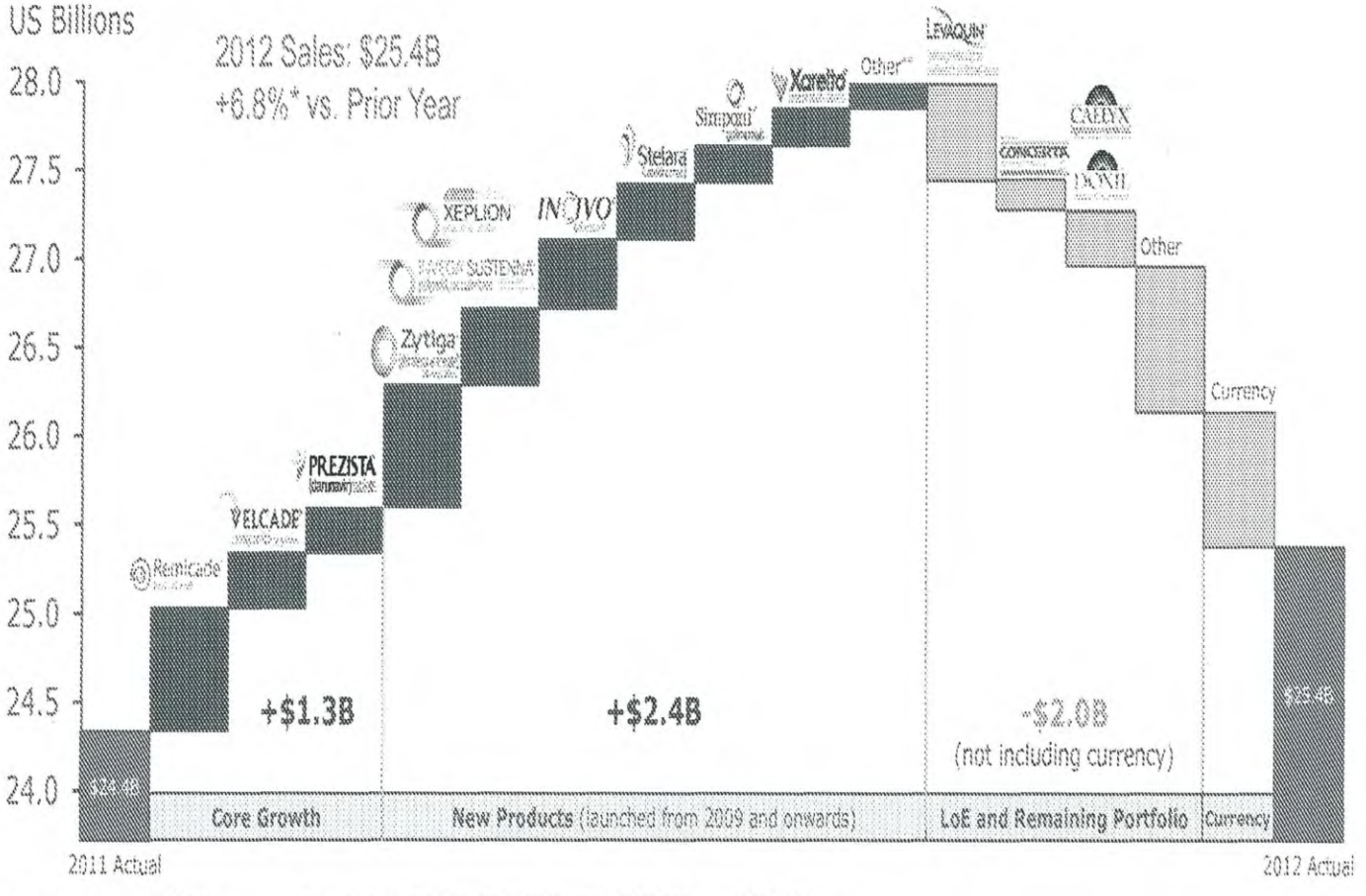
Strategic Framework

Johnson & Johnson

Strategic Framework



Robust Performance from Core Growth and New Products



*Operational change. **Other new products include NUCYNTA®, EDURANT®/COMPLERA®, and DACOGEN®.

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Core Growth Products Continue to Make a Strong Contribution

VELCADE® (bortezomib) FOR INJECTION

- Backbone of Multiple Myeloma treatment
  - Reached $1.5B in 2012 (+25%)*
  - Recently approved subcutaneous formulation
  - Label expansion planned in Mantle Cell Lymphoma

Q1 2013 SALES	Q1 YoY GROWTH*
$353MM	3%

PREZISTA® (darunavir) tablets

- Leading HIV Protease Inhibitor (PI), robust growth
  - Reached $1.4B in 2012 (+21%)*, #1 PI in Europe and US
  - New fixed-dose combination being developed with Gilead's cobicistat in Phase III

Q1 2013 SALES	Q1 YoY GROWTH*
$367MM	14%

Remicade® INFLIXIMAB

- Largest Johnson & Johnson brand, continued strong growth
  - Revenues over $6B in 2012 (+13%)*
  - 16 indications: 75% share of US Intravenous (IV) Immunology market[1]

Q1 2013 SALES	Q1 YoY GROWTH*
$1.6B	6%

Source: 1. IMS Health. * Operational change.

Immunology Portfolio Expanding on REMICADE® Legacy of Leadership

WW Market[1]		
2012	2017	CAGR
$35B	$52B	8%

Simponi® golimumab

Expanding Geographies and Indications

- Over $600MM in 2012 (+51%)*
- Additional FDA approval for moderately to severely active Ulcerative Colitis, May 2013
- Rheumatoid Arthritis IV formulation PDUFA July 2013

Q1 2013 SALES	Q1 YoY GROWTH*
$237MM	**

Remicade® INFLIXIMAB

Stelara® (ustekinumab)

Game-Changing, First-in-Class

- Crossed $1B threshold in 2012 (+42%)*
- 5-Year efficacy and safety data – 9,000 patient years of experience
- Psoriatic Arthritis Signs and Symptoms submitted 2012

Q1 2013 SALES	Q1 YoY GROWTH*
$346MM	57%

Sources: 1. EvaluatePharma, April 2013 (Immunology market includes small and large molecules for Rheumatoid Arthritis, Ankylosing Spondylitis, Lupus, Psoriatic Arthritis, Crohn's Disease, Ulcerative Colitis, and Psoriasis). * Operational change. ** Percent greater than 100%.

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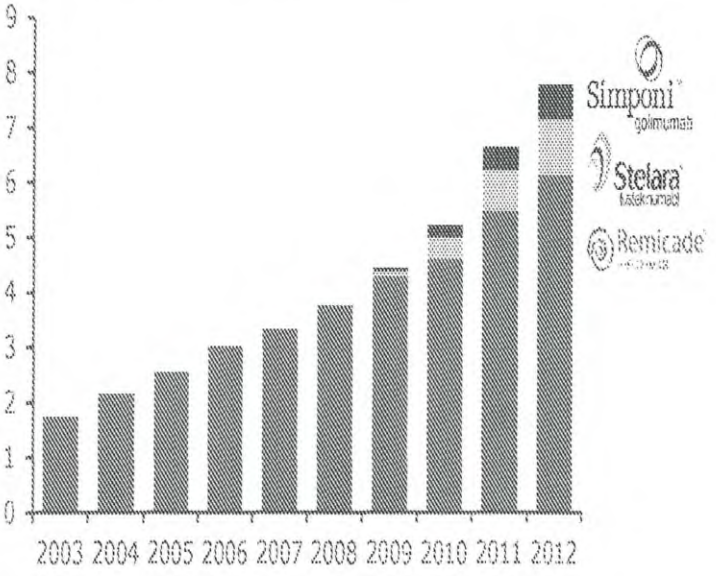
US Immunology Leader, Poised for Continued Growth

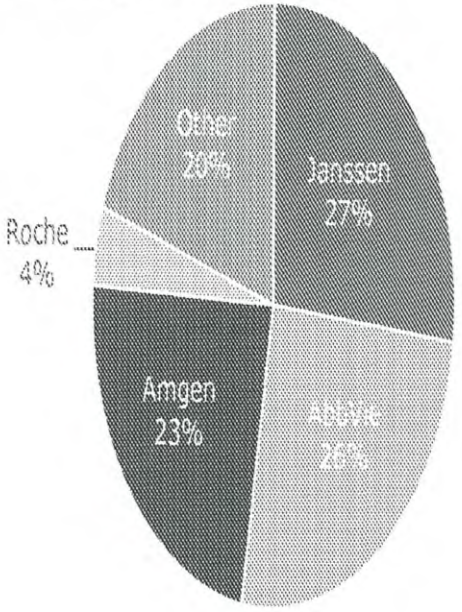
Total Immunology Products Delivered $7.9B in 2012;
19% Operational Compound Annual Growth Rate Since 2009

WW Immunology Portfolio Sales ($B)



Janssen Is #1 in US Immunology Sales and #2 Worldwide[1]

US Immunology Sales, 2012 ($17B)[1]



Source: 1. EvaluatePharma, May 2013 (Immunology market includes US small and large molecules for Rheumatoid Arthritis, Ankylosing Spondylitis, Lupus, Psoriatic Arthritis, Crohn's Disease, Ulcerative Colitis, and Psoriasis).

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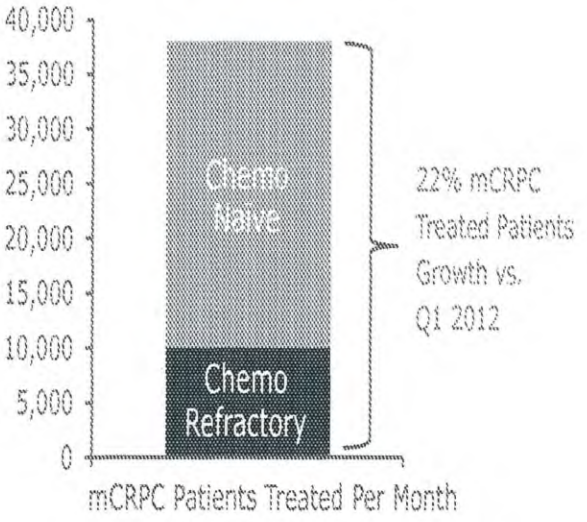
ZYTIGA®: Most Successful Oral Oncology Launch in History[1]

- Generated $961MM revenue in 2012
- Changed treatment paradigm for metastatic Castration-Resistant Prostate Cancer (mCRPC)
- Approved in 75+ countries for chemo refractory and more than 60,000 patients treated
- Approved in 40+ countries for chemo naïve (US/EU approvals December 2012)

WW Market[2]		
2012	2017	CAGR
$4.5B	$8.0B	12%

Q1 2013 SALES	Q1 YoY GROWTH*
$344MM	72%

Q1 2013 US Patient Population[3]



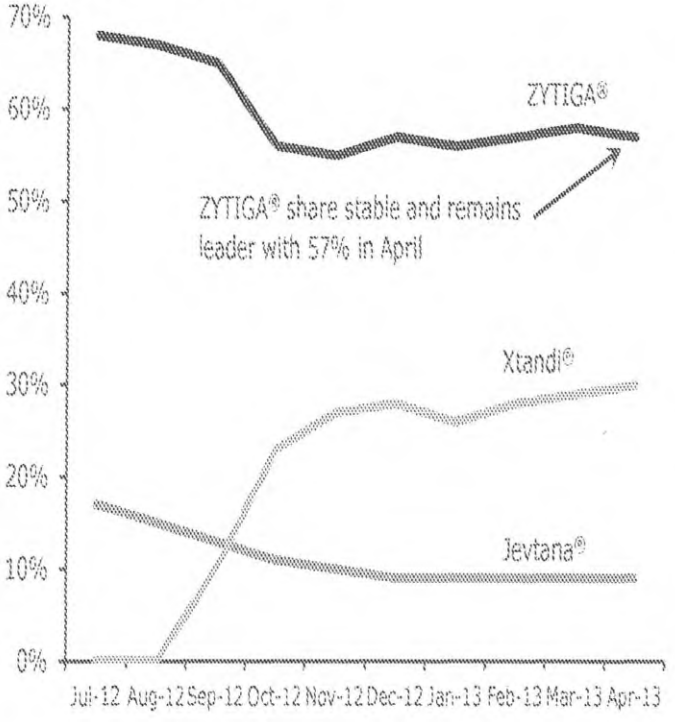
Sources: 1. EvaluatePharma, Oncology launch view orals, May 14, 2013. 2. EvaluatePharma, April 2013 (Prostate Cancer market). 3. IMS Health and internal analysis.
* Operational change.

Overall US Patient Share Continues to Grow

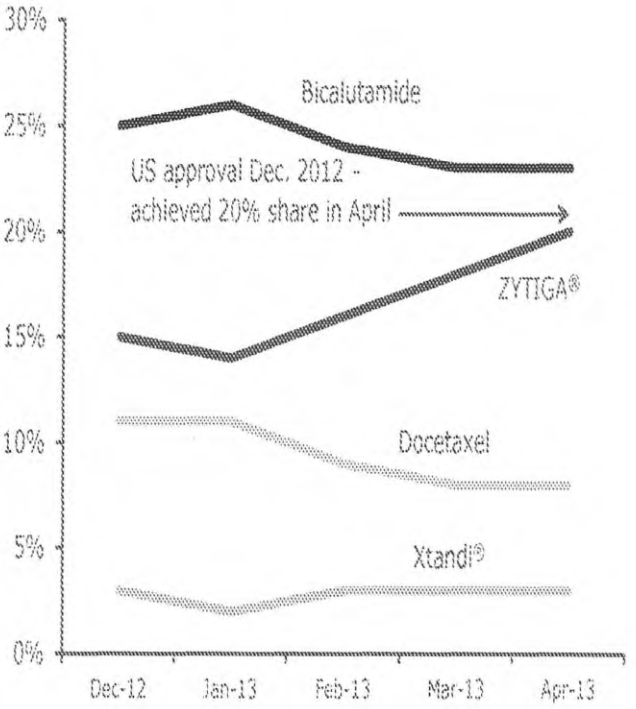
Total mCRPC Share in April Over 30%, Up ~3 Points from Q4 2012

Zytiga (abiraterone acetate) 250 mg tablets

Chemo Refractory



Chemo Naïve



Sources: ZYTIGA® - IMS DDD. Wolters Kluwer Health (WKH). Xtandi® - WKH data based on ZYTIGA® Xponent samples to IMS DDD universe (sample of claims from SPP/Pharmacy to Payer). Note: Patient share percentages are preliminary estimates based on limited data available. Patient level detailed sales data by indication only available on a 2 month lag (i.e., March data at the beginning of June).

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INCIVO®: Maintaining Leadership Position

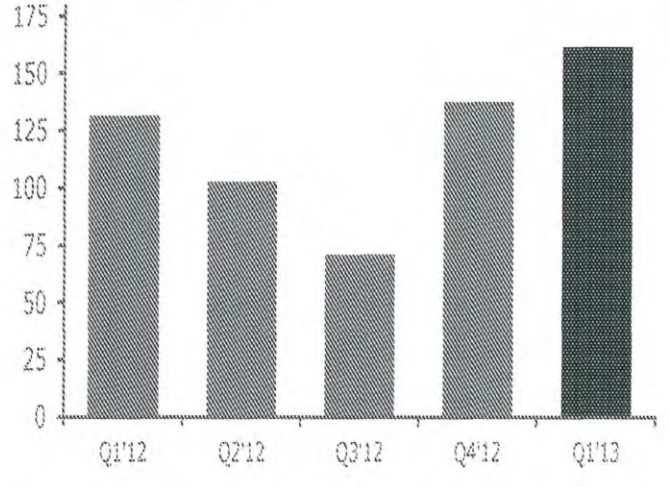
INCIVO® telaprevir

- EMA approved 2011; now launched in over 30 countries
- Maintaining strong lead vs. Victrelis® across Europe
- Received CHMP recommendation for twice-daily dosing April 2013

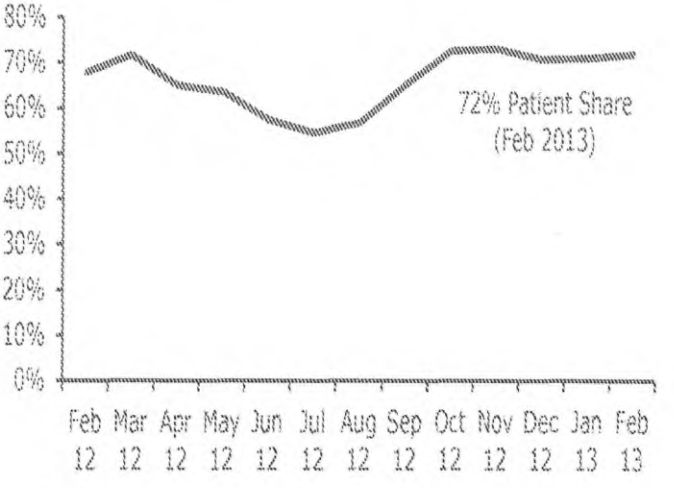
OUS Market[2]		
2012	2017	CAGR
$2.8B	$7.7B	22%

Q1 2013 SALES	Q1 YoY GROWTH[3]
$162MM	25%

INCIVO® Sales ($MM)



INCIVO® Patient Share (EMEA) – Direct-Acting Antivirals[1]



Sources: 1. IMS Health. 2. EvaluatePharma, April 2013 (HCV market excluding OTC products). 3 Operational change.

XARELTO®: Broadest Profile of Any Novel Oral Anticoagulant

Xarelto® rivaroxaban tablets

- Strong customer value proposition with once-a-day dosing convenience and multiple indications
- Broad market access
  - Over 90% formulary coverage for insured patients
  - 85% of Commercial and 85% of Part D have Tier 2 access and lowest branded co-pay
- Leader in the novel oral market[1]
  - Surpassed 1MM prescriptions in 2012
  - Over 1MM prescriptions already in 2013

US Market[2]		
2012	2017	CAGR
$2.2B	$5.6B	21%

Q1 2013 SALES	Q1 YoY GROWTH*
$158MM	**

6 FDA-Approved Indications

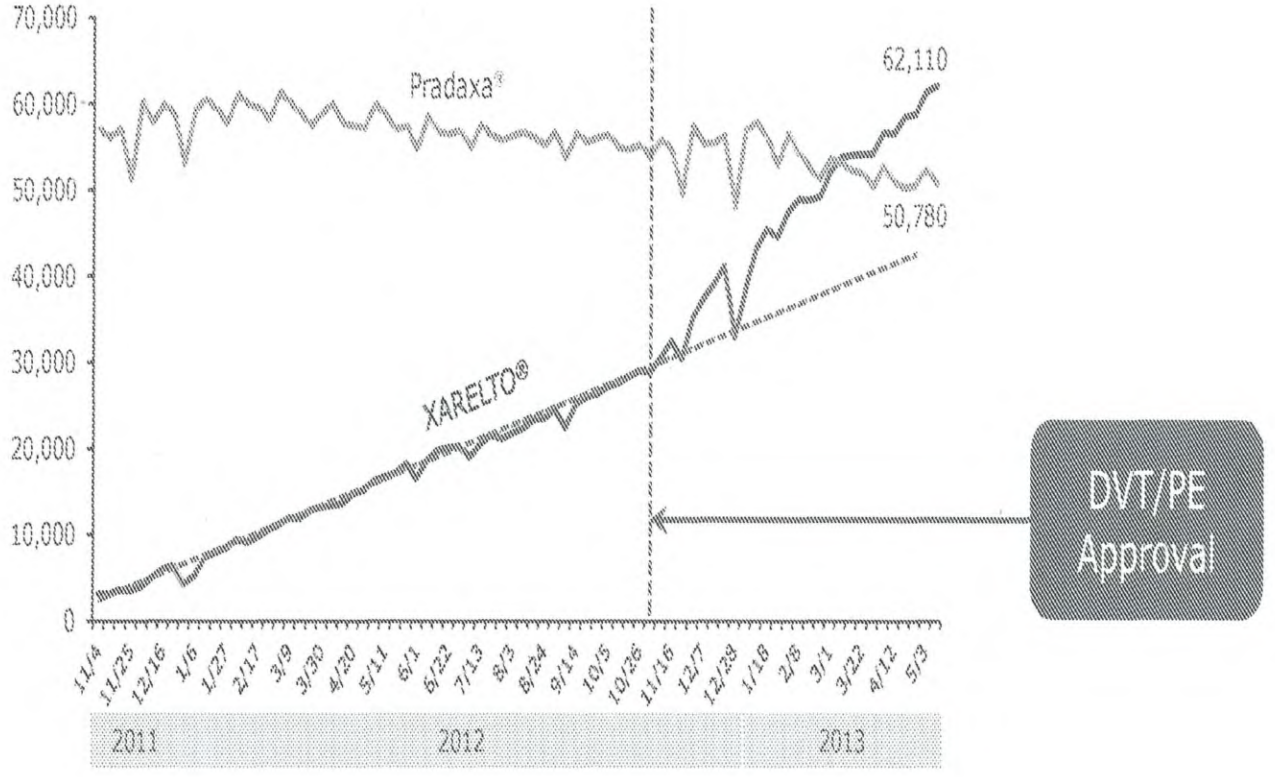
- Atrial Fibrillation (AF)
- Deep Vein Thrombosis (DVT)
- Pulmonary Embolism (PE)
- Risk of DVT/PE reoccurrence
- Prophylaxis of DVT/PE – Knee
- Prophylaxis of DVT/PE – Hip

Sources: 1. IMS Health. 2. EvaluatePharma, May 2013 (oral anticoagulants).
* Operational change. ** Percent greater than 100%.

Novel Oral Anticoagulant Leader in the US

Xarelto® rivaroxaban tablets

Novel Orals – US TRx Volume

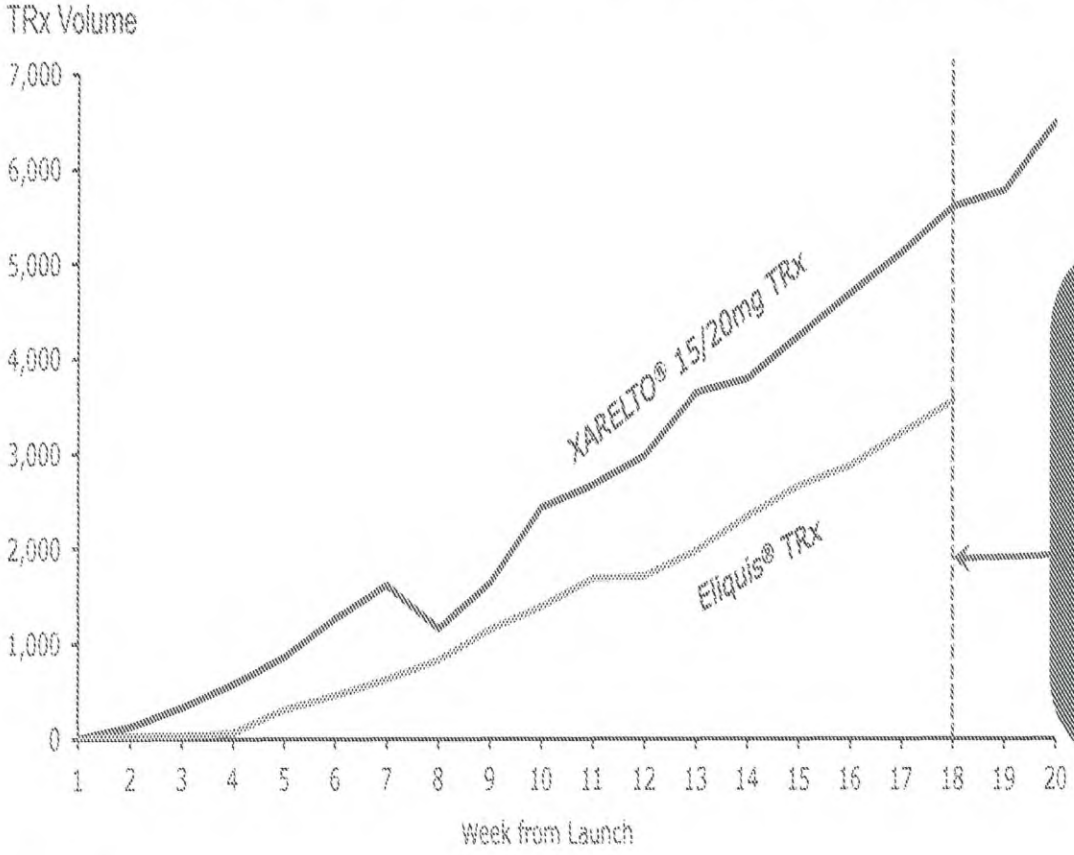


Source: IMS Health.

Unmatched Early Performance

Xarelto® rivaroxaban tablets

Factor Xa – US Atrial Fibrillation Launch Aligned Performance



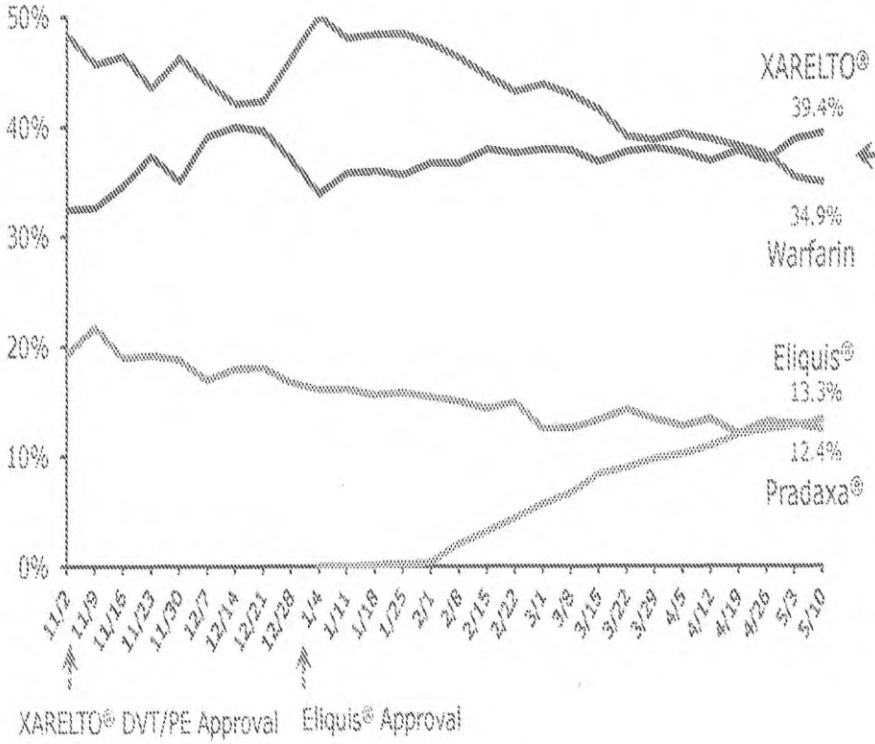
On a launch aligned basis, at week 18 XARELTO® had achieved over 70% greater cumulative prescription volume than Eliquis®

Source: IMS Health.
XARELTO® AF approval date: Nov 4, 2011. Eliquis® approval date: Dec 28, 2012.

Surpassing Warfarin Among Cardiologists

Xarelto® rivaroxaban tablets

US Oral Anti-Coagulant NBRx* Share in Cardiology



XARELTO® has overtaken warfarin in New-to-Brand share (NBRx)*

Source: IMS NPA Weekly, data through May 10, 2013.

* NBRx share includes new therapy starts, switch-to, and add-on prescriptions.

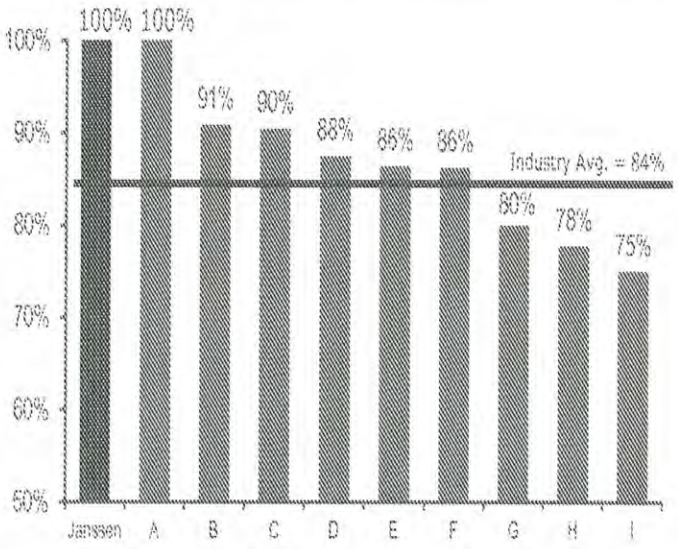
Best-in-Class Commercial Capabilities Have Unlocked the Potential of New Products

High Sales Force Effectiveness
8 of 14 sales forces assessed were rated as "best-in-class" by our customers[1]

Strong Net Promoter Scores
5 of 6 key brands ranked #1 vs. competitors[2]

Deep Market Access Expertise
100% success rate for NICE submissions since 2000[3]

NICE Health Technology Assessment Success Rate[3]



Sources: 1. Proprietary Sales Force Effectiveness and Activity Study, 2H 2012 conducted by Harris Interactive. 2. EU5 CONNECT Customer loyalty survey wave 3, Q4 2012, EU5, (VELCADE®, PREZISTA®, STELARA®, ZYTIGA®, INCIVO®, and XEPLION®). 3. Internal analysis of NICE Technology Appraisal Guidance.

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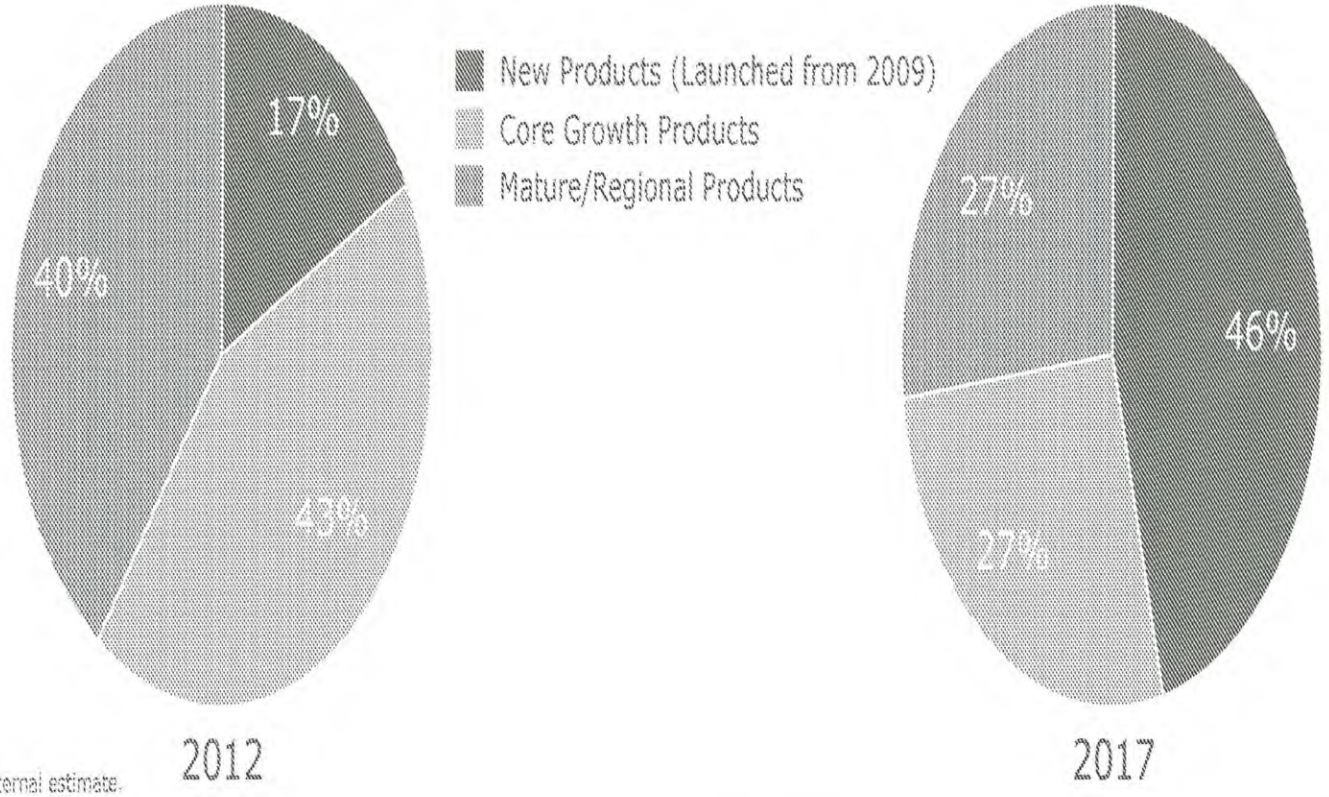
New Products Contributed $4.4B in 2012

Note: New Products include ZYTIGA®, INVEGA® SUSTENNA®/XEPLION®, INCIVO®, STELARA®, SIMPONI®, XARELTO®, NUCYNTA®, EDURANT®/COMPLERA®, and DACOGEN®.

New Products Expected to Make Up ~46% of a Well Balanced Portfolio in 2017

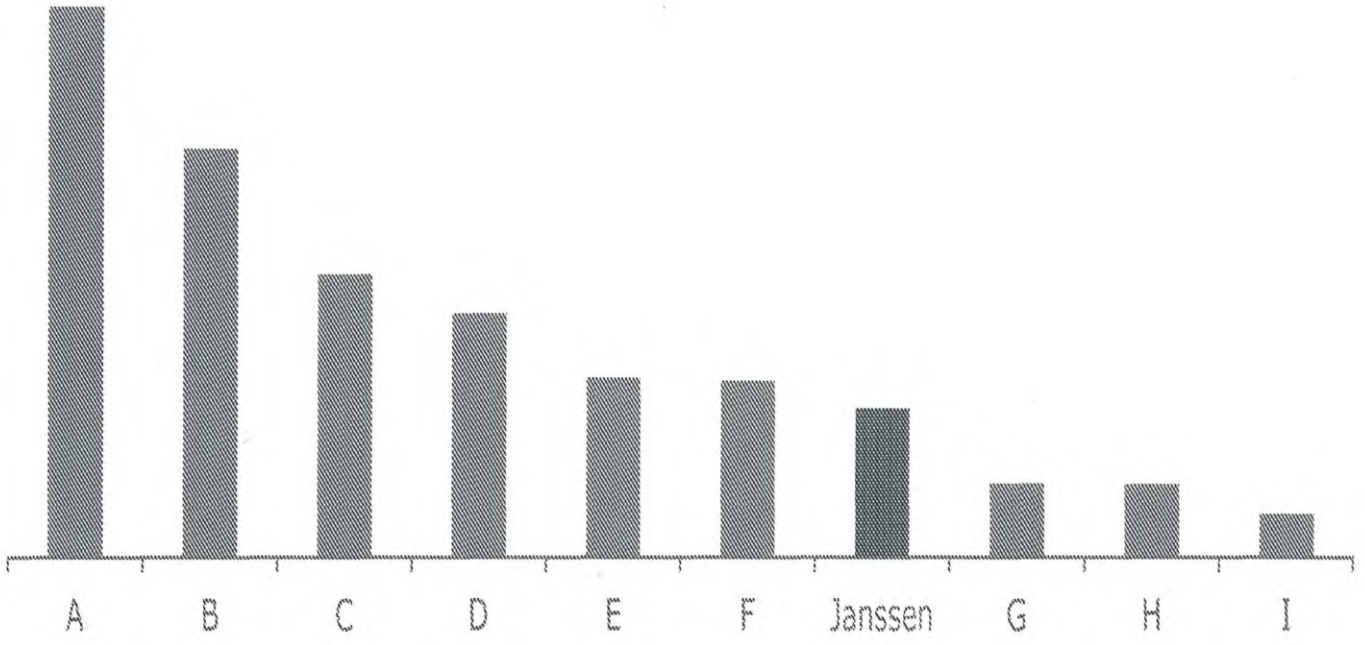
Sales as % of Total Pharmaceuticals



* Internal estimate.

Favorable Loss of Exclusivity Position from Refreshed Portfolio Helps Protect Future Revenues

Top 10 Global Pharmaceutical Companies – Potential 2013-2017 LoE Exposure



Source: IMS Health, April 2013 (included in analysis: US, Canada, Japan, Major EU markets, and S. Korea. Analysis excludes biologics).

Well Positioned for Potential Infliximab Biosimilars

- Expectations
  - Biosimilars compete like branded products rather than small molecule generics
  - Moderate impact in early years
- Infliximab patent situation
  - Potential 2015+ in Europe
  - Potential 2018+ in US

Janssen Strategies

- Support policies that promote patient safety and informed stakeholder decisions
- Leverage extensive REMICADE expertise and safety data from almost 2MM patients
- Develop innovative new therapies, both large and small molecule

Source: Internal assumptions.

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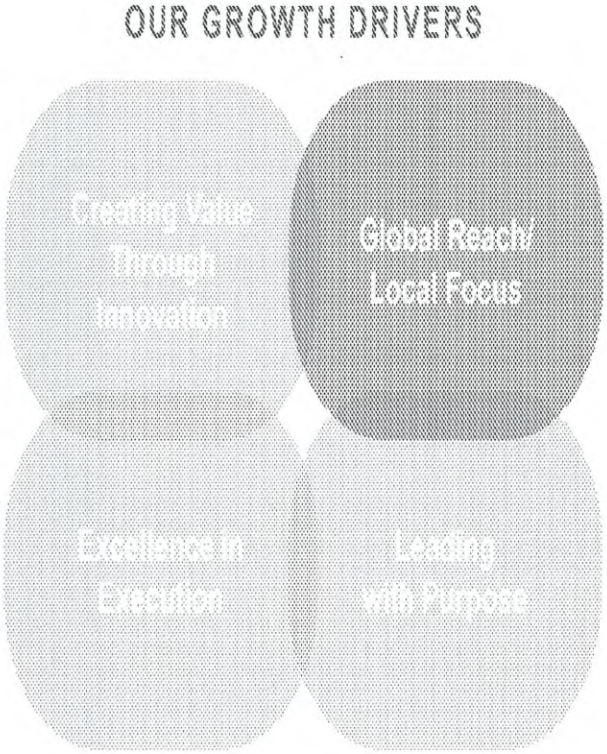
Strategic Framework



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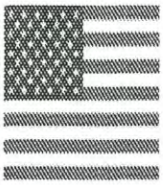
Fastest Growing Top 10 Global Pharmaceutical Company



RANK	COMPANY	GROWTH
#1	Janssen	12%
#2	Roche	7%
#3	AbbVie	5%
#4	Teva	1%
#5	Lilly	1%
Industry Average		-4%

RANK	COMPANY	GROWTH
#1	Janssen	7%
#2	AbbVie	5%
#3	Teva	4%
#4	Novartis	2%
#5	Merck	1%
Industry Average		1%

RANK	COMPANY	GROWTH
#1	Janssen	27%
#2	Teva	14%
#3	Roche	7%
#4	AZ	5%
#5	GSK	1%
Industry Average		0%

Source: IMS MIDAS as of Q4 2012 (vs. Q4 2011).

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Johnson & Johnson Continues to Lead the Pharmaceutical Industry in US Sales

Cumulative Sales from Products Launched from 2009 to March 2013

RANK	COMPANY	($MM)
1	JOHNSON & JOHNSON	$ 5,841 ★
2	NOVARTIS	$ 3,236
3	PFIZER	$ 3,062
4	SANOFI	$ 2,947
5	TAKEDA	$ 2,760
6	BMS	$ 2,715
7	VERTEX PHARMA	$ 2,530
8	BOEHRINGER INGELHEIM	$ 2,296
9	NOVO NORDISK	$ 2,249
10	GLAXOSMITHKLINE	$ 1,937

Source: IMS National Sales Perspectives, Mar 2013, Rx only.

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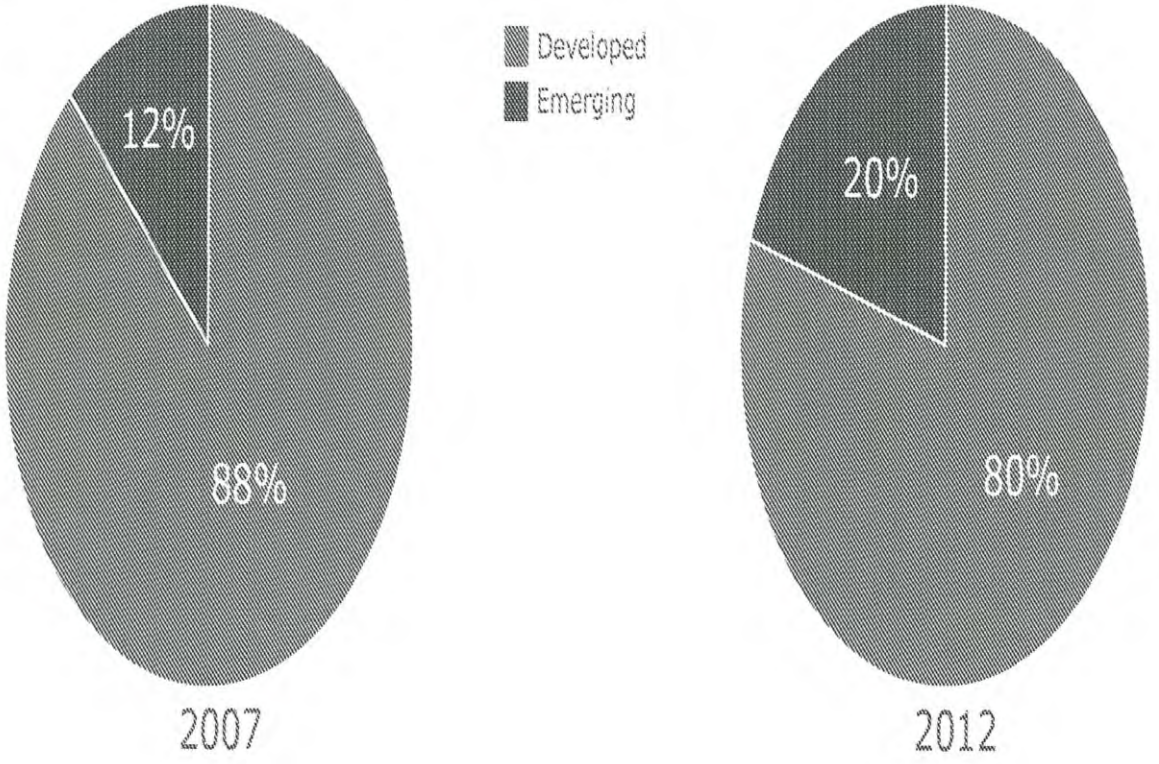
Core Growth and New Products Have Almost Doubled Footprint in Emerging Markets

Sales as % of Total Pharmaceuticals



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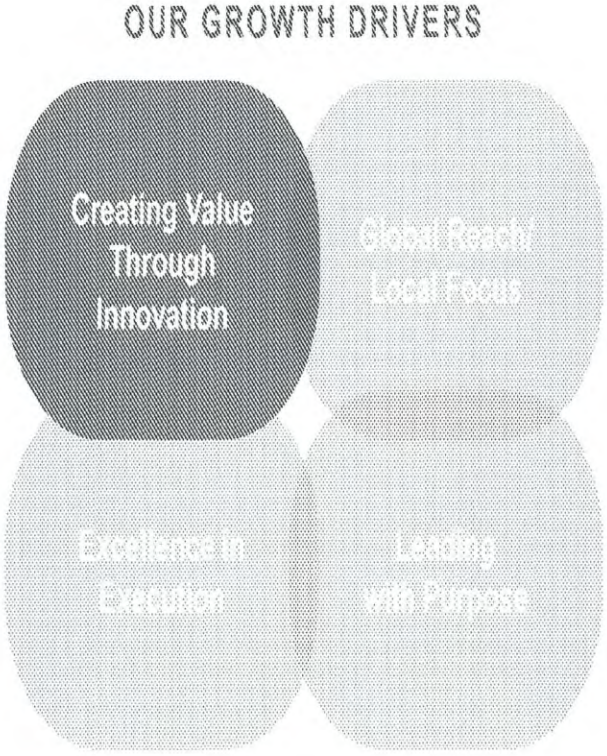
Strategic Framework



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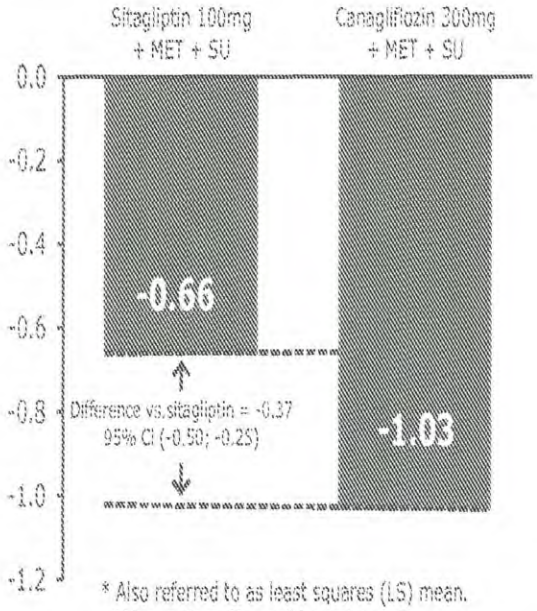
INVOKANA™: A New Approach in the Treatment of Type 2 Diabetes

Invokana
canagliflozin tablets

WW Market[1]		
2012	2017	CAGR
$14.5B	$30.6B	16%

- First-in-class SGLT2 inhibitor launched in April in collaboration with Diabetes Care franchise
- Oral, once-daily medication that reduces HbA_{1C}, body weight, and systolic blood pressure
- Extensive clinical program
- Filed fixed-dose combination with metformin (US – December 2012, EU – March 2013)
- Superiority at 300mg dose vs. Januvia® (sitagliptin) on HbA_{1C} reduction

Adjusted Mean Change* in HbA_{1C} from Baseline to Week 52[2]



Sources: 1. EvaluatePharma, April 2013 (diabetes market excluding Insulin).
2. Schernthaner G, et al. Diabetes Care. 2013 Apr 5. [Epub ahead of print].

* Also referred to as least squares (LS) mean.
Abbreviation: CI=confidence interval.

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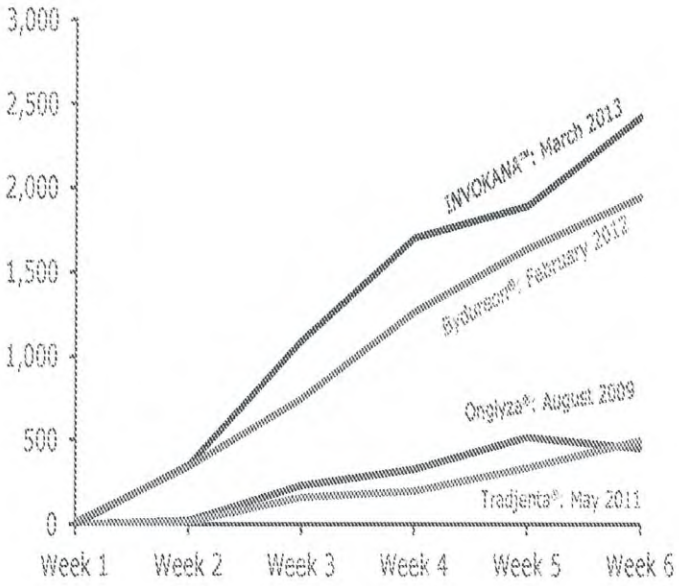
Strong Initial Market Reaction

Invokana™
canagliflozin tablets

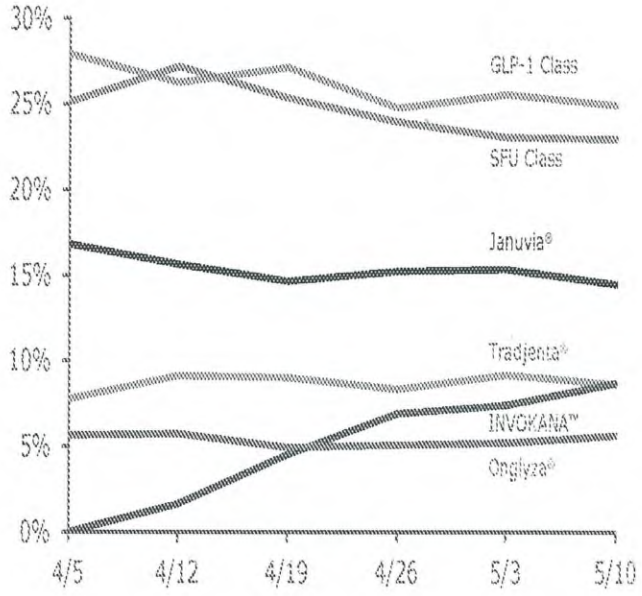
Strong Launch-Aligned Performance in the Early Weeks Following US Launch

US Launch Aligned TRx Volume



Nearly 9% NBRx Share Among US Endocrinologists in Week 6, Surpassing Onglyza® and Tradjenta®

US Total NBRx Share



Source: IMS NPA Weekly.

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Simeprevir: Next Generation HCV Treatment with Priority FDA Review

- Filed in Japan in February, US in March and EU in April; additional filings in process
- Potential best-in-class protease inhibitor
  - Efficacy across all patient populations with shorter duration of therapy for most patients
  - Safety/tolerability comparable to peg-interferon and ribavirin alone
  - Convenient once-daily dosing
- Opportunity in IFN-free regimens
  - COSMOS Ph 2 showed IFN-free efficacy rate 93-96%[1]
  - 5 IFN-free Phase 2 trials initiated with Simeprevir

WW Market[2]		
2012	2017	CAGR
$4.9B	$10.6B	17%

Significant Unmet Need

- High burden disease – long-term health problems and death
- 150 Million infected, only 25% diagnosed[3]

Sources: 1. Lawitz, et al. CROI 2013; abstract 155 LB.
2. EvaluatePharma, April 2013 (HCV market excluding OTC products). 3. CDC, WHO.

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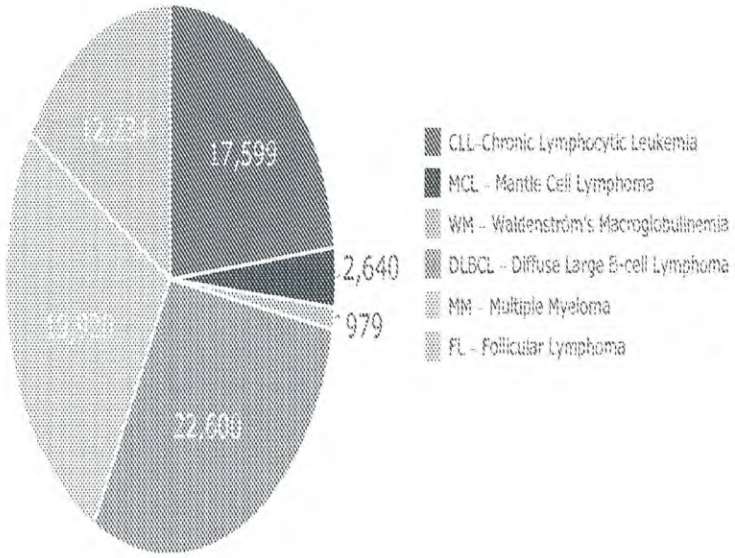
Ibrutinib: Granted Breakthrough Therapy Designations for Rel/Ref MCL, WM and 17p del CLL

- Highly differentiated, novel compound
  - Orally active, small molecule, targeted agent
  - Novel mechanism with compelling activity across several B-cell malignancies
  - Development in CLL, MCL, WM, DLBCL, FL, and MM
- WW license agreement with Pharmacyclics 50/50 profit and loss split
- Early Access Program announced May 2013
- MCL filing targeted before end of Q3 2013

WW Market[1]		
2012	2017	CAGR
$21.1B	$29.9B	7%

US Incidence[2]



Sources: 1. EvaluatePharma, April 2013 (Hematology market). 2. Decision Resources, 2009 and SEER data.

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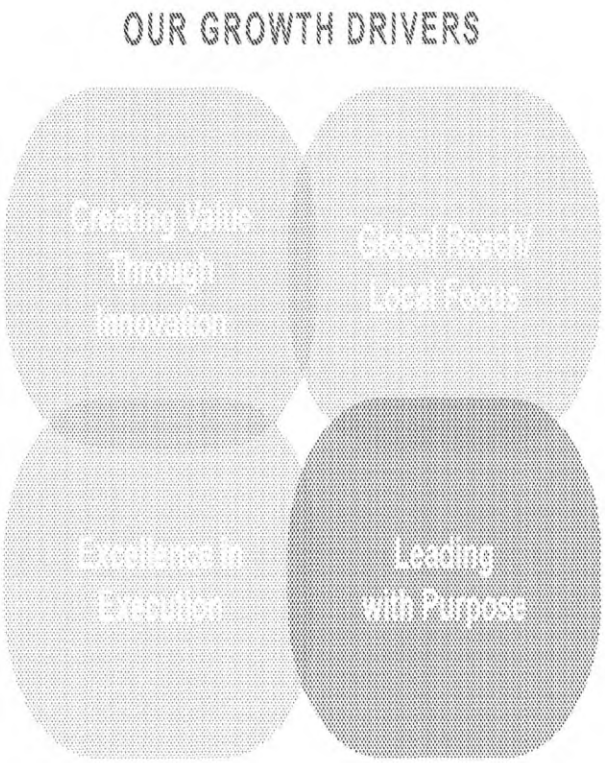
Strategic Framework



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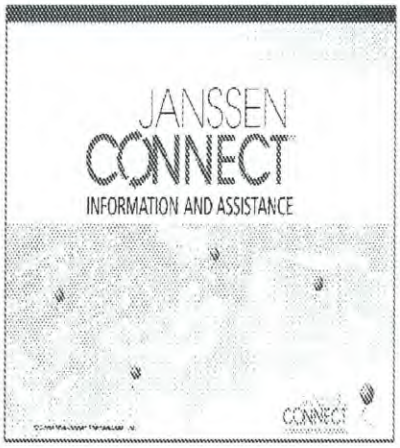
Improving Patient Care Through Innovation and Integration in Schizophrenia



Helping patients access and maintain appropriate treatment

Leveraging pharmaceuticals and diagnostics capabilities to improve patient care

INVEGA SUSTENNA® paliperidone palmitate

XEPLION®

Q1 2013 SALES	Q1 YoY GROWTH*
$284MM	76%

- Part of a $2.2B LAI antipsychotic franchise that grew 17% operationally in 2012
- Investigational new formulation requires only 4 injections per year

* Operational change (includes INVEGA® SUSTENNA®/XEPLION®).
LAI antipsychotic franchise includes INVEGA® SUSTENNA®/XEPLION® and RISPERDAL® CONSTA®.

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SIRTURO™: First New Mechanism for Multi-Drug-resistant Tuberculosis (MDR-TB) in 40 Years

"MDR-TB is a time bomb"
Margaret Chan, WHO Director General, Beijing, 2009

- Affects 630,000 worldwide[1]
- 150,000 deaths each year[2]
- 2MM new cases expected 2011-2015[3]
- ~90% untreated, only 50% cure rate[1]

斯耐瑞™
100mg

Innovative Models to Accelerate Patient Access and Improve Treatment Standards

- Registration efforts prioritized based on greatest need
- Appropriate use through responsible distribution and partnerships
- Equitable, tiered pricing approach

Sources: 1. WHO Global Tuberculosis Report 2012. 2. WHO 2011/2012 Tuberculosis Global Facts. 3. WHO Press Release, "Partners call for increased commitment to tackle MDR-TB," March 23 2011.

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Company Group Chairmen

Jane Griffiths
Company Group Chairman,
Europe, Middle East & Africa

Jennifer Taubert
Company Group Chairman,
North America

Kim Taylor
Company Group Chairman,
Asia Pacific

Key Takeaways

- Making a difference through transformational medical innovation
- Transforming our business with leading science and best-in-class commercial capabilities
- Enhancing pipeline to deliver the next wave of growth

Building on the Strong Momentum in Pharmaceuticals


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PMLiVE TOP PHARMA LIST

Data by GlobalData

Top 50 pharmaceutical products by global sales

The rankings of the top 50 pharmaceutical products have been compiled from GlobalData's pharmaceutical revenue figures. The rankings include figures for 2014, 2013, 2012 and 2011.

The PMLiVE Top Pharma List also features rankings of the 25 biggest pharmaceutical companies, based on their annual, global sales.

2014 2013 2012

#	Product	2014 ($m)	2013 ($m)	Growth ($m)	Growth (%)
1	Humira	13021	11105	1916	17
2	Sovaldi/Harvoni	12410	139	12271	8828
3	Remicade	10151	9900	251	3
4	Enbrel	9120	8894	226	3
5	Lantus	8152	7343	809	11
6	MabThera/Rituxan	7356	7410	-54	-1
7	Avastin	6841	6667	174	3
8	Seretide/Advair	6700	8356	-1656	-20
9	Herceptin	6690	6481	209	3
10	Crestor	6617	6960	-343	-5
11	Abilify	6416	9502	-3086	-32
12	Lyrica	5435	4838	597	12
13	Revlimid	4980	4280	700	16
14	Gleevec/Glivec	4746	4693	53	1
15	Spiriva	4722	4564	158	3
16	Neulasta	4596	4392	204	5
17	Prevnar 13	4464	3974	490	12
18	Nexium	4442	4551	-109	-2
19	Symbicort	4262	3929	333	8
20	Lucentis	4254	4184	70	2

21	Copaxone	4237	4328	-91	-2
22	Januvia	3931	4004	-73	-2
23	Xarelto	3679	2083	1596	77
24	Truvada	3528	3304	224	7
25	Atripla	3470	3649	-179	-5
26	Olmesartan franchise	3187	3761	-574	-15
27	Eylea	3034	2072	962	46
28	Avonex	3013	3006	7	0
29	NovoRapid	3012	2908	104	4
30	Gilenya	2934	2337	597	26
31	Tecfidera	2909	876	2033	232
32	Velcade	2881	2852	29	1
33	Zetia	2866	2879	-13	0
34	Alimta	2792	2703	89	3
35	Humalog	2785	2611	174	7
36	Lipitor	2766	3097	-331	-11
37	Celebrex	2699	2918	-219	-8
38	Plavix	2601	2644	-43	-2
39	Levemir	2454	1993	461	23
40	Rebif	2364	2396	-32	-1
41	Diovan/Co-Diovan	2345	3524	-1179	-33
42	Victoza	2318	2008	310	15
43	Olysio	2302	23	2279	9909
44	Cialis	2291	2159	132	6
45	Erbitux	2257	2204	53	2
46	Prograf	2249	2273	-24	-1
47	Zytiga	2237	1698	539	32
48	Soliris	2234	1551	683	44
49	Botox/Neuromodulator	2231	1982	249	13
50	Lovenox	2183	2188	-5	0

Note: The 2013 ranking uses 2013 exchange rates for both its 2013 and 2012 values, to remove the effect of currency fluctuations. The 2012 ranking similarly uses 2012 exchange rates.

GlobalData» Data by GlobalData

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