U.S. Postmarketing Commitments Table*

Name of Product	NDA Number	Description of Commitment	Date Commitment Given	FDA Projected Completion Date	Commitment Status
IMBRUVICA®	NDA 205552	Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of trial PCYC-1104-CA with a minimum follow-up of 24 months for each patient. If 24 months follow-up is not possible for certain patients, provide justification for each patient. In addition, submit detailed assessment information regarding all sites of extranodal disease at baseline and follow-up, including assessments for response and progression. Summarize extranodal disease characteristics at baseline and at time of progression. Request further documentation as necessary from clinical trial sites in order to summarize the details of the extranodal disease progression.	13 November 2013	Final Report Submission: 03/2015	Fulfilled
IMBRUVICA®	NDA 205552	Complete and submit the final results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765MCL3002) of ibrutinib in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma. Enrollment of approximately 520 patients is expected. The primary endpoint is progression-free survival as assessed by investigators. Overall survival is a key secondary endpoint.	13 November 2013	Final Report Submission: 03/2019	Ongoing
IMBRUVICA®	NDA 205552	Determine the effect of a broad range of concentrations of ibrutinib on the potential to inhibit platelet function by conducting in vitro studies. Assessment methods should include evaluation of effects on platelet aggregation, including GPIb-mediated aggregation. Evaluation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction (e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin).	13 November 2013	Final Report Submission: 12/2016	Ongoing
IMBRUVICA®	NDA 205552	Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs (Interim Report #1)	13 November 2013	#1 Interim Report Submission: 12/2014	Submitted
IMBRUVICA®	NDA 205552	Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs (Interim Report #2)	13 November 2013	#2 Interim Report Submission: 06/2015	Submitted
IMBRUVICA®	NDA 205552	Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs (Interim Report #3)	13 November 2013	#3 Interim Report Submission: 12/2015	Submitted

Name of Product	NDA Number	Description of Commitment	Date Commitment Given	FDA Projected Completion Date	Commitment Status
IMBRUVICA®	NDA 205552	Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs (Interim Report #4)	13 November 2013	#4 Interim Report Submission: 06/2016	Pending
IMBRUVICA®	NDA 205552	Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs (Interim Report #5)	13 November 2013	#5 Interim Report Submission: 12/2016	Pending
IMBRUVICA®	NDA 205552	Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs (Interim Report #6)	13 November 2013	#6 Interim Report Submission: 06/2017	Pending
IMBRUVICA®	NDA 205552	Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs (Interim Report #7)	13 November 2013	#7 Interim Report Submission: 12/2017	Pending
IMBRUVICA®	NDA 205552	Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with Imbruvica®, (ibrutinib) Capsules. The risks of special interest are major hemorrhagic events and their potential association with concomitant use of anti-platelet and/or anticoagulant drugs (Final Report)	13 November 2013	Final Report Submission: 11/2018	Pending
IMBRUVICA®	NDA 205552	Evaluate the effect of hepatic impairment on ibrutinib pharmacokinetics. Submit the final report for trial PCI-32765CLL1006 entitled, “An Open-Label, Multicenter, Pharmacokinetic Study of PCI-32765 in Subjects With Varying Degrees of Hepatic Impairment”.	13 November 2013	Final Report Submission: 12/2014	Fulfilled
IMBRUVICA®	NDA 205552	Determine effect of a strong CYP3A Inducer on ibrutinib pharmacokinetics. Submit the final report for trial PCI-32765CLL1010 entitled, “An Open-Label, Sequential Design Study to Assess the Effect of Rifampin on the Pharmacokinetics of PCI-32765 in Healthy Subjects”.	13 November 2013	Final Report Submission: 04/2014	Fulfilled
IMBRUVICA®	NDA 205552	Determine the effect of ibrutinib on the QT/QTc interval in healthy subjects on one or more therapeutic dose levels. Conduct and submit results of a thorough QT trial to evaluate the effects of ibrutinib on the QT /QTc interval.	13 November 2013	Final Report Submission: 12/2015	Submitted

Name of Product	NDA Number	Description of Commitment	Date Commitment Given	FDA Projected Completion Date	Commitment Status
IMBRUVICA®	NDA 205552	Submit the results of the completed randomized, open-label Phase 3 clinical trial (PCYC-1112-CA) of ibrutinib versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 391 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee.	12 February 2014	Final Report Submission: 06/2014	Fulfilled
IMBRUVICA®	NDA 205552	Complete and submit the results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765CLL3001) of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma. Enrollment of 578 patients was completed. The primary endpoint is progression-free survival as assessed by an Independent Review Committee	12 February 2014	Final Report Submission: 11/2016	Released
IMBRUVICA®	NDA 205552	Conduct a study to characterize the safety of long-term exposure to Imbruvica based on data and pooled analyses from trials of patients with mantle cell lymphoma and chronic lymphocytic leukemia. Submit 3-year, 4-year, and 5-year safety follow-up data and reports for a minimum population of 1000 patients treated with approved ibrutinib dosing regimens. Datasets should include patient level data on ibrutinib dosing, treatment-emergent adverse events, and treatment emergent laboratory information. This patient set may include approximately 350 patients who continue receiving long-term ibrutinib therapy after completion of primary analysis of the parent study, where study procedures are then limited to collect a minimum of Grade 3+ adverse events, available treatment emergent laboratory data, adverse events leading to treatment discontinuation and SAEs. Study reports should include analyses of adverse event categories listed in the current Warnings and Precautions section of the prescribing information, adverse events leading to treatment discontinuation, and serious adverse events. (Interim 3-year Data)	04 March 2016	Interim 3-year Data and Report Submission: 04/2017	Pending
IMBRUVICA®	NDA 205552	Conduct a study to characterize the safety of long-term exposure to Imbruvica based on data and pooled analyses from trials of patients with mantle cell lymphoma and chronic lymphocytic leukemia. Submit 3-year, 4-year, and 5-year safety follow-up data and reports for a minimum population of 1000 patients treated with approved ibrutinib dosing regimens. Datasets should include patient level data on ibrutinib dosing, treatment-emergent adverse events, and treatment emergent laboratory information. This patient set may include approximately 350 patients who continue receiving long-term ibrutinib therapy after completion of primary analysis of the parent study, where study procedures are then limited to collect a minimum of Grade 3+ adverse events, available treatment emergent laboratory data, adverse events leading to treatment discontinuation and SAEs. Study reports should include analyses of adverse event categories listed in the current Warnings and Precautions section of the prescribing information, adverse events leading to treatment discontinuation, and serious adverse events. (Interim 4-year Data)	04 March 2016	Interim 4-year Data and Report Submission: 04/2018	Pending

Name of Product	NDA Number	Description of Commitment	Date Commitment Given	FDA Projected Completion Date	Commitment Status
IMBRUVICA®	NDA 205552	Conduct a study to characterize the safety of long-term exposure to Imbruvica based on data and pooled analyses from trials of patients with mantle cell lymphoma and chronic lymphocytic leukemia. Submit 3-year, 4-year, and 5-year safety follow-up data and reports for a minimum population of 1000 patients treated with approved ibrutinib dosing regimens. Datasets should include patient level data on ibrutinib dosing, treatment-emergent adverse events, and treatment emergent laboratory information. This patient set may include approximately 350 patients who continue receiving long-term ibrutinib therapy after completion of primary analysis of the parent study, where study procedures are then limited to collect a minimum of Grade 3+ adverse events, available treatment emergent laboratory data, adverse events leading to treatment discontinuation and SAEs. Study reports should include analyses of adverse event categories listed in the current Warnings and Precautions section of the prescribing information, adverse events leading to treatment discontinuation, and serious adverse events. (Final Data)	04 March 2016	Final Data and Report Submission: 04/2019	Pending

*Chemistry Manufacturing and Controls (CMC) commitments are not included