イムブルビカカプセル 140mg
に関する資料

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略号一覧表

略号又は略称	名称及び内容
allo-HSCT	同種造血幹細胞移植（allogeneic hematopoietic stem cell transplantation）
BTK	ブルトン型チロシンキナーゼ（Bruton’s tyrosine kinase）
cGVHD	慢性移植片対宿主病（chronic graft versus host disease）
CI	カルシニューリン・インヒビター（calcineurin inhibitor）
CLL	慢性リンパ性白血病（chronic lymphocytic leukemia）
ITK	インターロイキン-2 誘導型 T 細胞キナーゼ（interleukin-2-inducible T-cell kinase）
MCL	マントル細胞リンパ腫（mantle cell lymphoma）
MZL	辺縁帯リンパ腫（marginal zone lymphoma）
NIH	National Institutes of Health
SLL	小リンパ球性リンパ腫（small lymphocytic lymphoma）
WM	原発性マクログロブリン血症（Waldenström's macroglobulinemia）

1.5　起原又は発見の経緯及び開発の経緯

イブルチニブは，Janssen Research & Development LLC と Pharmacyclics LLC（an AbbVie company）が共同開発しているファーストインクラスの強力な低分子経口ブルトン型チロシンキナーゼ（BTK）阻害薬であり，インターロイキン-2 誘導型 T 細胞キナーゼ（ITK）も共有結合により不可逆的に阻害する。

イブルチニブは抗悪性腫瘍薬として慢性リンパ性白血病（CLL）/小リンパ球性リンパ腫（SLL），マントル細胞リンパ腫（MCL），濾胞性リンパ腫，辺縁帯リンパ腫（MZL），原発性マクログロブリン血症（WM）等の B 細胞腫瘍患者を主な対象として国内外で広く開発が行われており，CLL/SLL，MCL，MZL，WM 等を適応として，米国及び欧州を含む約 100 カ国で承認を取得している。国内では，「慢性リンパ性白血病（小リンパ球性リンパ腫を含む）」及び「再発又は難治性のマントル細胞リンパ腫」の適応に対して製造販売承認を取得している。

慢性移植片対宿主病（cGVHD）は，同種造血幹細胞移植（allo-HSCT）後の合併症として発現する疾患であり，自己免疫疾患に類似した臨床徴候と症状を示し，ほぼ全ての組織に影響を及ぼす可能性がある。Allo-HSCT により移植の原因となった疾患が治癒する可能性がある一方で，cGVHD は重篤かつ致死的な疾患である[1) 2) 3) 4)]。

cGVHD の病態研究や新薬開発のための臨床試験を実施する上で，統一された診断及び重症度分類，奏効評価の基準が存在していなかったことが長年の課題であった[5)]。この課題を解決するため，2005 年に National Institutes of Health（NIH）のワーキンググループ（NIH Consensus Development Project）により cGVHD の診断及び重症度分類の基準，奏効評価，臨床試験デザイン等に関する提言が示され（NIH Consensus Development Project Criteria），2014 年に改訂された[6) 7)]。

cGVHD に対する一次治療の標準療法はステロイド全身療法又はステロイドとカルシニューリン・インヒビター（CI）の併用全身療法であるが，一次治療による治療効果が不十分で二次治療を必要とする患者に対する標準療法は確立されていない[8)]。国内で cGVHD に対して承認されている薬剤はステロイドと CI のみであるため，二次治療では，一次治療で使用されたステロイド又はステロイドと CI の併用の継続使用及び保険適用外の治療法という限られた治療選択肢の中で治療が行われている。加えて，長期にわたるステロイド投与による副作用も大きな問題となる。このため，二次治療において，有効性及び安全性が確立され，かつステロイドの減量が期待できるような新規の治療法が強く求められている。

cGVHD の発症機序は極めて多様と考えられ完全には明らかになっていないが，近年の報告から，cGVHD の発症には T 細胞だけでなく B 細胞の関与が示唆されている[9) 10) 11) 12)]。イブルチニブは，B 細胞の活性化に関与する BTK 及び T 細胞の活性化に関与する ITK の両方を阻害することから，cGVHD の発症機序に重要な B 細胞及び T 細胞の両方に作用する可能性があり，複数の cGVHD 動物モデルを用いた非臨床試験においてイブルチニブ投与による cGVHD の予防及び治療効果が認められている[13) 14)]。これらのことから，cGVHD に対する新規作用機序を有する治療薬としてイブルチニブの臨床開発が進められてきた。

海外では，ステロイド依存性又は抵抗性の cGVHD 患者を対象とした第 Ib/II 相試験（PCYC-1129-CA 試験，以下 1129 試験）の結果，NIH Consensus Development Project Criteria（2005）に基づくイブルチニブの臨床的有用性が示され，米国において 2016 年 6 月に orphan drug 及び

breakthrough therapy の指定を受け，2017 年 8 月に 1 種類以上の全身治療が効果不十分な成人 cGVHD 患者の治療薬として承認された。2020 年 12 月現在，cGVHD の二次治療に対する適応については 29 カ国で承認されている。

国内では，1129 試験の結果を踏まえ，青年期（12～17 歳）を含むステロイド依存性又は抵抗性の日本人 cGVHD 患者を対象とした第 III 相試験（54179060GVH3001 試験，以下 GVH3001 試験）を実施中である。GVH3001 試験の主要解析の結果，日本人患者でも 1129 試験と同様に，NIH Consensus Development Project Criteria（2014）に基づくイブルチニブの臨床的有用性が示された。

さらに海外において，1～21 歳の未治療又は 1 種類以上の全身治療で効果不十分な cGVHD 患者を対象とした第 I/II 相試験（PCYC-1146-IM 試験，以下 1146 試験）を実施中である。20[redacted] 年 [redacted] 月 [redacted] 日までに 1146 試験に登録された 12～1[redacted] 歳の cGVHD 患者 18 例に関する薬物動態及び安全性の中間解析の結果，イブルチニブの安全性プロファイルは許容可能であり，成人に対するイブルチニブの既知の安全性プロファイルと比較して新たな安全性シグナルは特定されなかった。

以上のとおり，1129 試験，GVH3001 試験及び 1146 試験において，青年期を含むステロイド依存性又は抵抗性の cGVHD 患者に対するイブルチニブの臨床的有用性が確認されたことから，青年期を含む「造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）」の効能・効果を追加することを目的として，医薬品製造販売承認事項一部変更承認申請（以下，本申請）を行うこととした。

なお，未治療の cGVHD に対しては，12 歳以上の未治療の cGVHD 患者を対象にステロイド併用時のイブルチニブの有効性及び安全性を評価する国際共同試験（PCYC-1140-IM 試験，以下 1140 試験）を実施中であり日本も参加している。1140 試験は主要解析が完了し，一部の副次評価項目についてイブルチニブの有用性を示唆する傾向が認められたものの，有効性の主要目的は達成されなかった。1140 試験において，成人患者，青年期患者ともにステロイド併用時のイブルチニブの忍容性が示され，新たな安全性シグナルは認められていない。1140 試験で有効性の主要目的が達成されなかったことから，国内外において未治療の cGVHD に対する薬事承認申請の予定はない。本申請では 1140 試験の結果を参考資料とし，cGVHD 患者におけるイブルチニブの安全性及び申請用法・用量の適切性の検討に 1140 試験の安全性及び薬物動態の結果を用いた。

また，イブルチニブは国内における cGVHD に対するアンメットメディカルニーズを満たし，医療上の必要性が高いと判断したため，2020 年 10 月に希少疾病用医薬品指定申請を行い，2020 年 12 月に指定された。

起原又は発見の経緯及び開発の経緯については，平成 13 年 6 月 21 日付医薬審発第 899 号医薬局審査管理課長通知「新医薬品の製造販売の承認申請に際し承認申請書に添付すべき資料の作成要領について」の別紙 2 の 5（1）項の記述をもとに，当該内容を主に第 2 部（5）に記載した（表 1.5-1）。また，本申請に関する開発の経緯について，非臨床試験及び臨床試験の一覧をそれぞれ表 1.5-2 及び表 1.5-3 に示す。

表 1.5-1 CTD 1.5 項の内容の記載場所

CTD Module 1.5 の内容	CTD Module 2 の記載場所
起原又は発見の経緯	2.5.1　製品開発の根拠
cGVHD の病態及び疫学	2.5.1.3　cGVHD の臨床的／病態生理学的側面
cGVHD の治療	2.5.1.4　cGVHD に対する治療の現状
開発の経緯	2.5.1.5　臨床開発経緯
非臨床試験の概略	2.4　非臨床試験の概括評価
申請効能・効果に対するイブルチニブの有用性	2.5.6　ベネフィットとリスクに関する結論

表 1.5-2 非臨床試験の一覧

試験項目		実施時期
毒性試験	がん原性試験	20[redacted]年[redacted]月～20[redacted]年[redacted]月

表 1.5-3 臨床試験の一覧

相	実施地域	対象	試験番号等	実施時期
Ib/II	海外	18 歳以上のステロイド依存性又は抵抗性の cGVHD 患者	PCYC-1129-CA（評価資料）	2014 年 7 月～2017 年 9 月
III	国内	12 歳以上のステロイド依存性又は抵抗性の日本人 cGVHD 患者	54179060GVH3001（評価資料）	2018 年 6 月～継続中
I/II	海外	パート B*に登録された 12～21 歳の未治療又は 1 種類以上の全身治療で効果不十分な cGVHD 患者（20[redacted]年[redacted]月[redacted]日までに登録され，イブルチニブの投与を受けた被験者）	PCYC-1146-IM（評価資料）	2018 年 12 月～継続中
III	国際共同	12 歳以上の未治療の cGVHD 患者	PCYC-1140-IM（参考資料）	2017 年 5 月～継続中

*PCYC-1146-IM 試験は，1～11 歳の cGVHD 患者の用量を決定するパート A と，1～21 歳の cGVHD 患者におけるイブルチニブの薬物動態及び安全性を評価するパート B から構成されている。

参考文献

1） Arai S, Jagasia M, Storer B, et al. Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH Consensus Criteria. Blood. 2011 Oct;118(15):4242-9.

2） Baird K, Pavletic SZ. Chronic graft versus host disease. Curr Opin Hematol. 2006 Nov;13(6):426-35.

3） Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2003 Apr;9(4):215-33.

4） Pidala J, Kim J, Anasetti C, et al. The global severity of chronic graft-versus-host disease, determined by National Institutes of Health consensus criteria, is associated with overall survival and non-relapse mortality. Haematologica. 2011 Nov;96(11):1678-84.

5） Pavletic SZ, Vogelsang GB. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: preface to the series. Biol Blood Marrow Transplant. 2005 Dec;11(12):943-4.

6） Pavletic SZ, Vogelsang GB, Lee SJ. 2014 National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: preface to the series. Biol Blood Marrow Transplant. 2015 Mar;21(3):387-8.

7） Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401.

8） 日本造血細胞移植学会. 造血細胞移植ガイドライン GVHD（第 4 版）. 平成 30 年 4 月 10 日. http://www.jshct.com/guideline/pdf/01_02_gvhd_ver04.pdf Accessed 24 Jun 2020.

9） Allen JL, Tata PV, Fore MS, et al. Increased BCR responsiveness in B cells from patients with chronic GVHD. Blood. 2014 Mar 27;123(13):2108-15.

10） Flynn R, Du J, Veenstra RG, et al. Increased T follicular helper cells and germinal center B cells are required for cGVHD and bronchiolitis obliterans. Blood. 2014 Jun 19;123(25):3988-98.

11） Johnston HF, Xu Y, Racine JJ, et al. Administration of anti-CD20 mAb is highly effective in preventing but ineffective in treating chronic graft-versus-host disease while preserving strong graft-versus-leukemia effects. Biol Blood Marrow Transplant. 2014 Aug;20(8):1089-103.

12） Sarantopoulos S, Blazar BR, Cutler C, et al. B cells in chronic graft-versus-host disease, Biol Blood Marrow Transplant. 2015 Jan; 21(1): 16-23.

13） Schutt SD, Fu J, Nguyen H, et al. Inhibition of BTK and ITK with ibrutinib is effective in the prevention of chronic graft-versus-host-disease in mice. PloS One. 2015 Sep 8;10(9):e0137641.

14） Dubovsky JA, Flynn R, Du J, et al. Ibrutinib treatment ameliorates murine chronic graft-versus-host disease. J Clin Invest. 2014 Nov:124(11):4867-76.

1.6　外国における使用状況等に関する資料

イブルチニブは，米国で MCL with at least one prior therapy の適応で 2013 年 11 月に世界で初めて承認され，約 100 カ国で承認を取得している。

慢性移植片対宿主病の二次治療に対する適応については，米国において 2017 年 8 月に承認され，2021 年 6 月時点で，29 カ国で承認されている。米国及び欧州における本剤の承認状況の概要を表 1.6-1 及び表 1.6-2 に示す。また，外国の添付文書として，米国及び欧州の添付文書，並びに企業中核データシート（CCDS）を添付する。

表 1.6-1 米国におけるイブルチニブの承認状況

販売名	IMBRUVICA (ibrutinib) capsules, for oral use IMBRUVICA (ibrutinib) tablets, for oral use
承認時期	2013 年 11 月
剤形・含量	カプセル：70 mg, 140 mg 錠剤：140 mg, 280 mg, 420 mg, 560 mg
効能・効果	**マントル細胞リンパ腫** IMBRUVICA は少なくとも 1 回の前治療歴を有する成人のマントル細胞リンパ腫（MCL）患者に対する治療を適応としている。 本適応症は，全奏効率に基づき迅速承認を取得したものである。検証的試験において臨床的利益が証明及び記述されることによって，本適応に対するさらなる承認が見込まれる。 **慢性リンパ性白血病/小リンパ球性リンパ腫** IMBRUVICA は成人の慢性リンパ性白血病（CLL）/小リンパ球性リンパ腫（SLL）患者に対する治療を適応としている。 **17p 欠損を有する慢性リンパ性白血病/小リンパ球性リンパ腫** IMBRUVICA は 17p 欠損を有する成人の慢性リンパ性白血病（CLL）/小リンパ球性リンパ腫（SLL）患者に対する治療を適応としている。 **ワルデンストレーム・マクログロブリン血症** IMBRUVICA は成人のワルデンストレーム・マクログロブリン血症（WM）患者に対する治療を適応としている。 **辺縁帯リンパ腫** IMBRUVICA は全身療法を必要とし，少なくとも 1 回の抗 CD20 併用療法による前治療歴を有する成人の辺縁帯リンパ腫（MZL）患者に対する治療を適応としている。 本適応症は，全奏効率に基づき迅速承認を取得したものである。検証的試験において臨床的利益が証明及び記述されることによって，本適応に対するさらなる承認が見込まれる。 **慢性移植片対宿主病** IMBRUVICA は 1 種以上の全身療法に失敗した成人の慢性移植片対宿主病（cGVHD）患者に対する治療を適応としている。
用法・用量	**推奨用量** <u>マントル細胞リンパ腫及び辺縁帯リンパ腫</u> MCL 患者及び MZL 患者に対する IMBRUVICA の推奨用量は 560 mg の 1 日 1 回，疾患進行又は不耐用な毒性がみられるまで経口投与である。 <u>慢性リンパ性白血病/小リンパ球性リンパ腫及びワルデンストレーム・マクログロブリン血症</u> CLL/SLL 患者及び WM 患者に対する IMBRUVICA の推奨用量は 420 mg の 1 日 1 回，疾患進行又は不耐用な毒性がみられるまで経口投与である。 CLL/SLL 患者に対しては，IMBRUVICA を単剤で，リツキシマブ又はオビヌツズマブと併用で，あるいはベンダムスチン及びリツキシマブ（BR）と併用で投与することができる。 WM 患者に対しては，IMBRUVICA を単剤又はリツキシマブと併用で投与することができる。 IMBRUVICA をリツキシマブ又はオビヌツズマブと併用する場合，同日に投与する場合はリツキシマブ又はオビヌツズマブを投与する前に IMBRUVICA を投与することを検討すること。

慢性移植片対宿主病
cGVHD 患者に対する IMBRUVICA の推奨用量は 420 mg の 1 日 1 回，cGVHD 進行，基礎悪性腫瘍の再発，又は不耐用な毒性がみられるまで経口投与である。
cGVHD に対する治療が不要になった場合は，個々の患者の医学的評価を考慮に入れた上で，IMBRUVICA の投与を中止すること。

投与
IMBRUVICA は毎日ほぼ同じ時間にコップ 1 杯の水で服用すること。
錠剤又はカプセルはそのまま飲み込むこと。カプセルを開けたり、割ったり、噛み砕いたりしないこと。錠剤を分割したり、砕いたり、噛み砕いたりしないこと。
規定された時刻に IMBRUVICA を服用しなかった場合、同日中の可能な限り速やかに服用し、翌日に通常のスケジュールに戻すこと。飲み忘れた分を補うために IMBRUVICA を追加で服用しないこと。

副作用に対する用量の調整
Grade 3 又は 4 の非血液学的毒性，感染症又は発熱を伴う Grade 3 又は 4 の好中球減少症，Grade 4 の血液学的毒性が発現した場合は IMBRUVICA を休薬すること。副作用が Grade 1 又はベースラインまで回復した後は，初回用量で IMBRUVICA の投与を再開してもよい。副作用が再度発現した場合， 1 日毎に 140 mg 減量する。必要に応じてさらに 140 mg の減量を考慮する。2 回の減量後にも副作用が持続又は再度発現した場合は，IMBRUVICA の投与を中止すること。

推奨される用量調整は以下のとおりである。

毒性の発現回数	**MCL 患者及び MZL 患者に対する回復後の用量調整 初回用量 = 560 mg**	**CLL/SLL 患者，WM 患者及び cGVHD 患者に対する回復後の用量調整 初回用量 = 420 mg**
1 回目	560 mg の 1 日 1 回投与で再開	420 mg の 1 日 1 回投与で再開
2 回目	420 mg の 1 日 1 回投与で再開	280 mg の 1 日 1 回投与で再開
3 回目	280 mg の 1 日 1 回投与で再開	140 mg の 1 日 1 回投与で再開
4 回目	IMBRUVICA の投与を中止	IMBRUVICA の投与を中止

CYP3A 阻害剤と併用する際の用量の調整
推奨される用量調整は以下のとおりである。

患者集団	**併用薬**	**IMBRUVICA の推奨用量**
B 細胞腫瘍	• 中程度の CYP3A 阻害剤	280 mg 1 日 1 回 推奨されるとおりに用量調整すること。
	• 200 mg 1 日 2 回のボリコナゾール • 100 mg 1 日 1 回，100 mg 1 日 2 回又は 200 mg 1 日 2 回の posaconazole 内用懸濁液	140 mg 1 日 1 回 推奨されるとおりに用量調整すること。
	• 200 mg 1 日 3 回又は 400 mg 1 日 2 回の posaconazole 内用懸濁液 • 300 mg 1 日 1 回の posaconazole 静注液 • 300 mg 1 日 1 回の posaconazole 遅延放出錠	70 mg 1 日 1 回 推奨されるとおりに休薬すること。

<table>
<tr><td></td><td>
<table>
<tr><td></td><td>• その他の強力な CYP3A 阻害剤</td><td>併用を避けること。
これらの阻害剤を短期間使用する場合は（例：抗感染症治療薬の投与を 7 日以下），IMBRUVICA を休薬すること。</td></tr>
<tr><td rowspan="4">慢性移植片対宿主病</td><td>• 中程度の CYP3A 阻害剤</td><td>420 mg 1 日 1 回
推奨されるとおりに用量を調整すること。</td></tr>
<tr><td>• 200 mg 1 日 2 回のボリコナゾール
• 100 mg 1 日 1 回，100 mg 1 日 2 回又は 200 mg 1 日 2 回の posaconazole 内用懸濁液</td><td>280 mg 1 日 1 回
推奨されるとおりに用量を調整すること。</td></tr>
<tr><td>• 200 mg 1 日 3 回又は 400 mg 1 日 2 回の posaconazole 内用懸濁液
• 300 mg 1 日 1 回の posaconazole 静注液
• 300 mg 1 日 1 回の posaconazole 遅延放出錠</td><td>140 mg 1 日 1 回
推奨されるとおりに休薬すること。</td></tr>
<tr><td>• その他の強力な CYP3A 阻害剤</td><td>併用を避けること。
これらの阻害剤を短期間使用する場合は（例：抗感染症治療薬の投与を 7 日以下），IMBRUVICA を休薬すること。</td></tr>
</table>
CYP3A 阻害剤の投与中止後は，以前の用量で IMBRUVICA の投与を再開する。

肝機能障害患者に対する用量調節
軽度肝機能障害患者（Child-Pugh 分類 A）で推奨される用量は 140 mg を 1 日 1 回とする。中等度の肝機能障害患者（Child-Pugh 分類 B）で推奨される用量は 70 mg を 1 日 1 回とする。高度の肝機能障害患者（Child-Pugh 分類 C）に対する IMBRUVICA の使用は避けること。
</td></tr>
<tr><td>禁忌</td><td>なし</td></tr>
<tr><td>警告及び使用上の注意</td><td>
警告及び注意
出血
IMBRUVICA の投与を受けた患者において致死的な出血事象が発現しており，大出血（Grade 3 以上，重篤，又は何らかの中枢神経系事象；例：頭蓋内出血［硬膜下血腫を含む］，消化管出血，血尿，処置後出血）が患者の 4%に発現し，27 件の臨床試験において IMBRUVICA の投与を受けた 2,838 例中 0.4%が死亡した。IMBRUVICA の投与を受けた患者のうち，挫傷及び点状出血を含む全 Grade の出血事象は 39%に発現し，挫傷及び点状出血を除く出血事象は 23%に発現した。
出血性イベントが発現する機序については明らかになっていない。
IMBRUVICA と抗凝固薬又は抗血小板薬を併用すると，重大な出血のリスクが増加する。臨床試験全体で，抗血小板療法又は抗凝固療法を受けずに IMBRUVICA の投与を受けた患者 2,838 例中 3.1%に重大な出血が認められた。抗凝固療法を伴う又は伴わない抗血小板療法の追加はこの割合を 4.4%に増加させ，抗血小板療法を伴う又は伴わない抗凝固療法の追加はこの割合を 6.1%に増加させた。IMBRUVICA と併用する場合，抗凝固療法又は抗血小板療法のリス
</td></tr>
</table>

	ク及びベネフィットを考慮すること。出血の徴候及び症状をモニタリングすること。 リスク・ベネフィットを考慮し，外科手術の種類及び出血のリスクに応じて，術前及び術後に少なくとも 3〜7 日間 IMBRUVICA を控えること。 **感染症** IMBRUVICA の投与による致死的及び非致死的な感染症（細菌感染，ウイルス感染，又は真菌感染を含む）の発現が認められている。臨床試験で IMBRUVICA の投与を受けた患者 1,476 例中 21%に Grade 3 以上の感染症が発現した。IMBRUVICA の投与を受けた患者において進行性多巣性白質脳症（PML）及びニューモシスチス・イロベチイ肺炎（PJP）が認められている。日和見感染のリスクが高い患者には，標準治療に従って，予防的投与を考慮すること。発熱及び感染について患者の観察及び評価を行い，それらの症状が現れた場合は適切な治療を行うこと。 **血球減少症** IMBRUVICA の単剤投与を受けた B 細胞腫瘍患者 645 例において，臨床検査値に基づき，Grade 3 又は 4 の好中球減少症が患者の 23%に，Grade 3 又は 4 の血小板減少症が 8%に，Grade 3 又は 4 の貧血が 3%に発現した。 月に 1 回，全血球数の測定を行うこと。 **不整脈及び心不全** IMBRUVICA の投与を受けた患者で，致死的及び重度の不整脈及び心不全が発現した。臨床試験において，IMBRUVICA の投与を受けた患者 1,476 例のうち，Grade 3 以上の心室性頻脈性不整脈が 0.2%，Grade 3 以上の心房細動及び心房粗動が 4%，Grade 3 以上の心不全が 1%に発現した。これらの事象は，心疾患のリスク因子，高血圧，急性感染症及び不整脈の既往歴を有する患者で特に発現している。 ベースライン時及びその後定期的に，不整脈及び心不全について患者を臨床的に観察すること。不整脈の症状（例：動悸，ふらつき，失神，胸部痛など）が発現した患者，又は新規に呼吸困難が発症した患者については心電図検査を実施する必要がある。不整脈及び心不全は適切に管理される必要がある。不整脈が持続する場合，IMBRUVICA 治療のリスク・ベネフィットを検討し用量の調整についてのガイドラインに従うこと。 **高血圧** 臨床試験で IMBRUVICA の投与を受けた 1,476 例中 19%に高血圧が発現した。Grade 3 以上の高血圧が患者の 8%に発現した。このうち 1,124 例のデータに基づくと，発現までの期間の中央値は 5.9 カ月（範囲 0.03 カ月〜24 カ月）であった。IMBRUVICA の投与を受けている患者の血圧をモニタリングし，IMBRUVICA の投与期間中は適宜降圧薬の投与を開始又は調節すること。 **二次性悪性腫瘍** 臨床試験で IMBRUVICA の投与を受けた 1,476 例の患者において，皮膚癌以外の悪性腫瘍（4%）を含む他の悪性腫瘍が発現している（10%）。最も多く認められた二次性悪性腫瘍は非黒色腫皮膚癌であった（6%）。 **腫瘍崩壊症候群** IMBRUVICA の治療による腫瘍崩壊症候群がまれに報告されている。ベースラインのリスク（例：高腫瘍量）の評価を行い，適切な予防措置を講じること。患者を十分に観察し，適切な治療を行うこと。

	胚・胎児毒性 非臨床試験の結果，IMBRUVICA は妊婦に投与した場合，胎児に害を及ぼすおそれがあることが示されている。妊娠ラット及び妊娠ウサギの器官形成期にイブルチニブを投与した際に血液悪性腫瘍患者での曝露量より 2～20 倍高い曝露量において，催奇形性を含む胚・胎児毒性が認められた。妊婦には胎児への潜在的リスクについて説明すること。妊娠可能な女性には，IMBRUVICA の投与中及び最終投与後 1 カ月間は有効な避妊法を使用するよう指示すること。

表 1.6-2 欧州におけるイブルチニブの承認状況

販売名	IMBRUVICA 140 mg hard capsules
承認時期	2014 年 10 月
剤形・含量	カプセル：140 mg
効能・効果	IMBRUVICA の単剤は再発又は難治性の成人マントル細胞リンパ腫（MCL）患者の治療を適応とする。 IMBRUVICA の単剤又はリツキシマブもしくはオビヌツズマブとの併用投与は未治療の成人慢性リンパ性白血病（CLL）患者の治療を適応とする。 IMBRUVICA の単剤又はベンダムスチン及びリツキシマブ（BR）との併用は少なくとも 1 回の前治療歴を有する成人 CLL 患者の治療を適応とする。 IMBRUVICA の単剤は少なくとも 1 回の前治療歴を有するワルデンストレーム・マクログロブリン血症（WM）成人患者又は化学免疫療法が不適応である WM 成人患者の一次治療を適応とする。IMBRUVICA とリツキシマブの併用投与は成人 WM 患者の治療を適応とする。
用法・用量	本剤を用いた治療は抗がん剤療法に精通している医師の下で開始し，そのような医師の監督の下で行うこと。 用法・用量 *MCL* MCL 患者に対する推奨用量は 560 mg（4 カプセル）の 1 日 1 回投与である。 *CLL 及び WM* CLL 及び WM 患者に対する推奨用量は，単剤又は併用で 420 mg（3 カプセル）の 1 日 1 回投与である。 投与は疾患進行が確認されるまで，又は患者が許容できない毒性が確認されるまで継続すること。 IMBRUVICA を抗 CD 20 抗体による治療と併用する場合，同日に投与する場合は抗 CD 20 抗体による治療療法の前に IMBRUVICA を投与することが推奨される。 用量調節 中程度又は強力な CYP3A4 阻害剤と本剤との併用により，イブルチニブの曝露量が増加する。 中程度の CYP3A4 阻害剤と併用する場合，イブルチニブの用量を 280 mg （2 カプセル）の 1 日 1 回投与まで減量すること。 強力な CYP3A4 阻害剤と併用する場合，イブルチニブの用量を 140 mg（1 カプセル）の 1 日 1 回投与まで減量するか，又は最長で 7 日間まで投与を中断すること。 Grade 3 以上の非血液学的毒性，感染症又は発熱を伴う Grade 3 以上の好中球減少症，Grade 4 の血液学的毒性の悪化又は新たな発現が認められた場合は本剤の投与を中止すること。毒性症状が Grade 1 又はベースラインまで回復した後は，初回用量で IMBRUVICA の投与を再開してもよい。毒性が再発した場合，1 日 1 回投与の用量を 1 カプセル分（1 日 140 mg）減量し，必要に応じてさらに 140 mg の減量を考慮する。2 回の用量減量後にも毒性が持続又は再発した場合は，本剤の投与を中止すること。

<table>
<tr><td></td><td>推奨される用量調節は以下のとおりである
<table>
<tr><th>毒性の発現回数</th><th>MCL 患者に対する回復後の用量調節</th><th>CLL/WM 患者に対する回復後の用量調節</th></tr>
<tr><td>1 回目</td><td>560 mg の 1 日 1 回投与で再開</td><td>420 mg の 1 日 1 回投与で再開</td></tr>
<tr><td>2 回目</td><td>420 mg の 1 日 1 回投与で再開</td><td>280 mg の 1 日 1 回投与で再開</td></tr>
<tr><td>3 回目</td><td>280 mg の 1 日 1 回投与で再開</td><td>140 mg の 1 日 1 回投与で再開</td></tr>
<tr><td>4 回目</td><td>本剤の投与を中止</td><td>本剤の投与を中止</td></tr>
</table>
飲み忘れ
予定された時刻に服用しなかった場合は，その日のうちできるだけ早く服用し，翌日に通常のスケジュールに戻すことができる。飲み忘れた分を補うために余分なカプセルを服用してはならない。

特別な患者集団
高齢者
高齢患者に対する特別な用量調節は不要である（65 歳以上）。

腎機能障害
腎機能障害患者を対象とした特別な臨床試験は実施していない。IMBRUVICA の臨床試験では，軽度又は中等度の腎機能障害を有する患者が治療を受けた。軽度又は中等度の腎機能障害患者に対する用量調節は不要である（クレアチニンクリアランスが 30 mL/min 超）。水分補給を維持し，血清クレアチニン値を定期的にモニタリングすべきである。
重度の腎機能障害患者（クレアチニンクリアランスが 30 mL/min 未満）には，ベネフィットがリスクを上回る場合にのみ IMBRUVICA を投与し，毒性の徴候について患者を注意深く観察すること。重度の腎機能障害患者又は透析患者のデータは得られていない。

肝機能障害
イブルチニブは肝臓で代謝される。肝機能障害患者を対象とした試験では，イブルチニブの曝露量の増加が示された。軽度の肝機能障害（Child-Pugh 分類 A）を有する患者に対する推奨用量は 280 mg/日（2 カプセル）である。中等度の肝機能障害を有する患者（Child-Pugh 分類 B）の場合，推奨用量は 140 mg/日（1 カプセル）である。IMBRUVICA の毒性の徴候について患者を観察し，必要に応じて用量調節を行うこと。重度の肝機能障害患者（Child-Pugh 分類 C）への IMBRUVICA の投与は推奨されない。

重度の心疾患
重度の心血管疾患を有する患者は IMBRUVICA の臨床試験から除外した。

小児集団
0 歳～18 歳の小児及び青少年における IMBRUVICA の安全性及び有効性は確立されていない。データは得られていない。

投与方法
IMBRUVICA は 1 日 1 回，コップ 1 杯の水とともに毎日ほぼ同じ時刻に経口投与すること。カプセルは水とともにそのまま飲み込み，開けたり，割ったり，噛み砕いたりしないこと。IMBRUVICA をグレープフルーツジュース又はセビリアオレンジと同時に服用しないこと。</td></tr>
<tr><td>禁忌</td><td>本剤の成分や添加物に対し過敏症の既往歴のある患者
本剤の投与を受けている患者に対するセント・ジョーンズ・ワート含有製剤の使用は禁忌である。</td></tr>
<tr><td>警告及び使用上の注意</td><td>出血関連事象
本剤の投与を受けた患者において，血小板減少症を伴う又は伴わない出血性イベントの発現が報告されている。軽度な出血性イベントとして挫傷，鼻出血，</td></tr>
</table>

	点状出血などが確認され，重度の出血性イベントとして死亡に至る消化管出血，頭蓋内出血，血尿が確認された。 ワルファリン又はその他のビタミンK拮抗薬と本剤を併用しないこと。 IMBRUVICA と併用して抗凝固薬又は血小板機能を阻害する薬剤（抗血小板薬）を使用すると，大出血のリスクが増加する。大出血のリスクは抗血小板薬よりも抗凝固薬の方が高かった。IMBRUVICA と併用する場合，抗凝固療法又は抗血小板療法のリスク及びベネフィットを考慮すること。出血の徴候及び症状をモニタリングすること。 魚油やビタミンE製剤などのサプリメントの摂取を避けること。 外科手術の種類および出血のリスクに応じて，手術前後少なくとも 3〜7 日間，本剤の投与を中止すること。 出血関連事象発現のメカニズムは完全には解明されていない。先天性の出血性素因のある患者を対象とした臨床試験は行われていない。 <u>白血球停滞</u> 本剤の投与を受けた患者において白血球症が報告されている。循環リンパ球数の増加（400,000/μL を超える）がリスクの上昇に起因している可能性がある。投与の一時的な中止を考慮すること。患者を注意深くモニタリングし，必要に応じて水分補給および／または細胞切除などの支持療法を行うこと。 <u>脾破裂</u> IMBRUVICA の投与中止後に脾破裂の症例が報告されている。IMBRUVICA の投与を中断又は中止する場合は，疾患の状態及び脾臓の大きさを注意深く観察すること（例：診察，超音波検査）。左上腹部痛又は肩先端痛を発症した患者を評価し，脾破裂の診断を考慮すべきである。 <u>感染症</u> 本剤の投与を受けた患者において感染症（敗血症，好中球減少性敗血症，細菌感染，ウイルス感染，真菌感染など）が確認されている。これらの感染症の中には入院や死亡に至る例も報告されている。致死的な感染症が発現した患者の多くが好中球減少症を伴っていた。発熱，肝機能検査異常，好中球減少症，感染症について患者をモニタリングし，必要に応じて適切な抗感染療法を行うこと。日和見感染のリスクが高い患者には，標準治療に従って，予防的投与を考慮すること。 イブルチニブの使用後に，アスペルギルス症，クリプトコッカス症及びニューモシスチス・イロベチイ感染を含む侵襲性真菌感染の症例が報告されている。報告された侵襲性真菌感染症の症例は致死的転帰と関連している。 免疫抑制療法による前治療又は併用療法においてイブルチニブの使用後に致死的症例を含む進行性多巣性白質脳症（PML）の症例が報告されている。医師は，神経，認知または行動上の徴候又は症状が新規発症又は悪化した患者に対する鑑別診断において PML を考慮すること。PML が疑われた場合は，適切な診断検査を実施し，PML が除外されるまで治療を中断すること。少しでも疑いが残っている場合は，神経科への紹介並びに MRI 検査（造影剤の使用が望ましい），JC ウイルス DNA に関する脳脊髄液（CSF）の検査及び神経学的評価の反復を含む適切な診断検査を考慮すること。 本剤の投与を受けた患者において，慢性化の可能性のある E 型肝炎の症例が報告されている。

	血球減少症 本剤の投与を受けた患者において Grade 3 又は Grade 4 の血球減少症（好中球減少症，血小板減少症，貧血）が報告されている。月に 1 回，全血球数の測定を行うこと。 間質性肺疾患（ILD） 本剤の投与を受けた患者において ILD 症例が報告されている。ILD を示す肺症状について患者をモニタリングすること。症状が発症した場合は，本剤の投与を中断し，ILD を適切に管理すること。症状が持続する場合は，本剤投与のリスクとベネフィットを考慮し，用量調節ガイドラインに従うこと。 不整脈及び心不全 本剤の投与を受けた患者において心房細動，心房粗動並びに心室性頻脈性不整脈及び心不全が報告されている。心房細動及び心房粗動は，特に心疾患リスク因子，高血圧，急性感染症，心房細動の既住歴を有する患者に報告されている。全ての患者に対し，不整脈及び心不全を含む心臓の症状を定期的に観察すること。不整脈の症状が発現した患者，又は新規に呼吸困難，浮動性めまい又は失神が発症した患者については臨床検査を行い，必要な場合には心電図（ECG）検査を実施する必要がある。 心室性頻脈性不整脈の徴候及び／又は症状が発症した患者に対しては，本剤の投与を一時的に中断し，本剤の投与再開前に，詳細な臨床上のベネフィット／リスク評価を実施すること。 抗凝固療法を必要とする心房細動の既住を有する患者に対しては，本剤の代替療法の使用を考慮すること。本剤の投与中に心房細動が発現した患者については血栓塞栓症のリスクについて十分な評価を行うこと。リスクの高い患者及び本剤の代替療法に適さない患者については，厳重に管理された抗凝固薬療法の実施を考慮すること。 IMBRUVICA 投与中は心不全の徴候及び症状について患者を観察すること。これらの症例の一部では，IMBRUVICA の中止又は減量後に心不全が回復又は改善した。 脳血管発作 IMBRUVICA の投与を受けた患者において，心房細動及び/又は高血圧の合併の有無を問わず，脳血管発作，一過性脳虚血発作及び虚血性脳卒中（死を含む）が報告されている。潜時が報告された症例のうち，IMBRUVICA の投与開始から虚血性中枢神経血管状態の発現までの期間は，ほとんどの症例で数カ月であったことから（1 カ月超が 78%，6 カ月超が 44%），患者を定期的にモニタリングする必要があることが示唆された。 腫瘍崩壊症候群 IMBRUVICA の治療による腫瘍崩壊症候群が報告されている。治療前に腫瘍量が多い患者は腫瘍崩壊症候群のリスクがある。患者の観察を十分行い，適切な予防措置を講じること。 非黒色腫皮膚癌 第Ⅲ相無作為化比較試験の統合データにおいて，対照薬の投与を受けた患者と比較して IMBRUVICA の投与を受けた患者においてより高い頻度の非黒色腫皮膚癌が報告されている。非黒色腫皮膚癌の発現に関して患者の観察を十分行うこと。 ウイルスの再活性化 本剤の投与を受けた患者において死亡例を含む B 型肝炎ウイルスの再活性化が報告されている。本剤の投与を開始する前に，B 型肝炎ウイルス（HBV）の状

	態を確定させること。HBV 感染検査陽性となった場合は，B 型肝炎の治療に精通した医師に紹介することが推奨される。B 型肝炎の血清検査陽性となった場合は，本剤の投与を開始する前に，肝疾患の専門医に紹介し，B 型肝炎ウイルスの再活性化を予防するための各国の標準治療に従って患者をモニタリング及び管理すること。 高血圧 IMBRUVICA の投与を受けた患者において高血圧が認められている。 IMBRUVICA の投与を受けている患者の血圧を定期的に観察し，IMBRUVICA の投与期間中は適宜降圧薬の投与を開始又は調節すること。 血球貪食性リンパ組織球症（HLH） IMBRUVICA の投与を受けた患者において，HLH（死亡例を含む）の症例が報告されている。HLH は，高度な全身性炎症の臨床徴候及び症状を特徴とする病的な免疫活性化による生命を脅かす症候群である。HLH は，発熱，肝脾腫，高トリグリセリド血症，血清フェリチン高値及び血球減少症を特徴とする。HLH の症状について患者に説明すること。病理的免疫活性化の初期症状を発現した患者は直ちに評価し，HLH の診断を考慮すべきである。 薬物相互作用 本剤と強力な又は中程度の CYP3A4 阻害剤との併用によってイブルチニブの曝露量が増加し，その結果として毒性発現のリスクが上昇する可能性がある。一方，本剤と CYP3A4 誘導剤との併用では，イブルチニブの曝露量が減少することで治療効果が減弱するおそれがある。そのため，本剤と強力な CYP3A4 阻害剤及び強力な又は中程度の CYP3A4 誘導剤との併用は可能な限り避け，治療上の有益性が危険性を明らかに上回ると判断される場合のみ併用投与を行うこと。CYP3A4 阻害剤をやむを得ず使用する必要がある場合は，本剤の毒性徴候について患者を注意深くモニタリングすること。CYP3A4 誘導剤をやむを得ず使用する必要がある場合は，本剤の治療効果減弱について患者を注意深くモニタリングすること。 妊娠可能な女性 妊娠可能な女性は，本剤の投与期間中は有効な避妊法をとること。

Janssen Research & Development, LLC

COMPANY CORE DATA SHEET

Ibrutinib (IMBRUVICA®)

[redacted]

以下，非公表のため2頁～61頁を省略

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1)	04/2020
Warnings and Precautions (5.1, 5.2, 5.3, 5.5, 5.6)	04/2020
Warnings and Precautions (5.4)	12/2020

----------INDICATIONS AND USAGE----------

IMBRUVICA is a kinase inhibitor indicated for the treatment of adult patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1).

  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) (1.2).
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion (1.3).
- Waldenström's macroglobulinemia (WM) (1.4).
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy (1.5).

  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy (1.6).

----------DOSAGE AND ADMINISTRATION----------

- MCL and MZL: 560 mg taken orally once daily (2.1).
- CLL/SLL, WM, and cGVHD: 420 mg taken orally once daily (2.1).

Dose should be taken orally with a glass of water. Do not open, break, or chew the capsules. Do not cut, crush, or chew the tablets (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 70 mg and 140 mg (3)

Tablets: 140 mg, 280 mg, 420 mg, and 560 mg (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hemorrhage: Monitor for bleeding and manage (5.1).
- Infections: Monitor patients for fever and infections, evaluate promptly, and treat (5.2).
- Cytopenias: Check complete blood counts monthly (5.3).
- Cardiac Arrhythmias and Cardiac Failure: Monitor for symptoms of arrhythmias and cardiac failure and manage (5.4).
- Hypertension: Monitor blood pressure and treat (5.5).
- Second Primary Malignancies: Other malignancies have occurred in patients, including skin cancers, and other carcinomas (5.6).
- Tumor Lysis Syndrome (TLS): Assess baseline risk and take precautions. Monitor and treat for TLS (5.7).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception (5.8, 8.1, 8.3).

----------ADVERSE REACTIONS----------

- The most common (≥30%) adverse reactions in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) are thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising(6).
- The most common (≥20%) adverse reactions in patients with cGVHD are fatigue, bruising, diarrhea, thrombocytopenia, muscle spasms, stomatitis, nausea, hemorrhage, anemia, and pneumonia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacyclics at 1-877-877-3536 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- CYP3A Inhibitors: Modify IMBRUVICA dose as described (2.3, 7.1).
- CYP3A Inducers: Avoid coadministration with strong CYP3A inducers (7.2).

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)
- Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA dose (2.4, 8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 12/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

IMBRUVICA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s) *[see Clinical Studies (14.1)]*.

1.2 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

1.3 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

1.4 Waldenström's Macroglobulinemia

IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

1.5 Marginal Zone Lymphoma

IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.4)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.6 Chronic Graft versus Host Disease

IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Mantle Cell Lymphoma and Marginal Zone Lymphoma

The recommended dosage of IMBRUVICA for MCL and MZL is 560 mg orally once daily until disease progression or unacceptable toxicity.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma and Waldenström's Macroglobulinemia

The recommended dosage of IMBRUVICA for CLL/SLL and WM is 420 mg orally once daily until disease progression or unacceptable toxicity.

For CLL/SLL, IMBRUVICA can be administered as a single agent, in combination with rituximab or obinutuzumab, or in combination with bendamustine and rituximab (BR).

For WM, IMBRUVICA can be administered as a single agent or in combination with rituximab.

When administering IMBRUVICA in combination with rituximab or obinutuzumab, consider administering IMBRUVICA prior to rituximab or obinutuzumab when given on the same day.

Chronic Graft versus Host Disease

The recommended dosage of IMBRUVICA for cGVHD is 420 mg orally once daily until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity. When a patient no longer requires therapy for the treatment of cGVHD, IMBRUVICA should be discontinued considering the medical assessment of the individual patient.

Administration

Administer IMBRUVICA at approximately the same time each day with a glass of water.

Swallow tablets or capsule whole. Do not open, break, or chew the capsules. Do not cut, crush, or chew the tablets.

If a dose of IMBRUVICA is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Do not take extra doses of IMBRUVICA to make up for the missed dose.

2.2 Dosage Modifications for Adverse Reactions

Interrupt IMBRUVICA therapy for any Grade 3 or 4 non-hematological toxicities, Grade 3 or 4 neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the adverse reaction has improved to Grade 1 or baseline (recovery), IMBRUVICA may be reinitiated at the starting dose. If the adverse reaction reoccurs, reduce dose by 140 mg per day. Consider a second reduction of dose by 140 mg as needed. If these adverse reactions persist or recur following two dose reductions, discontinue IMBRUVICA.

Recommended dose modifications are described below:

Toxicity Occurrence	**Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg**	**Dose Modification for CLL/SLL, WM, and cGVHD After Recovery Starting Dose = 420 mg**
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue IMBRUVICA	Discontinue IMBRUVICA

2.3 Dosage Modifications for Use with CYP3A Inhibitors

Recommended dosage modifications are described below *[see Drug Interactions (7.1)]*:

Patient Population	Coadministered Drug	Recommended IMBRUVICA Dosage
B-Cell Malignancies	• Moderate CYP3A inhibitor	280 mg once daily Modify dose as recommended *[see Dosage and Administration (2.2)]*.
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily Modify dose as recommended *[see Dosage and Administration (2.2)]*.
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole intravenously 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily Interrupt dose as recommended *[see Dosage and Administration (2.2)]*.
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.
Chronic Graft versus Host Disease	• Moderate CYP3A inhibitor	420 mg once daily Modify dose as recommended *[see Dosage and Administration (2.2)]*.
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	280 mg once daily Modify dose as recommended *[see Dosage and Administration (2.2)]*.
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole intravenously 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	140 mg once daily Interrupt dose as recommended *[see Dosage and Administration (2.2)]*.
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.

After discontinuation of a CYP3A inhibitor, resume previous dose of IMBRUVICA *[see Dosage and Administration (2.1), Drug Interactions (7.1)]*.

2.4 Dosage Modifications for Use in Hepatic Impairment

The recommended dosage is 140 mg daily for patients with mild hepatic impairment (Child-Pugh class A).

The recommended dosage is 70 mg daily for patients with moderate hepatic impairment (Child-Pugh class B).

Avoid the use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C) *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

Each 70 mg capsule is a yellow, opaque capsule marked with “ibr 70 mg” in black ink.

Each 140 mg capsule is a white, opaque capsule marked with “ibr 140 mg” in black ink.

Tablets:

Each 140 mg tablet is a yellow green to green round tablet debossed with “ibr” on one side and “140” on the other side.

Each 280 mg tablet is a purple oblong tablet debossed with “ibr” on one side and “280” on the other side.

Each 420 mg tablet is a yellow green to green oblong tablet debossed with “ibr” on one side and “420” on the other side.

Each 560 mg tablet is a yellow to orange oblong tablet debossed with “ibr” on one side and “560” on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal bleeding events have occurred in patients who received IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA, respectively.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received

IMBRUVICA without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14)]*.

5.2 Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA in clinical trials *[see Adverse Reactions (6.1, 6.2)]*. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

5.3 Cytopenias

In 645 patients with B-cell malignancies who received IMBRUVICA as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements.

Monitor complete blood counts monthly.

5.4 Cardiac Arrhythmias and Cardiac Failure

Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias *[see Adverse Reactions (6.1)]*.

At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.2)]*.

5.5 Hypertension

Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

5.6 Second Primary Malignancies

Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

5.7 Tumor Lysis Syndrome

Tumor lysis syndrome has been infrequently reported with IMBRUVICA. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

5.8 Embryo-Fetal Toxicity

Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose. *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Cardiac Arrhythmias and Cardiac Failure *[see Warnings and Precautions (5.4)]*
- Hypertension *[see Warnings and Precautions (5.5)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.6)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to IMBRUVICA in 6 trials as a single agent at 420 mg orally once daily in 475 patients and at 560 mg orally once daily in 174 patients and in 4 trials administered in combination with other drugs at 420 mg orally once daily in 827 patients. Among these 1,476 patients with B-cell malignancies who received IMBRUVICA, 87% were exposed for 6 months or longer and 68% were exposed for greater than one year. In this pooled safety population of 1,476 patients with B-cell malignancies, the most common adverse reactions (≥30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising.

Mantle Cell Lymphoma

The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most common adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal (ULN) occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	8†
	Skin infections	14	5
	Sinusitis	13	1
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	5†
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

† Includes one event with a fatal outcome.

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets decreased	57	17
Neutrophils decreased	47	29
Hemoglobin decreased	41	9

* Based on laboratory measurements and adverse reactions

Treatment-emergent Grade 4 thrombocytopenia (6%) and neutropenia (13%) occurred in patients.

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The data described below reflect exposure to IMBRUVICA in one single-arm, open-label clinical trial (Study 1102) and five randomized controlled clinical trials (RESONATE, RESONATE-2, HELIOS, iLLUMINATE, and E1912) in patients with CLL/SLL (n=2,016 total, including n=1,133 patients exposed to IMBRUVICA). In general, patients with creatinine

clearance (CLcr) ≤ 30 mL/min, AST or ALT ≥ 2.5 x ULN, or total bilirubin ≥ 1.5x ULN (unless of non-hepatic origin) were excluded from these trials. In Study E1912, patients with AST or ALT > 3 x ULN or total bilirubin > 2.5 x ULN were excluded. Study 1102 included 51 patients with previously treated CLL/SLL. RESONATE included 386 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab. RESONATE-2 included 267 randomized patients with treatment naïve CLL or SLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil. HELIOS included 574 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with BR or placebo in combination with BR. iLLUMINATE included 228 randomized patients with treatment naïve CLL/SLL who were 65 years or older or with coexisting medical conditions and received IMBRUVICA in combination with obinutuzumab or chlorambucil in combination with obinutuzumab. E1912 included 510 patients with previously untreated CLL/SLL who were 70 years or younger and received IMBRUVICA in combination with rituximab or received fludarabine, cyclophosphamide, and rituximab (FCR).

The most common adverse reactions in patients with CLL/SLL receiving IMBRUVICA (≥ 30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, bruising, and nausea.

Four to 10 percent of patients with CLL/SLL receiving IMBRUVICA discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, neutropenia, arthralgia, rash, and thrombocytopenia. Adverse reactions leading to dose reduction occurred in approximately 9% of patients.

Study 1102

Adverse reactions and laboratory abnormalities from Study 1102 (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Vascular disorders	Hypertension	16	8
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies	10	2[†]

[†]One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets decreased	69	12
Neutrophils decreased	53	26
Hemoglobin decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

Treatment-emergent Grade 4 thrombocytopenia (8%) and neutropenia (12%) occurred in patients.

RESONATE

Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Muscle spasms	13	0	8	0
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
General disorders and administration site conditions				
Pyrexia	24	2	15	2†
Respiratory, thoracic and mediastinal disorders				
Cough	19	0	23	1
Dyspnea	12	2	10	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2†
Pneumonia*	15	12†	13	10†
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

† Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils decreased	51	23	57	26
Platelets decreased	52	5	45	10
Hemoglobin decreased	36	0	21	0

Treatment-emergent Grade 4 thrombocytopenia (2% in the IMBRUVICA arm vs 3% in the ofatumumab arm) and neutropenia (8% in the IMBRUVICA arm vs 8% in the ofatumumab arm) occurred in patients.

RESONATE-2

Adverse reactions and laboratory abnormalities described below in Tables 7 and 8 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

Table 7: Adverse Reactions Reported in ⩾ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Nausea	22	1	39	1
Constipation	16	1	16	0
Stomatitis*	14	1	4	1
Vomiting	13	0	20	1
Abdominal pain	13	3	11	1
Dyspepsia	11	0	2	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
General disorders and administration site conditions				
Fatigue	30	1	38	5
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
Dyspnea	10	1	10	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Eye disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Infections and infestations				
Upper respiratory tract infection	17	2	17	2
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Vascular disorders				
Hypertension*	14	4	1	0
Nervous system disorders				
Headache	12	1	10	2
Dizziness	11	0	12	1
Investigations				
Weight decreased	10	0	12	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Table 8: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE-2

	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	55	28	67	31
Platelets Decreased	47	7	58	14
Hemoglobin Decreased	36	0	39	2

Treatment-emergent Grade 4 thrombocytopenia (1% in the IMBRUVICA arm vs 3% in the chlorambucil arm) and neutropenia (11% in the IMBRUVICA arm vs 12% in the chlorambucil arm) occurred in patients.

HELIOS

Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

Table 9: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

Body System Adverse Reaction	IMBRUVICA + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	56†
Thrombocytopenia*	34	16	26	16
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal pain	12	1	8	<1
Skin and subcutaneous tissue disorders				
Rash *	32	4	25	1
Bruising *	20	<1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular disorders				
Hemorrhage*	19	2†	9	1
Hypertension *	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%
† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia with a fatal outcome in the placebo + BR arm.

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR.

iLLUMINATE

Adverse reactions described below in Table 10 reflect exposure to IMBRUVICA + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

Table 10: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE

Body System Adverse Reaction	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	48	39	64	48
Thrombocytopenia*	36	19	28	11
Anemia	17	4	25	8
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Gastrointestinal disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Nausea	12	0	30	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Respiratory, thoracic and mediastinal disorders				
Cough	27	1	12	0
Injury, poisoning and procedural complications				
Infusion related reaction	25	2	58	8
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3

General disorders and administration site conditions				
Pyrexia	19	2	26	1
Fatigue	18	0	17	2
Peripheral edema	12	0	7	0
Infections and infestations				
Pneumonia*	16	9	9	4†
Upper respiratory tract infection	14	1	6	0
Skin infection*	13	1	3	0
Urinary tract infection	12	3	7	1
Nasopharyngitis	12	0	3	0
Conjunctivitis	11	0	2	0
Metabolism and nutrition disorders				
Hyperuricemia	13	1	0	0
Cardiac disorders				
Atrial fibrillation	12	5	0	0
Psychiatric disorders				
Insomnia	12	0	4	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

† Includes one event with a fatal outcome.

E1912

Adverse reactions described below in Table 11 reflect exposure to IMBRUVICA + rituximab with a median duration of 34.3 months and exposure to FCR with a median of 4.7 months in E1912 in patients with previously untreated CLL/SLL who were 70 years or younger.

Table 11: Adverse Reactions Reported in at Least 15% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in E1912

Body System Adverse Reaction	IMBRUVICA + Rituximab (N=352)		Fludarabine + Cyclophosphamide + Rituximab (N=158)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
General disorders and administration site conditions				
Fatigue	80	2	78	3
Peripheral edema	28	1	17	0
Pyrexia	27	1	27	1
Pain	23	2	8	0

Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	61	5	35	2
Arthralgia	41	5	10	1
Gastrointestinal disorders				
Diarrhea	53	4	27	1
Nausea	40	1	64	1
Stomatitis*	22	1	8	1
Abdominal pain*	19	2	10	1
Vomiting	18	2	28	0
Constipation	17	0	32	0
Skin and subcutaneous tissue disorders				
Rash*	49	4	29	5
Bruising*	36	1	4	1
Vascular disorders				
Hypertension*	42	19	22	6
Hemorrhage*	31	2	8	1
Nervous system disorders				
Headache	40	1	27	1
Dizziness	21	1	13	1
Peripheral neuropathy*	19	1	13	1
Respiratory, thoracic and mediastinal disorders				
Cough	32	0	25	0
Dyspnea	22	2	21	1
Infections and infestations				
Upper respiratory tract infection	29	1	19	2
Skin infection*	16	1	3	1
Metabolism and nutrition disorders				
Hyperuricemia	19	1	4	0
Decreased appetite	15	0	20	1
Psychiatric disorders				
Insomnia	16	1	19	1

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms

Table 12: Select Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving IMBRUVICA (E1912)

	IMBRUVICA + Rituximab (N=352)		Fludarabine + Cyclophosphamide + Rituximab (N=158)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology abnormalities				
Neutrophils decreased	53	30	70	44
Platelets decreased	43	7	69	25
Hemoglobin decreased	26	0	51	2
Chemistry abnormalities				
Creatinine increased	38	1	17	1
Bilirubin increased	30	2	15	0
AST increased	25	3	23	<1

Based on laboratory measurements per IWCLL criteria

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma

The data described below reflect exposure to IMBRUVICA in three single-arm open-label clinical trials (Study 1118, Study 1121, and INNOVATE monotherapy arm) and one randomized controlled trial (INNOVATE) in patients with WM or MZL, including a total n=307 patients overall and n=232 patients exposed to IMBRUVICA. Study 1118 included 63 patients with previously treated WM who received single agent IMBRUVICA. Study 1121 included 63 patients with previously treated MZL who received single agent IMBRUVICA. INNOVATE included 150 patients with treatment naïve or previously treated WM who received IMBRUVICA or placebo in combination with rituximab. The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received IMBRUVICA.

The most common adverse reactions in Studies 1118, 1121, and INNOVATE (≥ 20%) were thrombocytopenia, diarrhea, bruising, neutropenia, musculoskeletal pain, hemorrhage, anemia, rash, fatigue, and nausea.

Seven percent of patients receiving IMBRUVICA across Studies 1118, 1121, and INNOVATE discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were atrial fibrillation, interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 13% of patients.

Study 1118 and INNOVATE Monotherapy Arm

Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118 and 33 months in the INNOVATE Monotherapy Arm.

Table 13: Non-Hematologic Adverse Reactions in ⩾ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	38	2
	Nausea	21	0
	Stomatitis*	15	0
	Constipation	12	1
	Gastroesophageal reflux disease	12	0
Skin and subcutaneous tissue disorders	Bruising*	28	1
	Rash*	21	1
Vascular disorders	Hemorrhage*	28	0
	Hypertension*	14	4
General disorders and administrative site conditions	Fatigue	18	2
	Pyrexia	12	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	21	0
	Muscle spasms	19	0
Infections and infestations	Upper respiratory tract infection	19	0
	Skin infection*	18	3
	Sinusitis*	16	0
	Pneumonia*	13	5
Nervous system disorders	Headache	14	0
	Dizziness	13	0
Respiratory, thoracic and mediastinal disorders	Cough	13	0

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

	Percent of Patients (N=94)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	38	11
Neutrophils Decreased	43	16
Hemoglobin Decreased	21	6

Treatment-emergent Grade 4 thrombocytopenia (4%) and neutropenia (7%) occurred in patients.

INNOVATE

Adverse reactions described below in Table 15 reflect exposure to IMBRUVICA + R with a median duration of 25.8 months and exposure to placebo + R with a median duration of 15.5 months in patients with treatment naïve or previously treated WM in INNOVATE.

Table 15: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Skin and subcutaneous tissue disorders				
Bruising*	37	1	5	0
Rash*	24	1	11	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	35	4	21	3
Arthralgia	24	3	11	1
Muscle spasms	17	0	12	1
Vascular disorders				
Hemorrhage*	32	3	17	4[†]
Hypertension*	20	13	5	4
Gastrointestinal disorders				
Diarrhea	28	0	15	1
Nausea	21	0	12	0
Dyspepsia	16	0	1	0
Constipation	13	1	11	1
Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
Viral upper respiratory tract infection	11	0	7	0
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0
Blood and lymphatic system disorders				
Neutropenia*	16	12	11	4

Cardiac disorders				
Atrial fibrillation	15	12	3	1
Nervous system disorders				
Dizziness	11	0	7	0
Psychiatric disorders				
Insomnia	11	0	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes one event with a fatal outcome.

Grade 3 or 4 infusion related reactions were observed in 1% of patients treated with IR.

Study 1121

Adverse reactions and laboratory abnormalities described below in Tables 16 and 17 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 16: Non-Hematologic Adverse Reactions in ⩾ 10% in Patients with MZL in Study 1121 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
Skin and subcutaneous tissue disorders	Bruising *	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular disorders	Hemorrhage*	30	2†
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes one event with a fatal outcome.

Table 17: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets decreased	49	6
Hemoglobin decreased	43	13
Neutrophils decreased	22	13

Treatment-emergent Grade 4 thrombocytopenia (3%) and neutropenia (6%) occurred in patients.

Chronic Graft versus Host Disease

The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most common adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD trial discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 18 and 19 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 18: Non-Hematologic Adverse Reactions in ⩾ 10% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
General disorders and administration site conditions	Fatigue	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	14†
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	2
Metabolism and nutrition disorders	Hypokalemia	12	7

The system organ class and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.
† Includes 2 events with a fatal outcome.

Table 19: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets decreased	33	0
Neutrophils decreased	10	10
Hemoglobin decreased	24	2

Treatment-emergent Grade 4 neutropenia occurred in 2% of patients.

Additional Important Adverse Reactions

Cardiovascular Events

Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of ventricular

tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.3% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of atrial fibrillation and atrial flutter of any grade was 8.4% versus 1.6% and for Grade 3 or greater was 4.0% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of cardiac failure of any grade was 1.7% versus 0.5% and for Grade 3 or greater was 1.2% versus 0.3% in patients treated with IMBRUVICA compared to patients in the control arm.

The incidence of ischemic cerebrovascular events (cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack) of any grade was 1% versus 0.4% and Grade 3 or greater was 0.5% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm, respectively.

Diarrhea

In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), diarrhea of any grade occurred at a rate of 43% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. Less than 1% (0.3%) of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Based on data from 1,605 of these patients, the median time to first onset was 21 days (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively.

Visual Disturbance

In randomized controlled trials (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3).

Based on data from 1,605 of these patients, the median time to first onset was 91 days (range, 0 to 617) versus 100 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had

complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Long-Term Safety

The safety data from long-term treatment with IMBRUVICA over 5 years of 1,284 patients (treatment-naïve CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, relapsed/refractory MCL n=370, and WM n=106) were analyzed. The median treatment duration was 51 months (range, 0.2 to 98 months) for CLL/SLL, 11 months (range, 0 to 87 months) for MCL, and 47 months (range, 0.3 to 61 months) for WM. The cumulative rate of hypertension increased over time. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall incidence for the 5-year period was 11%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis, panniculitis, neutrophilic dermatoses
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

7 DRUG INTERACTIONS

7.1 Effect of CYP3A Inhibitors on Ibrutinib

The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors *[see Dosage and Administration (2.3)]*.

Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.3)]*.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

7.2 Effect of CYP3A Inducers on Ibrutinib

The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

IMBRUVICA can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Data)*. Advise pregnant women of the potential risk to a fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated

with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating IMBRUVICA.

Contraception

Females

IMBRUVICA can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month following the last dose.

8.4 Pediatric Use

The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

8.5 Geriatric Use

Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

8.6 Hepatic Impairment

Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Reduce the recommended dose when administering IMBRUVICA to patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients more frequently for adverse reactions of IMBRUVICA *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.7 Plasmapheresis

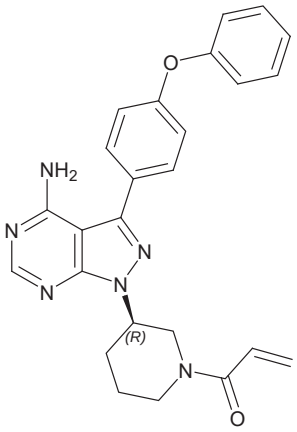
Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

10 OVERDOSAGE

There is no specific experience in the management of ibrutinib overdose in patients. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Closely monitor patients who ingest more than the recommended dosage and provide appropriate supportive treatment.

11 DESCRIPTION

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula $C_{25}H_{24}N_6O_2$ and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water. The chemical name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:



IMBRUVICA (ibrutinib) is available as immediate-release oral capsules and immediate-release oral tablets.

IMBRUVICA (ibrutinib) capsules for oral use are available in the following dosage strengths: 70 mg and 140 mg. Each capsule contains ibrutinib (active ingredient) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide (70 mg capsule only), and black ink.

IMBRUVICA (ibrutinib) tablets for oral use are available in the following dosage strengths: 140 mg, 280 mg, 420 mg, and 560 mg. Each tablet contains ibrutinib (active ingredient) and the

following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate. The film coating for each tablet contains ferrosoferric oxide (140 mg, 280 mg, and 420 mg tablets), polyvinyl alcohol, polyethylene glycol, red iron oxide (280 mg and 560 mg tablets), talc, titanium dioxide, and yellow iron oxide (140 mg, 420 mg, and 560 mg tablets).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

12.2 Pharmacodynamics

In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

In vitro Platelet Aggregation

Ibrutinib demonstrated inhibition of collagen-induced platelet aggregation, with IC50 values at 4.6 μM (2026 ng/mL), 0.8 μM (352 ng/mL), and 3 μM (1321 ng/mL) in blood samples from healthy donors, donors taking warfarin, and donors with severe renal dysfunction, respectively. Ibrutinib did not show meaningful inhibition of platelet aggregation for ADP, arachidonic acid, ristocetin, and TRAP-6.

Cardiac Electrophysiology

At a single dose 3 times the maximum recommended dose (1680 mg), IMBRUVICA did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Ibrutinib exposure increases with doses up to 840 mg (1.5 times the maximum approved recommended dosage) in patients with B-cell malignancies. The mean steady-state AUC (% coefficient of variation) observed in patients at 560 mg with MCL is 865 (69%) ng·h/mL and with MZL is 978 (82%) ng·h/mL, and in patients at 420 mg with CLL/SLL is 708 (71%) ng·h/mL, with WM is 707 (72%) ng·h/mL, and with cGVHD is 1159 (50%) ng·h/mL. Steady-state concentrations of ibrutinib without CYP3A inhibitors were achieved with an accumulation ratio of 1 to 1.6 after 1 week of multiple daily doses of 420 mg or 560 mg.

Absorption

Absolute bioavailability of ibrutinib in fasted condition was 2.9% (90% CI: 2.1, 3.9) in healthy subjects. Ibrutinib is absorbed after oral administration with a median T_{max} of 1 hour to 2 hours.

Effect of Food

The administration of IMBRUVICA with a high-fat and high-calorie meal (800 calories to 1,000 calories with approximately 50% of total caloric content of the meal from fat) increased ibrutinib C_{max} by 2- to 4-fold and AUC by approximately 2-fold, compared with administration of ibrutinib after overnight fasting.

In vitro studies suggest that ibrutinib is not a substrate of p-glycoprotein (P-gp) or breast cancer resistance protein (BCRP).

Distribution

Reversible binding of ibrutinib to human plasma protein *in vitro* was 97.3% with no concentration dependence in the range of 50 ng/mL to 1000 ng/mL. The volume of distribution (V_d) was 683 L, and the apparent volume of distribution at steady state ($V_{d,ss}/F$) was approximately 10,000 L.

Elimination

Intravenous clearance was 62 L/h in fasted conditions and 76 L/h in fed conditions. In line with the high first-pass effect, the apparent oral clearance is 2000 L/h in fasted conditions and 1000 L/h in fed conditions. The half-life of ibrutinib is 4 hours to 6 hours.

Metabolism

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8.

Excretion

Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled ibrutinib, 90% of radioactivity was excreted within 168 hours, with 80% excreted in the feces and less than 10% eliminated in urine. Unchanged ibrutinib accounted for 1% of the radiolabeled excreted dose in feces and none in urine, with the remainder of the excreted dose being metabolites.

Specific Populations

Age and Sex

Age and sex have no clinically meaningful effect on ibrutinib pharmacokinetics.

Patients with Renal Impairment

Mild and moderate renal impairment (creatinine clearance [CLcr] > 25 mL/min as estimated by Cockcroft-Gault equation) had no influence on the exposure of ibrutinib. No data is available in patients with severe renal impairment (CLcr < 25 mL/min) or in patients on dialysis.

Patients with Hepatic Impairment

The AUC of ibrutinib increased 2.7-fold in subjects with mild hepatic impairment (Child-Pugh class A), 8.2-fold in subjects with moderate hepatic impairment (Child-Pugh class B) and 9.8-fold in subjects with severe hepatic impairment (Child-Pugh class C) relative to subjects with normal liver function. The C_{max} of ibrutinib increased 5.2-fold in mild hepatic impairment, 8.8-fold in moderate hepatic impairment and 7-fold in severe hepatic impairment relative to subjects with normal liver function *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of multiple doses of ketoconazole (strong CYP3A inhibitor) increased the C_{max} of ibrutinib by 29-fold and AUC by 24-fold. The coadministration of multiple doses of voriconazole (strong CYP3A inhibitor) increased steady state C_{max} of ibrutinib by 6.7-fold and AUC by 5.7-fold. Simulations under fed conditions suggest that posaconazole (strong CYP3A inhibitor) may increase the AUC of ibrutinib 3-fold to 10-fold.

The coadministration of multiple doses of erythromycin (moderate CYP3A inhibitor) increased steady state C_{max} of ibrutinib by 3.4-fold and AUC by 3-fold.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of rifampin (strong CYP3A inducer) decreased the C_{max} of ibrutinib by more than 13-fold and AUC by more than 10-fold. Simulations suggest that efavirenz (moderate CYP3A inducer) may decrease the AUC of ibrutinib by 3-fold.

In Vitro Studies

Effect of Ibrutinib on CYP Substrates: In vitro studies suggest that ibrutinib and PCI-45227 are unlikely to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A at clinical doses. Both ibrutinib and PCI-45227 are unlikely to induce CYP1A2, CYP2B6 or CYP3A at clinical doses.

Effect of Ibrutinib on Substrates of Transporters: In vitro studies suggest that ibrutinib may inhibit BCRP and P-gp transport at clinical doses. The coadministration of oral P-gp or BCRP substrates with a narrow therapeutic index (e.g., digoxin, methotrexate) with IMBRUVICA may increase their concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ibrutinib was not carcinogenic in a 6-month rasH2 mouse study at oral doses up to 2000 mg/kg/day resulting in exposures approximately 23 (males) to 37 (females) times higher than the exposure in humans at a dose of 560 mg daily *[see Warnings and Precautions (5.6)]*.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Rats were administered oral daily doses of ibrutinib for 4 weeks prior to pairing and during pairing in males and 2 weeks prior to pairing and during pairing in females. Treatment of female rats continued following pregnancy up to gestation day (GD) 7, and treatment of male rats continued until end of study. No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED] 16 mg/kg).

14 CLINICAL STUDIES

14.1 Mantle Cell Lymphoma

The safety and efficacy of IMBRUVICA in patients with MCL who have received at least one prior therapy were evaluated in Study 1104 (NCT01236391), an open-label, multi-center, single-arm trial of 111 previously treated patients. IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR).

The median age was 68 years (range, 40 to 84 years), 77% were male, and 92% were White. At baseline, 89% of patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 11% with prior stem cell transplantation. At baseline, 39% of subjects had at least one tumor ≥ 5 cm, 49% had bone marrow involvement, and 54% had extranodal involvement at screening.

Responses to IMBRUVICA are shown in Table 20.

Table 20: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with MCL in Study 1104

	Total (N=111)
ORR (%)	65.8
95% CI (%)	(56.2, 74.5)
CR (%)	17.1
PR (%)	48.6
Median DOR months (95% CI)	17.5 (15.8, NE)

CI = confidence interval; CR = complete response; PR = partial response; NE = not evaluable

An Independent Review Committee (IRC) performed independent reading and interpretation of imaging scans. The IRC review demonstrated an ORR of 69%.

The median time to response was 1.9 months.

Lymphocytosis

Upon initiation of IMBRUVICA, a temporary increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 33% of patients in the MCL study. The onset of isolated lymphocytosis occurs during the first few weeks of IMBRUVICA therapy and resolves by a median of 8 weeks.

14.2 Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma

The safety and efficacy of IMBRUVICA in patients with CLL/SLL were demonstrated in one uncontrolled trial and five randomized, controlled trials.

Study 1102

Study 1102 (NCT01105247), an open-label, multi-center trial, was conducted in 48 previously treated CLL patients. IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The ORR and DOR were assessed using a modified version of the International Workshop on CLL Criteria by an Independent Review Committee.

The median age was 67 years (range, 37 to 82 years), 71% were male, and 94% were White. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 80 months and the median number of prior treatments was 4 (range, 1 to 12 treatments). At baseline, 46% of subjects had at least one tumor ≥ 5 cm.

The ORR was 58.3% (95% CI: 43.2%, 72.4%), all partial responses. None of the patients achieved a complete response. The DOR ranged from 5.6 to 24.2+ months. The median DOR was not reached.

RESONATE

The RESONATE study, a randomized, multicenter, open-label, phase 3 study of IMBRUVICA versus ofatumumab (NCT01578707), was conducted in patients with previously treated CLL or SLL. Patients (n=391) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression, or unacceptable toxicity or ofatumumab at an initial dose of 300 mg, followed one week later by a dose of 2000 mg weekly for 7 doses and then every 4 weeks for 4 additional doses. Fifty-seven patients randomized to ofatumumab crossed over following progression to receive IMBRUVICA.

The median age was 67 years (range, 30 to 88 years), 68% were male, and 90% were White. All patients had a baseline ECOG performance status of 0 or 1. The trial enrolled 373 patients with CLL and 18 patients with SLL. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range, 1 to 13 treatments). At baseline, 58% of patients had at least one tumor ≥ 5 cm. Thirty-two percent of patients had 17p deletion.

Efficacy results for RESONATE are shown in Table 21 and the Kaplan-Meier curves for PFS, assessed by an IRC according to IWCLL criteria, and OS are shown in Figures 1 and 2, respectively.

Table 21: Efficacy Results in Patients with CLL/SLL in RESONATE

Endpoint	IMBRUVICA N=195	Ofatumumab N=196
Progression Free Survival[b]		
Number of events (%)	35 (17.9)	111 (56.6)
Disease progression	26	93
Death events	9	18
Median (95% CI), months	NE	8.1 (7.2, 8.3)
HR (95% CI)	0.22 (0.15, 0.32)	
Overall Survival[a]		
Number of deaths (%)	16 (8.2)	33 (16.8)
HR (95% CI)	0.43 (0.24, 0.79)	
Overall Response Rate[b]	42.6%	4.1%

[a] Median OS not evaluable for either arm

[b] IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.

CI = confidence interval; HR = hazard ratio; NE = not evaluable

Figure 1: Kaplan-Meier Curve of Progression Free Survival (ITT Population) in Patients with CLL/SLL in RESONATE

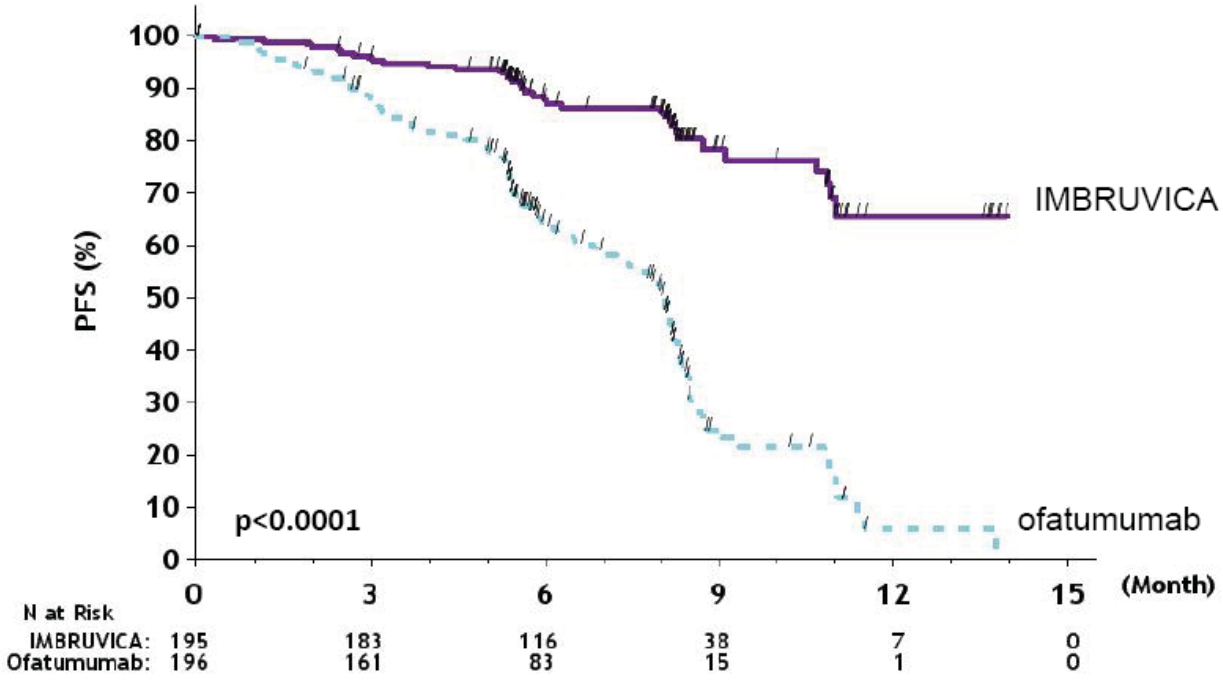
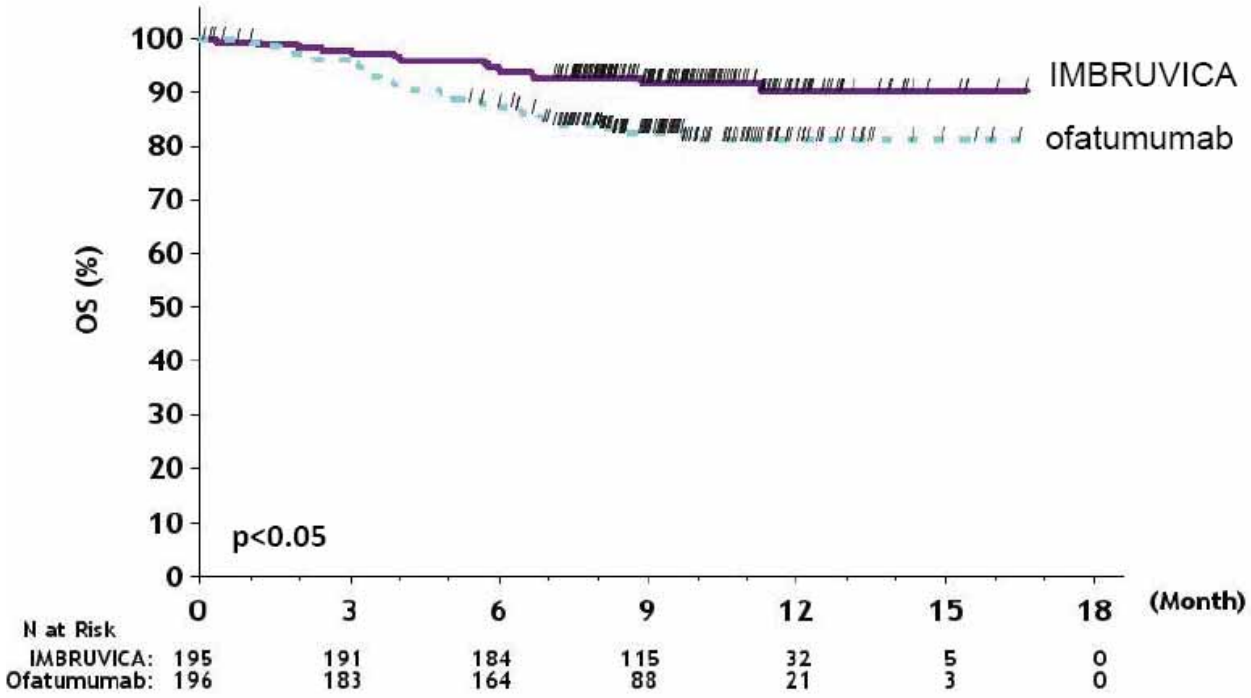


Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population) in Patients with CLL/SLL in RESONATE



63-Month Follow-Up

With an overall follow-up of 63 months, the median investigator-assessed PFS per IWCLL criteria was 44.1 months [95% CI (38.5, 56.9)] in the IMBRUVICA arm and 8.1 months [95% CI (7.8, 8.3)] in the ofatumumab arm, respectively. Overall response rate as assessed by investigators was 87.2% in the IMBRUVICA arm versus 22.4% in the ofatumumab arm.

CLL/SLL with 17p deletion (del 17p CLL/SLL) in RESONATE

RESONATE included 127 patients with del 17p CLL/SLL. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were White. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by an IRC. Efficacy results for del 17p CLL/SLL are shown in Table 22.

Table 22: Efficacy Results in Patients with del 17p CLL/SLL in RESONATE

Endpoint	IMBRUVICA N=63	Ofatumumab N=64
Progression Free Survival[a]		
Number of events (%)	16 (25.4)	38 (59.4)
Disease progression	12	31
Death events	4	7
Median (95% CI), months	NE	5.8 (5.3, 7.9)
HR (95% CI)	0.25 (0.14, 0.45)	
Overall Response Rate[a]	47.6%	4.7%

[a] IRC evaluated. All partial responses achieved; none of the patients achieved a complete response.
CI = confidence interval; HR = hazard ratio; NE = not evaluable

63-Month Follow-Up

With an overall follow-up of 63 months, the median investigator-assessed PFS in patients with del 17p per IWCLL criteria was 40.6 months [95% CI (25.4, 44.6)] in the IMBRUVICA arm and 6.2 months [95% CI (4.6, 8.1)] in the ofatumumab arm, respectively. Overall response rate as assessed by investigators in patients with del 17p was 88.9% in the IMBRUVICA arm versus 18.8% in the ofatumumab arm.

RESONATE-2

The RESONATE-2 study, a randomized, multicenter, open-label, phase 3 study of IMBRUVICA versus chlorambucil (NCT01722487), was conducted in patients with treatment naïve CLL or SLL who were 65 years of age or older. Patients (n = 269) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for a maximum of 12 cycles, with an allowance for intrapatient dose increases up to 0.8 mg/kg based on tolerability.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were White. Ninety one percent of patients had a baseline ECOG performance status of 0 or 1 and 9% had an ECOG performance status of 2. The trial enrolled 249 patients with CLL and 20 patients with SLL. At baseline, 20% of patients had 11q deletion. The most common reasons for initiating CLL therapy include: progressive marrow failure demonstrated by anemia and/or thrombocytopenia (38%), progressive or symptomatic lymphadenopathy (37%), progressive or symptomatic splenomegaly (30%), fatigue (27%) and night sweats (25%).

With a median follow-up of 28.1 months, there were 32 observed death events [11 (8.1%) and 21 (15.8%) in IMBRUVICA and chlorambucil treatment arms, respectively]. With 41% of patients switching from chlorambucil to IMBRUVICA, the overall survival analysis in the ITT patient population resulted in a statistically significant HR of 0.44 [95% CI (0.21, 0.92)] and 2-year survival rate estimates of 94.7% [95% CI (89.1, 97.4)] and 84.3% [95% CI (76.7, 89.6)] in the IMBRUVICA and chlorambucil arms, respectively.

Efficacy results for RESONATE-2 are shown in Table 23 and the Kaplan-Meier curve for PFS, assessed by an IRC according to IWCLL criteria is shown in Figure 3.

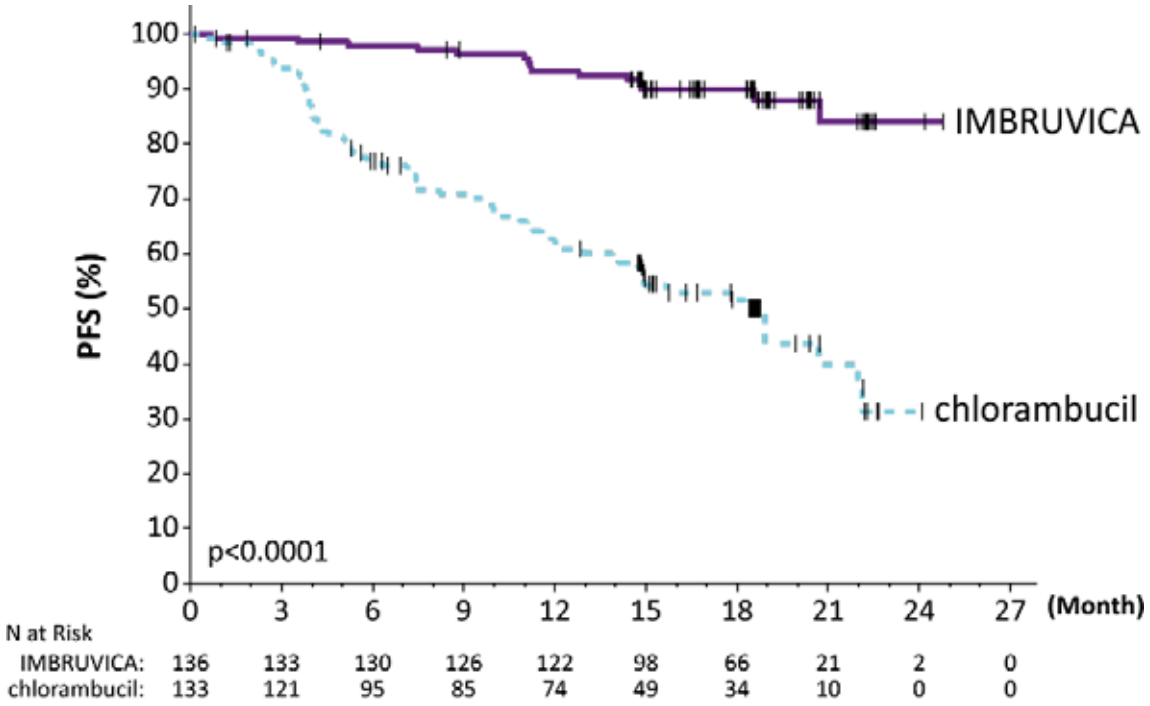
Table 23: Efficacy Results in Patients with CLL/SLL in RESONATE-2

Endpoint	IMBRUVICA N=136	Chlorambucil N=133
Progression Free Survival[a]		
Number of events (%)	15 (11.0)	64 (48.1)
Disease progression	12	57
Death events	3	7
Median (95% CI), months	NE	18.9 (14.1, 22.0)
HR[b] (95% CI)	0.16 (0.09, 0.28)	
Overall Response Rate[a] (CR + PR)	82.4%	35.3%
P-value	<0.0001	

[a] IRC evaluated; Five subjects (3.7%) in the IMBRUVICA arm and two subjects (1.5%) in the Chlorambucil arm achieved complete response

[b] HR = hazard ratio; NE = not evaluable

Figure 3: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL/SLL in RESONATE-2



55-Month Follow-Up

With an overall follow-up of 55 months, the median PFS was not reached in the IMBRUVICA arm.

HELIOS

The HELIOS study, a randomized, double-blind, placebo-controlled phase 3 study of IMBRUVICA in combination with bendamustine and rituximab (BR) (NCT01611090), was conducted in patients with previously treated CLL or SLL. Patients (n = 578) were randomized 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m^2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles, and all patients had a CLCr ≥ 40 mL/min at baseline. Rituximab was administered at a dose of 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1.

The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were White. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumor ≥ 5 cm and 26% presented with del11q.

Efficacy results for HELIOS are shown in Table 24 and the Kaplan-Meier curves for PFS are shown in Figure 4.

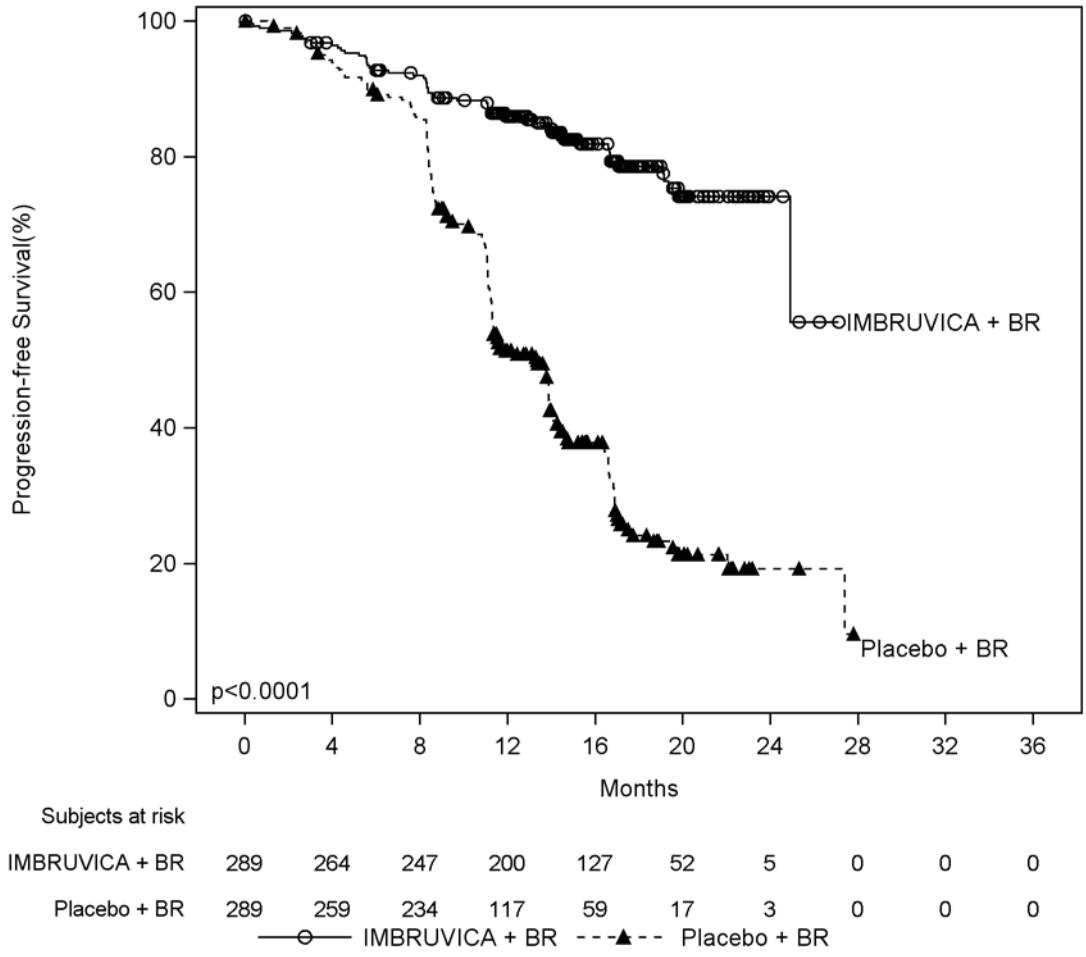
Table 24: Efficacy Results in Patients with CLL/SLL in HELIOS

Endpoint	IMBRUVICA + BR N=289	Placebo + BR N=289
Progression Free Survival[a]		
Number of events (%)	56 (19.4)	183 (63.3)
Median (95% CI), months	NE	13.3 (11.3, 13.9)
HR (95% CI)	0.20 (0.15, 0.28)	
Overall Response Rate[a]	82.7%	67.8%

[a] IRC evaluated, twenty-four subjects (8.3%) in the IMBRUVICA + BR arm and six subjects (2.1%) in the placebo + BR arm achieved complete response

BR = bendamustine and rituximab; CI = confidence interval; HR = hazard ratio; NE = not evaluable

Figure 4: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL/SLL in HELIOS



iLLUMINATE

The iLLUMINATE study, a randomized, multi-center, phase 3 study of IMBRUVICA in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab (NCT02264574), was conducted in patients with treatment naïve CLL or SLL. Patients were 65 years of age or older or < 65 years of age with coexisting medical conditions, reduced renal function as measured by creatinine clearance < 70 mL/min, or presence of del 17p/TP53 mutation. Patients (n = 229) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity or chlorambucil at a dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for 6 cycles. In both arms, patients received 1,000 mg of obinutuzumab on Days 1, 8, and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of obinutuzumab was divided between Day 1 (100 mg) and Day 2 (900 mg).

The median age was 71 years (range, 40 to 87 years), 64% were male, and 96% were White. All patients had a baseline ECOG performance status of 0 (48%) or 1-2 (52%). The trial enrolled 214 patients with CLL and 15 patients with SLL. At baseline, 65% of patients presented with

CLL/SLL with high risk factors (del 17p/TP53 mutation [18%], del 11q [15%], or unmutated immunoglobulin heavy-chain variable region (unmutated IGHV) [54%]). The most common reasons for initiating CLL therapy included: lymphadenopathy (38%), night sweats (34%), progressive marrow failure (31%), fatigue (29%), splenomegaly (25%), and progressive lymphocytosis (21%).

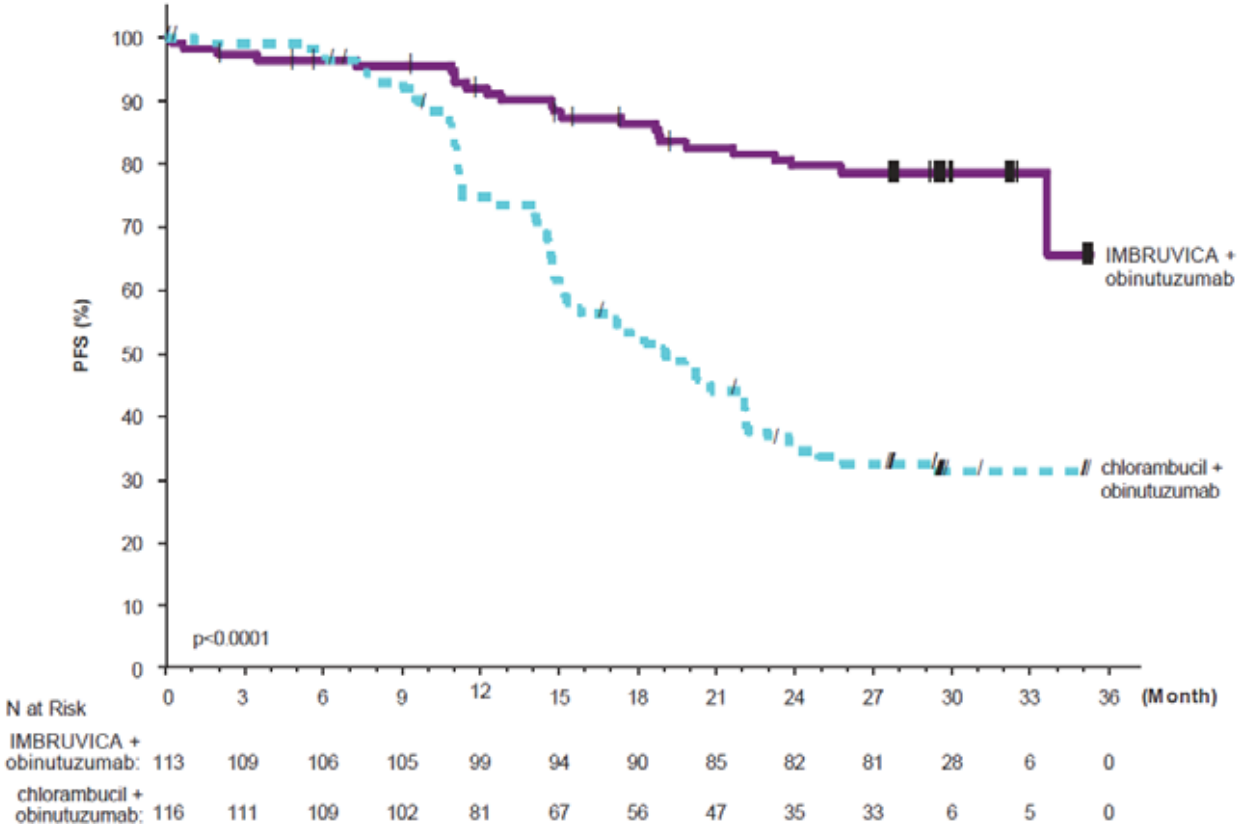
With a median follow-up time on study of 31 months, efficacy results for iLLUMINATE assessed by an IRC according to IWCLL criteria are shown in Table 25, and the Kaplan-Meier curve for PFS is shown in Figure 5.

Table 25: Efficacy Results in Patients with CLL/SLL in iLLUMINATE

Endpoint	IMBRUVICA + Obinutuzumab N=113	Chlorambucil + Obinutuzumab N=116
Progression Free Survival[a]		
Number of events (%)	24 (21)	74 (64)
Disease progression	11	64
Death events	13	10
Median (95% CI), months	NE	19.0 (15.1, 22.1)
HR (95% CI)	0.23 (0.15, 0.37)	
P-value[b]	<0.0001	
Overall Response Rate (%)[a]	88.5	73.3
CR[c] (%)	19.5	7.8
PR[d] (%)	69.0	65.5

[a] IRC-evaluated
[b] P-value is from unstratified log-rank test
[c] Includes 1 patient in the IMBRUVICA + obinutuzumab arm with a complete response with incomplete marrow recovery (CRi)
[d] PR = nPR +PR
HR = hazard ratio; NE = not evaluable

Figure 5: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL/SLL in iLLUMINATE



In the high risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), the PFS HR was 0.15 [95% CI (0.09, 0.27)].

E1912

The E1912 study, a randomized, multi-center, phase 3 study of IMBRUVICA in combination with rituximab versus standard fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy (NCT02048813), was conducted in adult patients who were 70 years or younger with previously untreated CLL or SLL requiring systemic therapy. All patients had a CLcr > 40 mL/min at baseline. Patients with 17p deletion were excluded. Patients (n =529) were randomized 2:1 to receive either IMBRUVICA plus rituximab or FCR. IMBRUVICA was administered at 420 mg daily until disease progression or unacceptable toxicity. Fludarabine was administered at a dose of 25 mg/m^2, and cyclophosphamide was administered at a dose of 250 mg/m^2, both on Days 1, 2, and 3 of Cycles 1-6. Rituximab was initiated in Cycle 2 for the IMBRUVICA plus rituximab arm and in Cycle 1 for the FCR arm and was administered at 50 mg/m^2 on Day 1 of the first cycle, 325 mg/m^2 on Day 2 of the first cycle, and 500 mg/m^2 on Day 1 of 5 subsequent cycles, for a total of 6 cycles. Each cycle was 28 days.

The median age was 58 years (range, 28 to 70 years), 67% were male, 90% were White and 98% had a ECOG performance status of 0-1. At baseline, 43% of patients were Rai stage 3 or 4 and

59% of patients presented with high risk factors (TP53 mutation [6%], del11q [22%], or unmutated IGHV [53%]).

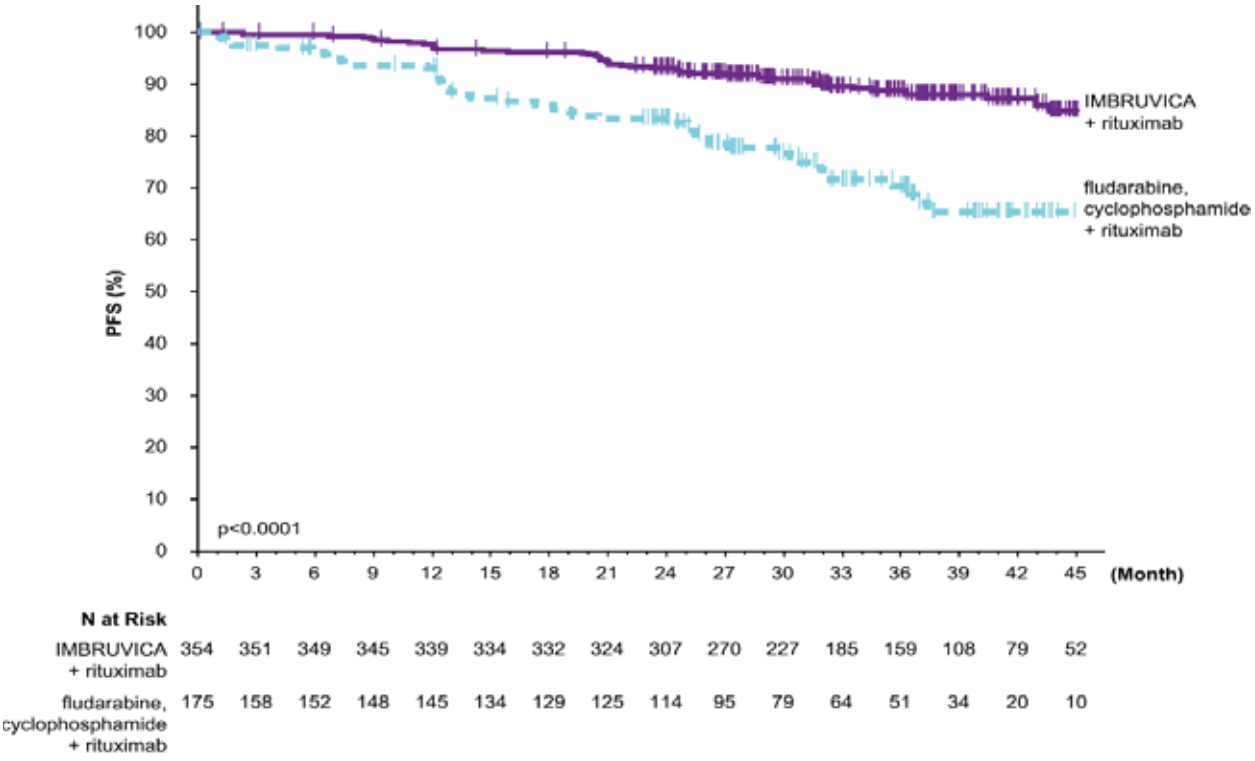
With a median follow-up time on study of 37 months, efficacy results for E1912 are shown in Table 26. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria is shown in Figure 6.

Table 26: Efficacy Results in Patients with CLL/SLL in E1912

Endpoint	IMBRUVICA + R N=354	FCR N=175
Progression Free Survival		
Number of events (%)	41 (12)	44 (25)
Disease progression	39	38
Death events	2	6
Median (95% CI), months	NE (49.4, NE)	NE (47.1, NE)
HR (95% CI)	0.34 (0.22, 0.52)	
P-value[a]	<0.0001	

[a] P-value is from unstratified log-rank test.
FCR = fludarabine, cyclophosphamide, and rituximab; HR = hazard ratio; R = rituximab; NE = not evaluable

Figure 6: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with CLL/SLL in E1912



With a median follow-up time on study of 49 months, median overall survival was not reached with a total of 23 deaths: 11 (3%) in the IMBRUVICA plus rituximab and 12 (7%) in the FCR treatment arms.

Lymphocytosis

Upon initiation of single-agent IMBRUVICA, an increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 66% of patients in the CLL studies. The onset of isolated lymphocytosis occurs during the first month of IMBRUVICA therapy and resolves by a median of 14 weeks (range, 0.1 to 104 weeks). When IMBRUVICA was administered in combination, lymphocytosis was 7% with IMBRUVICA + BR versus 6% with placebo + BR and 7% with IMBRUVICA + obinutuzumab versus 1% with chlorambucil + obinutuzumab.

14.3 Waldenström's Macroglobulinemia

The safety and efficacy of IMBRUVICA in patients with WM were demonstrated in two single-arm trials and one randomized, controlled trial.

Study 1118 and INNOVATE Monotherapy Arm

Study 1118 (NCT01614821), an open-label, multi-center, single-arm trial was conducted in 63 previously treated patients with WM. IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The responses were assessed by investigators and an IRC using criteria adopted from the International Workshop of Waldenström's Macroglobulinemia.

The median age was 63 years (range, 44 to 86 years), 76% were male, and 95% were White. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL (range, 0.7 to 8.4 g/dL).

Responses, defined as partial response or better, per IRC are shown in Table 27.

Table 27: Response Rate and Duration of Response (DOR) Based on IRC Assessment in Patients with WM in Study 1118

	Total (N=63)
Response rate (CR+VGPR+PR), (%)	61.9
95% CI (%)	(48.8, 73.9)
Complete Response (CR)	0
Very Good Partial Response (VGPR), (%)	11.1
Partial Response (PR), (%)	50.8
Median duration of response, months (range)	NE (2.8+, 18.8+)

CI = confidence interval; NE = not evaluable

The median time to response was 1.2 months (range, 0.7-13.4 months).

The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received single-agent IMBRUVICA. The median age was 67 years (range, 47 to 90 years). Eighty-one percent of patients had a baseline ECOG performance status of 0 or 1, and 19% had a baseline ECOG performance status of 2. The median number of prior treatments was 4 (range, 1 to 7 treatments). With an overall follow-up of 61 months, the response rate observed in the INNOVATE monotherapy arm per IRC assessment was 77% (0% CR, 29% VGPR, 48% PR). The median duration of response was 33 months (range, 2.4 to 60.2+ months).

INNOVATE

The INNOVATE study, a randomized, double-blind, placebo-controlled, phase 3 study of IMBRUVICA or placebo in combination with rituximab (NCT02165397), was conducted in treatment naïve or previously treated patients with WM. Patients (n = 150) were randomized 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with rituximab until disease progression or unacceptable toxicity. Rituximab was administered weekly at a dose of 375 mg/m^2 for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20). The major efficacy outcome measure is progression-free survival (PFS) assessed by an IRC with additional efficacy measure of response rate.

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were White. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment naïve, and 55% of patients were previously treated. Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status.

An exploratory analysis demonstrated a sustained hemoglobin improvement (defined as increase of ≥ 2 g/dL over baseline for at least 8 weeks without blood transfusions or growth factor support) in 65% of patients in the IMBRUVICA + R group and 39% of patients in the placebo + R group.

With an overall follow-up of 63 months, efficacy results as assessed by an IRC at the time of the final analysis for INNOVATE are shown in Table 28, and the Kaplan-Meier curves for PFS are shown in Figure 7.

Table 28: Efficacy Results in Patients with WM by IRC in INNOVATE (Final Analysis)

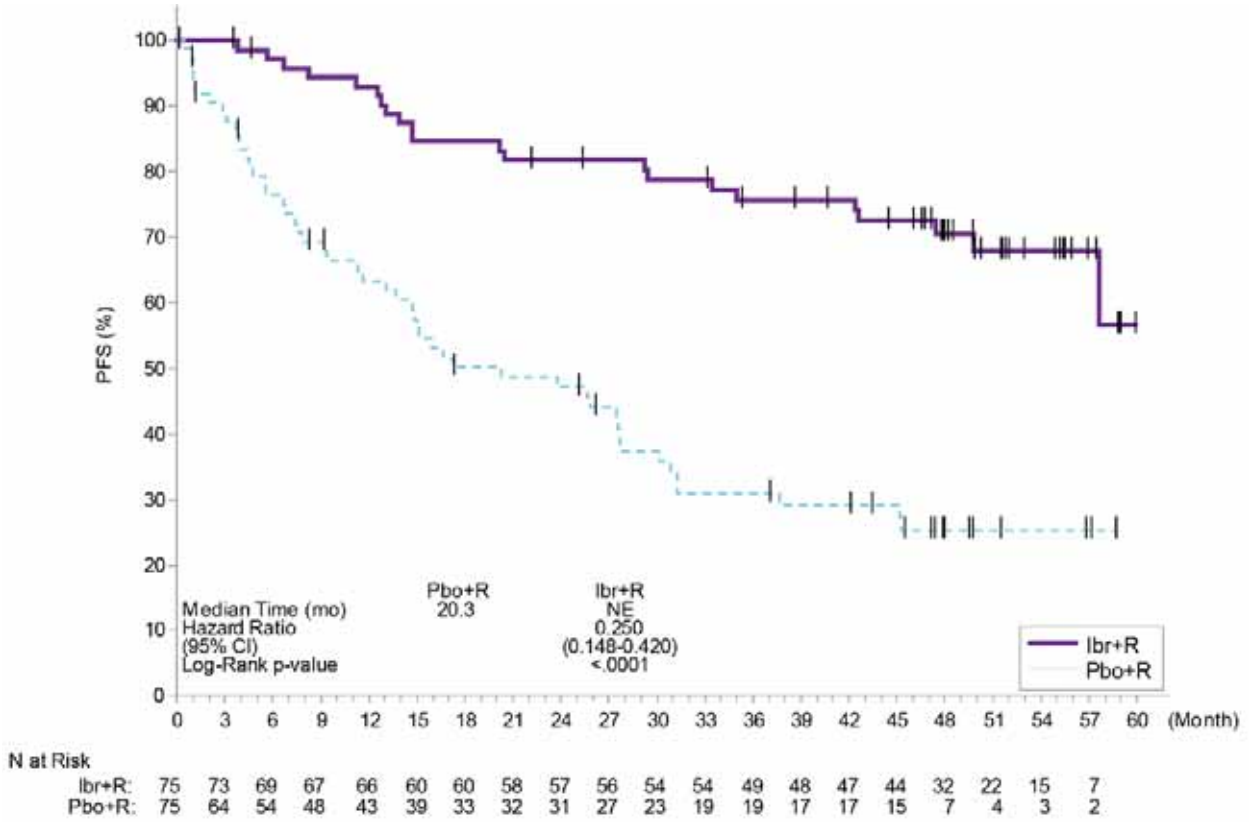
Endpoint	IMBRUVICA + R N=75	Placebo + R N=75
Progression Free Survival		
Number of events (%)	22 (29)	50 (67)
Median (95% CI), months	NE (57.7, NE)	20.3 (13.0, 27.6)
HR (95% CI)	0.25 (0.15, 0.42)	
P-value[a]	<0.0001	
Response Rate (CR+VGPR+PR)[b]	76%	31%
95% CI (%)	(65, 85)	(21, 42)
Complete Response (CR)	1%	1%
Very Good Partial Response (VGPR)	29%	4%
Partial Response (PR)	45%	25%
Median duration of response, months (range)	NE (1.9+, 58.9+)	NE (4.6+, 49.7+)

CI = confidence interval; HR = hazard ratio; NE = not evaluable; R = rituximab

[a] P-value is from the stratified log-rank test

[b] P-value associated with response rate was <0.0001

Figure 7: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Patients with WM in INNOVATE



Median overall survival was not reached for either treatment arm. With an overall follow-up of 63 months, 9 (12%) patients on IMBRUVICA + R and 10 (13.3%) patients on placebo + R had died. Forty-seven percent of patients randomized to the placebo + R arm crossed over to receive IMBRUVICA.

14.4 Marginal Zone Lymphoma

The safety and efficacy of IMBRUVICA in MZL were evaluated in Study 1121 (NCT01980628), an open-label, multi-center, single-arm trial of patients who received at least one prior therapy. IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. The responses were assessed by investigators and an IRC using criteria adopted from the International Working Group criteria for malignant lymphoma.

The efficacy analysis included 63 patients with 3 sub-types of MZL: mucosa-associated lymphoid tissue (MALT; N=32), nodal (N=17), and splenic (N=14). The median age was 66 years (range, 30 to 92 years), 59% were female, and 84% were White. Ninety two percent of patients had a baseline ECOG performance status of 0 or 1 and 8% had ECOG performance status 2. The median time since diagnosis was 3.8 years, and the median number of prior treatments was 2 (range, 1 to 9 treatments).

Responses per IRC are shown in Table 29.

Table 29: Overall Response Rate (ORR) and Duration of Response (DOR) Based on IRC Assessment in Patients with MZL in Study 1121

	Total (N=63)
Response rate (CR + PR), (%)	46.0%
95% CI (%)	(33.4, 59.1)
Complete Response (CR), (%)	3.2
Partial Response (PR), (%)	42.9
Median duration of response, months (range)	NE (16.7, NE)

CI = confidence interval; NE = not evaluable
Median follow-up time on study = 19.4 months

The median time to response was 4.5 months (range, 2.3 to 16.4 months). Overall response rates were 46.9%, 41.2%, and 50.0% for the 3 MZL sub-types (MALT, nodal, splenic), respectively.

14.5 Chronic Graft versus Host Disease

The safety and efficacy of IMBRUVICA in cGVHD were evaluated in Study 1129 (NCT02195869), an open-label, multi-center, single-arm trial of 42 patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. IMBRUVICA was administered orally at 420 mg once daily. The responses were assessed by investigators using the 2005 National Institute of Health (NIH) Consensus Panel Response Criteria with two modifications to align with the updated 2014 NIH Consensus Panel Response Criteria.

The median age was 56 years (range, 19 to 74 years), 52% were male, and 93% were White. The most common underlying malignancies leading to transplantation were acute lymphocytic

leukemia, acute myeloid leukemia, and CLL. The median time since cGVHD diagnosis was 14 months, the median number of prior cGVHD treatments was 2 (range, 1 to 3 treatments), and 60% of patients had a Karnofsky performance score of ≤ 80. The majority of patients (88 %) had at least 2 organs involved at baseline, with the most commonly involved organs being mouth (86%), skin (81%), and gastrointestinal tract (33%). The median daily corticosteroid dose (prednisone or prednisone equivalent) at baseline was 0.3 mg/kg/day, and 52% of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections were managed per institutional guidelines with 79% of patients receiving combinations of sulfonamides and trimethoprim and 64% receiving triazole derivatives.

Efficacy results are shown in Table 30.

Table 30: Best Overall Response Rate (ORR) and Sustained Response Rate Based on Investigator Assessment[a] in Patients with cGVHD in Study 1129

	Total (N=42)
ORR	28 (67%)
95% CI	(51%, 80%)
Complete Response (CR)	9 (21%)
Partial Response (PR)	19 (45%)
Sustained response rate[b]	20 (48%)

CI = confidence interval

[a] Investigator assessment based on the 2005 NIH Response Criteria with two modifications (added "not evaluable" for organs with non-cGVHD abnormalities, and organ score change from 0 to 1 was not considered disease progression)

[b] Sustained response rate is defined as the proportion of patients who achieved a CR or PR that was sustained for at least 20 weeks.

The median time to response coinciding with the first scheduled response assessment was 12.3 weeks (range, 4.1 to 42.1 weeks). Responses were seen across all organs involved for cGVHD (skin, mouth, gastrointestinal tract, and liver).

ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in Lee Symptom Scale overall summary score in 24% (10/42) of patients on at least 2 consecutive visits.

16 HOW SUPPLIED/STORAGE AND HANDLING

Capsules

The 70 mg capsules are supplied as yellow opaque capsules, marked with "ibr 70 mg" in black ink, in white HDPE bottles with a child-resistant closure:

- 28 capsules per bottle: NDC 57962-070-28

The 140 mg capsules are supplied as white opaque capsules, marked with "ibr 140 mg" in black ink, in white HDPE bottles with a child-resistant closure:

- 90 capsules per bottle: NDC 57962-140-09

- 120 capsules per bottle: NDC 57962-140-12

Store bottles at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F). Retain in original package until dispensing.

Tablets

The IMBRUVICA (ibrutinib) tablets are supplied in 4 strengths in the following packaging configurations:

- 140 mg tablets: Yellow green to green round tablets debossed with “ibr” on one side and “140” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-014-28
- 280 mg tablets: Purple oblong tablets debossed with “ibr” on one side and “280” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-280-28
- 420 mg tablets: Yellow green to green oblong tablets debossed with “ibr” on one side and “420” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-420-28
- 560 mg tablets: Yellow to orange oblong tablets debossed with “ibr” on one side and “560” on the other side. Carton of one folded blister card containing two 14-count blister strips for a total of 28 tablets: NDC 57962-560-28

Store tablets in original packaging at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions (5.1)]*.
- *Infections:*
  Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions (5.2)]*.
- *Cardiac arrhythmias and cardiac failure:*
  Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema *[see Warnings and Precautions (5.4)]*.
- *Hypertension:*

Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions* (5.5)].

- *Second primary malignancies:*
  Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions (5.6)]*.
- *Tumor lysis syndrome:*
  Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions (5.7)]*.
- *Embryo-fetal toxicity:*
  Advise women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

  Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose *[see Use in Specific Populations (8.3)]*.

  Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.
- *Lactation:*

  Advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day *[see Dosage and Administration (2.1)]*.
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose *[see Dosage and Administration (2.1)]*.
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions (6)]*. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7)]*.

- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration *[see Adverse Reactions (6.1)]*.

Active ingredient made in China.

Distributed and Marketed by:
Pharmacyclics LLC
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent *http://www.imbruvica.com*
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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 140 mg of ibrutinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

White opaque, hard capsule of 22 mm in length, marked with “ibr 140 mg” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMBRUVICA as a single agent is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

IMBRUVICA as a single agent or in combination with rituximab or obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

IMBRUVICA as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

IMBRUVICA as a single agent is indicated for the treatment of adult patients with Waldenström’s macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with WM.

4.2 Posology and method of administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology
MCL
The recommended dose for the treatment of MCL is 560 mg (four capsules) once daily.

CLL and WM
The recommended dose for the treatment of CLL and WM, either as a single agent or in combination, is 420 mg (three capsules) once daily (for details of the combination regimens, see section 5.1).

Treatment should continue until disease progression or no longer tolerated by the patient.

When administering IMBRUVICA in combination with anti-CD20 therapy, it is recommended to administer IMBRUVICA prior to anti-CD20 therapy when given on the same day.

Dose adjustments
Moderate and strong CYP3A4 inhibitors increase the exposure of ibrutinib (see sections 4.4 and 4.5).

The dose of ibrutinib should be reduced to 280 mg once daily (two capsules) when used concomitantly with moderate CYP3A4 inhibitors.

The dose of ibrutinib should be reduced to 140 mg once daily (one capsule) or withheld for up to 7 days when it is used concomitantly with strong CYP3A4 inhibitors.

IMBRUVICA therapy should be withheld for any new onset or worsening grade ≥3 non-haematological toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, the once daily dose should be reduced by one capsule (140 mg). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue the medicinal product.

Recommended dose modifications are described below:

Toxicity occurrence	**MCL dose modification after recovery**	**CLL/WM dose modification after recovery**
First	restart at 560 mg daily	restart at 420 mg daily
Second	restart at 420 mg daily	restart at 280 mg daily
Third	restart at 280 mg daily	restart at 140 mg daily
Fourth	discontinue IMBRUVICA	discontinue IMBRUVICA

Missed dose
If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose.

Special populations
Elderly
No specific dose adjustment is required for elderly patients (aged ≥65 years).

Renal impairment
No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in IMBRUVICA clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained and serum creatinine levels monitored periodically. Administer IMBRUVICA to patients with severe renal impairment (<30 mL/min creatinine clearance) only if the benefit outweighs the risk and monitor patients closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis (see section 5.2).

Hepatic impairment
Ibrutinib is metabolised in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure (see section 5.2). For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with severe hepatic impairment (Child-Pugh class C).

Severe cardiac disease
Patients with severe cardiovascular disease were excluded from IMBRUVICA clinical studies.

Paediatric population
The safety and efficacy of IMBRUVICA in children and adolescents aged 0 to 18 years have not been established. No data are available.

Method of administration
IMBRUVICA should be administered orally once daily with a glass of water approximately at the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. IMBRUVICA must not be taken with grapefruit juice or Seville oranges (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use of preparations containing St. John's Wort is contraindicated in patients treated with IMBRUVICA.

4.4 Special warnings and precautions for use

Bleeding-related events
There have been reports of bleeding events in patients treated with IMBRUVICA, both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial haemorrhage, and haematuria.

Warfarin or other vitamin K antagonists should not be administered concomitantly with IMBRUVICA.

Use of either anticoagulants or medicinal products that inhibit platelet function (antiplatelet agents) concomitantly with IMBRUVICA increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Supplements such as fish oil and vitamin E preparations should be avoided.

IMBRUVICA should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

The mechanism for the bleeding-related events is not fully understood. Patients with congenital bleeding diathesis have not been studied.

Leukostasis
Cases of leukostasis have been reported in patients treated with IMBRUVICA. A high number of circulating lymphocytes (>400,000/mcL) may confer increased risk. Consider temporarily withholding IMBRUVICA. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Splenic rupture
Cases of splenic rupture have been reported following discontinuation of IMBRUVICA treatment. Disease status and spleen size should be carefully monitored (e.g. clinical examination, ultrasound) when IMBRUVICA treatment is interrupted or ceased. Patients who develop left upper abdominal or shoulder tip pain should be evaluated and a diagnosis of splenic rupture should be considered.

Infections
Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) were observed in patients treated with IMBRUVICA. Some of these infections have been associated with hospitalisation

and death. Most patients with fatal infections also had neutropenia. Patients should be monitored for fever, abnormal liver function tests, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Cases of invasive fungal infections, including cases of Aspergillosis, Cryptococcosis and Pneumocystis jiroveci infections have been reported following the use of ibrutinib. Reported cases of invasive fungal infections have been associated with fatal outcomes.

Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of ibrutinib within the context of a prior or concomitant immunosuppressive therapy. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.

Cases of hepatitis E, which may be chronic, have occurred in patients treated with IMBRUVICA.

Cytopenias
Treatment-emergent grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients treated with IMBRUVICA. Monitor complete blood counts monthly.

Interstitial Lung Disease (ILD)
Cases of ILD have been reported in patients treated with IMBRUVICA. Monitor patients for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt IMBRUVICA and manage ILD appropriately. If symptoms persist, consider the risks and benefits of IMBRUVICA treatment and follow the dose modification guidelines.

Cardiac arrhythmia and cardiac failure
Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia and cardiac failure have been reported in patients treated with IMBRUVICA. Cases of atrial fibrillation and atrial flutter have been reported particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor all patients clinically for cardiac manifestations, including cardiac arrhythmia and cardiac failure. Patients who develop arrhythmic symptoms or new onset of dyspnoea, dizziness or fainting should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed.

In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, IMBRUVICA should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.

In patients with preexisting atrial fibrillation requiring anticoagulant therapy, alternative treatment options to IMBRUVICA should be considered. In patients who develop atrial fibrillation on therapy with IMBRUVICA a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to IMBRUVICA are non-suitable, tightly controlled treatment with anticoagulants should be considered.

Patients should be monitored for signs and symptoms of cardiac failure during IMBRUVICA treatment. In some of these cases cardiac failure resolved or improved after IMBRUVICA withdrawal or dose reduction.

Cerebrovascular accidents
Cases of cerebrovascular accident, transient ischaemic attack and ischaemic stroke including fatalities have been reported in patients treated with IMBRUVICA, with and without concomitant atrial fibrillation and/or hypertension. Among cases with reported latency, the initiation of treatment with

IMBRUVICA to the onset of ischaemic central nervous vascular conditions was in the most cases after several months (more than 1 month in 78% and more than 6 months in 44% of cases) emphasising the need for regular monitoring of patients (please see section 4.4 Cardiac arrhythmia and Hypertension and section 4.8).

Tumour lysis syndrome
Tumour lysis syndrome has been reported with IMBRUVICA therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions.

Non-melanoma skin cancer
Non-melanoma skin cancers were reported more frequently in patients treated with IMBRUVICA than in patients treated with comparators in pooled comparative randomised phase 3 studies. Monitor patients for the appearance of non-melanoma skin cancer.

Viral reactivation
Cases of hepatitis B reactivation, including fatal events, have been reported in patients receiving IMBRUVICA. Hepatitis B virus (HBV) status should be established before initiating treatment with IMBRUVICA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Hypertension
Hypertension has occurred in patients treated with IMBRUVICA (see section 4.8). Regularly monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust antihypertensive medication throughout treatment with IMBRUVICA as appropriate.

Haemophagocytic lymphohistiocytosis (HLH)
Cases of HLH (including fatal cases) have been reported in patients treated with IMBRUVICA. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of extreme systemic inflammation. HLH is characterised by fever, hepatosplenomegaly, hypertriglyceridaemia, high serum ferritin and cytopenias. Patients should be informed about symptoms of HLH. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered.

Drug-drug interactions
Co-administration of strong or moderate CYP3A4 inhibitors with IMBRUVICA may lead to increased ibrutinib exposure and consequently a higher risk for toxicity. On the contrary, co-administration of CYP3A4 inducers may lead to decreased IMBRUVICA exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of IMBRUVICA with strong CYP3A4 inhibitors and strong or moderate CYP3A4 inducers should be avoided whenever possible and co-administration should only be considered when the potential benefits clearly outweigh the potential risks. Patients should be closely monitored for signs of IMBRUVICA toxicity if a CYP3A4 inhibitor must be used (see sections 4.2 and 4.5). If a CYP3A4 inducer must be used, closely monitor patients for signs of IMBRUVICA lack of efficacy.

Women of childbearing potential
Women of childbearing potential must use a highly effective method of contraception while taking IMBRUVICA (see section 4.6).

Excipients with known effect
Each capsule contains less than 1 mmol sodium (23 mg), and is essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Ibrutinib is primarily metabolised by cytochrome P450 enzyme 3A4 (CYP3A4).

Agents that may increase ibrutinib plasma concentrations
Concomitant use of IMBRUVICA and medicinal products that strongly or moderately inhibit CYP3A4 can increase ibrutinib exposure and strong CYP3A4 inhibitors should be avoided.

Strong CYP3A4 inhibitors
Co-administration of ketoconazole, a very strong CYP3A4 inhibitor, in 18 fasted healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by 29- and 24-fold, respectively. Simulations using fasted conditions suggested that the strong CYP3A4 inhibitor clarithromycin may increase the AUC of ibrutinib by a factor of 14. In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the strong CYP3A4 inhibitor voriconazole increased C_{max} by 6.7-fold and AUC by 5.7-fold. Strong inhibitors of CYP3A4 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodon, cobicistat, voriconazole and posaconazole) should be avoided. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the IMBRUVICA dose to 140 mg (one capsule) for the duration of the inhibitor use or withhold IMBRUVICA temporarily (for 7 days or less). Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Moderate CYP3A4 inhibitors
In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the CYP3A4 inhibitor erythromycin increased C_{max} by 3.4-fold and AUC by 3.0-fold. If a moderate CYP3A4 inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone and dronedarone) is indicated, reduce IMBRUVICA dose to 280 mg (two capsules) for the duration of the inhibitor use. Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Mild CYP3A4 inhibitors
Simulations using fasted conditions suggested that the mild CYP3A4 inhibitors azithromycin and fluvoxamine may increase the AUC of ibrutinib by <2-fold. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed.

Co-administration of grapefruit juice, containing CYP3A4 inhibitors, in eight healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by approximately 4- and 2-fold, respectively. Grapefruit and Seville oranges should be avoided during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A4 (see section 4.2).

Agents that may decrease ibrutinib plasma concentrations
Administration of IMBRUVICA with inducers of CYP3A4 can decrease ibrutinib plasma concentrations.

Co-administration of rifampicin, a strong CYP3A4 inducer, in 18 fasted healthy subjects, decreased exposure (C_{max} and AUC) of ibrutinib by 92 and 90%, respectively. Avoid concomitant use of strong or moderate CYP3A4 inducers (e.g., carbamazepine, rifampicin, phenytoin). Preparations containing St. John's Wort are contraindicated during treatment with IMBRUVICA, as efficacy may be reduced. Consider alternative agents with less CYP3A4 induction. If the benefit outweighs the risk and a strong or moderate CYP3A4 inducer must be used, monitor patient closely for lack of efficacy (see sections 4.3 and 4.4). Mild inducers may be used concomitantly with IMBRUVICA, however, patients should be monitored for potential lack of efficacy.

Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. A lower C_{max} was observed in fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days (see section 5.2). There is no evidence that the lower C_{max} would have clinical significance, and medicinal products that increase stomach pH (e.g., proton pump inhibitors) have been used without restrictions in the pivotal clinical studies.

Agents that may have their plasma concentrations altered by ibrutinib
Ibrutinib is a P-gp and breast cancer resistance protein (BCRP) inhibitor *in vitro*. As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. To minimise the potential for an interaction in the GI tract, oral narrow therapeutic range, P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after IMBRUVICA. Ibrutinib may also inhibit BCRP in the liver and increase the exposure of medicinal products that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

In a drug interaction study in patients with B-cell malignancies, a single 560 mg dose of ibrutinib did not have a clinically meaningful effect on the exposure of the CYP3A4 substrate midazolam. In the same study, 2 weeks of treatment with ibrutinib at 560 mg daily had no clinically relevant effect on the pharmacokinetics of oral contraceptives (ethinylestradiol and levonorgestrel), the CYP3A4 substrate midazolam, nor the CYP2B6 substrate bupropion.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in females
Based on findings in animals, IMBRUVICA may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking IMBRUVICA and for three months after stopping treatment.

Pregnancy
IMBRUVICA should not be used during pregnancy. There are no data from the use of IMBRUVICA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding
It is not known whether ibrutinib or its metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with IMBRUVICA.

Fertility
No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED] 16 mg/kg/day) (see section 5.3). No human data on the effects of ibrutinib on fertility are available.

4.7 Effects on ability to drive and use machines

IMBRUVICA has minor influence on the ability to drive and use machines.

Fatigue, dizziness and asthenia have been reported in some patients taking IMBRUVICA and should be considered when assessing a patient's ability to drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly occurring adverse reactions (≥20%) were diarrhoea, neutropenia, musculoskeletal pain, rash, haemorrhage (e.g., bruising), thrombocytopenia, nausea, pyrexia, arthralgia, and upper respiratory tract infection. The most common grade 3/4 adverse reactions (≥5%) were neutropenia, lymphocytosis, thrombocytopenia, pneumonia, and hypertension.

Tabulated list of adverse reactions
The safety profile is based on pooled data from 1552 patients treated with IMBRUVICA in three phase 2 clinical studies and seven randomised phase 3 studies and from post-marketing experience. Patients treated for MCL in clinical studies received IMBRUVICA at 560 mg once daily and patients treated for CLL or WM in clinical studies received IMBRUVICA at 420 mg once daily. All patients in clinical studies received IMBRUVICA until disease progression or no longer tolerated. The median

duration of IMBRUVICA treatment across the pooled dataset was 17.4 months. The median duration of treatment for CLL/SLL was 18.2 months (up to 52 months); MCL was 11.7 months (up to 28 months); WM was 21.6 months (up to 37 months).

Adverse reactions in patients treated with ibrutinib for B-cell malignancies and post-marketing adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported in clinical studies or during post marketing surveillance in patients with B-cell malignancies[†]

System organ class	Frequency (All grades)	Adverse reactions	All Grades (%)	Grade ≥3 (%)
Infections and infestations	Very common	Pneumonia[*#]	14	8
		Upper respiratory tract infection	20	1
		Skin infection[*]	15	3
	Common	Sepsis[*#]	4	3
		Urinary tract infection	9	2
		Sinusitis[*]	10	1
	Uncommon	Cryptococcal infections[*]	<1	0
		Pneumocystis infections[*#]	1	<1
		Aspergillus infections[*]	<1	<1
		Hepatitis B reactivation[@#]	<1	<1
Neoplasms benign and malignant (incl cysts and polyps)	Common	Non-melanoma skin cancer[*]	6	1
		Basal cell carcinoma	4	<1
		Squamous cell carcinoma	2	<1
Blood and lymphatic system disorders	Very common	Neutropenia[*]	38	29
		Thrombocytopenia[*]	32	9
		Lymphocytosis[*]	19	14
	Common	Febrile neutropenia	4	4
		Leukocytosis	5	4
	Rare	Leukostasis syndrome	<1	<1
Immune system disorders	Common	Interstitial lung disease[*,#,a]	2	<1
Metabolism and nutrition disorders	Very common	Hyperuricaemia	10	1
	Uncommon	Tumour lysis syndrome[a]	1	1
Nervous system disorders	Very common	Dizziness	12	<1
		Headache	19	1
	Common	Peripheral neuropathy[*,a]	8	<1
	Uncommon	Cerebrovascular accident[a,#]	<1	<1
		Transient ischaemic attack[a]	<1	<1
	Rare	Ischaemic stroke[a,#]	<1	<1
Eye disorders	Common	Vision blurred	7	0
Cardiac disorders	Common	Cardiac failure[a,*,#]	2	1
		Atrial fibrillation	7	4
		Ventricular tachyarrhythmia[*,a,#]	1	<1
Vascular disorders	Very common	Haemorrhage[*#]	32	1
		Bruising[*]	25	1
		Hypertension[*]	18	8
	Common	Epistaxis	8	<1
		Petechiae	6	0
	Uncommon	Subdural haematoma[#]	1	<1

Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation	42 14 14 28 16	3 1 1 1 <1
Hepatobiliary disorders	Uncommon	Hepatic failure*,a #	<1	<1
Skin and subcutaneous tissue disorders	Very common	Rash*	35	3
	Common	Urticaria[a] Erythema[a] Onychoclasis[a]	1 2 3	<1 0 0
	Uncommon	Angioedema[a] Panniculitis*,a Neutrophilic dermatoses*, a	<1 <1 <1	<1 <1 <1
	Not known	Stevens-Johnson syndrome[a]	Not known	Not known
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Muscle spasms Musculoskeletal pain*	20 14 37	2 <1 3
General disorders and administration site conditions	Very common	Pyrexia Oedema peripheral	22 18	1 1
Investigations	Very common	Blood creatinine increased	11	<1

† Frequencies are rounded to the nearest integer.

* Includes multiple adverse reaction terms.

Includes events with fatal outcome.

@ Lower level term (LLT) used for selection.

a Spontaneous reports from post-marketing experience.

Description of selected adverse reactions

Discontinuation and dose reduction due to adverse reactions

Of the 1552 patients treated with IMBRUVICA for B-cell malignancies, 6% discontinued treatment primarily due to adverse reactions. These included pneumonia, atrial fibrillation, thrombocytopenia, haemorrhage, neutropenia, rash, and arthralgia. Adverse reactions leading to dose reduction occurred in approximately 8% of patients.

Elderly

Of the 1552 patients treated with IMBRUVICA, 52% were 65 years of age or older. Grade 3 or higher pneumonia (12% of patients age ≥65 versus 5% of patients <65 years) and thrombocytopenia (12% of patients age ≥65 years versus 6% of patients <65 years) occurred more frequently among elderly patients treated with IMBRUVICA.

Long-term safety

The safety data from long-term treatment with IMBRUVICA over 5 years from 1284 patients (treatment-naïve CLL/SLL n = 162, relapsed/refractory CLL/SLL n = 646, relapsed/refractory MCL n = 370, and WM n = 106) were analysed. The median duration of treatment for CLL/SLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of patients receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of patients receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for WM was 47 months (range, 0.3 to 61 months) with 78% and 46% of patients receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of IMBRUVICA-exposed patients remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall incidence for the 5-year period was 11%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are limited data on the effects of IMBRUVICA overdose. No maximum tolerated dose was reached in the phase 1 study in which patients received up to 12.5 mg/kg/day (1,400 mg/day). In a separate study, one healthy subject who received a dose of 1,680 mg experienced reversible grade 4 hepatic enzyme increases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. There is no specific antidote for IMBRUVICA. Patients who ingested more than the recommended dose should be closely monitored and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EL01.

Mechanism of action
Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including MCL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and CLL. BTK's pivotal role in signalling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis and adhesion. Preclinical studies have shown that ibrutinib effectively inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

Lymphocytosis
Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count >5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in about three fourths of patients with CLL treated with IMBRUVICA. This effect has also been observed in about one third of patients with relapsed or refractory MCL treated with IMBRUVICA. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of IMBRUVICA therapy and typically resolves within a median of 8.0 weeks in patients with MCL and 14 weeks in patients with CLL. A large increase in the number of circulating lymphocytes (e.g., >400,000/mcL) has been observed in some patients.

Lymphocytosis was not observed in patients with WM treated with IMBRUVICA.

In vitro platelet aggregation
In an *in vitro* study, ibrutinib demonstrated inhibition of collagen-induced platelet aggregation. Ibrutinib did not show meaningful inhibition of platelet aggregation using other agonists of platelet aggregation.

Effect on QT/QTc interval and cardiac electrophysiology
The effect of ibrutinib on the QTc interval was evaluated in 20 healthy male and female subjects in a randomised, double-blind thorough QT study with placebo and positive controls. At a supratherapeutic dose of 1,680 mg, ibrutinib did not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the baseline adjusted mean differences between ibrutinib and placebo was below 10 ms. In this same study, a concentration dependent shortening in the QTc interval was observed (-5.3 ms [90% CI: -9.4, -1.1] at a C_{max} of 719 ng/mL following the supratherapeutic dose of 1,680 mg).

Clinical efficacy and safety

MCL

The safety and efficacy of IMBRUVICA in patients with relapsed or refractory MCL were evaluated in a single open-label, multi-center phase 2 study (PCYC-1104-CA) of 111 patients. The median age was 68 years (range: 40 to 84 years), 77% were male and 92% were Caucasian. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater were excluded from the study. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range: 1 to 5 treatments), including 35% with prior high-dose chemotherapy, 43% with prior bortezomib, 24% with prior lenalidomide, and 11% with prior autologous or allogeneic stem cell transplant. At baseline, 39% of patients had bulky disease (≥5 cm), 49% had high-risk score by Simplified MCL International Prognostic Index (MIPI), and 72% had advanced disease (extranodal and/or bone marrow involvement) at screening.

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumour response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to IMBRUVICA are shown in Table 2.

Table 2: ORR and DOR in patients with relapsed or refractory MCL (Study PCYC-1104-CA)

	Total N=111
ORR (%)	67.6
95% CI (%)	(58.0; 76.1)
CR (%)	20.7
PR (%)	46.8
Median DOR (CR+PR) (months)	17.5 (15.8, NR)
Median time to initial response, months (range)	1.9 (1.4-13.7)
Median time to CR, months (range)	5.5 (1.7-11.5)

CI=confidence interval; CR=complete response; DOR=duration of response; ORR=overall response rate; PR=partial response; NR=not reached

The efficacy data was further evaluated by an Independent Review Committee (IRC) demonstrating an ORR of 69%, with a 21% complete response (CR) rate and a 48% partial response (PR) rate. The IRC estimated median DOR was 19.6 months.

The overall response to IMBRUVICA was independent of prior treatment including bortezomib and lenalidomide or underlying risk/prognostic factors, bulky disease, gender or age.

The safety and efficacy of IMBRUVICA were demonstrated in a randomised phase 3, open-label, multicenter study including 280 patients with MCL who received at least one prior therapy (Study MCL3001). Patients were randomised 1:1 to receive either IMBRUVICA orally at 560 mg once daily for 21 days or temsirolimus intravenously at 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Treatment on both arms continued until disease progression or unacceptable toxicity. The median age was 68 years (range, 34; 88 years), 74% were male and 87% were Caucasian. The median time since diagnosis was 43 months, and median number of prior treatments was 2 (range: 1 to 9 treatments), including 51% with prior high-dose chemotherapy, 18% with prior bortezomib, 5% with prior lenalidomide, and 24% with prior stem cell transplant. At baseline, 53% of patients had bulky disease (≥5 cm), 21% had high-risk score by Simplified MIPI, 60% had extranodal disease and 54% had bone marrow involvement at screening.

Progression-free survival (PFS) was assessed by IRC according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. Efficacy results for Study MCL3001 are shown in Table 3 and the Kaplan-Meier curve for PFS in Figure 1.

Table 3: Efficacy Results in patients with relapsed or refractory MCL (Study MCL3001)

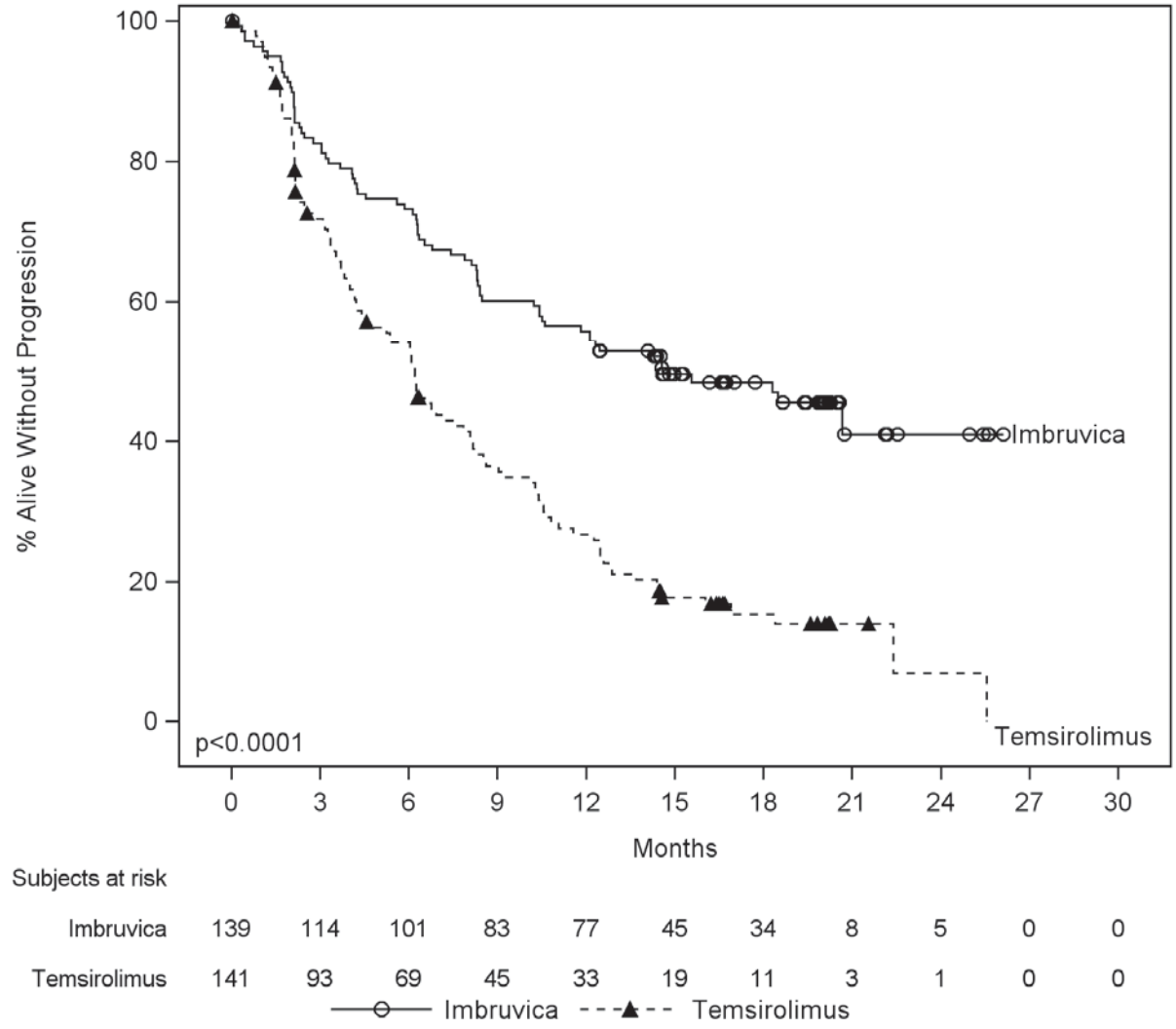
Endpoint	IMBRUVICA N=139	Temsirolimus N=141
PFS[a]		
Median PFS (95% CI), (months)	14.6 (10.4, NE)	6.2 (4.2, 7.9)
	HR=0.43 [95% CI: 0.32, 0.58]	
ORR (%)	71.9	40.4
p-value	p<0.0001	

NE=not estimable; HR=hazard ratio; CI=confidence interval; ORR=overall response rate; PFS=progression-free survival

[a] IRC evaluated.

A smaller proportion of patients treated with ibrutinib experienced a clinically meaningful worsening of lymphoma symptoms versus temsirolimus (27% versus 52%) and time to worsening of symptoms occurred more slowly with ibrutinib versus temsirolimus (HR 0.27, p<0.0001).

Figure 1: Kaplan-Meier curve of PFS (ITT Population) in Study MCL3001



CLL

Patients previously untreated for CLL

Single agent

A randomised, multicenter, open-label phase 3 study (PCYC-1115-CA) of IMBRUVICA versus chlorambucil was conducted in patients with treatment-naïve CLL who were 65 years of age or older. Patients between 65 and 70 years of age were required to have at least one comorbidity that precluded the use of frontline chemo-immunotherapy with fludarabine, cyclophosphamide, and rituximab. Patients (n=269) were randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on days 1 and 15

of each 28-day cycle for a maximum of 12 cycles, with an allowance for intrapatient dose increases up to 0.8 mg/kg based on tolerability. After confirmed disease progression, patients on chlorambucil were able to crossover to ibrutinib.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety one percent of patients had a baseline ECOG performance status of 0 or 1 and 9% had an ECOG performance status of 2. The study enrolled 269 patients with CLL. At baseline, 45% had advanced clinical stage (Rai Stage III or IV), 35% of patients had at least one tumor ≥5 cm, 39% with baseline anaemia, 23% with baseline thrombocytopenia, 65% had elevated β2 microglobulin >3500 mcg/L, 47% had a CrCL <60 mL/min, 20% of patients presented with del11q, 6% of patients presented with del17p/tumor protein 53 (TP53) mutation, and 44% of patients presented with unmutated immunoglobulin heavy chain variable region (IGHV).

Progression free survival (PFS) as assessed by IRC according to International Workshop on CLL (IWCLL) criteria indicated an 84% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. Efficacy results for Study PCYC-1115-CA are shown in Table 4 and the Kaplan-Meier curves for PFS and OS are shown in Figures 2 and 3, respectively.

There was a statistically significant sustained platelet or haemoglobin improvement in the ITT population in favor of ibrutinib versus chlorambucil. In patients with baseline cytopenias, sustained haematologic improvement was: platelets 77.1% versus 42.9%; haemoglobin 84.3% versus 45.5% for ibrutinib and chlorambucil respectively.

Table 4: Efficacy results in Study PCYC-1115-CA

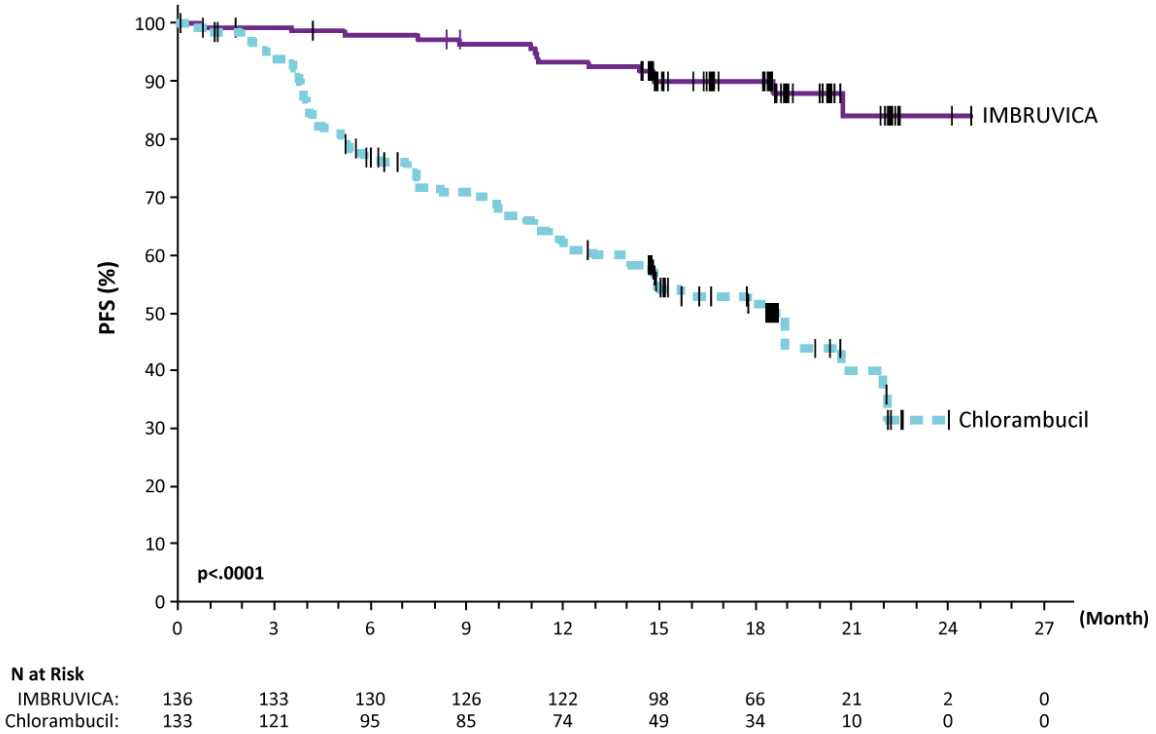
Endpoint	**IMBRUVICA N=136**	**Chlorambucil N=133**
PFS[a]		
Number of events (%)	15 (11.0)	64 (48.1)
Median (95% CI), months	Not reached	18.9 (14.1, 22.0)
HR (95% CI)	0.161 (0.091, 0.283)	
ORR[a] (CR+PR)	82.4%	35.3%
P-value	<0.0001	
OS[b]		
Number of deaths (%)	3 (2.2)	17 (12.8)
HR (95% CI)	0.163 (0.048, 0.558)	

CI=confidence interval; HR=hazard ratio; CR=complete response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response

[a] IRC evaluated, median follow-up 18.4 months.

[b] Median OS not reached for both arms. p<0.005 for OS

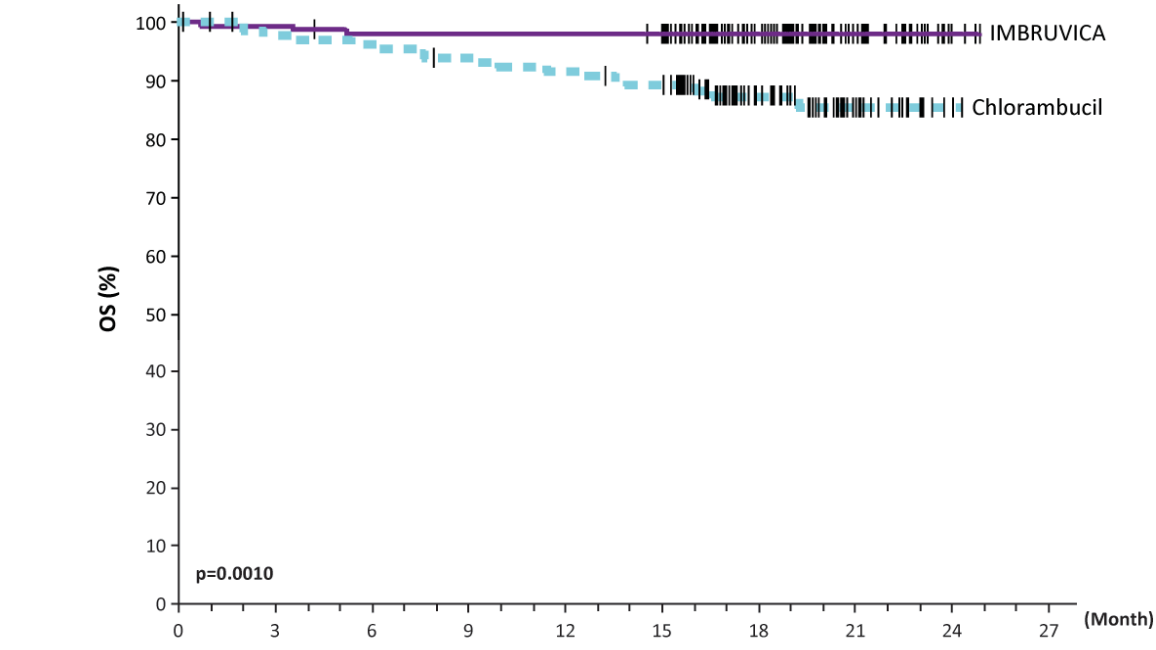
Figure 2: Kaplan-Meier curve of PFS (ITT Population) in Study PCYC-1115-CA



N at Risk

IMBRUVICA:	136	133	130	126	122	98	66	21	2	0
Chlorambucil:	133	121	95	85	74	49	34	10	0	0

Figure 3: Kaplan-Meier curve of OS (ITT Population) in Study PCYC-1115-CA



N at Risk

IMBRUVICA:	136	134	131	131	131	128	74	32	4	0
Chlorambucil:	133	127	125	121	118	113	62	24	1	0

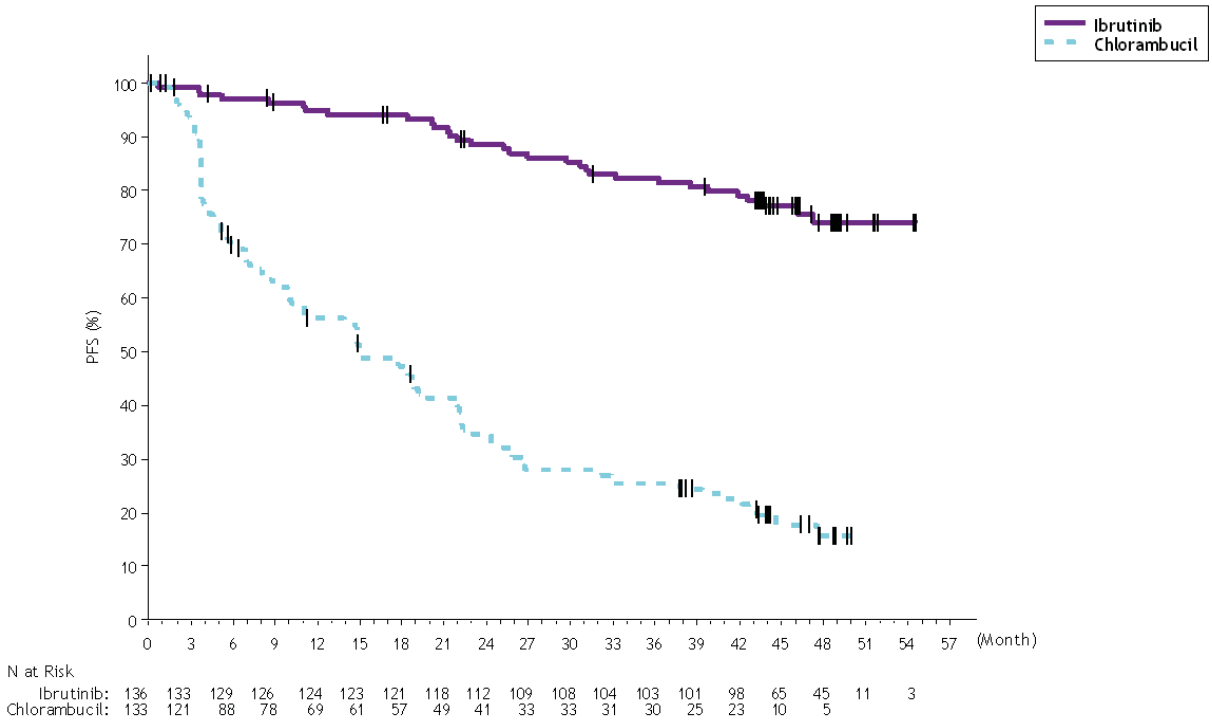
48-month follow-up

With a median follow-up time on study of 48 months in Study PCYC-1115-CA and its extension study, an 86% reduction in the risk of death or progression by investigator assessment was observed

for patients in the IMBRUVICA arm. The median investigator-assessed PFS was not reached in the IMBRUVICA arm and was 15 months [95% CI (10.22, 19.35)] in the chlorambucil arm; (HR=0.14 [95% CI (0.09, 0.21)]). The 4-year PFS estimate was 73.9% in the IMBRUVICA arm and 15.5% in the chlorambucil arm, respectively. The updated Kaplan-Meier curve for PFS is shown in Figure 4. The investigator-assessed ORR was 91.2% in the IMBRUVICA arm versus 36.8% in the chlorambucil arm. The CR rate according to IWCLL criteria was 16.2% in the IMBRUVICA arm versus 3.0% in the chlorambucil arm. At the time of long-term follow-up, a total of 73 subjects (54.9%) originally randomised to the chlorambucil arm subsequently received ibrutinib as cross-over treatment. The Kaplan-Meier landmark estimate for OS at 48-months was 85.5% in the IMBRUVICA arm.

The treatment effect of ibrutinib in Study PCYC-1115-CA was consistent across high-risk patients with del17p/TP53 mutation, del11q, and/or unmutated IGHV.

Figure 4: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1115-CA with 48 Months Follow-up



Combination therapy

The safety and efficacy of IMBRUVICA in patients with previously untreated CLL/SLL were further evaluated in a randomised, multi-center, open-label, phase 3 study (PCYC-1130-CA) of IMBRUVICA in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab. The study enrolled patients who were 65 years of age or older or <65 years of age with coexisting medical conditions, reduced renal function as measured by creatinine clearance <70 mL/min, or presence of del17p/TP53 mutation. Patients (n=229) were randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity or chlorambucil at a dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for 6 cycles. In both arms, patients received 1000 mg of obinutuzumab on Days 1, 8 and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg).

The median age was 71 years (range, 40 to 87 years), 64% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (48%) or 1-2 (52%). At baseline, 52% had advanced clinical stage (Rai Stage III or IV), 32% of patients had bulky disease (≥5 cm), 44% with baseline anaemia, 22% with baseline thrombocytopenia, 28% had a CrCL <60 mL/min, and the median Cumulative Illness Rating Score for Geriatrics (CIRS-G) was 4 (range, 0 to 12). At baseline,

65% of patients presented with CLL/SLL with high risk factors (del17p/TP53 mutation [18%], del11q [15%], or unmutated IGHV [54%]).

Progression-free survival (PFS) was assessed by IRC according to IWCLL criteria indicated a 77% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. With a median follow-up time on study of 31 months, the median PFS was not reached in the IMBRUVICA+obinutuzumab arm and was 19 months in the chlorambucil+obinutuzumab arm. Efficacy results for Study PCYC-1130-CA are shown in Table 5 and the Kaplan-Meier curve for PFS is shown in Figure 5.

Table 5: Efficacy results in Study PCYC-1130-CA

Endpoint	**IMBRUVICA+Obinutuzumab N=113**	**Chlorambucil+Obinutuzumab N=116**
Progression Free Survival[a]		
Number of events (%)	24 (21.2)	74 (63.8)
Median (95% CI), months	Not reached	19.0 (15.1, 22.1)
HR (95% CI)	0.23 (0.15, 0.37)	
Overall Response Rate[a] (%)	88.5	73.3
CR[b]	19.5	7.8
PR[c]	69.0	65.5

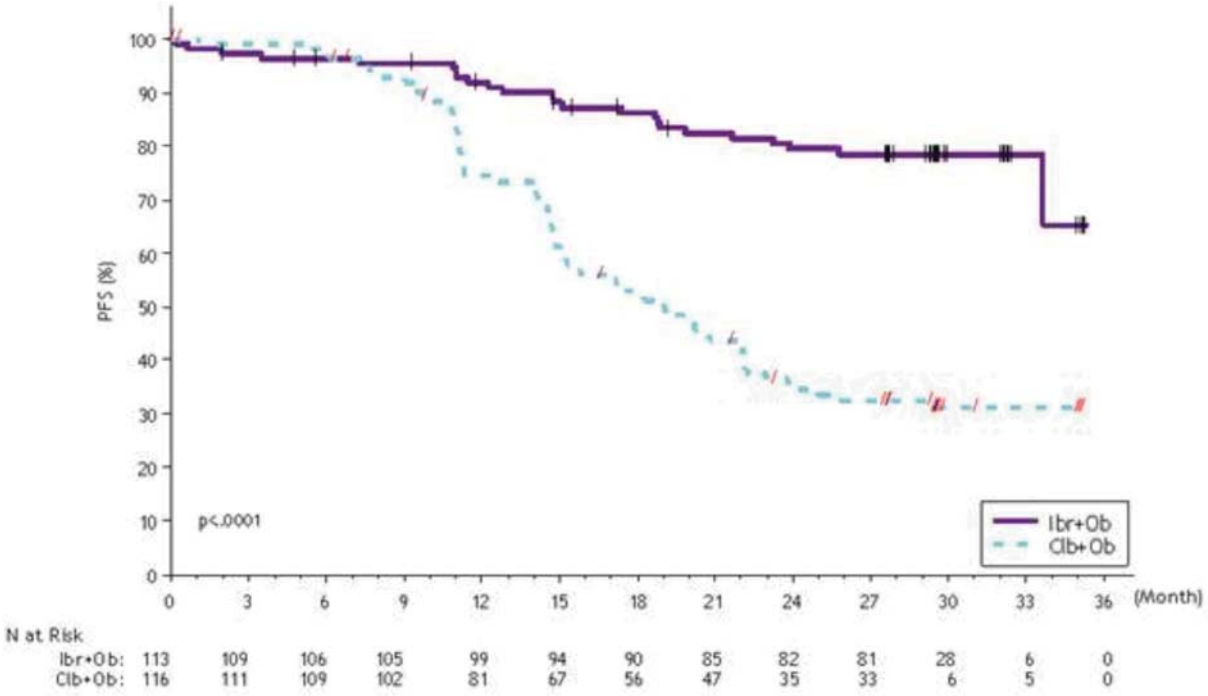
CI=confidence interval; HR=hazard ratio; CR=complete response; PR=partial response.

[a] IRC evaluated.

[b] Includes 1 patient in the IMBRUVICA+obinutuzumab arm with a complete response with incomplete marrow recovery (CRi).

[c] PR=PR+nPR.

Figure 5: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1130-CA



The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (del17p/TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.15 [95% CI (0.09, 0.27)], as shown in Table 6. The 2-year PFS rate estimates for the high-risk CLL/SLL population were 78.8% [95% CI (67.3, 86.7)] and 15.5% [95% CI (8.1, 25.2)] in the IMBRUVICA+obinutuzumab and chlorambucil+obinutuzumab arms, respectively.

Table 6: Subgroup Analysis of PFS (Study PCYC-1130-CA)

	N	Hazard Ratio	95% CI
All subjects	229	0.231	0.145, 0.367
High risk (del17p/TP53/del11q/unmutated IGHV)			
Yes	148	0.154	0.087, 0.270
No	81	0.521	0.221, 1.231
Del17p/TP53			
Yes	41	0.109	0.031, 0.380
No	188	0.275	0.166, 0.455
FISH			
Del17p	32	0.141	0.039, 0.506
Del11q	35	0.131	0.030, 0.573
Others	162	0.302	0.176, 0.520
Unmutated IGHV			
Yes	123	0.150	0.084, 0.269
No	91	0.300	0.120, 0.749
Age			
<65	46	0.293	0.122, 0.705
≥65	183	0.215	0.125, 0.372
Bulky disease			
<5 cm	154	0.289	0.161, 0.521
≥5 cm	74	0.184	0.085, 0.398
Rai stage			
0/I/II	110	0.221	0.115, 0.424
III/IV	119	0.246	0.127, 0.477
ECOG per CRF			
0	110	0.226	0.110, 0.464
1-2	119	0.239	0.130, 0.438

Hazard ratio based on non-stratified analysis

Any grade infusion-related reactions were observed in 25% of patients treated with IMBRUVICA+obinutuzumab and 58% of patients treated with chlorambucil+obinutuzumab. Grade 3 or higher or serious infusion-related reactions were observed in 3% of patients treated with IMBRUVICA+obinutuzumab and 9% of patients treated with chlorambucil+obinutuzumab.

The safety and efficacy of IMBRUVICA in patients with previously untreated CLL or SLL were further evaluated in a randomised, multi-center, open-label, phase 3 study (E1912) of IMBRUVICA in combination with rituximab (IR) versus standard fludarabine, cyclophosphamide, and rituximab (FCR) chemo-immunotherapy. The study enrolled previously untreated patients with CLL or SLL who were 70 years or younger. Patients with del17p were excluded from the study. Patients (n=529) were randomised 2:1 to receive either IR or FCR. IMBRUVICA was administered at a dose of 420 mg daily until disease progression or unacceptable toxicity. Fludarabine was administered at a dose of 25 mg/m^2, and cyclophosphamide was administered at a dose of 250 mg/m^2, both on Days 1, 2, and 3 of Cycles 1-6. Rituximab was initiated in Cycle 2 for the IR arm and in Cycle 1 for the FCR arm and was administered at a dose of 50 mg/m^2 on Day 1 of the first cycle, 325 mg/m^2 on Day 2 of the first cycle, and 500 mg/m^2 on Day 1 of 5 subsequent cycles, for a total of 6 cycles. Each cycle was 28 days.

The median age was 58 years (range, 28 to 70 years), 67% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1 (98%) or 2 (2%). At baseline, 43% of patients presented with Rai Stage III or IV, and 59% of patients presented with CLL/SLL with high risk factors (TP53 mutation [6%], del11q [22%], or unmutated IGHV [53%]).

With a median follow-up time on study of 37 months, efficacy results for E1912 are shown in Table 7. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria, and OS are shown in Figures 6 and 7, respectively.

Table 7: Efficacy results in Study E1912

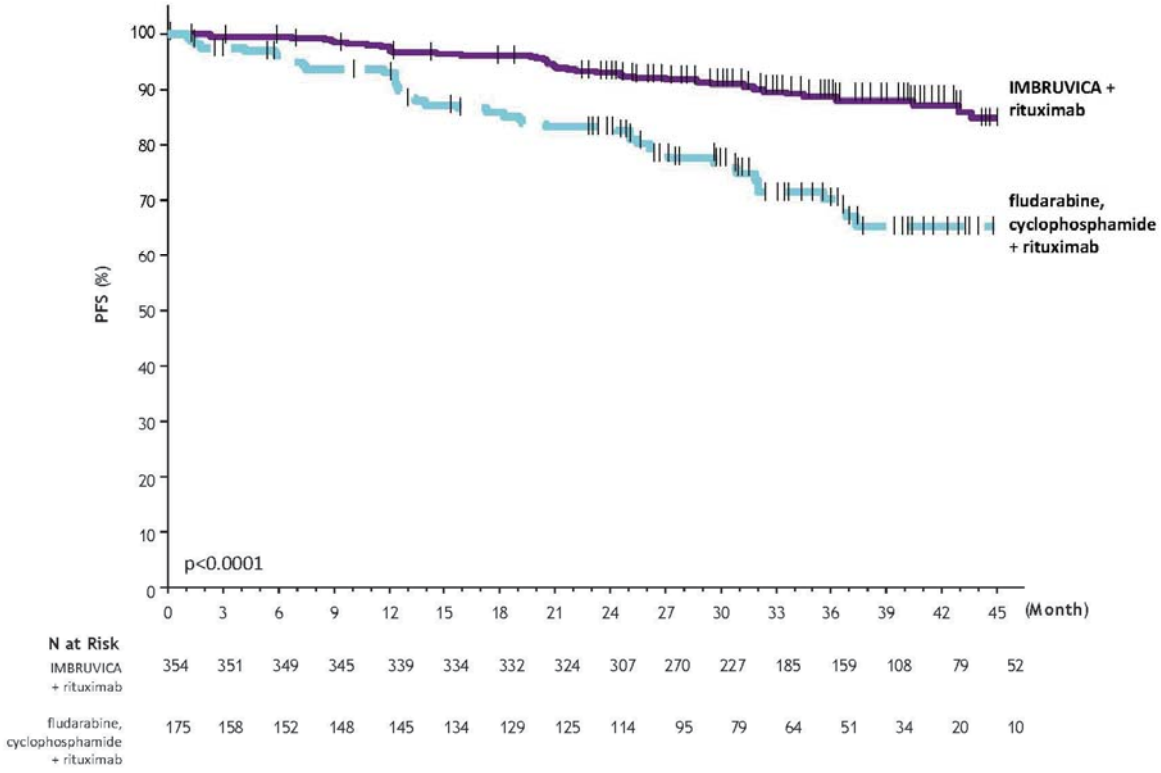
Endpoint	Ibrutinib+rituximab (IR) N=354	Fludarabine, Cyclophosphamide, and Rituximab (FCR) N=175
Progression Free Survival		
Number of events (%)	41 (12)	44 (25)
Disease progression	39	38
Death events	2	6
Median (95% CI), months	NE (49.4, NE)	NE (47.1, NE)
HR (95% CI)	0.34 (0.22, 0.52)	
P-value[a]	<0.0001	
Overall Survival		
Number of deaths (%)	4 (1)	10 (6)
HR (95% CI)	0.17 (0.05, 0.54)	
P-value[a]	0.0007	
Overall Response Rate[b] (%)	96.9	85.7

[a] P-value is from unstratified log-rank test.

[b] Investigator evaluated.

HR = hazard ratio; NE = not evaluable

Figure 6: Kaplan-Meier Curve of PFS (ITT Population) in Study E1912



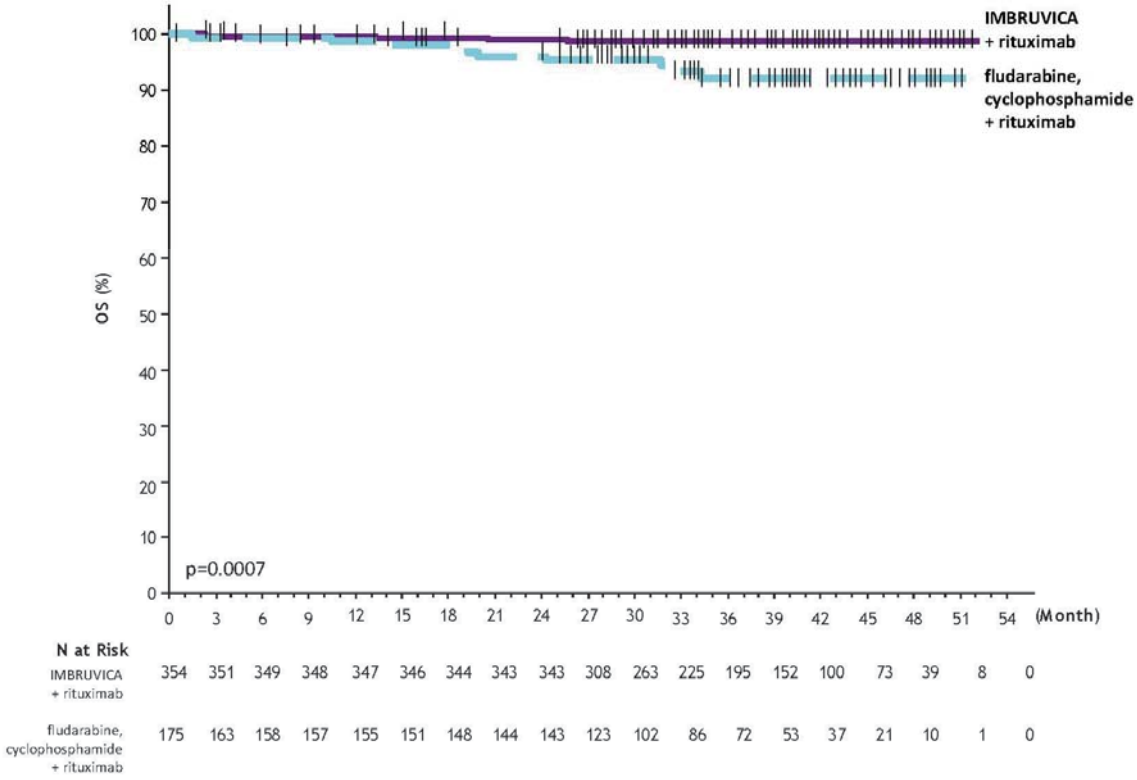
The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.40)], p <0.0001, as shown in Table 8. The 3-year PFS rate estimates for the high-risk CLL/SLL population were 90.4% [95% CI (85.4, 93.7)] and 60.3% [95% CI (46.2, 71.8)] in the IR and FCR arms, respectively.

Table 8: Subgroup Analysis of PFS (Study E1912)

	N	Hazard Ratio	95% CI
All subjects	529	0.340	0.222, 0.522
High risk (TP53/del11q/unmutated IGHV)			
Yes	313	0.231	0.132, 0.404
No	216	0.568	0.292, 1.105
del11q			
Yes	117	0.199	0.088, 0.453
No	410	0.433	0.260, 0.722
Unmutated IGHV			
Yes	281	0.233	0.129, 0.421
No	112	0.741	0.276, 1.993
Bulky disease			
<5 cm	316	0.393	0.217, 0.711
≥5 cm	194	0.257	0.134, 0.494
Rai stage			
0/I/II	301	0.398	0.224, 0.708
III/IV	228	0.281	0.148, 0.534
ECOG			
0	335	0.242	0.138, 0.422
1-2	194	0.551	0.271, 1.118

Hazard ratio based on non-stratified analysis

Figure 7: Kaplan-Meier Curve of OS (ITT Population) in Study E1912



Patients with CLL who received at least one prior therapy
Single agent
The safety and efficacy of IMBRUVICA in patients with CLL were demonstrated in one uncontrolled study and one randomised, controlled study. The open-label, multi-center study (PCYC-1102-CA) included 51 patients with relapsed or refractory CLL, who received 420 mg once daily. IMBRUVICA was administered until disease progression or unacceptable toxicity. The median age was 68 years (range: 37 to 82 years), median time since diagnosis was 80 months, and median number of prior

treatments was 4 (range: 1 to 12 treatments), including 92.2% with a prior nucleoside analog, 98.0% with prior rituximab, 86.3% with a prior alkylator, 39.2% with prior bendamustine and 19.6% with prior ofatumumab. At baseline, 39.2% of patients had Rai Stage IV, 45.1% had bulky disease (≥5 cm), 35.3% had deletion 17p and 31.4% had deletion 11q.

ORR was assessed according to the 2008 IWCLL criteria by investigators and IRC. At a median duration follow up of 16.4 months, the ORR by IRC for the 51 relapsed or refractory patients was 64.7% (95% CI: 50.1%; 77.6%), all PRs. The ORR including PR with lymphocytosis was 70.6%. Median time to response was 1.9 months. The DOR ranged from 3.9 to 24.2+ months. The median DOR was not reached.

A randomised, multi-center, open-label phase 3 study of IMBRUVICA versus ofatumumab (PCYC-1112-CA) was conducted in patients with relapsed or refractory CLL. Patients (n=391) were randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or ofatumumab for up to 12 doses (300/2,000 mg). Fifty-seven patients randomised to ofatumumab crossed over following progression to receive IMBRUVICA. The median age was 67 years (range: 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range: 1 to 13 treatments). At baseline, 58% of patients had at least one tumour ≥5 cm. Thirty-two percent of patients had deletion 17p (with 50% of patients having deletion 17p/TP53 mutation), 24% had 11q deletion, and 47% of patients had unmutated IGHV.

Progression free survival (PFS) as assessed by an IRC according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA arm. Analysis of OS demonstrated a 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study PCYC-1112-CA are shown in Table 9.

Table 9: Efficacy results in patients with CLL (Study PCYC-1112-CA)

Endpoint	**IMBRUVICA N=195**	**Ofatumumab N=196**
Median PFS	Not reached	8.1 months
	HR=0.215 [95% CI: 0.146; 0.317]	
OS[a]	HR=0.434 [95% CI: 0.238; 0.789][b] HR=0.387 [95% CI: 0.216; 0.695][c]	
ORR[d, e] (%)	42.6	4.1
ORR including PR with lymphocytosis[d] (%)	62.6	4.1

HR=hazard ratio; CI=confidence interval; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response

[a] Median OS not reached for both arms. p<0.005 for OS.

[b] Patients randomised to ofatumumab were censored when starting IMBRUVICA if applicable.

[c] Sensitivity analysis in which crossover patients from the ofatumumab arm were not censored at the date of first dose of IMBRUVICA.

[d] Per IRC. Repeat CT scans required to confirm response.

[e] All PRs achieved; p<0.0001 for ORR.

Median follow-up time on study=9 months

The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Table 10).

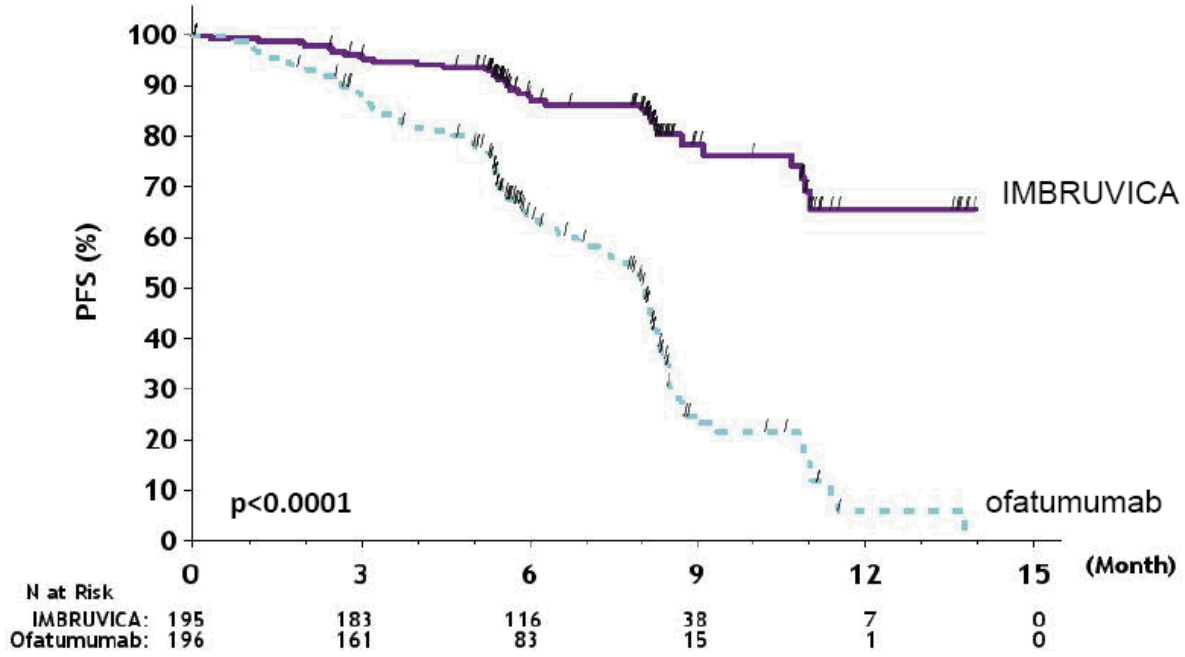
Table 10: Subgroup analysis of PFS (Study PCYC-1112-CA)

	N	Hazard Ratio	95% CI
All subjects	391	0.210	(0.143; 0.308)
Del17P			
Yes	127	0.247	(0.136; 0.450)
No	264	0.194	(0.117; 0.323)
Refractory disease to purine analog			
Yes	175	0.178	(0.100; 0.320)
No	216	0.242	(0.145; 0.404)
Age			
<65	152	0.166	(0.088; 0.315)
≥65	239	0.243	(0.149; 0.395)
Number of prior lines			
<3	198	0.189	(0.100; 0.358)
≥3	193	0.212	(0.130; 0.344)
Bulky disease			
<5 cm	163	0.237	(0.127; 0.442)
≥5 cm	225	0.191	(0.117; 0.311)

Hazard ratio based on non-stratified analysis

The Kaplan-Meier curve for PFS is shown in Figure 8.

Figure 8: Kaplan-Meier curve of PFS (ITT Population) in Study PCYC-1112-CA



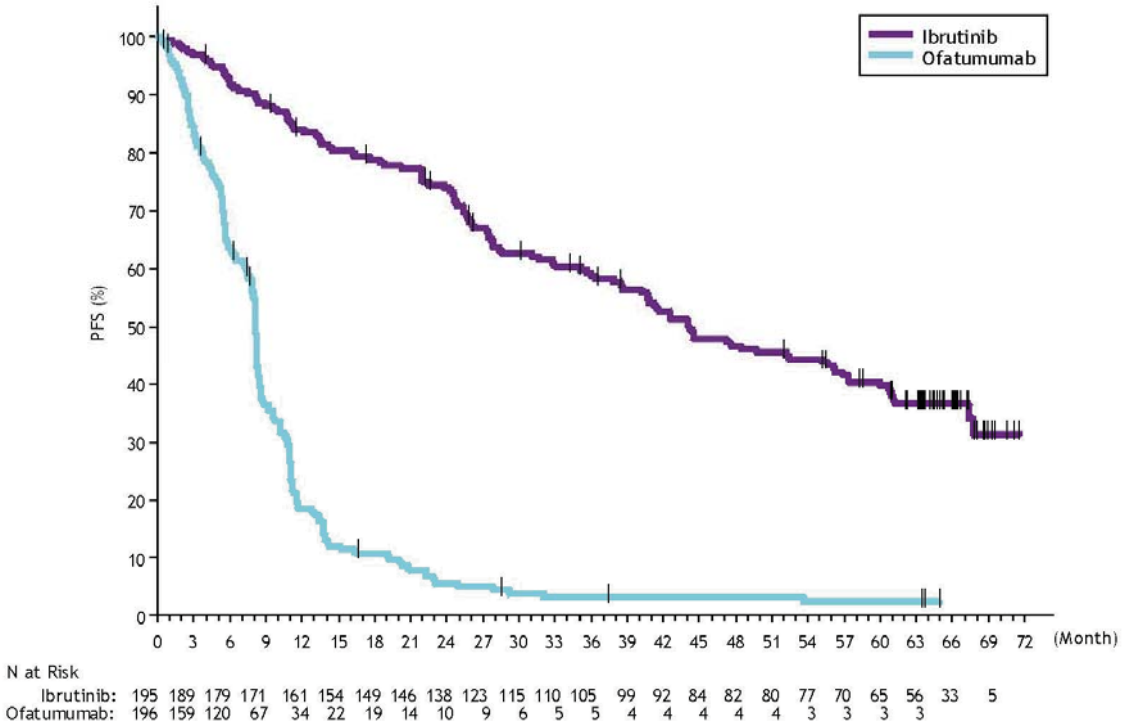
Final Analysis at 65-month follow-up

With a median follow-up time on study of 65 months in Study PCYC-1112-CA, an 85% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The median investigator-assessed PFS according to IWCLL criteria was 44.1 months [95% CI (38.47, 56.18)] in the IMBRUVICA arm and 8.1 months [95% CI (7.79, 8.25)] in the ofatumumab arm, respectively; HR=0.15 [95% CI (0.11, 0.20)]. The updated Kaplan-Meier curve for PFS is shown in Figure 9. The investigator-assessed ORR in the IMBRUVICA arm was 87.7% versus 22.4% in the ofatumumab arm. At the time of final analysis, 133 (67.9%) of the 196 subjects originally randomised to the ofatumumab treatment arm had crossed over to ibrutinib treatment. The median investigator-assessed PFS2 (time from randomisation until PFS event after first subsequent anti-neoplastic therapy) according to IWCLL criteria was 65.4 months [95% CI (51.61, not estimable)] in the IMBRUVICA arm and 38.5 months [95% CI (19.98, 47.24)] in the ofatumumab

arm, respectively; HR=0.54 [95% CI (0.41, 0.71)]. The median OS was 67.7 months [95% CI (61.0, not estimable)] in the IMBRUVICA arm.

The treatment effect of ibrutinib in Study PCYC-1112-CA was consistent across high-risk patients with deletion 17p/TP53 mutation, deletion 11q, and/or unmutated IGHV.

Figure 9: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1112-CA at Final Analysis with 65 Months Follow-up



Combination therapy
The safety and efficacy of IMBRUVICA in patients previously treated for CLL were further evaluated in a randomised, multicenter, double-blinded phase 3 study of IMBRUVICA in combination with BR versus placebo+BR (Study CLL3001). Patients (n=578) were randomised 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m^2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1. Ninety patients randomised to placebo+BR crossed over to receive IMBRUVICA following IRC confirmed progression. The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 6 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumour ≥5 cm, 26% had del11q.

Progression free survival (PFS) was assessed by IRC according to IWCLL criteria. Efficacy results for Study CLL3001 are shown in Table 11.

Table 11: Efficacy Results in patients with CLL (Study CLL3001)

Endpoint	IMBRUVICA+BR N=289	Placebo+BR N=289
PFS[a]		
Median (95% CI), months	Not reached	13.3 (11.3, 13.9)
	HR=0.203 [95% CI: 0.150, 0.276]	
ORR[b] %	82.7	67.8
OS[c]	HR=0.628 [95% CI: 0.385, 1.024]	

CI=confidence interval; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

[a] IRC evaluated.

[b] IRC evaluated, ORR (complete response, complete response with incomplete marrow recovery, nodular partial response, partial response).

[c] Median OS not reached for both arms.

WM

Single agent

The safety and efficacy of IMBRUVICA in WM (IgM-excreting lymphoplasmacytic lymphoma) were evaluated in an open-label, multi-center, single-arm trial of 63 previously treated patients. The median age was 63 years (range: 44 to 86 years), 76% were male, and 95% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range: 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL, and 60% of patients were anaemic (haemoglobin ≤11 g/dL or 6.8 mmol/L).

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The primary endpoint in this study was ORR per investigator assessment. The ORR and DOR were assessed using criteria adopted from the Third International Workshop of WM. Responses to IMBRUVICA are shown in Table 12.

Table 12: ORR and DOR in patients with WM

	Total (N=63)
ORR (%)	87.3
95% CI (%)	(76.5, 94.4)
VGPR (%)	14.3
PR (%)	55.6
MR (%)	17.5
Median DOR months (range)	NR (0.03+, 18.8+)

CI=confidence interval; DOR=duration of response; NR=not reached; MR=minor response; PR=partial response; VGPR=very good partial response; ORR=MR+PR+VGPR
Median follow-up time on study=14.8 months

The median time to response was 1.0 month (range: 0.7-13.4 months).
Efficacy results were also assessed by an IRC demonstrating an ORR of 83%, with a 11% VGPR rate and a 51% PR rate.

Combination therapy

The safety and efficacy of IMBRUVICA in WM were further evaluated in patients with treatment-naïve or previously treated WM in a randomised, multicenter, double-blinded phase 3 study of IMBRUVICA in combination with rituximab versus placebo in combination with rituximab (PCYC-1127-CA). Patients (n=150) were randomised 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with rituximab until disease progression or unacceptable toxicity. Rituximab was administered weekly at a dose of 375 mg/m^2 for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20).

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment-naïve, and 55% of patients were previously treated. The median time since diagnosis was 52.6 months

(treatment-naïve patients=6.5 months and previously treated patients=94.3 months). Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), 63% of patients were anaemic (haemoglobin ≤11 g/dL or 6.8 mmol/L) and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status.

At the primary analysis, with a median follow-up of 26.5 months, the IRC-assessed PFS hazard ratio was 0.20 [95% CI (0.11, 0.38)]. PFS hazard ratios for treatment-naïve patients, previously treated patients, and patients with or without MYD88 L265P mutations were consistent with the PFS hazard ratio for the ITT population.

Grade 3 or 4 infusion-related reactions were observed in 1% of patients treated with IMBRUVICA+rituximab and 16% of patients treated with placebo+rituximab.

Tumor flare in the form of IgM increase occurred in 8.0% of subjects in the IMBRUVICA+rituximab arm and 46.7% of subjects in the placebo+rituximab arm.

Final Analysis at 63-month follow-up
With an overall follow-up of 63 months, efficacy results as assessed by an IRC at the time of the final analysis for PCYC-1127-CA are shown in Table 13 and the Kaplan-Meier curve for PFS is shown in Figure 10. PFS hazard ratios for treatment-naïve patients (0.31 [95% CI (0.14, 0.69)]) and previously treated patients (0.22 [95% CI (0.11, 0.43)]) were consistent with the PFS hazard ratio for the ITT population.

Table 13: Efficacy results in Study PCYC-1127-CA (Final Analysis[*])

Endpoint	IMBRUVICA + R N=75	Placebo + R N=75
Progression Free Survival[a, b]		
Number of events (%)	22 (29)	50 (67)
Median (95% CI), months	Not reached	20.3 (13.0, 27.6)
HR (95% CI)	0.25 (0.15, 0.42)	
P-value	<0.0001	
Time to next treatment		
Median (95% CI), months	Not reached	18.1 (11.1, 33.1)
HR (95% CI)	0.1 (0.05, 0.21)	
Best Overall Response (%)		
CR	1.3	1.3
VGPR	29.3	4.0
PR	45.3	25.3
MR	16.0	13.3
Overall Response Rate[c] (CR, VGPR, PR, MR) (%)	69 (92.0)	33 (44.0)
Median duration of overall response, months (range)	Not reached (2.7, 58.9+)	27.6 (1.9, 55.9+)
Response Rate (CR, VGPR, PR)[c, d] (%)	57 (76.0)	23 (30.7)
Median duration of response, months (range)	Not reached (1.9+, 58.9+)	Not reached (4.6, 49.7+)
Rate of Sustained Hemoglobin Improvement[c, e] (%)	77.3	42.7

CI = confidence interval; CR = complete response; HR = hazard ratio; MR = minor response; PR = partial response; R = Rituximab; VGPR = very good partial response

* Median follow-up time on study = 49.7 months.

[a] IRC evaluated.

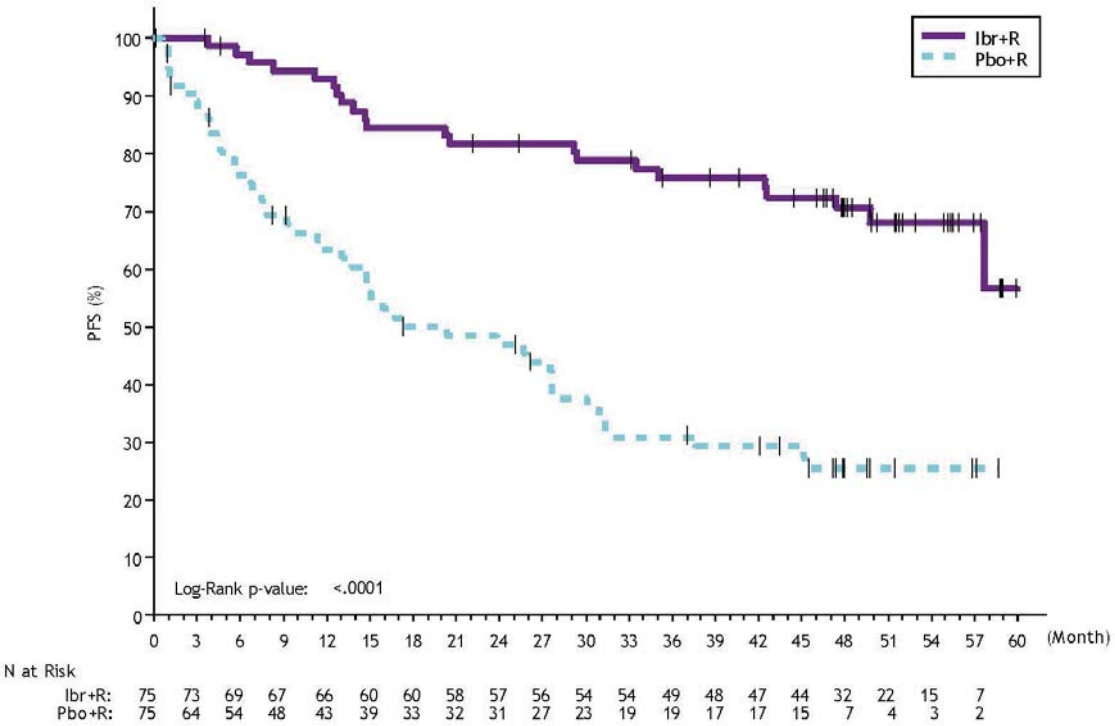
[b] 4-year PFS estimates were 70.6% [95% CI (58.1, 80.0)] in the IMBRUVICA + R arm versus 25.3% [95% CI (15.3, 36.6)] in the placebo + R arm.

[c] p-value associated with response rate was <0.0001.

[d] Response rate was 76% vs 41% in treatment-naïve patients and 76% vs 22% in previously treated patients for the IMBRUVICA + R arm vs the placebo + R arm, respectively.

[e] Defined as increase of ≥2 g/dL over baseline regardless of baseline value, or an increase to >11 g/dL with a ≥0.5 g/dL improvement if baseline was ≤11 g/dL.

Figure 10: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1127-CA (Final Analysis)



Study PCYC-1127-CA had a separate monotherapy arm of 31 patients with previously treated WM who failed prior rituximab-containing therapy and received single agent IMBRUVICA. The median age was 67 years (range, 47 to 90 years). Eighty-one percent of patients had a baseline ECOG performance status of 0 or 1, and 19% had a baseline ECOG performance status of 2. The median number of prior treatments was 4 (range, 1 to 7 treatments). With an overall follow-up of 61 months, the response rate observed in Study PCYC-1127-CA monotherapy arm per IRC assessment was 77% (0% CR, 29% VGPR, 48% PR). The median duration of response was 33 months (range, 2.4 to 60.2+ months). The overall response rate per IRC observed in the monotherapy arm was 87% (0% CR, 29% VGPR, 48% PR, 10% MR). The median duration of overall response was 39 months (range, 2.07 to 60.2+ months).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with IMBRUVICA in all subsets of the paediatric population in MCL, CLL and lymphoplasmacytic lymphoma (LPL) (for information on paediatric use, see section 4.2).

5.2 Pharmacokinetic properties

Absorption

Ibrutinib is rapidly absorbed after oral administration with a median T_{max} of 1 to 2 hours. Absolute bioavailability in fasted condition (n=8) was 2.9% (90% CI=2.1 – 3.9) and doubled when combined

with a meal. Pharmacokinetics of ibrutinib does not significantly differ in patients with different B-cell malignancies. Ibrutinib exposure increases with doses up to 840 mg. The steady state AUC observed in patients at 560 mg is (mean ± standard deviation) 953 ± 705 ng h/mL. Administration of ibrutinib in fasted condition resulted in approximately 60% of exposure (AUC_{last}) as compared to either 30 minutes before, 30 minutes after (fed condition) or 2 hours after a high fat breakfast.

Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. In fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days, compared to ibrutinib alone, geometric mean ratios (90% CI) were 83% (68-102%), 92% (78-110%), and 38% (26-53%) for AUC_{0-24}, AUC_{last}, and C_{max}, respectively.

Distribution
Reversible binding of ibrutinib to human plasma protein *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1,000 ng/mL. The apparent volume of distribution at steady state ($V_{d, ss}/F$) was approximately 10,000 L.

Metabolism
Ibrutinib is metabolised primarily by CYP3A4 to produce a dihydrodiol metabolite with an inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Involvement of CYP2D6 in the metabolism of ibrutinib appears to be minimal.

Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

Elimination
Apparent clearance (CL/F) is approximately 1,000 L/h. The half-life of ibrutinib is 4 to 13 hours. After a single oral administration of radiolabeled [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the faeces and <10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in faeces and none in urine.

Special populations
Elderly
Population pharmacokinetics indicated that age does not significantly influence ibrutinib clearance from the circulation.

Paediatric population
No pharmacokinetic studies were performed with IMBRUVICA in patients under 18 years of age.

Gender
Population pharmacokinetics data indicated that gender does not significantly influence ibrutinib clearance from the circulation.

Race
There are insufficient data to evaluate the potential effect of race on ibrutinib pharmacokinetics.

Body weight
Population pharmacokinetics data indicated that body weight (range: 41-146 kg; mean [SD]: 83 [19 kg]) had a negligible effect on ibrutinib clearance.

Renal impairment
Ibrutinib has minimal renal clearance; urinary excretion of metabolites is <10% of the dose. No specific studies have been conducted to date in subjects with impaired renal function. There are no data in patients with severe renal impairment or patients on dialysis (see section 4.2).

Hepatic impairment
Ibrutinib is metabolised in the liver. A hepatic impairment trial was performed in non-cancer subjects administered a single dose of 140 mg of medicinal product under fasting conditions. The effect of

impaired liver function varied substantially between individuals, but on average a 2.7-, 8.2-, and 9.8-fold increase in ibrutinib exposure (AUC_{last}) was observed in subjects with mild (n=6, Child-Pugh class A), moderate (n=10, Child-Pugh class B) and severe (n=8, Child-Pugh class C) hepatic impairment, respectively. The free fraction of ibrutinib also increased with degree of impairment, with 3.0, 3.8 and 4.8% in subjects with mild, moderate and severe liver impairment, respectively, compared to 3.3% in plasma from matched healthy controls within this study. The corresponding increase in unbound ibrutinib exposure ($AUC_{unbound, last}$) is estimated to be 4.1-, 9.8-, and 13-fold in subjects with mild, moderate, and severe hepatic impairment, respectively (see section 4.2).

Co-administration with transport substrates/inhibitors
In vitro studies indicated that ibrutinib is not a substrate of P-gp, nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is an *in vitro* inhibitor of P-gp and BCRP (see section 4.5).

5.3 Preclinical safety data

The following adverse effects were seen in studies of 13-weeks duration in rats and dogs. Ibrutinib was found to induce gastrointestinal effects (soft faeces/diarrhoea and/or inflammation) and lymphoid depletion in rats and dogs with a No Observed Adverse Effect Level (NOAEL) of 30 mg/kg/day in both species. Based on mean exposure (AUC) at the 560 mg/day clinical dose, AUC ratios were 2.6 and 21 at the NOAEL in male and female rats, and 0.4 and 1.8 at the NOAEL in male and female dogs, respectively. Lowest Observed Effect Level (LOEL) (60 mg/kg/day) margins in the dog are 3.6-fold (males) and 2.3-fold (females). In rats, moderate pancreatic acinar cell atrophy (considered adverse) was observed at doses of ≥100 mg/kg in male rats (AUC exposure margin of 2.6-fold) and not observed in females at doses up to 300 mg/kg/day (AUC exposure margin of 21.3-fold). Mildly decreased trabecular and cortical bone was seen in female rats administered ≥100 mg/kg/day (AUC exposure margin of 20.3-fold). All gastrointestinal, lymphoid and bone findings recovered following recovery periods of 6-13 weeks. Pancreatic findings partially recovered during comparable reversal periods.

Juvenile toxicity studies have not been conducted.

Carcinogenicity/genotoxicity
Ibrutinib was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse at oral doses up to 2000 mg/kg/day with an exposure margin of approximately 23 (males) to 37 (females) times the human AUC of ibrutinib at a dose of 560 mg daily.
Ibrutinib has no genotoxic properties when tested in bacteria, mammalian cells or in mice.

Reproductive toxicity
In pregnant rats, ibrutinib at a dose of 80 mg/kg/day was associated with increased post-implantation loss and increased visceral (heart and major vessels) malformations and skeletal variations with an exposure margin 14 times the AUC found in patients at a daily dose of 560 mg. At a dose of ≥40 mg/kg/day, ibrutinib was associated with decreased foetal weights (AUC ratio of ≥5.6 as compared to daily dose of 560 mg in patients). Consequently the foetal NOAEL was 10 mg/kg/day (approximately 1.3 times the AUC of ibrutinib at a dose of 560 mg daily) (see section 4.6).

In pregnant rabbits, ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal malformations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased post-implantation loss. Ibrutinib caused malformations in rabbits at a dose of 15 mg/kg/day (approximately 2.0 times the exposure (AUC) in patients with MCL administered ibrutinib 560 mg daily and 2.8 times the exposure in patients with CLL or WM receiving ibrutinib dose 420 mg per day). Consequently the foetal NOAEL was 5 mg/kg/day (approximately 0.7 times the AUC of ibrutinib at a dose of 560 mg daily) (see section 4.6).

Fertility
No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (HED 16 mg/kg/day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose
Sodium lauril sulfate (E487)

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac
Black iron oxide (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with a child-resistant polypropylene closure.

Each carton contains one bottle of either 90 or 120 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/001 (90 hard capsules)
EU/1/14/945/002 (120 hard capsules)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 October 2014
Date of latest renewal: 25 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg film-coated tablets
IMBRUVICA 280 mg film-coated tablets
IMBRUVICA 420 mg film-coated tablets
IMBRUVICA 560 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMBRUVICA 140 mg film-coated tablets
Each film-coated tablet contains 140 mg of ibrutinib.

Excipients with known effect
Each 140 mg film-coated tablet contains 28 mg of lactose monohydrate.

IMBRUVICA 280 mg film-coated tablets
Each film-coated tablet contains 280 mg of ibrutinib.

Excipients with known effect
Each 280 mg film-coated tablet contains 56 mg of lactose monohydrate.

IMBRUVICA 420 mg film-coated tablets
Each film-coated tablet contains 420 mg of ibrutinib.

Excipients with known effect
Each 420 mg film-coated tablet contains 84 mg of lactose monohydrate.

IMBRUVICA 560 mg film-coated tablets
Each film-coated tablet contains 560 mg of ibrutinib.

Excipients with known effect
Each 560 mg film-coated tablet contains 112 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

IMBRUVICA 140 mg film-coated tablets
Yellow-green to green round tablets (9 mm), debossed with “ibr” on one side and “140” on the other side.

IMBRUVICA 280 mg film-coated tablets
Purple oblong tablets (15 mm in length and 7 mm in width), debossed with “ibr” on one side and “280” on the other side.

IMBRUVICA 420 mg film-coated tablets
Yellow-green to green oblong tablets (17.5 mm in length and 7.4 mm in width), debossed with “ibr” on one side and “420” on the other side.

IMBRUVICA 560 mg film-coated tablets
Yellow to orange oblong tablets (19 mm in length and 8.1 mm in width), debossed with “ibr” on one side and “560” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMBRUVICA as a single agent is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

IMBRUVICA as a single agent or in combination with rituximab or obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

IMBRUVICA as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

IMBRUVICA as a single agent is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with WM.

4.2 Posology and method of administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology
MCL
The recommended dose for the treatment of MCL is 560 mg once daily.

CLL and WM
The recommended dose for the treatment of CLL and WM, either as a single agent or in combination, is 420 mg once daily (for details of the combination regimens, see section 5.1).

Treatment should continue until disease progression or no longer tolerated by the patient.

When administering IMBRUVICA in combination with anti-CD20 therapy, it is recommended to administer IMBRUVICA prior to anti-CD20 therapy when given on the same day.

Dose adjustments
Moderate and strong CYP3A4 inhibitors increase the exposure of ibrutinib (see sections 4.4 and 4.5).

The dose of ibrutinib should be reduced to 280 mg once daily when used concomitantly with moderate CYP3A4 inhibitors.

The dose of ibrutinib should be reduced to 140 mg once daily or withheld for up to 7 days when it is used concomitantly with strong CYP3A4 inhibitors.

IMBRUVICA therapy should be withheld for any new onset or worsening grade ≥3 non-haematological toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, the once daily dose should be reduced by 140 mg. A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue the medicinal product.

Recommended dose modifications are described below:

Toxicity occurrence	MCL dose modification after recovery	CLL/WM dose modification after recovery
First	restart at 560 mg daily	restart at 420 mg daily
Second	restart at 420 mg daily	restart at 280 mg daily
Third	restart at 280 mg daily	restart at 140 mg daily
Fourth	discontinue IMBRUVICA	discontinue IMBRUVICA

Missed dose
If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra tablets to make up the missed dose.

Special populations
Elderly
No specific dose adjustment is required for elderly patients (aged ≥65 years).

Renal impairment
No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in IMBRUVICA clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained and serum creatinine levels monitored periodically. Administer IMBRUVICA to patients with severe renal impairment (<30 mL/min creatinine clearance) only if the benefit outweighs the risk and monitor patients closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis (see section 5.2).

Hepatic impairment
Ibrutinib is metabolised in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure (see section 5.2). For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily. For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily. Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with severe hepatic impairment (Child-Pugh class C).

Severe cardiac disease
Patients with severe cardiovascular disease were excluded from IMBRUVICA clinical studies.

Paediatric population
The safety and efficacy of IMBRUVICA in children and adolescents aged 0 to 18 years have not been established. No data are available.

Method of administration
IMBRUVICA should be administered orally once daily with a glass of water approximately at the same time each day. The tablets should be swallowed whole with water and should not be broken or chewed. IMBRUVICA must not be taken with grapefruit juice or Seville oranges (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Use of preparations containing St. John’s Wort is contraindicated in patients treated with IMBRUVICA.

4.4 Special warnings and precautions for use

Bleeding-related events
There have been reports of bleeding events in patients treated with IMBRUVICA, both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial haemorrhage, and haematuria.

Warfarin or other vitamin K antagonists should not be administered concomitantly with IMBRUVICA.

Use of either anticoagulants or medicinal products that inhibit platelet function (antiplatelet agents) concomitantly with IMBRUVICA increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Supplements such as fish oil and vitamin E preparations should be avoided.

IMBRUVICA should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

The mechanism for the bleeding-related events is not fully understood. Patients with congenital bleeding diathesis have not been studied.

Leukostasis
Cases of leukostasis have been reported in patients treated with IMBRUVICA. A high number of circulating lymphocytes (>400,000/mcL) may confer increased risk. Consider temporarily withholding IMBRUVICA. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Splenic rupture
Cases of splenic rupture have been reported following discontinuation of IMBRUVICA treatment. Disease status and spleen size should be carefully monitored (e.g. clinical examination, ultrasound) when IMBRUVICA treatment is interrupted or ceased. Patients who develop left upper abdominal or shoulder tip pain should be evaluated and a diagnosis of splenic rupture should be considered.

Infections
Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) were observed in patients treated with IMBRUVICA. Some of these infections have been associated with hospitalisation and death. Most patients with fatal infections also had neutropenia. Patients should be monitored for fever, abnormal liver function tests, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Cases of invasive fungal infections, including cases of Aspergillosis, Cryptococcosis and Pneumocystis jiroveci infections have been reported following the use of ibrutinib. Reported cases of invasive fungal infections have been associated with fatal outcomes.

Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of ibrutinib within the context of a prior or concomitant immunosuppressive therapy. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.

Cases of hepatitis E, which may be chronic, have occurred in patients treated with IMBRUVICA.

Cytopenias
Treatment-emergent grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients treated with IMBRUVICA. Monitor complete blood counts monthly.

Interstitial Lung Disease (ILD)
Cases of ILD have been reported in patients treated with IMBRUVICA. Monitor patients for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt IMBRUVICA and manage ILD appropriately. If symptoms persist, consider the risks and benefits of IMBRUVICA treatment and follow the dose modification guidelines.

Cardiac arrhythmia and cardiac failure
Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia and cardiac failure have been reported in patients treated with IMBRUVICA. Cases of atrial fibrillation and atrial flutter have been reported particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor all patients clinically for cardiac manifestations, including cardiac arrhythmia and cardiac failure. Patients who develop arrhythmic symptoms or new onset of dyspnoea, dizziness or fainting should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed.

In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, IMBRUVICA should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.

In patients with preexisting atrial fibrillation requiring anticoagulant therapy, alternative treatment options to IMBRUVICA should be considered. In patients who develop atrial fibrillation on therapy with IMBRUVICA a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to IMBRUVICA are non-suitable, tightly controlled treatment with anticoagulants should be considered.

Patients should be monitored for signs and symptoms of cardiac failure during IMBRUVICA treatment. In some of these cases cardiac failure resolved or improved after IMBRUVICA withdrawal or dose reduction.

Cerebrovascular accidents
Cases of cerebrovascular accident, transient ischaemic attack and ischaemic stroke including fatalities have been reported in patients treated with IMBRUVICA, with and without concomitant atrial fibrillation and/or hypertension. Among cases with reported latency, the initiation of treatment with IMBRUVICA to the onset of ischaemic central nervous vascular conditions was in the most cases after several months (more than 1 month in 78% and more than 6 months in 44% of cases) emphasising the need for regular monitoring of patients (please see section 4.4 Cardiac arrhythmia and Hypertension and section 4.8).

Tumour lysis syndrome
Tumour lysis syndrome has been reported with IMBRUVICA therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions.

Non-melanoma skin cancer
Non-melanoma skin cancers were reported more frequently in patients treated with IMBRUVICA than in patients treated with comparators in pooled comparative randomised phase 3 studies. Monitor patients for the appearance of non-melanoma skin cancer.

Viral reactivation
Cases of hepatitis B reactivation, including fatal events, have been reported in patients receiving IMBRUVICA. Hepatitis B virus (HBV) status should be established before initiating treatment with

IMBRUVICA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Hypertension
Hypertension has occurred in patients treated with IMBRUVICA (see section 4.8). Regularly monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust antihypertensive medication throughout treatment with IMBRUVICA as appropriate.

Haemophagocytic lymphohistiocytosis (HLH)
Cases of HLH (including fatal cases) have been reported in patients treated with IMBRUVICA. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of extreme systemic inflammation. HLH is characterised by fever, hepatosplenomegaly, hypertriglyceridaemia, high serum ferritin and cytopenias. Patients should be informed about symptoms of HLH. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered.

Drug-drug interactions
Co-administration of strong or moderate CYP3A4 inhibitors with IMBRUVICA may lead to increased ibrutinib exposure and consequently a higher risk for toxicity. On the contrary, co-administration of CYP3A4 inducers may lead to decreased IMBRUVICA exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of IMBRUVICA with strong CYP3A4 inhibitors and strong or moderate CYP3A4 inducers should be avoided whenever possible and co-administration should only be considered when the potential benefits clearly outweigh the potential risks. Patients should be closely monitored for signs of IMBRUVICA toxicity if a CYP3A4 inhibitor must be used (see sections 4.2 and 4.5). If a CYP3A4 inducer must be used, closely monitor patients for signs of IMBRUVICA lack of efficacy.

Women of childbearing potential
Women of childbearing potential must use a highly effective method of contraception while taking IMBRUVICA (see section 4.6).

Excipients with known effect
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Each film-coated tablet contains less than 1 mmol sodium (23 mg), and is essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Ibrutinib is primarily metabolised by cytochrome P450 enzyme 3A4 (CYP3A4).

Agents that may increase ibrutinib plasma concentrations
Concomitant use of IMBRUVICA and medicinal products that strongly or moderately inhibit CYP3A4 can increase ibrutinib exposure and strong CYP3A4 inhibitors should be avoided.

Strong CYP3A4 inhibitors
Co-administration of ketoconazole, a very strong CYP3A4 inhibitor, in 18 fasted healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by 29- and 24-fold, respectively. Simulations using fasted conditions suggested that the strong CYP3A4 inhibitor clarithromycin may increase the AUC of ibrutinib by a factor of 14. In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the strong CYP3A4 inhibitor voriconazole increased C_{max} by 6.7-fold and AUC by 5.7-fold. Strong inhibitors of CYP3A4 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodon, cobicistat, voriconazole and posaconazole) should be avoided. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the IMBRUVICA dose to 140 mg for the duration of the inhibitor use or

withhold IMBRUVICA temporarily (for 7 days or less). Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Moderate CYP3A4 inhibitors
In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the CYP3A4 inhibitor erythromycin increased C_{max} by 3.4-fold and AUC by 3.0-fold. If a moderate CYP3A4 inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone and dronedarone) is indicated, reduce IMBRUVICA dose to 280 mg for the duration of the inhibitor use. Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Mild CYP3A4 inhibitors
Simulations using fasted conditions suggested that the mild CYP3A4 inhibitors azithromycin and fluvoxamine may increase the AUC of ibrutinib by <2-fold. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed.

Co-administration of grapefruit juice, containing CYP3A4 inhibitors, in eight healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by approximately 4- and 2-fold, respectively. Grapefruit and Seville oranges should be avoided during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A4 (see section 4.2).

Agents that may decrease ibrutinib plasma concentrations
Administration of IMBRUVICA with inducers of CYP3A4 can decrease ibrutinib plasma concentrations.

Co-administration of rifampicin, a strong CYP3A4 inducer, in 18 fasted healthy subjects, decreased exposure (C_{max} and AUC) of ibrutinib by 92 and 90%, respectively. Avoid concomitant use of strong or moderate CYP3A4 inducers (e.g., carbamazepine, rifampicin, phenytoin). Preparations containing St. John's Wort are contraindicated during treatment with IMBRUVICA, as efficacy may be reduced. Consider alternative agents with less CYP3A4 induction. If the benefit outweighs the risk and a strong or moderate CYP3A4 inducer must be used, monitor patient closely for lack of efficacy (see sections 4.3 and 4.4). Mild inducers may be used concomitantly with IMBRUVICA, however, patients should be monitored for potential lack of efficacy.

Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. A lower C_{max} was observed in fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days (see section 5.2). There is no evidence that the lower C_{max} would have clinical significance, and medicinal products that increase stomach pH (e.g., proton pump inhibitors) have been used without restrictions in the pivotal clinical studies.

Agents that may have their plasma concentrations altered by ibrutinib
Ibrutinib is a P-gp and breast cancer resistance protein (BCRP) inhibitor *in vitro*. As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. To minimise the potential for an interaction in the GI tract, oral narrow therapeutic range, P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after IMBRUVICA. Ibrutinib may also inhibit BCRP in the liver and increase the exposure of medicinal products that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

In a drug interaction study in patients with B-cell malignancies, a single 560 mg dose of ibrutinib did not have a clinically meaningful effect on the exposure of the CYP3A4 substrate midazolam. In the same study, 2 weeks of treatment with ibrutinib at 560 mg daily had no clinically relevant effect on the pharmacokinetics of oral contraceptives (ethinylestradiol and levonorgestrel), the CYP3A4 substrate midazolam, nor the CYP2B6 substrate bupropion.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in females
Based on findings in animals, IMBRUVICA may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking IMBRUVICA and for three months after stopping treatment.

Pregnancy
IMBRUVICA should not be used during pregnancy. There are no data from the use of IMBRUVICA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding
It is not known whether ibrutinib or its metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with IMBRUVICA.

Fertility
No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED] 16 mg/kg/day) (see section 5.3). No human data on the effects of ibrutinib on fertility are available.

4.7 Effects on ability to drive and use machines

IMBRUVICA has minor influence on the ability to drive and use machines.

Fatigue, dizziness and asthenia have been reported in some patients taking IMBRUVICA and should be considered when assessing a patient's ability to drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly occurring adverse reactions (≥20%) were diarrhoea, neutropenia, musculoskeletal pain, rash, haemorrhage (e.g., bruising), thrombocytopenia, nausea, pyrexia, arthralgia, and upper respiratory tract infection. The most common grade 3/4 adverse reactions (≥5%) were neutropenia, lymphocytosis, thrombocytopenia, pneumonia, and hypertension.

Tabulated list of adverse reactions
The safety profile is based on pooled data from 1552 patients treated with IMBRUVICA in three phase 2 clinical studies and seven randomised phase 3 studies and from post-marketing experience. Patients treated for MCL in clinical studies received IMBRUVICA at 560 mg once daily and patients treated for CLL or WM in clinical studies received IMBRUVICA at 420 mg once daily. All patients in clinical studies received IMBRUVICA until disease progression or no longer tolerated. The median duration of IMBRUVICA treatment across the pooled dataset was 17.4 months. The median duration of treatment for CLL/SLL was 18.2 months (up to 52 months); MCL was 11.7 months (up to 28 months); WM was 21.6 months (up to 37 months).

Adverse reactions in patients treated with ibrutinib for B-cell malignancies and post-marketing adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported in clinical studies or during post marketing surveillance in patients with B-cell malignancies[†]

System organ class	Frequency (All grades)	Adverse reactions	All Grades (%)	Grade ≥3 (%)
Infections and infestations	Very common	Pneumonia[*#]	14	8
		Upper respiratory tract infection	20	1
		Skin infection[*]	15	3
	Common	Sepsis[*#]	4	3
		Urinary tract infection	9	2
		Sinusitis[*]	10	1
	Uncommon	Cryptococcal infections[*]	<1	0
		Pneumocystis infections[*#]	1	<1
		Aspergillus infections[*]	<1	<1
		Hepatitis B reactivation[@#]	<1	<1
Neoplasms benign and malignant (incl cysts and polyps)	Common	Non-melanoma skin cancer[*]	6	1
		Basal cell carcinoma	4	<1
		Squamous cell carcinoma	2	<1
Blood and lymphatic system disorders	Very common	Neutropenia[*]	38	29
		Thrombocytopenia[*]	32	9
		Lymphocytosis[*]	19	14
	Common	Febrile neutropenia	4	4
		Leukocytosis	5	4
	Rare	Leukostasis syndrome	<1	<1
Immune system disorders	Common	Interstitial lung disease[*,#,a]	2	<1
Metabolism and nutrition disorders	Very common	Hyperuricaemia	10	1
	Uncommon	Tumour lysis syndrome[a]	1	1
Nervous system disorders	Very common	Dizziness	12	<1
		Headache	19	1
	Common	Peripheral neuropathy[*,a]	8	<1
	Uncommon	Cerebrovascular accident[a, #]	<1	<1
		Transient ischaemic attack[a]	<1	<1
	Rare	Ischaemic stroke[a, #]	<1	<1
Eye disorders	Common	Vision blurred	7	0
Cardiac disorders	Common	Cardiac failure[a,*, #]	2	1
		Atrial fibrillation	7	4
		Ventricular tachyarrhythmia[*,a,#]	1	<1
Vascular disorders	Very common	Haemorrhage[*#]	32	1
		Bruising[*]	25	1
		Hypertension[*]	18	8
	Common	Epistaxis	8	<1
		Petechiae	6	0
	Uncommon	Subdural haematoma[#]	1	<1

Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation	42 14 14 28 16	3 1 1 1 <1
Hepatobiliary disorders	Uncommon	Hepatic failure*,a #	<1	<1
Skin and subcutaneous tissue disorders	Very common	Rash*	35	3
	Common	Urticaria[a] Erythema[a] Onychoclasis[a]	1 2 3	<1 0 0
	Uncommon	Angioedema[a] Panniculitis*,a Neutrophilic dermatoses*, a	<1 <1 <1	<1 <1 <1
	Not known	Stevens-Johnson syndrome[a]	Not known	Not known
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Muscle spasms Musculoskeletal pain*	20 14 37	2 <1 3
General disorders and administration site conditions	Very common	Pyrexia Oedema peripheral	22 18	1 1
Investigations	Very common	Blood creatinine increased	11	<1

† Frequencies are rounded to the nearest integer.

* Includes multiple adverse reaction terms.

Includes events with fatal outcome.

@ Lower level term (LLT) used for selection.

a Spontaneous reports from post-marketing experience.

Description of selected adverse reactions

Discontinuation and dose reduction due to adverse reactions

Of the 1552 patients treated with IMBRUVICA for B-cell malignancies, 6% discontinued treatment primarily due to adverse reactions. These included pneumonia, atrial fibrillation, thrombocytopenia, haemorrhage, neutropenia, rash, and arthralgia. Adverse reactions leading to dose reduction occurred in approximately 8% of patients.

Elderly

Of the 1552 patients treated with IMBRUVICA, 52% were 65 years of age or older. Grade 3 or higher pneumonia (12% of patients age ≥65 versus 5% of patients <65 years) and thrombocytopenia (12% of patients age ≥65 years versus 6% of patients <65 years) occurred more frequently among elderly patients treated with IMBRUVICA.

Long-term safety

The safety data from long-term treatment with IMBRUVICA over 5 years from 1284 patients (treatment-naïve CLL/SLL n = 162, relapsed/refractory CLL/SLL n = 646, relapsed/refractory MCL n = 370, and WM n = 106) were analysed. The median duration of treatment for CLL/SLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of patients receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of patients receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for WM was 47 months (range, 0.3 to 61 months) with 78% and 46% of patients receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of IMBRUVICA-exposed patients remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall incidence for the 5-year period was 11%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are limited data on the effects of IMBRUVICA overdose. No maximum tolerated dose was reached in the phase 1 study in which patients received up to 12.5 mg/kg/day (1,400 mg/day). In a separate study, one healthy subject who received a dose of 1,680 mg experienced reversible grade 4 hepatic enzyme increases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. There is no specific antidote for IMBRUVICA. Patients who ingested more than the recommended dose should be closely monitored and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EL01.

Mechanism of action
Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including MCL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and CLL. BTK's pivotal role in signalling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis and adhesion. Preclinical studies have shown that ibrutinib effectively inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

Lymphocytosis
Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count >5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in about three fourths of patients with CLL treated with IMBRUVICA. This effect has also been observed in about one third of patients with relapsed or refractory MCL treated with IMBRUVICA. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of IMBRUVICA therapy and typically resolves within a median of 8.0 weeks in patients with MCL and 14 weeks in patients with CLL. A large increase in the number of circulating lymphocytes (e.g., >400,000/mcL) has been observed in some patients.

Lymphocytosis was not observed in patients with WM treated with IMBRUVICA.

In vitro platelet aggregation
In an *in vitro* study, ibrutinib demonstrated inhibition of collagen-induced platelet aggregation. Ibrutinib did not show meaningful inhibition of platelet aggregation using other agonists of platelet aggregation.

Effect on QT/QTc interval and cardiac electrophysiology
The effect of ibrutinib on the QTc interval was evaluated in 20 healthy male and female subjects in a randomised, double-blind thorough QT study with placebo and positive controls. At a supratherapeutic dose of 1,680 mg, ibrutinib did not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the baseline adjusted mean differences between ibrutinib and placebo was below 10 ms. In this same study, a concentration dependent shortening in the QTc interval was observed (-5.3 ms [90% CI: -9.4, -1.1] at a C_{max} of 719 ng/mL following the supratherapeutic dose of 1,680 mg).

Clinical efficacy and safety

MCL

The safety and efficacy of IMBRUVICA in patients with relapsed or refractory MCL were evaluated in a single open-label, multi-center phase 2 study (PCYC-1104-CA) of 111 patients. The median age was 68 years (range: 40 to 84 years), 77% were male and 92% were Caucasian. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater were excluded from the study. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range: 1 to 5 treatments), including 35% with prior high-dose chemotherapy, 43% with prior bortezomib, 24% with prior lenalidomide, and 11% with prior autologous or allogeneic stem cell transplant. At baseline, 39% of patients had bulky disease (≥5 cm), 49% had high-risk score by Simplified MCL International Prognostic Index (MIPI), and 72% had advanced disease (extranodal and/or bone marrow involvement) at screening.

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumour response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to IMBRUVICA are shown in Table 2.

Table 2: ORR and DOR in patients with relapsed or refractory MCL (Study PCYC-1104-CA)

	Total N=111
ORR (%)	67.6
95% CI (%)	(58.0; 76.1)
CR (%)	20.7
PR (%)	46.8
Median DOR (CR+PR) (months)	17.5 (15.8, NR)
Median time to initial response, months (range)	1.9 (1.4-13.7)
Median time to CR, months (range)	5.5 (1.7-11.5)

CI=confidence interval; CR=complete response; DOR=duration of response; ORR=overall response rate; PR=partial response; NR=not reached

The efficacy data was further evaluated by an Independent Review Committee (IRC) demonstrating an ORR of 69%, with a 21% complete response (CR) rate and a 48% partial response (PR) rate. The IRC estimated median DOR was 19.6 months.

The overall response to IMBRUVICA was independent of prior treatment including bortezomib and lenalidomide or underlying risk/prognostic factors, bulky disease, gender or age.

The safety and efficacy of IMBRUVICA were demonstrated in a randomised phase 3, open-label, multicenter study including 280 patients with MCL who received at least one prior therapy (Study MCL3001). Patients were randomised 1:1 to receive either IMBRUVICA orally at 560 mg once daily for 21 days or temsirolimus intravenously at 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Treatment on both arms continued until disease progression or unacceptable toxicity. The median age was 68 years (range, 34; 88 years), 74% were male and 87% were Caucasian. The median time since diagnosis was 43 months, and median number of prior treatments was 2 (range: 1 to 9 treatments), including 51% with prior high-dose chemotherapy, 18% with prior bortezomib, 5% with prior lenalidomide, and 24% with prior stem cell transplant. At baseline, 53% of patients had bulky disease (≥5 cm), 21% had high-risk score by Simplified MIPI, 60% had extranodal disease and 54% had bone marrow involvement at screening.

Progression-free survival (PFS) was assessed by IRC according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. Efficacy results for Study MCL3001 are shown in Table 3 and the Kaplan-Meier curve for PFS in Figure 1.

Table 3: Efficacy Results in patients with relapsed or refractory MCL (Study MCL3001)

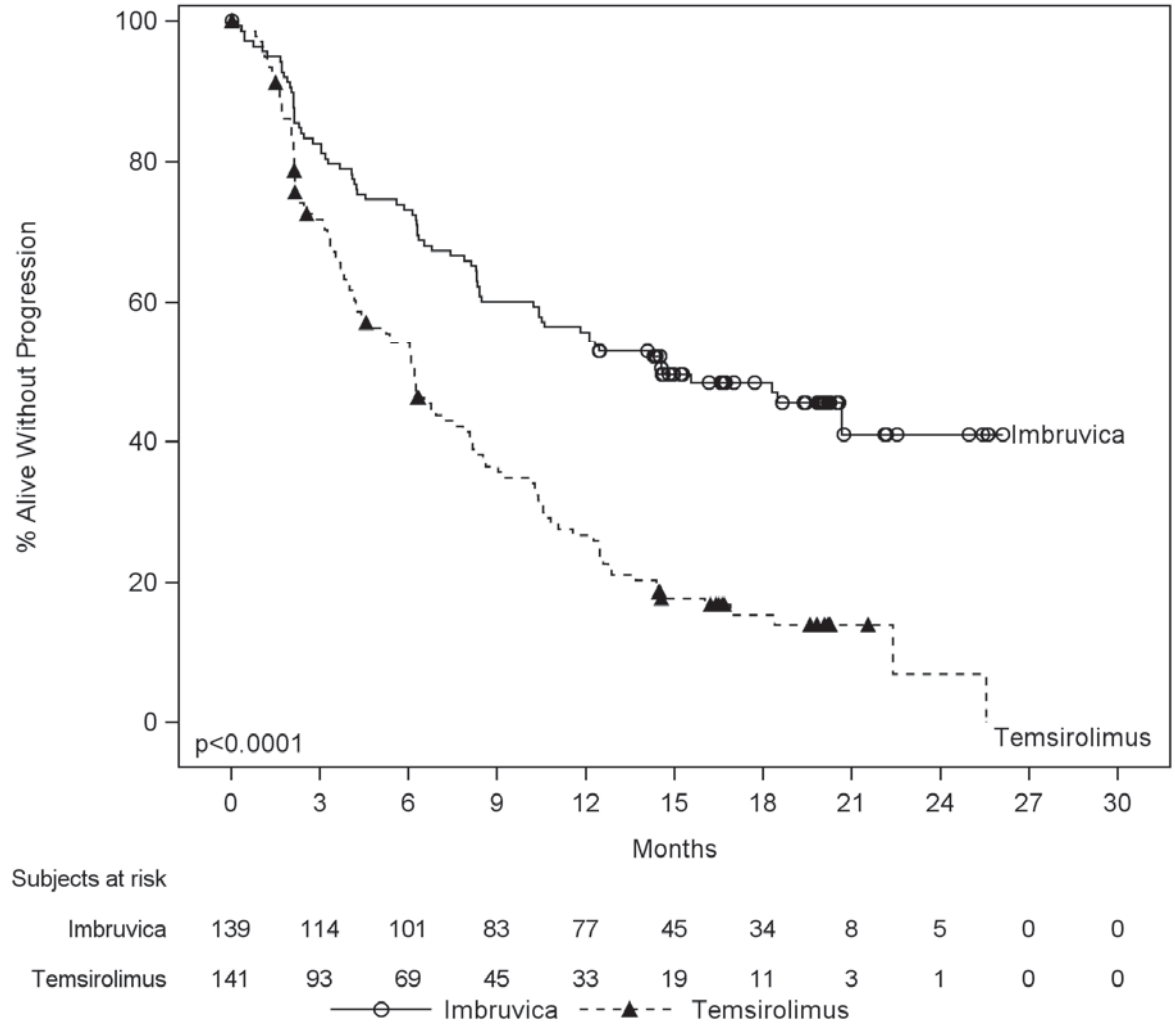
Endpoint	IMBRUVICA N=139	Temsirolimus N=141
PFS[a]		
Median PFS (95% CI), (months)	14.6 (10.4, NE)	6.2 (4.2, 7.9)
	HR=0.43 [95% CI: 0.32, 0.58]	
ORR (%)	71.9	40.4
p-value	p<0.0001	

NE=not estimable; HR=hazard ratio; CI=confidence interval; ORR=overall response rate; PFS=progression-free survival

[a] IRC evaluated.

A smaller proportion of patients treated with ibrutinib experienced a clinically meaningful worsening of lymphoma symptoms versus temsirolimus (27% versus 52%) and time to worsening of symptoms occurred more slowly with ibrutinib versus temsirolimus (HR 0.27, p<0.0001).

Figure 1: Kaplan-Meier curve of PFS (ITT Population) in Study MCL3001



CLL

Patients previously untreated for CLL

Single agent

A randomised, multicenter, open-label phase 3 study (PCYC-1115-CA) of IMBRUVICA versus chlorambucil was conducted in patients with treatment-naïve CLL who were 65 years of age or older. Patients between 65 and 70 years of age were required to have at least one comorbidity that precluded the use of frontline chemo-immunotherapy with fludarabine, cyclophosphamide, and rituximab. Patients (n=269) were randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on days 1 and

15 of each 28-day cycle for a maximum of 12 cycles, with an allowance for intrapatient dose increases up to 0.8 mg/kg based on tolerability. After confirmed disease progression, patients on chlorambucil were able to crossover to ibrutinib.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety one percent of patients had a baseline ECOG performance status of 0 or 1 and 9% had an ECOG performance status of 2. The study enrolled 269 patients with CLL. At baseline, 45% had advanced clinical stage (Rai Stage III or IV), 35% of patients had at least one tumor ≥5 cm, 39% with baseline anaemia, 23% with baseline thrombocytopenia, 65% had elevated β2 microglobulin >3500 mcg/L, 47% had a CrCL<60 mL/min, 20% of patients presented with del11q, 6% of patients presented with del17p/tumor protein 53 (TP53) mutation, and 44% of patients presented with unmutated immunoglobulin heavy chain variable region (IGHV).

Progression free survival (PFS) as assessed by IRC according to International Workshop on CLL (IWCLL) criteria indicated an 84% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. Efficacy results for Study PCYC-1115-CA are shown in Table 4 and the Kaplan-Meier curves for PFS and OS are shown in Figures 2 and 3, respectively.

There was a statistically significant sustained platelet or haemoglobin improvement in the ITT population in favor of ibrutinib versus chlorambucil. In patients with baseline cytopenias, sustained haematologic improvement was: platelets 77.1% versus 42.9%; haemoglobin 84.3% versus 45.5% for ibrutinib and chlorambucil respectively.

Table 4: Efficacy results in Study PCYC-1115-CA

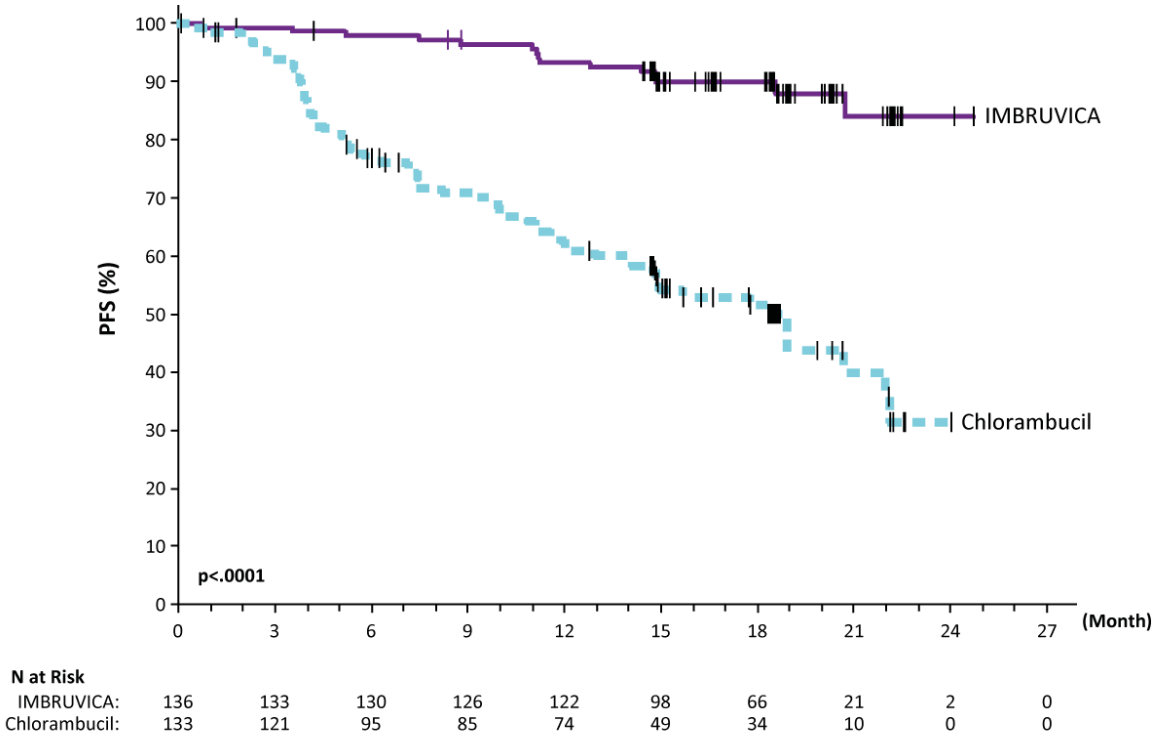
Endpoint	**IMBRUVICA N=136**	**Chlorambucil N=133**
PFS[a]		
Number of events (%)	15 (11.0)	64 (48.1)
Median (95% CI), months	Not reached	18.9 (14.1, 22.0)
HR (95% CI)	0.161 (0.091, 0.283)	
ORR[a] (CR+PR)	82.4%	35.3%
P-value	<0.0001	
OS[b]		
Number of deaths (%)	3 (2.2)	17 (12.8)
HR (95% CI)	0.163 (0.048, 0.558)	

CI=confidence interval; HR=hazard ratio; CR=complete response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response

[a] IRC evaluated, median follow-up 18.4 months.

[b] Median OS not reached for both arms. p<0.005 for OS

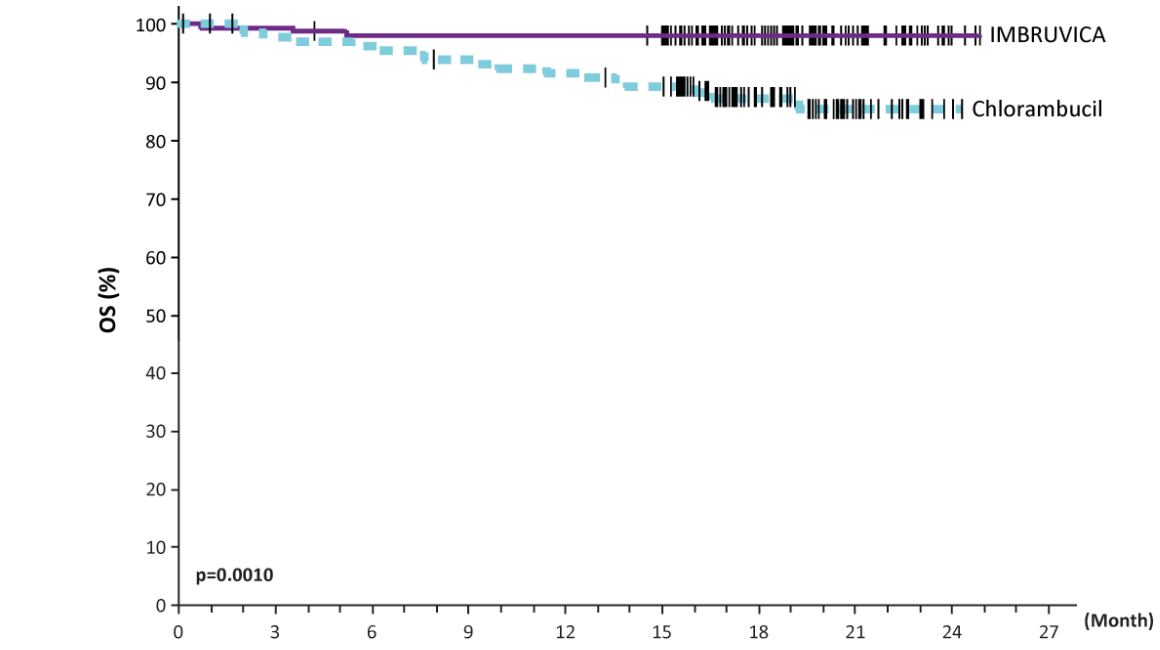
Figure 2: Kaplan-Meier curve of PFS (ITT Population) in Study PCYC-1115-CA



N at Risk

IMBRUVICA:	136	133	130	126	122	98	66	21	2	0
Chlorambucil:	133	121	95	85	74	49	34	10	0	0

Figure 3: Kaplan-Meier curve of OS (ITT Population) in Study PCYC-1115-CA



N at Risk

IMBRUVICA:	136	134	131	131	131	128	74	32	4	0
Chlorambucil:	133	127	125	121	118	113	62	24	1	0

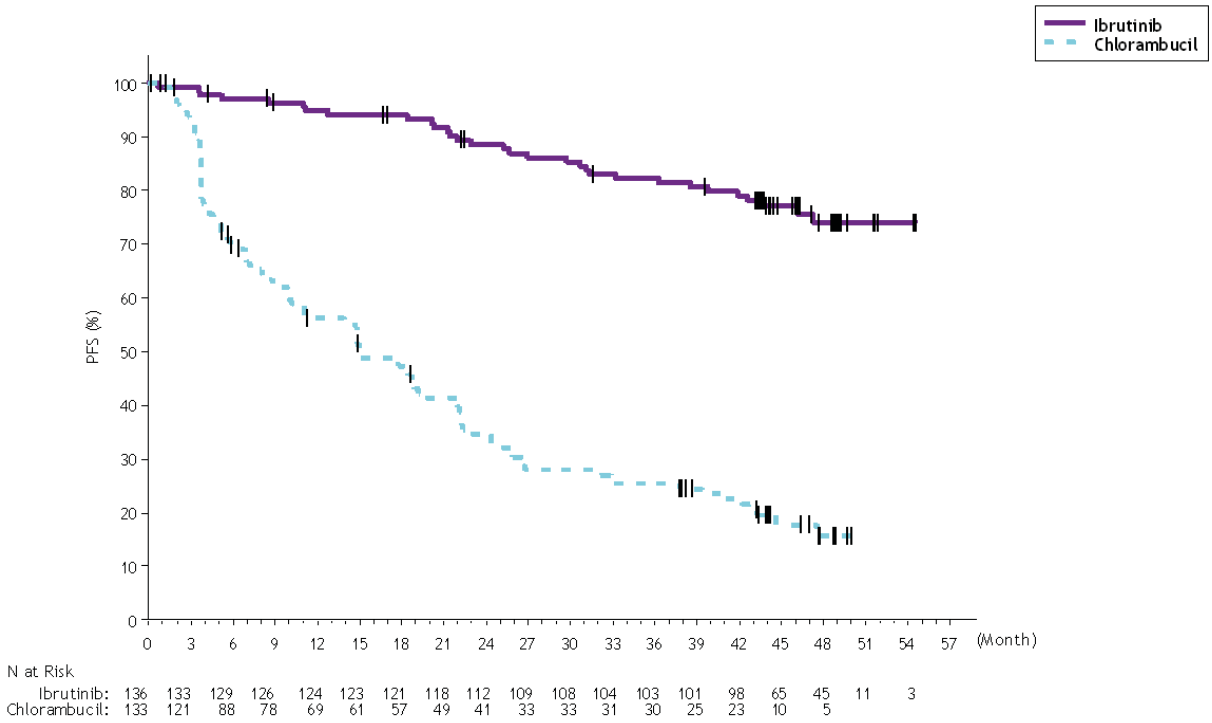
48-month follow-up

With a median follow-up time on study of 48 months in Study PCYC-1115-CA and its extension study, an 86% reduction in the risk of death or progression by investigator assessment was observed

for patients in the IMBRUVICA arm. The median investigator-assessed PFS was not reached in the IMBRUVICA arm and was 15 months [95% CI (10.22, 19.35)] in the chlorambucil arm; (HR=0.14 [95% CI (0.09, 0.21)]). The 4-year PFS estimate was 73.9% in the IMBRUVICA arm and 15.5% in the chlorambucil arm, respectively. The updated Kaplan-Meier curve for PFS is shown in Figure 4. The investigator-assessed ORR was 91.2% in the IMBRUVICA arm versus 36.8% in the chlorambucil arm. The CR rate according to IWCLL criteria was 16.2% in the IMBRUVICA arm versus 3.0% in the chlorambucil arm. At the time of long-term follow-up, a total of 73 subjects (54.9%) originally randomised to the chlorambucil arm subsequently received ibrutinib as cross-over treatment. The Kaplan-Meier landmark estimate for OS at 48-months was 85.5% in the IMBRUVICA arm.

The treatment effect of ibrutinib in Study PCYC-1115-CA was consistent across high-risk patients with del17p/TP53 mutation, del11q, and/or unmutated IGHV.

Figure 4: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1115-CA with 48 Months Follow-up



Combination therapy

The safety and efficacy of IMBRUVICA in patients with previously untreated CLL/SLL were further evaluated in a randomised, multi-center, open-label, phase 3 study (PCYC-1130-CA) of IMBRUVICA in combination with obinutuzumab versus chlorambucil in combination with obinutuzumab. The study enrolled patients who were 65 years of age or older or <65 years of age with coexisting medical conditions, reduced renal function as measured by creatinine clearance <70 mL/min, or presence of del17p/TP53 mutation. Patients (n=229) were randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity or chlorambucil at a dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for 6 cycles. In both arms, patients received 1000 mg of obinutuzumab on Days 1, 8 and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg).

The median age was 71 years (range, 40 to 87 years), 64% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (48%) or 1-2 (52%). At baseline, 52% had advanced clinical stage (Rai Stage III or IV), 32% of patients had bulky disease (≥5 cm), 44% with baseline anaemia, 22% with baseline thrombocytopenia, 28% had a CrCL <60 mL/min, and the median Cumulative Illness Rating Score for Geriatrics (CIRS-G) was 4 (range, 0 to 12). At baseline,

65% of patients presented with CLL/SLL with high risk factors (del17p/TP53 mutation [18%], del11q [15%], or unmutated IGHV [54%]).

Progression-free survival (PFS) was assessed by IRC according to IWCLL criteria indicated a 77% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. With a median follow-up time on study of 31 months, the median PFS was not reached in the IMBRUVICA+obinutuzumab arm and was 19 months in the chlorambucil+obinutuzumab arm. Efficacy results for Study PCYC-1130-CA are shown in Table 5 and the Kaplan-Meier curve for PFS is shown in Figure 5.

Table 5: Efficacy results in Study PCYC-1130-CA

Endpoint	**IMBRUVICA+Obinutuzumab N=113**	**Chlorambucil+Obinutuzumab N=116**
Progression Free Survival[a]		
Number of events (%)	24 (21.2)	74 (63.8)
Median (95% CI), months	Not reached	19.0 (15.1, 22.1)
HR (95% CI)	0.23 (0.15, 0.37)	
Overall Response Rate[a] (%)	88.5	73.3
CR[b]	19.5	7.8
PR[c]	69.0	65.5

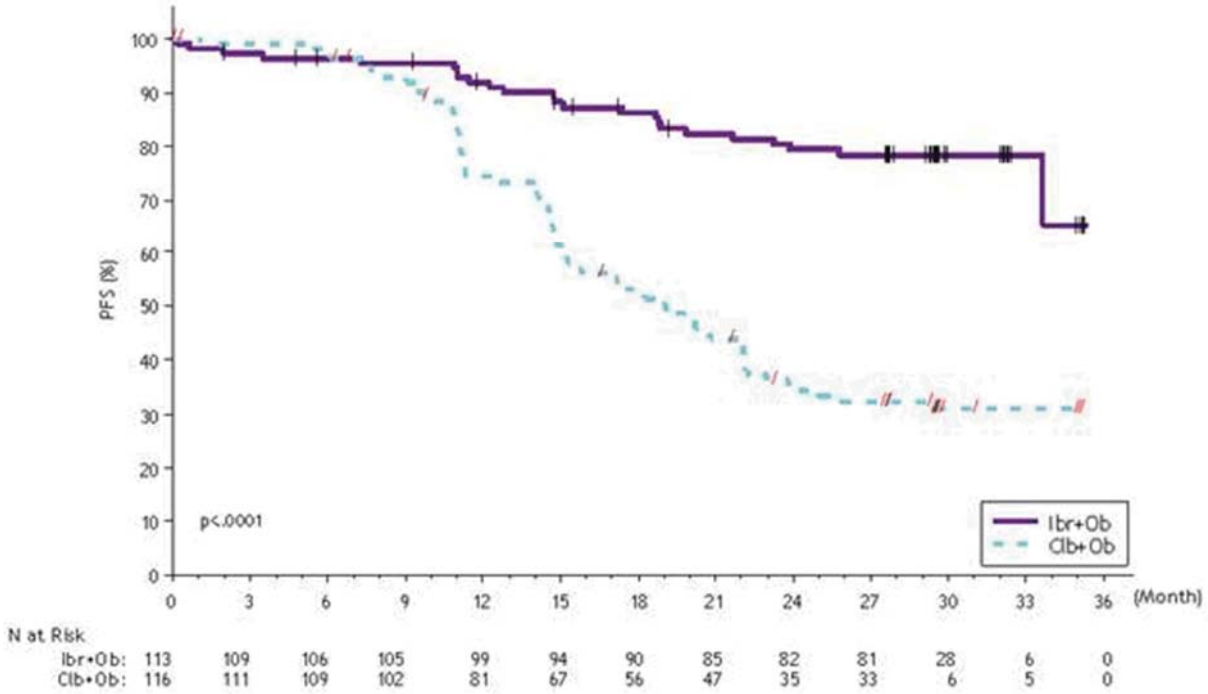
CI=confidence interval; HR=hazard ratio; CR=complete response; PR=partial response.

[a] IRC evaluated.

[b] Includes 1 patient in the IMBRUVICA+obinutuzumab arm with a complete response with incomplete marrow recovery (CRi).

[c] PR=PR+nPR.

Figure 5: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1130-CA



The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (del17p/TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.15 [95% CI (0.09, 0.27)], as shown in Table 6. The 2-year PFS rate estimates for the high-risk CLL/SLL population were 78.8% [95% CI (67.3, 86.7)] and 15.5% [95% CI (8.1, 25.2)] in the IMBRUVICA+obinutuzumab and chlorambucil+obinutuzumab arms, respectively.

Table 6: Subgroup Analysis of PFS (Study PCYC-1130-CA)

	N	Hazard Ratio	95% CI
All subjects	229	0.231	0.145, 0.367
High risk (del17p/TP53/del11q/unmutated IGHV)			
Yes	148	0.154	0.087, 0.270
No	81	0.521	0.221, 1.231
Del17p/TP53			
Yes	41	0.109	0.031, 0.380
No	188	0.275	0.166, 0.455
FISH			
Del17p	32	0.141	0.039, 0.506
Del11q	35	0.131	0.030, 0.573
Others	162	0.302	0.176, 0.520
Unmutated IGHV			
Yes	123	0.150	0.084, 0.269
No	91	0.300	0.120, 0.749
Age			
<65	46	0.293	0.122, 0.705
≥65	183	0.215	0.125, 0.372
Bulky disease			
<5 cm	154	0.289	0.161, 0.521
≥5 cm	74	0.184	0.085, 0.398
Rai stage			
0/I/II	110	0.221	0.115, 0.424
III/IV	119	0.246	0.127, 0.477
ECOG per CRF			
0	110	0.226	0.110, 0.464
1-2	119	0.239	0.130, 0.438

Hazard ratio based on non-stratified analysis

Any grade infusion-related reactions were observed in 25% of patients treated with IMBRUVICA+obinutuzumab and 58% of patients treated with chlorambucil+obinutuzumab. Grade 3 or higher or serious infusion-related reactions were observed in 3% of patients treated with IMBRUVICA+obinutuzumab and 9% of patients treated with chlorambucil+obinutuzumab.

The safety and efficacy of IMBRUVICA in patients with previously untreated CLL or SLL were further evaluated in a randomised, multi-center, open-label, phase 3 study (E1912) of IMBRUVICA in combination with rituximab (IR) versus standard fludarabine, cyclophosphamide, and rituximab (FCR) chemo-immunotherapy. The study enrolled previously untreated patients with CLL or SLL who were 70 years or younger. Patients with del17p were excluded from the study. Patients (n=529) were randomised 2:1 to receive either IR or FCR. IMBRUVICA was administered at a dose of 420 mg daily until disease progression or unacceptable toxicity. Fludarabine was administered at a dose of 25 mg/m^2, and cyclophosphamide was administered at a dose of 250 mg/m^2, both on Days 1, 2, and 3 of Cycles 1-6. Rituximab was initiated in Cycle 2 for the IR arm and in Cycle 1 for the FCR arm and was administered at a dose of 50 mg/m^2 on Day 1 of the first cycle, 325 mg/m^2 on Day 2 of the first cycle, and 500 mg/m^2 on Day 1 of 5 subsequent cycles, for a total of 6 cycles. Each cycle was 28 days.

The median age was 58 years (range, 28 to 70 years), 67% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1 (98%) or 2 (2%). At baseline, 43% of patients presented with Rai Stage III or IV, and 59% of patients presented with CLL/SLL with high risk factors (TP53 mutation [6%], del11q [22%], or unmutated IGHV [53%]).

With a median follow-up time on study of 37 months, efficacy results for E1912 are shown in Table 7. The Kaplan-Meier curves for PFS, assessed according to IWCLL criteria, and OS are shown in Figures 6 and 7, respectively.

Table 7: Efficacy results in Study E1912

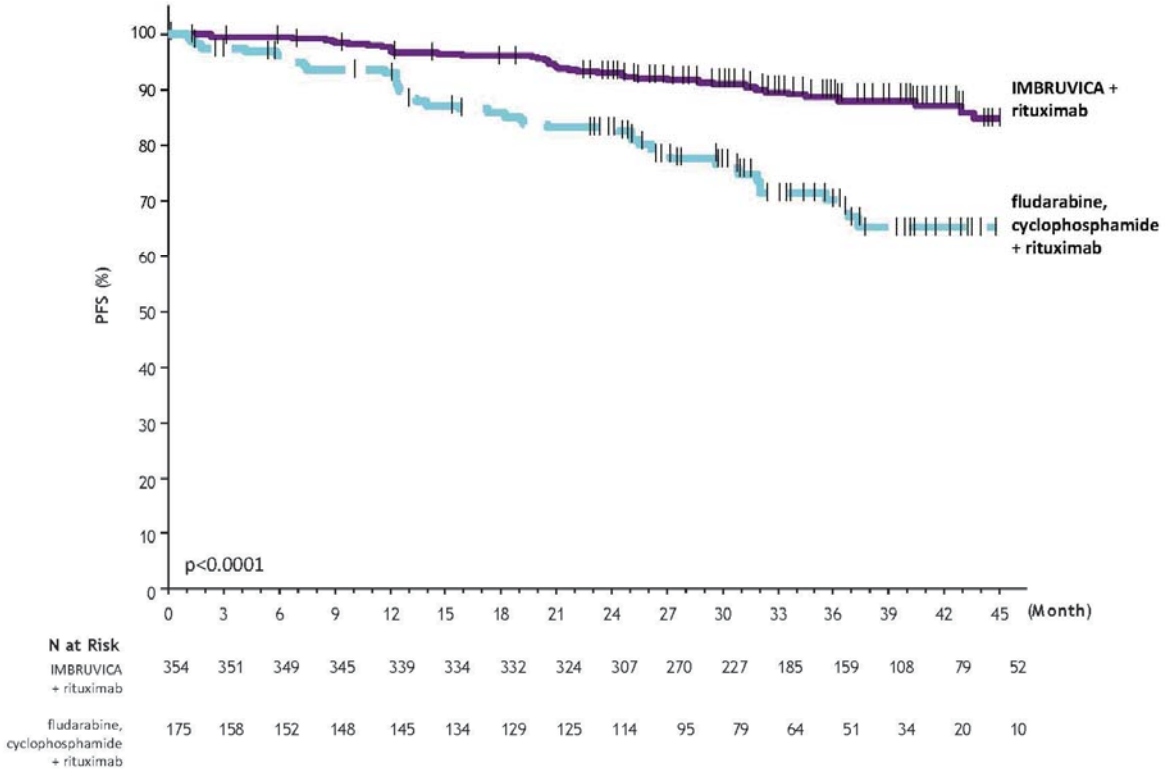
Endpoint	Ibrutinib+rituximab (IR) N=354	Fludarabine, Cyclophosphamide, and Rituximab (FCR) N=175
Progression Free Survival		
Number of events (%)	41 (12)	44 (25)
Disease progression	39	38
Death events	2	6
Median (95% CI), months	NE (49.4, NE)	NE (47.1, NE)
HR (95% CI)	0.34 (0.22, 0.52)	
P-value[a]	<0.0001	
Overall Survival		
Number of deaths (%)	4 (1)	10 (6)
HR (95% CI)	0.17 (0.05, 0.54)	
P-value[a]	0.0007	
Overall Response Rate[b] (%)	96.9	85.7

[a] P-value is from unstratified log-rank test.

[b] Investigator evaluated.

HR = hazard ratio; NE = not evaluable

Figure 6: Kaplan-Meier Curve of PFS (ITT Population) in Study E1912



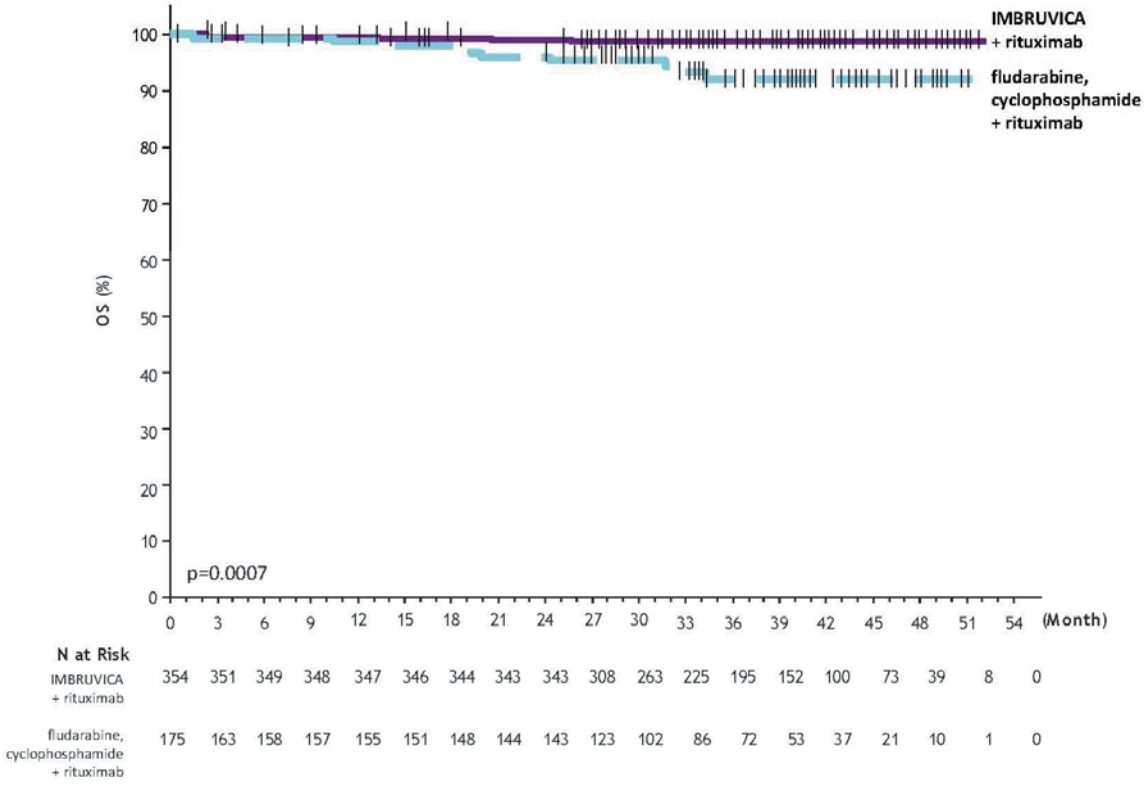
The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (TP53 mutation, del11q, or unmutated IGHV), with a PFS HR of 0.23 [95% CI (0.13, 0.40)], p <0.0001, as shown in Table 8. The 3-year PFS rate estimates for the high-risk CLL/SLL population were 90.4% [95% CI (85.4, 93.7)] and 60.3% [95% CI (46.2, 71.8)] in the IR and FCR arms, respectively.

Table 8: Subgroup Analysis of PFS (Study E1912)

	N	Hazard Ratio	95% CI
All subjects	529	0.340	0.222, 0.522
High risk (TP53/del11q/unmutated IGHV)			
Yes	313	0.231	0.132, 0.404
No	216	0.568	0.292, 1.105
del11q			
Yes	117	0.199	0.088, 0.453
No	410	0.433	0.260, 0.722
Unmutated IGHV			
Yes	281	0.233	0.129, 0.421
No	112	0.741	0.276, 1.993
Bulky disease			
<5 cm	316	0.393	0.217, 0.711
≥5 cm	194	0.257	0.134, 0.494
Rai stage			
0/I/II	301	0.398	0.224, 0.708
III/IV	228	0.281	0.148, 0.534
ECOG			
0	335	0.242	0.138, 0.422
1-2	194	0.551	0.271, 1.118

Hazard ratio based on non-stratified analysis

Figure 7: Kaplan-Meier Curve of OS (ITT Population) in Study E1912



Patients with CLL who received at least one prior therapy
Single agent
The safety and efficacy of IMBRUVICA in patients with CLL were demonstrated in one uncontrolled study and one randomised, controlled study. The open-label, multi-center study (PCYC-1102-CA) included 51 patients with relapsed or refractory CLL, who received 420 mg once daily. IMBRUVICA was administered until disease progression or unacceptable toxicity. The median age was 68 years (range: 37 to 82 years), median time since diagnosis was 80 months, and median number of prior

treatments was 4 (range: 1 to 12 treatments), including 92.2% with a prior nucleoside analog, 98.0% with prior rituximab, 86.3% with a prior alkylator, 39.2% with prior bendamustine and 19.6% with prior ofatumumab. At baseline, 39.2% of patients had Rai Stage IV, 45.1% had bulky disease (≥5 cm), 35.3% had deletion 17p and 31.4% had deletion 11q.

ORR was assessed according to the 2008 IWCLL criteria by investigators and IRC. At a median duration follow up of 16.4 months, the ORR by IRC for the 51 relapsed or refractory patients was 64.7% (95% CI: 50.1%; 77.6%), all PRs. The ORR including PR with lymphocytosis was 70.6%. Median time to response was 1.9 months. The DOR ranged from 3.9 to 24.2+ months. The median DOR was not reached.

A randomised, multi-center, open-label phase 3 study of IMBRUVICA versus ofatumumab (PCYC-1112-CA) was conducted in patients with relapsed or refractory CLL. Patients (n=391) were randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or ofatumumab for up to 12 doses (300/2,000 mg). Fifty-seven patients randomised to ofatumumab crossed over following progression to receive IMBRUVICA. The median age was 67 years (range: 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range: 1 to 13 treatments). At baseline, 58% of patients had at least one tumour ≥5 cm. Thirty-two percent of patients had deletion 17p (with 50% of patients having deletion 17p/TP53 mutation), 24% had 11q deletion, and 47% of patients had unmutated IGHV.

Progression free survival (PFS) as assessed by an IRC according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA arm. Analysis of OS demonstrated a 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study PCYC-1112-CA are shown in Table 9.

Table 9: Efficacy results in patients with CLL (Study PCYC-1112-CA)

Endpoint	**IMBRUVICA N=195**	**Ofatumumab N=196**
Median PFS	Not reached	8.1 months
	HR=0.215 [95% CI: 0.146; 0.317]	
OS[a]	HR=0.434 [95% CI: 0.238; 0.789][b] HR=0.387 [95% CI: 0.216; 0.695][c]	
ORR[d, e] (%)	42.6	4.1
ORR including PR with lymphocytosis[d] (%)	62.6	4.1

HR=hazard ratio; CI=confidence interval; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response

[a] Median OS not reached for both arms. p<0.005 for OS.

[b] Patients randomised to ofatumumab were censored when starting IMBRUVICA if applicable.

[c] Sensitivity analysis in which crossover patients from the ofatumumab arm were not censored at the date of first dose of IMBRUVICA.

[d] Per IRC. Repeat CT scans required to confirm response.

[e] All PRs achieved; p<0.0001 for ORR.

Median follow-up time on study=9 months

The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Table 10).

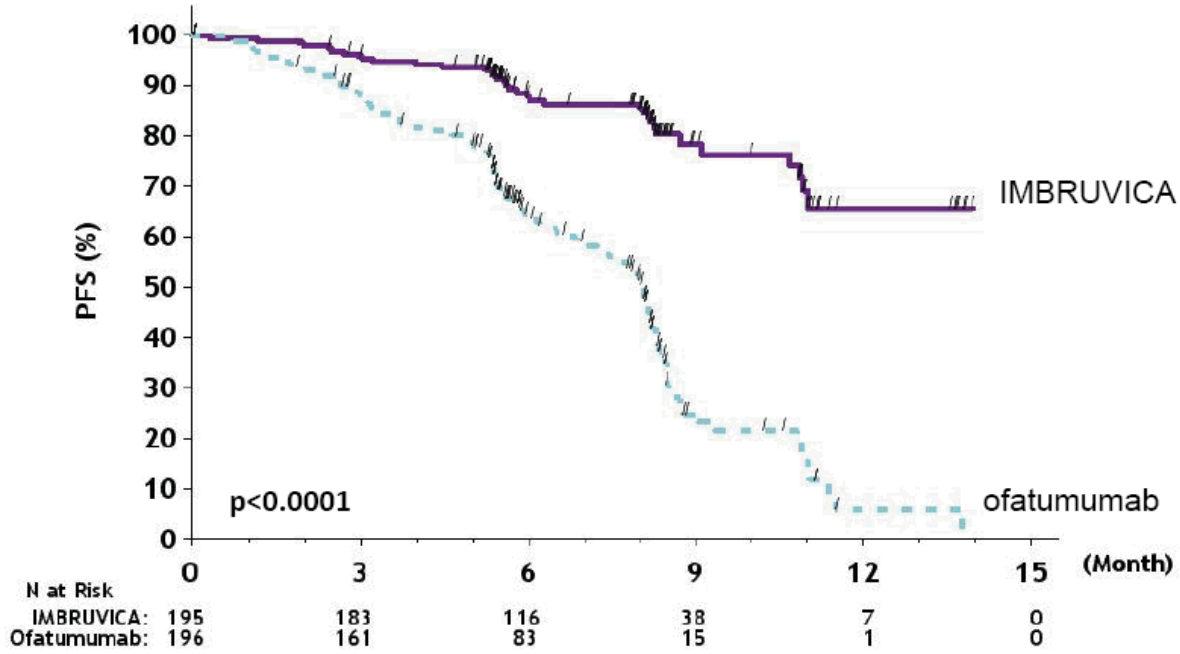
Table 10: Subgroup analysis of PFS (Study PCYC-1112-CA)

	N	Hazard Ratio	95% CI
All subjects	391	0.210	(0.143; 0.308)
Del17P			
Yes	127	0.247	(0.136; 0.450)
No	264	0.194	(0.117; 0.323)
Refractory disease to purine analog			
Yes	175	0.178	(0.100; 0.320)
No	216	0.242	(0.145; 0.404)
Age			
<65	152	0.166	(0.088; 0.315)
≥65	239	0.243	(0.149; 0.395)
Number of prior lines			
<3	198	0.189	(0.100; 0.358)
≥3	193	0.212	(0.130; 0.344)
Bulky disease			
<5 cm	163	0.237	(0.127; 0.442)
≥5 cm	225	0.191	(0.117; 0.311)

Hazard ratio based on non-stratified analysis

The Kaplan-Meier curve for PFS is shown in Figure 8.

Figure 8: Kaplan-Meier curve of PFS (ITT Population) in Study PCYC-1112- CA



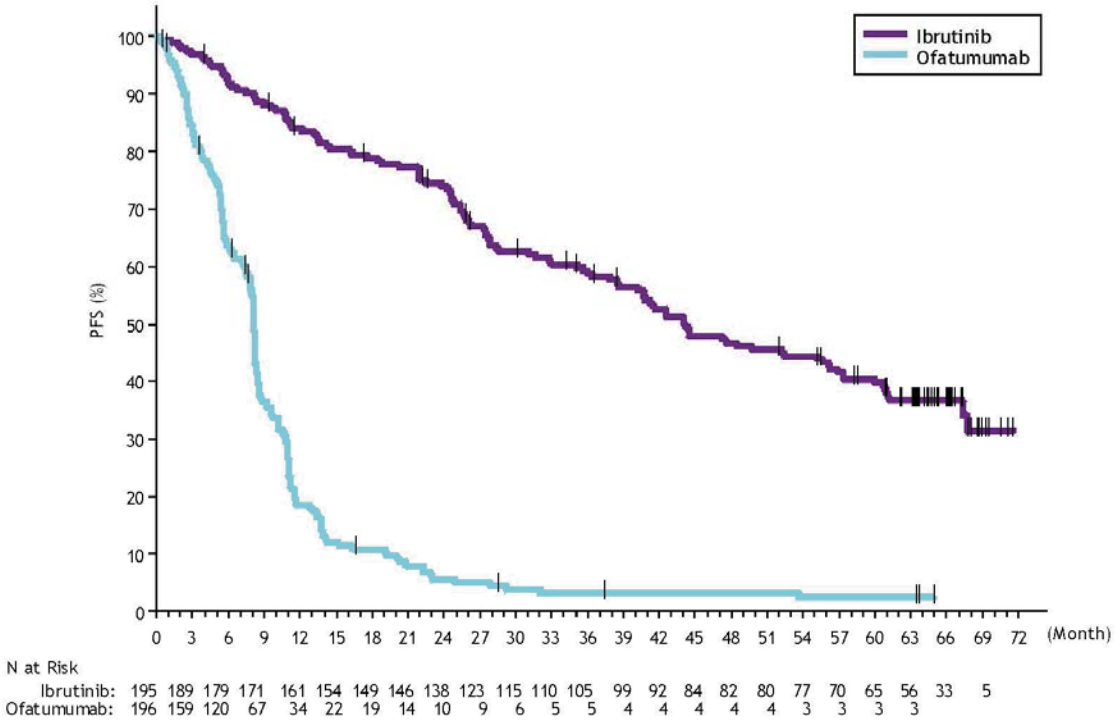
Final Analysis at 65-month follow-up

With a median follow-up time on study of 65 months in Study PCYC-1112-CA, an 85% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The median investigator-assessed PFS according to IWCLL criteria was 44.1 months [95% CI (38.47, 56.18)] in the IMBRUVICA arm and 8.1 months [95% CI (7.79, 8.25)] in the ofatumumab arm, respectively; HR=0.15 [95% CI (0.11, 0.20)]. The updated Kaplan-Meier curve for PFS is shown in Figure 9. The investigator-assessed ORR in the IMBRUVICA arm was 87.7% versus 22.4% in the ofatumumab arm. At the time of final analysis, 133 (67.9%) of the 196 subjects originally randomised to the ofatumumab treatment arm had crossed over to ibrutinib treatment. The median investigator-assessed PFS2 (time from randomisation until PFS event after first subsequent anti-neoplastic therapy) according to IWCLL criteria was 65.4 months [95% CI (51.61, not estimable)] in the IMBRUVICA arm and 38.5 months [95% CI (19.98, 47.24)] in the ofatumumab

arm, respectively; HR=0.54 [95% CI (0.41, 0.71)]. The median OS was 67.7 months [95% CI (61.0, not estimable)] in the IMBRUVICA arm.

The treatment effect of ibrutinib in Study PCYC-1112-CA was consistent across high-risk patients with deletion 17p/TP53 mutation, deletion 11q, and/or unmutated IGHV.

Figure 9: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1112-CA at Final Analysis with 65 months Follow-up



Combination therapy

The safety and efficacy of IMBRUVICA in patients previously treated for CLL were further evaluated in a randomised, multicenter, double-blinded phase 3 study of IMBRUVICA in combination with BR versus placebo+BR (Study CLL3001). Patients (n=578) were randomised 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m^2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1. Ninety patients randomised to placebo+BR crossed over to receive IMBRUVICA following IRC confirmed progression. The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 6 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumour ≥5 cm, 26% had del11q.

Progression free survival (PFS) was assessed by IRC according to IWCLL criteria. Efficacy results for Study CLL3001 are shown in Table 11.

Table 11: Efficacy Results in patients with CLL (Study CLL3001)

Endpoint	IMBRUVICA+BR N=289	Placebo+BR N=289
PFS[a]		
Median (95% CI), months	Not reached	13.3 (11.3, 13.9)
	HR=0.203 [95% CI: 0.150, 0.276]	
ORR[b] %	82.7	67.8
OS[c]	HR=0.628 [95% CI: 0.385, 1.024]	

CI=confidence interval; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

[a] IRC evaluated.

[b] IRC evaluated, ORR (complete response, complete response with incomplete marrow recovery, nodular partial response, partial response).

[c] Median OS not reached for both arms.

WM

Single agent

The safety and efficacy of IMBRUVICA in WM (IgM-excreting lymphoplasmacytic lymphoma) were evaluated in an open-label, multi-center, single-arm trial of 63 previously treated patients. The median age was 63 years (range: 44 to 86 years), 76% were male, and 95% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range: 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL, and 60% of patients were anaemic (haemoglobin ≤11 g/dL or 6.8 mmol/L).

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The primary endpoint in this study was ORR per investigator assessment. The ORR and DOR were assessed using criteria adopted from the Third International Workshop of WM. Responses to IMBRUVICA are shown in Table 12.

Table 12: ORR and DOR in patients with WM

	Total (N=63)
ORR (%)	87.3
95% CI (%)	(76.5, 94.4)
VGPR (%)	14.3
PR (%)	55.6
MR (%)	17.5
Median DOR months (range)	NR (0.03+, 18.8+)

CI=confidence interval; DOR=duration of response; NR=not reached; MR=minor response; PR=partial response; VGPR=very good partial response; ORR=MR+PR+VGPR
Median follow-up time on study=14.8 months

The median time to response was 1.0 month (range: 0.7-13.4 months).
Efficacy results were also assessed by an IRC demonstrating an ORR of 83%, with a 11% VGPR rate and a 51% PR rate.

Combination therapy

The safety and efficacy of IMBRUVICA in WM were further evaluated in patients with treatment-naïve or previously treated WM in a randomised, multicenter, double-blinded phase 3 study of IMBRUVICA in combination with rituximab versus placebo in combination with rituximab (PCYC-1127-CA). Patients (n=150) were randomised 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with rituximab until disease progression or unacceptable toxicity. Rituximab was administered weekly at a dose of 375 mg/m^2 for 4 consecutive weeks (weeks 1-4) followed by a second course of weekly rituximab for 4 consecutive weeks (weeks 17-20).

The median age was 69 years (range, 36 to 89 years), 66% were male, and 79% were Caucasian. Ninety-three percent of patients had a baseline ECOG performance status of 0 or 1, and 7% of patients had a baseline ECOG performance status of 2. Forty-five percent of patients were treatment-naïve, and 55% of patients were previously treated. The median time since diagnosis was 52.6 months (treatment-

naïve patients=6.5 months and previously treated patients=94.3 months). Among previously treated patients, the median number of prior treatments was 2 (range, 1 to 6 treatments). At baseline, the median serum IgM value was 3.2 g/dL (range, 0.6 to 8.3 g/dL), 63% of patients were anaemic (haemoglobin ≤11 g/dL or 6.8 mmol/L) and MYD88 L265P mutations were present in 77% of patients, absent in 13% of patients, and 9% of patients were not evaluable for mutation status.

At the primary analysis, with a median follow-up of 26.5 months, the IRC-assessed PFS hazard ratio was 0.20 [95% CI (0.11, 0.38)]. PFS hazard ratios for treatment-naïve patients, previously treated patients, and patients with or without MYD88 L265P mutations were consistent with the PFS hazard ratio for the ITT population.

Grade 3 or 4 infusion-related reactions were observed in 1% of patients treated with IMBRUVICA+rituximab and 16% of patients treated with placebo+rituximab.

Tumor flare in the form of IgM increase occurred in 8.0% of subjects in the IMBRUVICA+rituximab arm and 46.7% of subjects in the placebo+rituximab arm.

Final Analysis at 63-month follow-up
With an overall follow-up of 63 months, efficacy results as assessed by an IRC at the time of the final analysis for PCYC-1127-CA are shown in Table 13 and the Kaplan-Meier curve for PFS is shown in Figure 10. PFS hazard ratios for treatment-naïve patients (0.31 [95% CI (0.14, 0.69)]) and previously treated patients (0.22 [95% CI (0.11, 0.43)]) were consistent with the PFS hazard ratio for the ITT population.

Table 13: Efficacy results in Study PCYC-1127-CA (Final Analysis[*])

Endpoint	IMBRUVICA + R N=75	Placebo + R N=75
Progression Free Survival[a, b]		
Number of events (%)	22 (29)	50 (67)
Median (95% CI), months	Not reached	20.3 (13.0, 27.6)
HR (95% CI)	0.25 (0.15, 0.42)	
P-value	<0.0001	
Time to next treatment		
Median (95% CI), months	Not reached	18.1 (11.1, 33.1)
HR (95% CI)	0.1 (0.05, 0.21)	
Best Overall Response (%)		
CR	1.3	1.3
VGPR	29.3	4.0
PR	45.3	25.3
MR	16.0	13.3
Overall Response Rate[c] (CR, VGPR, PR, MR) (%)	69 (92.0)	33 (44.0)
Median duration of overall response, months (range)	Not reached (2.7, 58.9+)	27.6 (1.9, 55.9+)
Response Rate (CR, VGPR, PR)[c, d] (%)	57 (76.0)	23 (30.7)
Median duration of response, months (range)	Not reached (1.9+, 58.9+)	Not reached (4.6, 49.7+)
Rate of Sustained Hemoglobin Improvement[c, e] (%)	77.3	42.7

CI = confidence interval; CR = complete response; HR = hazard ratio; MR = minor response; PR = partial response; R = Rituximab; VGPR = very good partial response

* Median follow-up time on study = 49.7 months.

[a] IRC evaluated.

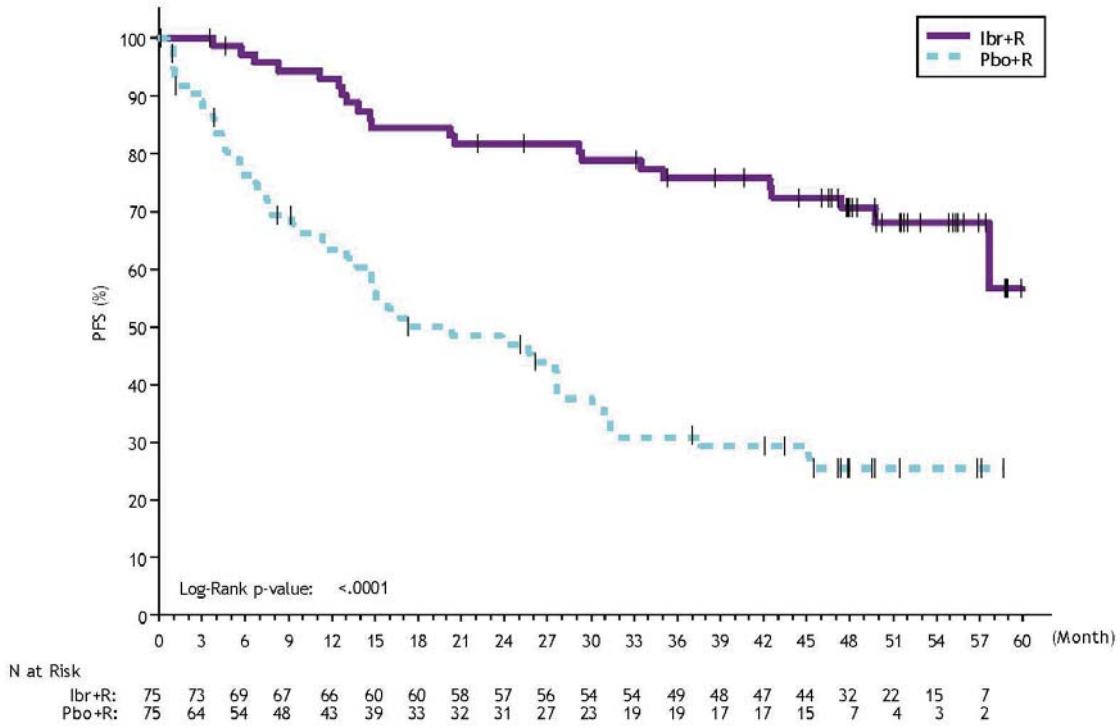
[b] 4-year PFS estimates were 70.6% [95% CI (58.1, 80.0)] in the IMBRUVICA + R arm versus 25.3% [95% CI (15.3, 36.6)] in the placebo + R arm.

[c] p-value associated with response rate was <0.0001.

[d] Response rate was 76% vs 41% in treatment-naïve patients and 76% vs 22% in previously treated patients for the IMBRUVICA + R arm vs the placebo + R arm, respectively.

[e] Defined as increase of ≥2 g/dL over baseline regardless of baseline value, or an increase to >11 g/dL with a ≥0.5 g/dL improvement if baseline was ≤11 g/dL.

Figure 10: Kaplan-Meier Curve of PFS (ITT Population) in Study PCYC-1127-CA (Final Analysis)



Study PCYC-1127-CA had a separate monotherapy arm of 31 patients with previously treated WM who failed prior rituximab-containing therapy and received single agent IMBRUVICA. The median age was 67 years (range, 47 to 90 years). Eighty-one percent of patients had a baseline ECOG performance status of 0 or 1, and 19% had a baseline ECOG performance status of 2. The median number of prior treatments was 4 (range, 1 to 7 treatments). With an overall follow-up of 61 months, the response rate observed in Study PCYC-1127-CA monotherapy arm per IRC assessment was 77% (0% CR, 29% VGPR, 48% PR). The median duration of response was 33 months (range, 2.4 to 60.2+ months). The overall response rate per IRC observed in the monotherapy arm was 87% (0% CR, 29% VGPR, 48% PR, 10% MR). The median duration of overall response was 39 months (range, 2.07 to 60.2+ months).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with IMBRUVICA in all subsets of the paediatric population in MCL, CLL and lymphoplasmacytic lymphoma (LPL) (for information on paediatric use, see section 4.2).

5.2 Pharmacokinetic properties

Absorption

Ibrutinib is rapidly absorbed after oral administration with a median T_{max} of 1 to 2 hours. Absolute bioavailability in fasted condition (n=8) was 2.9% (90% CI=2.1 – 3.9) and doubled when combined

with a meal. Pharmacokinetics of ibrutinib does not significantly differ in patients with different B-cell malignancies. Ibrutinib exposure increases with doses up to 840 mg. The steady state AUC observed in patients at 560 mg is (mean ± standard deviation) 953 ± 705 ng h/mL. Administration of ibrutinib in fasted condition resulted in approximately 60% of exposure (AUC_{last}) as compared to either 30 minutes before, 30 minutes after (fed condition) or 2 hours after a high fat breakfast.

Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. In fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days, compared to ibrutinib alone, geometric mean ratios (90% CI) were 83% (68-102%), 92% (78-110%), and 38% (26-53%) for AUC_{0-24}, AUC_{last}, and C_{max}, respectively.

Distribution
Reversible binding of ibrutinib to human plasma protein *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1,000 ng/mL. The apparent volume of distribution at steady state ($V_{d, ss}/F$) was approximately 10,000 L.

Metabolism
Ibrutinib is metabolised primarily by CYP3A4 to produce a dihydrodiol metabolite with an inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Involvement of CYP2D6 in the metabolism of ibrutinib appears to be minimal.

Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

Elimination
Apparent clearance (CL/F) is approximately 1,000 L/h. The half-life of ibrutinib is 4 to 13 hours. After a single oral administration of radiolabeled [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the faeces and <10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in faeces and none in urine.

Special populations
Elderly
Population pharmacokinetics indicated that age does not significantly influence ibrutinib clearance from the circulation.

Paediatric population
No pharmacokinetic studies were performed with IMBRUVICA in patients under 18 years of age.

Gender
Population pharmacokinetics data indicated that gender does not significantly influence ibrutinib clearance from the circulation.

Race
There are insufficient data to evaluate the potential effect of race on ibrutinib pharmacokinetics.

Body weight
Population pharmacokinetics data indicated that body weight (range: 41-146 kg; mean [SD]: 83 [19 kg]) had a negligible effect on ibrutinib clearance.

Renal impairment
Ibrutinib has minimal renal clearance; urinary excretion of metabolites is <10% of the dose. No specific studies have been conducted to date in subjects with impaired renal function. There are no data in patients with severe renal impairment or patients on dialysis (see section 4.2).

Hepatic impairment
Ibrutinib is metabolised in the liver. A hepatic impairment trial was performed in non-cancer subjects administered a single dose of 140 mg of medicinal product under fasting conditions. The effect of

impaired liver function varied substantially between individuals, but on average a 2.7-, 8.2-, and 9.8-fold increase in ibrutinib exposure (AUC_{last}) was observed in subjects with mild (n=6, Child-Pugh class A), moderate (n=10, Child-Pugh class B) and severe (n=8, Child-Pugh class C) hepatic impairment, respectively. The free fraction of ibrutinib also increased with degree of impairment, with 3.0, 3.8 and 4.8% in subjects with mild, moderate and severe liver impairment, respectively, compared to 3.3% in plasma from matched healthy controls within this study. The corresponding increase in unbound ibrutinib exposure ($AUC_{unbound, last}$) is estimated to be 4.1-, 9.8-, and 13-fold in subjects with mild, moderate, and severe hepatic impairment, respectively (see section 4.2).

Co-administration with transport substrates/inhibitors
In vitro studies indicated that ibrutinib is not a substrate of P-gp, nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is an *in vitro* inhibitor of P-gp and BCRP (see section 4.5).

5.3 Preclinical safety data

The following adverse effects were seen in studies of 13-weeks duration in rats and dogs. Ibrutinib was found to induce gastrointestinal effects (soft faeces/diarrhoea and/or inflammation) and lymphoid depletion in rats and dogs with a No Observed Adverse Effect Level (NOAEL) of 30 mg/kg/day in both species. Based on mean exposure (AUC) at the 560 mg/day clinical dose, AUC ratios were 2.6 and 21 at the NOAEL in male and female rats, and 0.4 and 1.8 at the NOAEL in male and female dogs, respectively. Lowest Observed Effect Level (LOEL) (60 mg/kg/day) margins in the dog are 3.6-fold (males) and 2.3-fold (females). In rats, moderate pancreatic acinar cell atrophy (considered adverse) was observed at doses of ≥100 mg/kg in male rats (AUC exposure margin of 2.6-fold) and not observed in females at doses up to 300 mg/kg/day (AUC exposure margin of 21.3-fold). Mildly decreased trabecular and cortical bone was seen in female rats administered ≥100 mg/kg/day (AUC exposure margin of 20.3-fold). All gastrointestinal, lymphoid and bone findings recovered following recovery periods of 6-13 weeks. Pancreatic findings partially recovered during comparable reversal periods.

Juvenile toxicity studies have not been conducted.

Carcinogenicity/genotoxicity
Ibrutinib was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse at oral doses up to 2000 mg/kg/day with an exposure margin of approximately 23 (males) to 37 (females) times the human AUC of ibrutinib at a dose of 560 mg daily.
Ibrutinib has no genotoxic properties when tested in bacteria, mammalian cells or in mice.

Reproductive toxicity
In pregnant rats, ibrutinib at a dose of 80 mg/kg/day was associated with increased post-implantation loss and increased visceral (heart and major vessels) malformations and skeletal variations with an exposure margin 14 times the AUC found in patients at a daily dose of 560 mg. At a dose of ≥40 mg/kg/day, ibrutinib was associated with decreased foetal weights (AUC ratio of ≥5.6 as compared to daily dose of 560 mg in patients). Consequently the foetal NOAEL was 10 mg/kg/day (approximately 1.3 times the AUC of ibrutinib at a dose of 560 mg daily) (see section 4.6).

In pregnant rabbits, ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal malformations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased post-implantation loss. Ibrutinib caused malformations in rabbits at a dose of 15 mg/kg/day (approximately 2.0 times the exposure (AUC) in patients with MCL administered ibrutinib 560 mg daily and 2.8 times the exposure in patients with CLL or WM receiving ibrutinib dose 420 mg per day). Consequently the foetal NOAEL was 5 mg/kg/day (approximately 0.7 times the AUC of ibrutinib at a dose of 560 mg daily) (see section 4.6).

Fertility
No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (HED 16 mg/kg/day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Colloidal anhydrous silica
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Povidone
Sodium lauril sulfate (E487)

Film-coat
IMBRUVICA 140 mg film-coated tablets and IMBRUVICA 420 mg film-coated tablets
Macrogol
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Black iron oxide (E172)
Yellow iron oxide (E172)

IMBRUVICA 280 mg film-coated tablets
Macrogol
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Black iron oxide (E172)
Red iron oxide (E172)

IMBRUVICA 560 mg film-coated tablets
Macrogol
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinyl chloride (PVC) laminated with polychlorotrifluoroethylene (PCTFE)/aluminium blister of 14 film-coated tablets in a cardboard wallet. Each carton contains (28 film-coated tablets) 2 wallets.

Polyvinyl chloride (PVC) laminated with polychlorotrifluoroethylene (PCTFE)/aluminium blister of 10 film-coated tablets in a cardboard wallet. Each carton contains (30 film-coated tablets) 3 wallets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

IMBRUVICA 140 mg film-coated tablets
EU/1/14/945/007 – 28 tablets (2 wallet packs of 14)
EU/1/14/945/008 – 30 tablets (3 wallet packs of 10)

IMBRUVICA 280 mg film-coated tablets
EU/1/14/945/009 – 28 tablets (2 wallet packs of 14)
EU/1/14/945/010 – 30 tablets (3 wallet packs of 10)

IMBRUVICA 420 mg film-coated tablets
EU/1/14/945/011 – 28 tablets (2 wallet packs of 14)
EU/1/14/945/005 – 30 tablets (3 wallet packs of 10)

IMBRUVICA 560 mg film-coated tablets
EU/1/14/945/012 – 28 tablets (2 wallet packs of 14)
EU/1/14/945/006 – 30 tablets (3 wallet packs of 10)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 October 2014
Date of latest renewal: 25 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

IMBRUVICA Hard Capsules
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

IMBRUVICA Film-Coated Tablets
Janssen-Cilag SpA
Via C. Janssen,
Loc. Borgo S. Michele,
04100 Latina,
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 140 MG CAPSULE

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg hard capsules
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 140 mg of ibrutinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/001 (90 hard capsules)
EU/1/14/945/002 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 140 MG CAPSULE

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg capsules
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 140 mg of ibrutinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/001 (90 hard capsules)
EU/1/14/945/002 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 140 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 140 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/007 (28 tablets)
EU/1/14/945/008 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 140 MG TABLET (28 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 140 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Oral use

HOW TO TAKE IMBRUVICA
Use as directed by your physician.
Take IMBRUVICA tablet by mouth, at about the same time each day, with a glass of water.
Swallow the tablet whole. Do not break or chew.
If you miss a dose of IMBRUVICA, take it as soon as you remember on the same day. Do not take extra doses to make up the missed dose.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 140 MG TABLET (30 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 140 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

When you take a tablet, fill in the day of the week or the date in the space provided.

HOW TO TAKE IMBRUVICA
Use as directed by your physician.
Take IMBRUVICA tablet by mouth, at about the same time each day, with a glass of water.
Swallow the tablet whole. Do not break or chew.
If you miss a dose of IMBRUVICA, take it as soon as you remember on the same day. Do not take extra doses to make up the missed dose.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 140 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg tablets
ibrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 280 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 280 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 280 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/009 (28 tablets)
EU/1/14/945/010 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 280 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 280 MG TABLET (28 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 280 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 280 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Oral use

HOW TO TAKE IMBRUVICA
Use as directed by your physician.
Take IMBRUVICA tablet by mouth, at about the same time each day, with a glass of water.
Swallow the tablet whole. Do not break or chew.
If you miss a dose of IMBRUVICA, take it as soon as you remember on the same day. Do not take extra doses to make up the missed dose.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 280 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 280 MG TABLET (30 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 280 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 280 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

When you take a tablet, fill in the day of the week or the date in the space provided.

HOW TO TAKE IMBRUVICA
Use as directed by your physician.
Take IMBRUVICA tablet by mouth, at about the same time each day, with a glass of water.
Swallow the tablet whole. Do not break or chew.
If you miss a dose of IMBRUVICA, take it as soon as you remember on the same day. Do not take extra doses to make up the missed dose.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 280 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 280 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 280 mg tablets
ibrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 420 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 420 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 420 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/011 (28 tablets)
EU/1/14/945/005 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 420 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 420 MG TABLET (28 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 420 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 420 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Oral use

HOW TO TAKE IMBRUVICA
Use as directed by your physician.
Take IMBRUVICA tablet by mouth, at about the same time each day, with a glass of water.
Swallow the tablet whole. Do not break or chew.
If you miss a dose of IMBRUVICA, take it as soon as you remember on the same day. Do not take extra doses to make up the missed dose.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 420 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 420 MG TABLET (30 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 420 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 420 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

When you take a tablet, fill in the day of the week or the date in the space provided.

HOW TO TAKE IMBRUVICA
Use as directed by your physician.
Take IMBRUVICA tablet by mouth, at about the same time each day, with a glass of water.
Swallow the tablet whole. Do not break or chew.
If you miss a dose of IMBRUVICA, take it as soon as you remember on the same day. Do not take extra doses to make up the missed dose.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 420 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 420 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 420 mg tablets
ibrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 560 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 560 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 560 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/012 (28 tablets)
EU/1/14/945/006 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 560 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 560 MG TABLET (28 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 560 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 560 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Oral use

HOW TO TAKE IMBRUVICA
Use as directed by your physician.
Take IMBRUVICA tablet by mouth, at about the same time each day, with a glass of water.
Swallow the tablet whole. Do not break or chew.
If you miss a dose of IMBRUVICA, take it as soon as you remember on the same day. Do not take extra doses to make up the missed dose.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 560 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 560 MG TABLET (30 days)

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 560 mg film-coated tablets
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 560 mg of ibrutinib

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

When you take a tablet, fill in the day of the week or the date in the space provided.

HOW TO TAKE IMBRUVICA
Use as directed by your physician.
Take IMBRUVICA tablet by mouth, at about the same time each day, with a glass of water.
Swallow the tablet whole. Do not break or chew.
If you miss a dose of IMBRUVICA, take it as soon as you remember on the same day. Do not take extra doses to make up the missed dose.

Flip open the pack. Push tablet through from other side.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imbruvica 560 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 560 MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 560 mg tablets
ibrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

IMBRUVICA 140 mg hard capsules
ibrutinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMBRUVICA is and what it is used for
2. What you need to know before you take IMBRUVICA
3. How to take IMBRUVICA
4. Possible side effects
5. How to store IMBRUVICA
6. Contents of the pack and other information

1. What IMBRUVICA is and what it is used for

What IMBRUVICA is
IMBRUVICA is an anticancer medicine that contains the active substance ibrutinib. It belongs to a class of medicines called protein kinase inhibitors.

What IMBRUVICA is used for
It is used to treat the following blood cancers in adults:
- Mantle cell lymphoma (MCL), a type of cancer affecting the lymph nodes, when the disease has come back or has not responded to treatment.
- Chronic lymphocytic leukaemia (CLL) a type of cancer affecting white blood cells called lymphocytes that also involves the lymph nodes. IMBRUVICA is used in patients who have not previously been treated for CLL or when the disease has come back or has not responded to treatment.
- Waldenström's macroglobulinaemia (WM), a type of cancer affecting white blood cells called lymphocytes. It is used in patients who have not previously been treated for WM or when the disease has come back or has not responded to treatment or in patients for whom chemotherapy given together with an antibody is not a suitable therapy.

How IMBRUVICA works
In MCL, CLL and WM, IMBRUVICA works by blocking Bruton's tyrosine kinase, a protein in the body that helps these cancer cells grow and survive. By blocking this protein, IMBRUVICA helps kill and reduce the number of cancer cells. It also slows down the worsening of the cancer.

2. What you need to know before you take IMBRUVICA

Do not take IMBRUVICA
- if you are allergic to ibrutinib or any of the other ingredients of this medicine (listed in section 6)
- if you are taking a herbal medicine called St. John's Wort, used for depression. If you are not sure about this, talk to your doctor, pharmacist or nurse before taking this medicine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking IMBRUVICA:

- if you have ever had unusual bruising or bleeding or are on any medicines or supplements that increase your risk of bleeding (see section **"Other medicines and IMBRUVICA"**)
- if you have irregular heart beat or have a history of irregular heart beat or severe heart failure, or if you feel any of the following: shortness of breath, weakness, dizziness, light-headedness, fainting or near fainting, chest pain or swollen legs
- if you have liver or kidney problems
- if you have high blood pressure
- if you have recently had any surgery, especially if this might affect how you absorb food or medicines from your stomach or gut
- if you are planning to have any surgery– your doctor may ask you to stop taking IMBRUVICA for a short time (3 to 7 days) before and after your surgery.
- if you have ever had or might now have a hepatitis B infection. This is because IMBRUVICA could cause hepatitis B to become active again, which can be fatal. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking this medicine.

When taking IMBRUVICA, tell your doctor immediately if you notice or someone notices in you: memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare but serious brain infection which can be fatal (Progressive Multifocal Leukoencephalopathy or PML).

Tell your doctor immediately if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke.

Tell your doctor immediately if you develop left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of rupture of the spleen) after you stop taking IMBRUVICA.

Tell your doctor immediately if you notice breathlessness, difficulty breathing when lying down, swelling of the feet, ankles or legs and weakness/tiredness (these may be signs of heart failure) during treatment with IMBRUVICA.

You may experience viral, bacterial, or fungal infections during treatment with IMBRUVICA. Contact your doctor if you have fever, chills, weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath, yellowing of the skin or eyes (jaundice). These could be signs of an infection.

Haemophagocytic lymphohistiocytosis
There have been rare reports of excessive activation of white blood cells associated with inflammation (haemophagocytic lymphohistiocytosis), which can be fatal if not diagnosed and treated early. If you experience multiple symptoms such as fever, swollen glands, bruising, or skin rash, contact your doctor immediately.

Tests and check-ups before and during treatment
Tumour lysis syndrome (TLS): Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or another healthcare provider may do blood tests to check for TLS.

Lymphocytosis: Laboratory tests may show an increase in white blood cells (called "lymphocytes") in your blood in the first few weeks of treatment. This is expected and may last for a few months. This does not necessarily mean that your blood cancer is getting worse. Your doctor will check your blood

counts before or during the treatment and in rare cases they may need to give you another medicine. Talk to your doctor about what your test results mean.

Children and adolescents
IMBRUVICA should not be used in children and adolescents. This is because it has not been studied in these age groups.

Other medicines and IMBRUVICA
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, herbal medicines and supplements. This is because IMBRUVICA may affect the way some other medicines work. Also some other medicines can affect the way IMBRUVICA works.

IMBRUVICA may make you bleed more easily. This means you should tell your doctor if you take other medicines that increase your risk of bleeding. This includes:
- acetyl salicylic acid and non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen or naproxen
- blood thinners such as warfarin, heparin or other medicines for blood clots
- supplements that may increase your risk of bleeding such as fish oil, vitamin E or flaxseed.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

Also tell your doctor if you take any of the following medicines – The effects of IMBRUVICA or other medicines may be influenced if you take IMBRUVICA together with any of the following medicines:
- medicines called antibiotics to treat bacterial infections – clarithromycin, telithromycin, ciprofloxacin, erythromycin or rifampicin
- medicines for fungal infections – posaconazole, ketoconazole, itraconazole, fluconazole or voriconazole
- medicines for HIV infection – ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, or fosamprenavir
- medicines to prevent nausea and vomiting associated with chemotherapy - aprepitant
- medicines for depression - nefazodon
- medicines called kinase inhibitors for treatment of other cancers – crizotinib or imatinib
- medicines called calcium channel blockers for high blood pressure or chest pain – diltiazem or verapamil
- medicines called statins to treat high cholesterol - rosuvastatin
- heart medicines/anti-arrhythmics – amiodarone or dronedarone
- medicines to prevent seizures or to treat epilepsy, or medicines to treat a painful condition of the face called trigeminal neuralgia – carbamazepine or phenytoin.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

If you are taking digoxin, a medicine used for heart problems, or methotrexate, a medicine used to treat other cancers and to reduce the activity of the immune system (e.g., for rheumatoid arthritis or psoriasis), it should be taken at least 6 hours before or after IMBRUVICA.

IMBRUVICA with food
Do not take IMBRUVICA with grapefruit or Seville oranges (bitter oranges) – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because it can increase the amount of IMBRUVICA in your blood.

Pregnancy and breast-feeding
Do not get pregnant while you are taking this medicine. IMBRUVICA should not be used during pregnancy. There is no information about the safety of IMBRUVICA in pregnant women.

Women of childbearing age must use a highly effective method of birth control during and up to three months after receiving IMBRUVICA, to avoid becoming pregnant while being treated with IMBRUVICA.

- Tell your doctor immediately if you become pregnant.
- Do not breast-feed while you are taking this medicine.

Driving and using machines
You may feel tired or dizzy after taking IMBRUVICA, which may affect your ability to drive or use any tools or machines.

IMBRUVICA contains sodium
IMBRUVICA contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take IMBRUVICA

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
Mantle cell lymphoma (MCL)
The recommended dose of IMBRUVICA is four capsules (560 mg) once a day.

Chronic lymphocytic leukaemia (CLL)/Waldenström's macroglobulinaemia (WM)
The recommended dose of IMBRUVICA is three capsules (420 mg) once a day.

Your doctor may adjust your dose.

Taking this medicine
- Take the capsules orally (by mouth) with a glass of water.
- Take the capsules about the same time each day.
- Swallow the capsules whole. Do not open, break or chew them.

If you take more IMBRUVICA than you should
If you take more IMBRUVICA than you should, talk to a doctor or go to a hospital straight away. Take the capsules and this leaflet with you.

If you forget to take IMBRUVICA
- If you miss a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.
- Do not take a double dose to make up for a forgotten dose.
- If you are not sure, talk to your doctor, pharmacist or nurse about when to take your next dose.

If you stop taking IMBRUVICA
Do not stop taking this medicine unless your doctor tells you.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects may happen with this medicine:

Stop taking IMBRUVICA and tell a doctor straight away if you notice any of the following side effects:
itchy bumpy rash, difficulty breathing, swelling of your face, lips, tongue or throat – you may be having an allergic reaction to the medicine.

Tell a doctor straight away if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath – these could be signs of an infection (viral, bacterial or fungal). These could include infections of the nose, sinus or throat (upper respiratory tract infection), or lung, or skin.
- bruising or increased tendency of bruising.
- mouth sores
- feeling dizzy
- headache
- constipation
- feeling or being sick (nausea or vomiting)
- diarrhoea, your doctor may need to give you a fluid and salt replacement or another medicine
- skin rash
- painful arms or legs
- back pain or joint pain
- muscle cramps, aches or spasms
- low number of cells that help blood clot (platelets), very low number of white blood cells – shown in blood tests
- an increase in the number or proportion of white blood cells shown in blood tests
- high level of "uric acid" in the blood (shown in blood tests), which may cause gout
- swollen hands, ankles or feet
- high blood pressure
- increased level of "creatinine" in the blood.

Common (may affect up to 1 in 10 people)
- severe infections throughout the body (sepsis)
- infections of the urinary tract
- nose bleeds, small red or purple spots caused by bleeding under the skin
- blood in your stomach, gut, stools or urine, heavier periods, or bleeding that you cannot stop from an injury
- heart failure
- fast heart rate, missed heart beats, weak or uneven pulse, lightheadedness, shortness of breath, chest discomfort (symptoms of heart rhythm problems)
- low white blood cell counts with fever (febrile neutropenia)
- non-melanoma skin cancer, most frequently squamous cell and basal cell skin cancer
- blurred vision
- redness of the skin
- inflammation within the lungs that may lead to permanent damage
- breaking of the nails
- weakness, numbness, tingling or pain in your hands or feet or other parts of the body (peripheral neuropathy).

Uncommon (may affect up to 1 in 100 people)
- liver failure, including events with fatal outcome
- severe fungal infections
- confusion, headache with slurred speech or feeling faint – these could be signs of serious internal bleeding in your brain

- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment (tumour lysis syndrome)
- allergic reaction, sometimes severe, that may include a swollen face, lip, mouth, tongue or throat, difficulty swallowing or breathing, itchy rash (hives)
- inflammation of the fatty tissue underneath the skin
- temporary episode of decreased brain or nerve function caused by loss of blood flow, stroke
- painful skin ulceration (pyoderma gangrenosum) or red, raised painful patches on the skin, fever and an increase in white blood cells (these may be signs of acute febrile neutrophilic dermatosis or Sweet's syndrome).

Rare (may affect up to 1 in 1,000 people)
- severely increased white blood cell count that may cause cells to clump together.

Not known (frequency cannot be estimated from available data)
- severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMBRUVICA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IMBRUVICA contains
- The active substance is ibrutinib. Each hard capsule contains 140 mg of ibrutinib.
- The other ingredients are:
  - capsule content: croscarmellose sodium, magnesium stearate, microcrystalline cellulose and sodium lauril sulfate (E487)
  - capsule shell: gelatin and titanium dioxide (E171)
  - printing ink: shellac, black iron oxide (E172), and propylene glycol (E1520).

What IMBRUVICA looks like and contents of the pack
IMBRUVICA are white opaque, hard capsules marked with "ibr 140 mg" in black ink on one side. The capsules are provided in a plastic bottle with a child resistant polypropylene closure. Each bottle contains either 90 or 120 capsules. Each pack contains one bottle.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: +32 14 64 94 11
janssen@jacbe.jnj.com

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

България
„Джонсън & Джонсън България" ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: +32 14 64 94 11
janssen@jacbe.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel: +420 227 012 227

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Danmark
Janssen-Cilag A/S
Tlf: +45 4594 8282
jacdk@its.jnj.com

Malta
AM MANGION LTD.
Tel: +356 2397 6000

Deutschland
Janssen-Cilag GmbH
Tel: +49 2137 955 955
jancil@its.jnj.com

Nederland
Janssen-Cilag B.V.
Tel: +31 76 711 1111
janssen@jacnl.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική A.E.B.E.
Τηλ: +30 210 80 90 000

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.:+48 22 237 60 00

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: +353 1 800 709 122

Ísland
Janssen-Cilag AB
c/o Vistor hf
Sími: +354 535 7000
janssen@vistor.is

Italia
Janssen-Cilag SpA
Tel: 800 688 777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel.: +386 1 401 18 00
Janssen_safety_slo@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

United Kingdom (Northern Ireland)
Janssen Sciences Ireland UC
Tel: +44 1 494 567 444

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient

IMBRUVICA 140 mg film-coated tablets
IMBRUVICA 280 mg film-coated tablets
IMBRUVICA 420 mg film-coated tablets
IMBRUVICA 560 mg film-coated tablets
ibrutinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMBRUVICA is and what it is used for
2. What you need to know before you take IMBRUVICA
3. How to take IMBRUVICA
4. Possible side effects
5. How to store IMBRUVICA
6. Contents of the pack and other information

1. What IMBRUVICA is and what it is used for

What IMBRUVICA is
IMBRUVICA is an anticancer medicine that contains the active substance ibrutinib. It belongs to a class of medicines called protein kinase inhibitors.

What IMBRUVICA is used for
It is used to treat the following blood cancers in adults:
- Mantle cell lymphoma (MCL), a type of cancer affecting the lymph nodes, when the disease has come back or has not responded to treatment.
- Chronic lymphocytic leukaemia (CLL) a type of cancer affecting white blood cells called lymphocytes that also involves the lymph nodes. IMBRUVICA is used in patients who have not previously been treated for CLL or when the disease has come back or has not responded to treatment.
- Waldenström's macroglobulinaemia (WM), a type of cancer affecting white blood cells called lymphocytes. It is used in patients who have not previously been treated for WM or when the disease has come back or has not responded to treatment or in patients for whom chemotherapy given together with an antibody is not a suitable therapy.

How IMBRUVICA works
In MCL, CLL and WM, IMBRUVICA works by blocking Bruton's tyrosine kinase, a protein in the body that helps these cancer cells grow and survive. By blocking this protein, IMBRUVICA helps kill and reduce the number of cancer cells. It also slows down the worsening of the cancer.

2. What you need to know before you take IMBRUVICA

Do not take IMBRUVICA
- if you are allergic to ibrutinib or any of the other ingredients of this medicine (listed in section 6)

- if you are taking a herbal medicine called St. John's Wort, used for depression. If you are not sure about this, talk to your doctor, pharmacist or nurse before taking this medicine.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking IMBRUVICA:
- if you have ever had unusual bruising or bleeding or are on any medicines or supplements that increase your risk of bleeding (see section **"Other medicines and IMBRUVICA"**)
- if you have irregular heart beat or have a history of irregular heart beat or severe heart failure, or if you feel any of the following: shortness of breath, weakness, dizziness, light-headedness, fainting or near fainting, chest pain or swollen legs
- if you have liver or kidney problems
- if you have high blood pressure
- if you have recently had any surgery, especially if this might affect how you absorb food or medicines from your stomach or gut
- if you are planning to have any surgery– your doctor may ask you to stop taking IMBRUVICA for a short time (3 to 7 days) before and after your surgery.
- if you have ever had or might now have a hepatitis B infection. This is because IMBRUVICA could cause hepatitis B to become active again, which can be fatal. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking this medicine.

When taking IMBRUVICA, tell your doctor immediately if you notice or someone notices in you: memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare but serious brain infection which can be fatal (Progressive Multifocal Leukoencephalopathy or PML).

Tell your doctor immediately if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke.

Tell your doctor immediately if you develop left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of rupture of the spleen) after you stop taking IMBRUVICA.

Tell your doctor immediately if you notice breathlessness, difficulty breathing when lying down, swelling of the feet, ankles or legs and weakness/tiredness (these may be signs of heart failure) during treatment with IMBRUVICA.

You may experience viral, bacterial, or fungal infections during treatment with IMBRUVICA. Contact your doctor if you have fever, chills, weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath, yellowing of the skin or eyes (jaundice). These could be signs of an infection.

Haemophagocytic lymphohistiocytosis
There have been rare reports of excessive activation of white blood cells associated with inflammation (haemophagocytic lymphohistiocytosis), which can be fatal if not diagnosed and treated early. If you experience multiple symptoms such as fever, swollen glands, bruising, or skin rash, contact your doctor immediately.

Tests and check-ups before and during treatment
Tumour lysis syndrome (TLS): Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or another healthcare provider may do blood tests to check for TLS.

Lymphocytosis: Laboratory tests may show an increase in white blood cells (called “lymphocytes”) in your blood in the first few weeks of treatment. This is expected and may last for a few months. This does not necessarily mean that your blood cancer is getting worse. Your doctor will check your blood counts before or during the treatment and in rare cases they may need to give you another medicine. Talk to your doctor about what your test results mean.

Children and adolescents
IMBRUVICA should not be used in children and adolescents. This is because it has not been studied in these age groups.

Other medicines and IMBRUVICA
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, herbal medicines and supplements. This is because IMBRUVICA may affect the way some other medicines work. Also some other medicines can affect the way IMBRUVICA works.

IMBRUVICA may make you bleed more easily. This means you should tell your doctor if you take other medicines that increase your risk of bleeding. This includes:
- acetyl salicylic acid and non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen or naproxen
- blood thinners such as warfarin, heparin or other medicines for blood clots
- supplements that may increase your risk of bleeding such as fish oil, vitamin E or flaxseed.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

Also tell your doctor if you take any of the following medicines – The effects of IMBRUVICA or other medicines may be influenced if you take IMBRUVICA together with any of the following medicines:
- medicines called antibiotics to treat bacterial infections – clarithromycin, telithromycin, ciprofloxacin, erythromycin or rifampicin
- medicines for fungal infections – posaconazole, ketoconazole, itraconazole, fluconazole or voriconazole
- medicines for HIV infection – ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, or fosamprenavir
- medicines to prevent nausea and vomiting associated with chemotherapy - aprepitant
- medicines for depression - nefazodon
- medicines called kinase inhibitors for treatment of other cancers – crizotinib or imatinib
- medicines called calcium channel blockers for high blood pressure or chest pain – diltiazem or verapamil
- medicines called statins to treat high cholesterol - rosuvastatin
- heart medicines/anti-arrhythmics – amiodarone or dronedarone
- medicines to prevent seizures or to treat epilepsy, or medicines to treat a painful condition of the face called trigeminal neuralgia – carbamazepine or phenytoin.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

If you are taking digoxin, a medicine used for heart problems, or methotrexate, a medicine used to treat other cancers and to reduce the activity of the immune system (e.g., for rheumatoid arthritis or psoriasis), it should be taken at least 6 hours before or after IMBRUVICA.

IMBRUVICA with food
Do not take IMBRUVICA with grapefruit or Seville oranges (bitter oranges) – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because it can increase the amount of IMBRUVICA in your blood.

Pregnancy and breast-feeding
Do not get pregnant while you are taking this medicine. IMBRUVICA should not be used during pregnancy. There is no information about the safety of IMBRUVICA in pregnant women.

Women of childbearing age must use a highly effective method of birth control during and up to three months after receiving IMBRUVICA, to avoid becoming pregnant while being treated with IMBRUVICA.

- Tell your doctor immediately if you become pregnant.
- Do not breast-feed while you are taking this medicine.

Driving and using machines
You may feel tired or dizzy after taking IMBRUVICA, which may affect your ability to drive or use any tools or machines.

IMBRUVICA contains lactose
IMBRUVICA contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

IMBRUVICA contains sodium
IMBRUVICA contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take IMBRUVICA

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take
Mantle cell lymphoma (MCL)
The recommended dose of IMBRUVICA is 560 mg once a day.

Chronic lymphocytic leukaemia (CLL)/Waldenström's macroglobulinaemia (WM)
The recommended dose of IMBRUVICA is 420 mg once a day.

Your doctor may adjust your dose.

Taking this medicine
- Take the tablets orally (by mouth) with a glass of water.
- Take the tablets about the same time each day.
- Swallow the tablets whole. Do not break or chew them.

If you take more IMBRUVICA than you should
If you take more IMBRUVICA than you should, talk to a doctor or go to a hospital straight away. Take the tablets and this leaflet with you.

If you forget to take IMBRUVICA
- If you miss a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.
- Do not take a double dose to make up for a forgotten dose.
- If you are not sure, talk to your doctor, pharmacist or nurse about when to take your next dose.

If you stop taking IMBRUVICA
Do not stop taking this medicine unless your doctor tells you.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects may happen with this medicine:

Stop taking IMBRUVICA and tell a doctor straight away if you notice any of the following side effects:
itchy bumpy rash, difficulty breathing, swelling of your face, lips, tongue or throat – you may be having an allergic reaction to the medicine.

Tell a doctor straight away if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath – these could be signs of an infection (viral, bacterial or fungal). These could include infections of the nose, sinus or throat (upper respiratory tract infection), or lung, or skin.
- bruising or increased tendency of bruising.
- mouth sores
- feeling dizzy
- headache
- constipation
- feeling or being sick (nausea or vomiting)
- diarrhoea, your doctor may need to give you a fluid and salt replacement or another medicine
- skin rash
- painful arms or legs
- back pain or joint pain
- muscle cramps, aches or spasms
- low number of cells that help blood clot (platelets), very low number of white blood cells – shown in blood tests
- an increase in the number or proportion of white blood cells shown in blood tests
- high level of "uric acid" in the blood (shown in blood tests), which may cause gout
- swollen hands, ankles or feet
- high blood pressure
- increased level of "creatinine" in the blood.

Common (may affect up to 1 in 10 people)
- severe infections throughout the body (sepsis)
- infections of the urinary tract
- nose bleeds, small red or purple spots caused by bleeding under the skin
- blood in your stomach, gut, stools or urine, heavier periods, or bleeding that you cannot stop from an injury
- heart failure
- fast heart rate, missed heart beats, weak or uneven pulse, lightheadedness, shortness of breath, chest discomfort (symptoms of heart rhythm problems)
- low white blood cell counts with fever (febrile neutropenia)
- non-melanoma skin cancer, most frequently squamous cell and basal cell skin cancer
- blurred vision
- redness of the skin
- inflammation within the lungs that may lead to permanent damage
- breaking of the nails
- weakness, numbness, tingling or pain in your hands or feet or other parts of the body (peripheral neuropathy).

Uncommon (may affect up to 1 in 100 people)
- liver failure, including events with fatal outcome
- severe fungal infections
- confusion, headache with slurred speech or feeling faint – these could be signs of serious internal bleeding in your brain
- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment (tumour lysis syndrome)
- allergic reaction, sometimes severe, that may include a swollen face, lip, mouth, tongue or throat, difficulty swallowing or breathing, itchy rash (hives)
- inflammation of the fatty tissue underneath the skin
- temporary episode of decreased brain or nerve function caused by loss of blood flow, stroke
- painful skin ulceration (pyoderma gangrenosum) or red, raised painful patches on the skin, fever and an increase in white blood cells (these may be signs of acute febrile neutrophilic dermatosis or Sweet's syndrome).

Rare (may affect up to 1 in 1,000 people)
- severely increased white blood cell count that may cause cells to clump together.

Not known (frequency cannot be estimated from available data)
- severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMBRUVICA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IMBRUVICA contains
- The active substance is ibrutinib.
  - IMBRUVICA 140 mg film-coated tablets: Each tablet contains 140 mg of ibrutinib.
  - IMBRUVICA 280 mg film-coated tablets: Each tablet contains 280 mg of ibrutinib.
  - IMBRUVICA 420 mg film-coated tablets: Each tablet contains 420 mg of ibrutinib.
  - IMBRUVICA 560 mg film-coated tablets: Each tablet contains 560 mg of ibrutinib.
- The other ingredients are:
- Tablet core: colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate (see section 2 **"IMBRUVICA contains lactose"**), magnesium stearate, microcrystalline cellulose, povidone, sodium lauril sulfate (E487).
- Tablet film-coat: polyvinyl alcohol, macrogol, talc, titanium dioxide (E171);

IMBRUVICA 140 mg and IMBRUVICA 420 mg film-coated tablets also contain black iron oxide (E172) and yellow iron oxide (E172);
IMBRUVICA 280 mg film-coated tablets also contain black iron oxide (E172) and red iron oxide (E172);
IMBRUVICA 560 mg film-coated tablets also contain red iron oxide (E172) and yellow iron oxide (E172).

What IMBRUVICA looks like and contents of the pack
IMBRUVICA 140 mg film-coated tablets
Yellow-green to green round (9 mm) tablets, written with “ibr” on one side and “140” on the other side. Each 28 day carton contains 28 film-coated tablets in 2 cardboard wallets of 14 film-coated tablets each. Each 30 day carton contains 30 film-coated tablets in 3 cardboard wallets of 10 film-coated tablets each.

IMBRUVICA 280 mg film-coated tablets
Purple oblong (15 mm in length and 7 mm in width), written with “ibr” on one side and “280” on the other side. Each 28 day carton contains 28 film-coated tablets in 2 cardboard wallets of 14 film-coated tablets each. Each 30 day carton contains 30 film-coated tablets in 3 cardboard wallets of 10 film-coated tablets each.

IMBRUVICA 420 mg film-coated tablets
Yellow-green to green oblong tablets (17.5 mm in length and 7.4 mm in width), written with “ibr” on one side and “420” on the other side. Each 28 day carton contains 28 film-coated tablets in 2 cardboard wallets of 14 film-coated tablets each. Each 30 day carton contains 30 film-coated tablets in 3 cardboard wallets of 10 film-coated tablets each.

IMBRUVICA 560 mg film-coated tablets
Yellow to orange oblong tablets (19 mm in length and 8.1 mm in width), written with “ibr” on one side and “560” on the other side. Each 28 day carton contains 28 film-coated tablets in 2 cardboard wallets of 14 film-coated tablets each. Each 30 day carton contains 30 film-coated tablets in 3 cardboard wallets of 10 film-coated tablets each.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen-Cilag SpA
Via C. Janssen,
Loc. Borgo S. Michele,
04100 Latina,
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: +32 14 64 94 11
janssen@jacbe.jnj.com

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

България
„Джонсън & Джонсън България” ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel: +420 227 012 227

Danmark
Janssen-Cilag A/S
Tlf: +45 4594 8282
jacdk@its.jnj.com

Deutschland
Janssen-Cilag GmbH
Tel: +49 2137 955 955
jancil@its.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική A.E.B.E.
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: +353 1 800 709 122

Ísland
Janssen-Cilag AB
c/o Vistor hf
Sími: +354 535 7000
janssen@vistor.is

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: +32 14 64 94 11
janssen@jacbe.jnj.com

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Malta
AM MANGION LTD.
Tel: +356 2397 6000

Nederland
Janssen-Cilag B.V.
Tel: +31 76 711 1111
janssen@jacnl.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.:+48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel.: +386 1 401 18 00
Janssen_safety_slo@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Italia
Janssen-Cilag SpA
Tel: 800 688 777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

United Kingdom (Northern Ireland)
Janssen Sciences Ireland UC
Tel: +44 1 494 567 444

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

1.7　同種同効品一覧表

販売名	イムブルビカカプセル 140mg	グラセプターカプセル 0.5mg，同カプセル 1 mg，同カプセル 5 mg	ネオーラル 10mg カプセル，同 25mg カプセル，同 50mg カプセル	プログラフカプセル 0.5mg，同カプセル 1 mg プログラフカプセル 5mg
一般名	イブルチニブ	タクロリムス水和物	シクロスポリン	タクロリムス水和物
会社名	ヤンセンファーマ株式会社	製造販売：アステラス製薬株式会社	製造販売：ノバルティスファーマ株式会社	製造販売：アステラス製薬株式会社
効能又は効果	○慢性リンパ性白血病（小リンパ球性リンパ腫を含む） ○再発又は難治性のマントル細胞リンパ腫 ○造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）	○下記の臓器移植における拒絶反応の抑制 腎移植、肝移植、心移植、肺移植、膵移植、小腸移植 ○骨髄移植における拒絶反応及び移植片対宿主病の抑制	〈ネオーラル10mgカプセル〉 〈ネオーラル25mgカプセル〉 〈ネオーラル50mgカプセル〉 ○下記の臓器移植における拒絶反応の抑制 腎移植、肝移植、心移植、肺移植、膵移植、小腸移植 ○骨髄移植における拒絶反応及び移植片対宿主病の抑制 ○ベーチェット病（眼症状のある場合）、及びその他の非感染性ぶどう膜炎（既存治療で効果不十分であり、視力低下のおそれのある活動性の中間部又は後部の非感染性ぶどう膜炎に限る） ○尋常性乾癬（皮疹が全身の30%以上に及ぶものあるいは難治性の場合）、膿疱性乾癬、乾癬性紅皮症、関節症性乾癬 ○再生不良性貧血、赤芽球癆 ○ネフローゼ症候群（頻回再発型あるいはステロイドに抵抗性を示す場合） ○全身型重症筋無力症（胸腺摘出後の治療において、ステロイド剤の投与が効果不十分、又は副作用により困難な場合） ○アトピー性皮膚炎（既存治療で十分な効果が得られない患者）	プログラフカプセル 0.5mg，同カプセル 1 mg ○下記の臓器移植における拒絶反応の抑制 腎移植、肝移植、心移植、肺移植、膵移植、小腸移植 ○骨髄移植における拒絶反応及び移植片対宿主病の抑制 ○重症筋無力症 ○関節リウマチ（既存治療で効果不十分な場合に限る） ○ループス腎炎（ステロイド剤の投与が効果不十分、又は副作用により困難な場合） ○難治性（ステロイド抵抗性、ステロイド依存性）の活動期潰瘍性大腸炎（中等症～重症に限る） ○多発性筋炎・皮膚筋炎に合併する間質性肺炎 プログラフカプセル 5mg ○下記の臓器移植における拒絶反応の抑制 腎移植、肝移植、心移植、肺移植、膵移植、小腸移植 ○骨髄移植における拒絶反応及び移植片対宿主病の抑制 ○難治性（ステロイド抵抗性、ステロイド依存性）の活動期潰瘍性大腸炎（中等症～重症に限る）
添付文書改訂日	—	2019 年 6 月改訂	2020 年 2 月改訂	2020 年 4 月改訂（プログラフカプセル 0.5mg，同カプセル 1 mg） 2019 年 6 月改訂（プログラフカプセル 5mg）

最新の添付文書を参照すること

2021年5月改訂（第2版）からの変更箇所（下線：追記箇所、取消線：削除箇所）

貯　　法：室温保存
有効期間：24ヵ月

日本標準商品分類番号
874291

抗悪性腫瘍剤（ブルトン型チロシンキナーゼ阻害剤）

劇薬
処方箋医薬品※

イブルチニブカプセル

イムブルビカ®カプセル140mg

IMBRUVICA® Capsules

※注意－医師等の処方箋により使用すること

承認番号	22800AMX00387000
販売開始	2016年5月

1. 警告

本剤は、緊急時に十分に対応できる医療施設において、造血器悪性腫瘍の治療又は造血幹細胞移植に対して十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

2.1 本剤の成分に対し過敏症の既往歴のある患者
2.2 中等度以上の肝機能障害のある患者［9.3.1、16.6.1参照］
2.3 ケトコナゾール、イトラコナゾール、クラリスロマイシンを投与中の患者［10.1、16.7.1、16.7.7参照］
2.4 妊婦又は妊娠している可能性のある女性［9.5参照］

3. 組成・性状

3.1 組成

販売名	イムブルビカカプセル140mg
有効成分	（1カプセル中） イブルチニブ140mg
添加剤	（内容物）結晶セルロース、クロスカルメロースナトリウム、ラウリル硫酸ナトリウム、ステアリン酸マグネシウム （カプセル本体）酸化チタン、ゼラチン

3.2 製剤の性状

色・剤形	白色不透明の0号硬カプセル
外形・大きさ	 長さ：21.7mm　直径：7.6mm　重量：426mg
識別コード	ibr　140mg

4. 効能又は効果

〇慢性リンパ性白血病（小リンパ球性リンパ腫を含む）
〇再発又は難治性のマントル細胞リンパ腫
〇造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）

5. 効能又は効果に関連する注意

〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）〉

5.1 未治療の慢性リンパ性白血病（小リンパ球性リンパ腫を含む）の場合、「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。

〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉

5.2 「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。

6. 用法及び用量

〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）〉

通常、成人にはイブルチニブとして420mgを1日1回経口投与する。なお、患者の状態により適宜減量する。

〈再発又は難治性のマントル細胞リンパ腫〉

通常、成人にはイブルチニブとして560mgを1日1回経口投与する。なお、患者の状態により適宜減量する。

〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉

通常、成人及び12歳以上の小児にはイブルチニブとして420mgを1日1回経口投与する。なお、患者の状態により適宜減量する。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 Grade 3[注)]以上の副作用が発現した場合には、Grade 1以下に回復するまで本剤を休薬すること。再開する場合には、以下の目安を参考に減量又は中止すること。

注）CTCAE（Common Terminology Criteria for Adverse Events）version 4.0に準じる。

用量調節の目安

発現回数	回復後の再開時投与量	
	慢性リンパ性白血病 慢性移植片対宿主病	マントル細胞リンパ腫
1回	1日1回420mg	1日1回560mg
2回	1日1回280mg	1日1回420mg
3回	1日1回140mg	1日1回280mg
4回	投与中止	

7.2 ~~3~~ ボリコナゾールと併用する場合には、本剤の血中濃度が上昇するおそれがあるため、イブルチニブとして140mgを1日1回経口投与すること。［10.2、16.7.2参照］以下のCYP3A阻害作用を有する薬剤を併用する場合には、本剤の血中濃度が上昇するおそれがあるため、併用薬に応じて次のように投与すること。

CYP3A阻害剤との併用時の用量調節基準

効能又は効果	併用薬	投与方法
慢性リンパ性白血病（小リンパ球性リンパ腫を含む）、再発又は難治性のマントル細胞リンパ腫	ボリコナゾール	イブルチニブとして140mgを1日1回経口投与すること。［10.2、16.7.2参照］
	ポサコナゾール	イブルチニブとして140mgを1日1回経口投与すること。［10.2、16.7.7参照］
造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）	ボリコナゾール	イブルチニブとして280mgを1日1回経口投与すること。［10.2参照］
	ポサコナゾール	イブルチニブとして140mgを1日1回経口投与すること。［10.2、16.7.7参照］

〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）、再発又は難治性のマントル細胞リンパ腫〉

7.3 ~~2~~ 本剤と他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。

〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉

7.4 治療にあたっては経過を十分に観察し、漫然と投与を継続しないこと。

8. 重要な基本的注意

8.1 本剤投与時に外科的処置に伴う大量出血が報告されていることから、本剤投与中に手術や侵襲的手技を実施する患者に対しては本剤の投与中断を考慮すること。

8.2 肺炎、敗血症等の重篤な感染症や日和見感染が発現又は悪化することがあり、B型肝炎ウイルス、結核、帯状疱疹等が再活性化するおそれがあるので、本剤投与に先立って肝炎ウイルス、結核等の感染の有無を確認すること。本剤投与前に適切な処置を行い、本剤投与中は感染症の発現又は増悪に十分注意すること。［9.1.1、11.1.3参照］

8.3 貧血、好中球減少症、血小板減少症等の重篤な骨髄抑制があ

らわれることがあるので、本剤投与に際しては定期的に血液検査を行うこと。[9.1.2、11.1.5 参照]

8.4 重篤な不整脈が発現又は悪化することがあるので、本剤投与に際しては定期的に心機能検査（十二誘導心電図検査等）を行うこと。[9.1.3、11.1.6 参照]

8.5 腫瘍崩壊症候群があらわれることがあるので、血清中電解質濃度及び腎機能検査を行うなど、患者の状態を十分に観察すること。[11.1.7 参照]

8.6 肝不全、ALT、AST、ビリルビン等の上昇を伴う肝機能障害があらわれることがあるので、本剤投与に際しては定期的に肝機能検査を行うこと。[11.1.10 参照]

8.7 間質性肺疾患があらわれることがあるので、息切れ、呼吸困難、咳嗽、発熱等の臨床症状を十分に観察すること。[11.1.11 参照]

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 感染症を合併している患者

骨髄抑制等により、感染症が増悪するおそれがある。[8.2、11.1.3 参照]

9.1.2 重篤な骨髄機能低下のある患者

血球減少を増悪させ重篤化させるおそれがある。[8.3、11.1.5 参照]

9.1.3 不整脈のある患者又はその既往歴のある患者

心房細動等の不整脈があらわれることがある。[8.4、11.1.6 参照]

9.2 腎機能障害患者

9.2.1 重度の腎機能障害のある患者

重度の腎機能障害のある患者を対象とした臨床試験は実施していない。

9.3 肝機能障害患者

9.3.1 中等度以上の肝機能障害患者

投与しないこと。血中濃度が著しく上昇する。[2.2、16.6.1 参照]

9.3.2 軽度の肝機能障害患者

減量を考慮するとともに、患者の状態をより慎重に観察し、有害事象の発現に十分注意すること。血中濃度が上昇する。[16.6.1 参照]

9.4 生殖能を有する者

妊娠可能な女性に対しては、本剤投与中及び投与終了後一定期間は適切な避妊を行うよう指導すること。[9.5 参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には投与しないこと。動物実験で胚致死作用（ラット及びウサギ）、及び催奇形性（ラット：心血管系の奇形、ウサギ：胸骨分節の癒合）が報告されている。[2.4、9.4 参照]

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。ヒトにおける乳汁中への移行は不明である。

9.7 小児等

〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）、再発又は難治性のマントル細胞リンパ腫〉

9.7.1 小児等を対象とした臨床試験は実施していない。

〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉

9.7.2 12 歳未満の小児等を対象とした臨床試験は実施していない。

9.8 高齢者

海外臨床試験において、65 歳以上の患者で、Grade 3 注) 以上の有害事象、肺炎、尿路感染、心房細動、白血球増加症等の発現率が高かった。

注)CTCAE(Common Terminology Criteria for Adverse Events)version 4.0 に準じる。

10. 相互作用

本剤は主に CYP3A により代謝される。

10.1 併用禁忌（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
ケトコナゾール（経口剤：国内未発売） イトラコナゾール イトリゾール クラリスロマイシン クラリス、クラリシッド [2.3、16.7.1、16.7.7 参照]	本剤の血中濃度が上昇し、副作用が増強されるおそれがある。	これらの薬剤の CYP3A 阻害作用により、本剤の代謝が阻害される。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP3A 阻害作用を有する薬剤 インジナビル ネルフィナビル リトナビル含有製剤 サキナビル コビシスタット含有製剤 アタザナビル ダルナビル ホスアンプレナビル テラプレビル ボリコナゾール [7.2、16.7.2 参照] ポサコナゾール [7.2、16.7.7 参照] フルコナゾール エリスロマイシン [16.7.3 参照] シプロフロキサシン ジルチアゼム [16.7.7 参照] ベラパミル アミオダロン アプレピタント	本剤の血中濃度が上昇し、副作用が増強されるおそれがあるので、CYP3A 阻害作用のない薬剤への代替を考慮すること。やむを得ず併用する際には、本剤の減量を考慮するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	これらの薬剤の CYP3A 阻害作用により、本剤の代謝が阻害される。
グレープフルーツ含有食品 [16.7.5 参照]	本剤の血中濃度が上昇し、副作用が増強されるおそれがあるので、摂取しないよう注意すること。	食品中に CYP3A 阻害作用を有する成分が含まれている。
CYP3A 誘導作用を有する薬剤 カルバマゼピン リファンピシン フェニトイン [16.7.4、16.7.7 参照]	本剤の血中濃度が低下し、効果が減弱するおそれがあるので、CYP3A 誘導作用のない薬剤への代替を考慮すること。	これらの薬剤の CYP3A 誘導作用により、本剤の代謝が促進される。
セイヨウオトギリソウ（St. John’s Wort、セント・ジョーンズ・ワート）含有食品	本剤の血中濃度が低下し、効果が減弱するおそれがあるので、摂取しないよう注意すること。	食品中に CYP3A 誘導作用を有する成分が含まれている。
抗凝固剤 抗血小板剤	出血のおそれがある。	出血のリスクを増強させるおそれがある。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 出血

脳出血（0.2%）、消化管出血（0.4%）等の重篤な出血があらわれることがあり、死亡に至った例が報告されている。

11.1.2 白血球症（頻度不明）

頭蓋内出血、嗜眠、不安定歩行、頭痛等を伴う白血球症があらわれることがある。

11.1.3 感染症

肺炎（8.9%）、敗血症（2.3%）等の重篤な感染症があらわれることがある。また、B 型肝炎ウイルス、結核、帯状疱疹等の再活性化があらわれることがある。[8.2、9.1.1 参照]

11.1.4 進行性多巣性白質脳症（PML）（頻度不明）

本剤投与中及び投与終了後は患者の状態を十分に観察すること。意識障害、認知障害、麻痺症状（片麻痺、四肢麻痺）、言語障害等の症状があらわれた場合には、MRI による画像診断及び脳脊髄液検査を行うとともに、投与を中止するなどの適切な処置を行うこと。

11.1.5 骨髄抑制

貧血（9.6%）、好中球減少症（12.5%）、血小板減少症（9.8%）等の重篤な骨髄抑制があらわれることがある。[8.3、9.1.2 参照]

11.1.6 不整脈

心房細動（2.7%）、心房粗動（0.5%）、心室性不整脈（頻度不明）等の重篤な不整脈があらわれることがある。[8.4、9.1.3 参照]

11.1.7 腫瘍崩壊症候群（0.2%）

異常が認められた場合には、直ちに投与を中止し、適切な処置（生理食塩液、高尿酸血症治療剤の投与等）を行うとともに、症状が回復するまで患者の状態を十分に観察すること。なお、重篤な腫瘍崩壊症候群が遅発性にあらわれることがある。[8.5 参照]

11.1.8 過敏症（0.2%）

アナフィラキシー等の重篤な過敏症があらわれることがある。

11.1.9 皮膚粘膜眼症候群（Stevens-Johnson 症候群）（頻度不明）

11.1.10 肝不全、肝機能障害（頻度不明）

肝不全、ALT、AST、ビリルビン等の上昇を伴う肝機能障害があらわれることがある。[8.6 参照]

11.1.11 間質性肺疾患（0.5%）

異常が認められた場合には、胸部 X 線、胸部 CT 等の検査を実施すること。間質性肺疾患が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。[8.7 参照]

11.2 その他の副作用

	10%以上	10%未満 5%以上	5%未満	頻度不明
感染症及び寄生虫症		上気道感染	~~上気道感染、~~皮膚感染、尿路感染、副鼻腔炎	
良性、悪性及び詳細不明の新生物（嚢胞及びポリープを含む）			扁平上皮癌、基底細胞癌	前立腺癌、悪性黒色腫、リンパ腫、骨髄異形成症候群
血液及びリンパ系障害			白血球増加症、リンパ球増加症、発熱性好中球減少症	
代謝及び栄養障害			食欲減退、高尿酸血症、低カリウム血症、脱水、低ナトリウム血症	
神経系障害		頭痛	浮動性めまい、末梢性ニューロパチー	
眼障害注)			霧視、眼乾燥、流涙増加、視力低下、結膜炎	
血管障害			高血圧	
呼吸器、胸郭及び縦隔障害			鼻出血、咳嗽、呼吸困難	
胃腸障害	下痢（28.5%）、悪心	口内炎、嘔吐~~、便秘~~	便秘、消化不良、腹痛、胃食道逆流性疾患	
皮膚及び皮下組織障害	発疹、挫傷	点状出血	そう痒症、爪破損、紅斑、蕁麻疹、血管浮腫	脂肪織炎、急性熱性好中球性皮膚症（Sweet 症候群）
筋骨格系及び結合組織障害		関節痛、筋痙縮、筋骨格痛		関節障害
一般・全身障害及び投与部位の状態	疲労	発熱	末梢性浮腫、無力症、硬膜下血腫	
傷害、中毒及び処置合併症			転倒	

注） 眼の異常があらわれた場合には、直ちに眼科的検査を行うなどの適切な処置を行うこと。

14. 適用上の注意

14.1 薬剤交付時の注意

PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

15. その他の注意

15.1 臨床使用に基づく情報

イブルチニブの血中濃度の上昇に伴い、出血事象の発現率が高くなる傾向が認められたとの報告がある。

16. 薬物動態

16.1 血中濃度

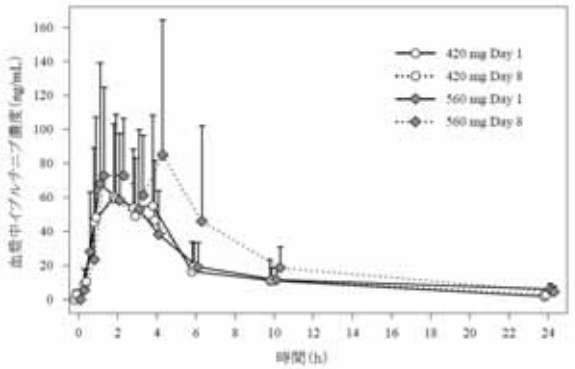
16.1.1 ~~単回投与及び反復投与~~再発又は難治性成熟 B 細胞性腫瘍患者

再発又は難治性成熟 B 細胞性腫瘍患者にイブルチニブ 140mg 注1) ～560mg を単回又は反復経口投与したとき、血漿中イブルチニブ濃度は用量によらず、投与後 1～2 時間（中央値）に最高濃度に達し、4～9 時間（平均値）の消失半減期で消失した。血漿中イブルチニブの C_{max} 及び AUC は個体間変動が大きいが、用量の増加に伴って増加した。反復経口投与による累積率は 1.6 未満であった。[1)]

再発又は難治性成熟 B 細胞性腫瘍患者にイブルチニブを単回又は反復経口投与したときの薬物動態パラメータ［平均値（標準偏差）］

測定日	用量（mg）	n	C_{max}（ng/mL）	t_{max} a)（h）	AUC_{last}（ng･h/mL）	$t_{1/2}$（h）
1日目	140	3	42.53 ± 23.74	2.02 (1.98, 3.95)	203.64 ± 128.60	3.90 ± 1.67
	280	3	68.47 ± 14.09	1.82 (1.00, 1.97)	339.21 ± 72.42	5.64 ± 1.50
	420	9	87.33 ± 62.15	1.97 (1.00, 3.98)	381.73 ± 265.26	6.99 b) ± 3.34
	560	6	94.57 ± 65.43	1.48 (0.98, 3.92)	419.09 ± 238.74	7.35、5.33 c)
8日目	420	8	77.50 ± 58.11	2.00 (0.95, 3.97)	383.17 ± 189.61	4.60 b) ± 1.86
	560	6	105.47 ± 68.60	2.00 (0.97, 4.00)	638.96 ± 476.16	6.39、4.23 c)

算術平均値±標準偏差、a)：中央値（範囲）、b)：n=6、c)：個別値（n=2）



再発又は難治性成熟 B 細胞性腫瘍患者にイブルチニブ 420mg 又は 560mg を単回（Day 1）又は反復（Day 8）経口投与したときの血漿中イブルチニブ濃度推移（平均値+標準偏差）

16.1.2 造血幹細胞移植後の慢性移植片対宿主病患者

12 歳以上のステロイド依存性又は抵抗性の日本人慢性移植片対宿主病患者にイブルチニブ 140 注1) ～420mg を 1 日 1 回反復経口投与したとき、血漿中イブルチニブ濃度は下表のとおりであった。[2)]

慢性移植片対宿主病患者にイブルチニブを反復経口投与したときの薬物動態パラメータ

	測定日	用量（mg）	n	C_{max}（ng/mL）	t_{max} a)（h）	AUC_{last}（ng･h/mL）	$t_{1/2}$ a)（h）
中程度以上の CYP3A 阻害剤併用なし	Week1 1 日目	420	7	386 ± 166	2.08 (1.78, 4.50)	1843 ± 1146	4.86 (4.42, 5.15) b)
	Week2 1 日目	420	7	275 ± 171	4.08 (1.85, 5.28)	2102 ± 938	3.83, 10.2 c)

ボリコナゾール併用	Week1 1日目	280	4	399 ± 126	3.83 (1.78, 5.75)	4003 ± 1586	4.88 c)
	Week2 1日目	280	4	432 ± 374	3.87 (1.75, 5.43)	2970 ± 2201	N/A
フルコナゾール併用	Week1 1日目	420	8	628 ± 526	3.91 (1.97, 4.25)	5134 ± 4173	N/A
	Week2 1日目	420	8	678 ± 701	3.95 (1.82, 5.17)	6235 ± 5875	4.33, 4.56 c)

算術平均値±標準偏差、N/A：報告対象となるデータなし
a)：中央値（範囲）、b)：n=3、c)：個別値

12 歳以上の日本人及び外国人慢性移植片対宿主病患者にイブルチニブ 140 注1) ～420mg を 1 日 1 回反復経口投与したとき、血漿中イブルチニブ濃度は下表のとおりであった。2)

慢性移植片対宿主病患者にイブルチニブを反復経口投与したときの薬物動態パラメータ

	測定日	用量 (mg)	n	C_{max} (ng/mL)	t_{max} a) (h)	AUC_{last} (ng･h/mL)	$t_{1/2}$ a) (h)
中程度以上のCYP3A阻害剤併用なし	Week2 1日目	420	23	235 ± 261	2.00 (0.880, 6.05)	1313 ± 1017 b)	4.10 (1.34, 10.1) c)
	Week2 1日目	140 d)	1	158	1.00	388	5.51
ボリコナゾール併用	Week2 1日目	280	12	436 ± 292	2.00 (0.930, 5.00)	2934 ± 1805	4.04 (2.47, 9.04) e)
	Week2 1日目	140	3	322 ± 258	2.22 (1.00, 4.00)	1610, 1010 f)	ND
ポサコナゾール併用	Week2 1日目	420 g)	2	98.4, 241	3.92, 1.75	1060 h)	ND
	Week2 1日目	280	13	289 ± 296	2.00 (1.88, 6.00)	1979 ± 1205 i)	4.70 (4.02, 5.70) j)
	Week2 1日目	140	10	140 ± 124	2.83 (1.87, 5.38)	915 ± 617	4.97 (4.95, 5.88) k)
フルコナゾール併用	Week2 1日目	420	6	629 ± 480	2.05 (1.12, 4.08)	3662 ± 2392	4.92 (4.46, 5.39) k)
	Week2 1日目	280	4	242 ± 93.9	2.99 (1.92, 5.08)	1638 ± 819	5.49 h)

算術平均値±標準偏差、ND：算出されず
a)：中央値（範囲）、b)：n=20、c)：n=10、d)：イブルチニブの減量を要する併用薬の併用はなかったが 140mg に減量された、e)：n=7、f)：n=2、g)：イブルチニブを減量されなかった、h)：n=1、i)：n=12、j)：n=5、k)：n=4

注 1) CYP3A 阻害作用を有するボリコナゾール又はポサコナゾール併用時並びに副作用発現時は減量することとされた。

16.2 吸収

16.2.1 絶対的バイオアベイラビリティ及び食事の影響

健康成人にイブルチニブ 560mg を絶食時注 2) 及び食前 30 分に経口投与し、経口投与の 2 時間後に ^{13}C-イブルチニブ（100 μg）を静脈内投与したときの絶対的バイオアベイラビリティはそれぞれ、2.9%（90%CI：2.1～3.9%）及び 7.6%（90%CI：6.4～9.0%）であった 23)。健康成人にイブルチニブ 420mg を経口投与したときの C_{max} 及び AUC_{last} は、食前 30 分、食後 30 分又は食後 2 時間に投与したときと比較して絶食時注 2) にはそれぞれ約 30～40%及び約 60%に低下した 34)。再発又は難治性慢性リンパ性白血病/小リンパ球性リンパ腫患者にイブルチニブ 420mg を経口投与したときの C_{max} 及び AUC_{0-24h} は、食事の 30 分以上前又は 2 時間以上後に経口投与（modified fasting 投与）したときと比較して絶食時注 2) にはそれぞれ約 40%及び約 60～70%に低下した 45)。（外国人データ）

16.3 分布

イブルチニブのヒト血漿蛋白結合率は 97.3%であり、検討された濃度域（*in vitro*、50～1000ng/mL）で概ね一定であった 56)。健康成人に ^{13}C-イブルチニブ（100 μg）を静脈内投与したときの定常状態における分布容積は 683L 23)、再発又は難治性慢性リンパ性白血病/小リンパ球性リンパ腫患者にイブルチニブ 420mg を単回経口投与したときのみかけの分布容積（Vdz/F）は 10837L であった 45)。（外国人データ）

16.4 代謝

イブルチニブは主に CYP3A4/5 により代謝される（*in vitro*）67)、78)。主な代謝物であるジヒドロジオール体は、ブルトン型チロシンキナーゼ（BTK）に対してイブルチニブの約 1/15 の阻害活性を示す 89)。ジヒドロジオール体の定常状態における曝露量は、イブルチニブと同程度であった 1)。

16.5 排泄

健康成人に ^{14}C-イブルチニブ 1480kBq を含むイブルチニブ 140mg 注 1) を単回経口投与したとき、放射能の約 90%が 168 時間以内に回収され、糞中では 80%、尿中では 10%以下であった。イブルチニブの回収率は、糞中で 1%、尿中には認められなかった 910)。健康成人に ^{13}C-イブルチニブ（100 μg）を静脈内投与したときの全身クリアランス（CL）は、絶食時及び食前 30 分においてそれぞれ 62 及び 76L/h であった 23)。健康成人にイブルチニブ 560mg を経口投与したときのみかけの全身クリアランス（CL/F）は、絶食時及び食前 30 分においてそれぞれ 1572 及び 875L/h であった 23)。（外国人データ）

16.6 特定の背景を有する患者

16.6.1 肝機能障害

軽度の肝機能障害（Child-Pugh 分類 A）患者 6 例、中等度の肝機能障害（Child-Pugh 分類 B）患者 10 例及び重度の肝機能障害（Child-Pugh 分類 C）患者 8 例にイブルチニブ 140mg 注 1) を単回経口投与したときの AUC_{last} の幾何平均値は正常肝機能被験者と比較して 2.7、8.2 及び 9.8 倍高かった。また、非結合分画も肝機能障害の程度に応じてわずかに増加し、非結合型イブルチニブの AUC_{last} はそれぞれ 4.1、9.8 及び 13 倍増加すると推定される 1011)。（外国人データ）［2.2、9.3.1、9.3.2 参照］

16.6.2 12 歳以上の小児

〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉

12 歳以上の慢性移植片対宿主病患者を対象とした国内外の臨床成績における血漿中イブルチニブ濃度（162 例、1,281 測定時点）に基づき母集団薬物動態解析を実施した。イブルチニブ 420mg を 1 日 1 回経口投与したとき、薬物動態パラメータの推定値は、小児と成人で同程度であった。

16.7 薬物相互作用

16.7.1 ケトコナゾール

健康成人（18 例）に CYP3A の阻害作用を有するケトコナゾール（経口剤：国内未発売）400mg（4～9 日目に投与）とイブルチニブ 120mg 及び 40mg 注 1)（それぞれ 1 日目及び 7 日目に投与）を併用投与（絶食時）したとき、イブルチニブの C_{max} 及び AUC はそれぞれ約 29 及び 24 倍増加した 1112)。（外国人データ）［2.3、10.1 参照］

16.7.2 ボリコナゾール

B 細胞性腫瘍患者（26 例）に CYP3A の阻害作用を有するボリコナゾール 200mg 1 日 2 回とイブルチニブ 140mg 1 日 1 回注 1) を併用投与したとき、イブルチニブの C_{max} 及び AUC はそれぞれ約 6.7 及び 5.7 倍増加した 1213)。（外国人データ）［7.2、10.2 参照］

16.7.3 エリスロマイシン

B 細胞性腫瘍患者（25 例）に CYP3A の阻害作用を有するエリスロマイシン 500mg 1 日 3 回とイブルチニブ 140mg 1 日 1 回注 1) を併用投与したとき、イブルチニブの C_{max} 及び AUC はそれぞれ約 3.4 及び 3.0 倍増加した 1213)。（外国人データ）［10.2 参照］

16.7.4 リファンピシン

健康成人（18 例）に CYP3A の誘導作用を有するリファンピシン 600mg（4～13 日目に投与）とイブルチニブ 560mg（1 日目及び 11 日目に投与）を併用投与（絶食時）したとき、イブルチニブの C_{max} 及び AUC はそれぞれ約 1/13 及び 1/10 以下に減少した 1314)。（外国人データ）［10.2 参照］

16.7.5 グレープフルーツジュース

健康成人（8 例）に CYP3A の阻害作用を有するグレープフルーツジュースとイブルチニブ 140mg 注 1) を併用投与（非絶食時）したとき、イブルチニブの C_{max} 及び AUC はそれぞれ約 3.6 及び 2.1 倍増加した 23)。（外国人データ）［10.2 参照］

16.7.6 オメプラゾール

健康成人（20 例）にプロトンポンプ阻害剤であるオメプラゾール 40mg（3～7 日目に投与）とイブルチニブ 560mg（1 日目及び 7 日目に投与）を併用投与（絶食時）したとき、イブルチニブの C_{max} は約 38%に減少したが、AUC に顕著な変化は認められなかった 1415)。（外国人データ）

16.7.7 生理学的薬物動態モデルによるシミュレーション

イブルチニブ 140mg 注 1) と CYP3A 阻害作用を有するイトラコナゾール、クラリスロマイシン、ポサコナゾール及びジルチアゼムを併用投与（非絶食時）した場合、イブルチニブの AUC はそれぞれ、約 15、11、8.3 及び 4.4 倍増加することが推定された。イブルチニブ 560mg と CYP3A 阻害作用を有するフルボキサミン及びアジスロマイシンを併用投与（非絶食時）した場合、イブルチニブの AUC はそれぞれ、約 1.7 及び 1.5 倍増加することが推定された。イブルチニブ 560mg と CYP3A 誘導作用を有するカルバマゼピン及びエファビレンツを併用投与（非絶食時）した場合、イブルチニブの AUC はそれぞれ、

約 1/6 及び 1/3 に減少することが推定された。[15][16]［2.3、7.2、10.1、10.2 参照］

注 1）本剤の承認された用法・用量は、「420mg 又は 560mg を 1 日 1 回経口投与する」である。

注 2）一晩絶食後にイブルチニブを経口投与し、その後 4 時間絶食。

17. 臨床成績

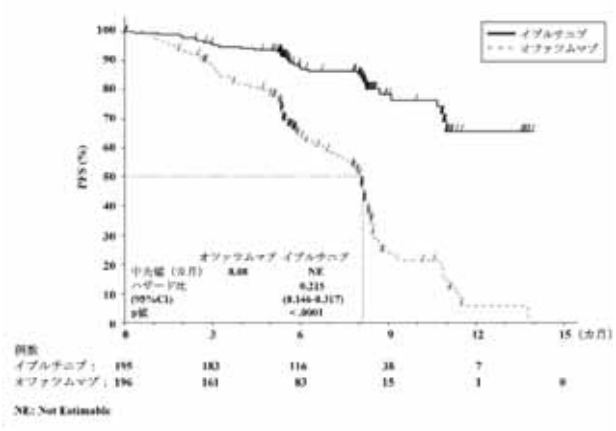
17.1 有効性及び安全性に関する試験

〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）〉

17.1.1 海外臨床試験成績（第Ⅲ相試験：PCYC-1112-CA 試験）

1 レジメン以上の前治療歴を有する再発又は難治性慢性リンパ性白血病/小リンパ球性リンパ腫患者を対象とし、オファツムマブを対照として本剤 420mg を 1 日 1 回、食事の 30 分以上前又は 2 時間以上後に投与（modified fasting 投与）した。有効性の成績は以下のとおりであった。なお、当該試験に組み入れられた患者の内訳は慢性リンパ性白血病患者が 185 例、小リンパ球性リンパ腫患者が 10 例であった。[16][17]

本剤が投与された 195 例中 177 例（90.8%）に副作用が認められた。主な副作用は、下痢 70 例（35.9%）、悪心 35 例（17.9%）、好中球減少症 31 例（15.9%）、関節痛 28 例（14.4%）、発疹 24 例（12.3%）等であった。



無増悪生存期間（PFS）の Kaplan-Meier 曲線

17.1.2 国内臨床試験成績（第Ⅰ相試験：PCI-32765-JPN-101 試験）

再発又は難治性成熟 B 細胞性腫瘍患者を対象とし、本剤を経口投与した。このうち本剤 420mg を 1 日 1 回投与した慢性リンパ性白血病/小リンパ球性リンパ腫患者（8 例）では、7 例がカットオフ時点[注]で本剤の投与を継続していた。奏効率は 62.5%（5/8 例）であった（95%CI：24.5～91.5%）。[1]

本剤が投与された 8 例全例（100%）に副作用が認められた。主な副作用は、好中球減少症 4 例（50.0%）、貧血 4 例（50.0%）、発疹 3 例（37.5%）、口内炎 3 例（37.5%）等であった。

注）最終登録患者が 175 日間の投与を完了した時点。

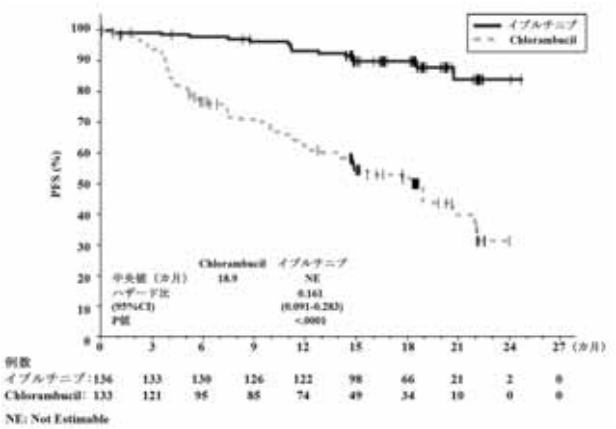
17.1.3 海外臨床試験成績（第Ⅲ相試験：PCYC-1115-CA 試験）

未治療の慢性リンパ性白血病/小リンパ球性リンパ腫患者[注 1)]を対象とし、chlorambucil [注 2)] を対照として本剤 420mg を 1 日 1 回投与した。有効性の成績は以下のとおりであった。なお、当該試験に組み入れられた患者の内訳は慢性リンパ性白血病患者が 123 例、小リンパ球性リンパ腫患者が 13 例であった[17][18]。

本剤が投与された 135 例中 114 例（84.4%）に副作用が認められた。主な副作用は、下痢 44 例（32.6%）、悪心 18 例（13.3%）、好中球減少症 16 例（11.9%）、発疹 14 例（10.4%）等であった。

注 1）フルダラビンリン酸エステル、シクロホスファミド水和物及びリツキシマブ（遺伝子組換え）の併用投与の適応とならず、かつ 17 番染色体短腕欠失を有さない患者。

注 2）本邦では、承認されていない。



無増悪生存期間（PFS）の Kaplan-Meier 曲線

17.1.4 国内臨床試験成績（第Ⅰ相試験：54179060LEU1001 試験）

未治療の慢性リンパ性白血病/小リンパ球性リンパ腫患者[注)]を対象とし、本剤 420mg を 1 日 1 回投与した。奏効率は 75.0%（6/8 例）であった（95%CI：34.9～96.8%）。[18][19]

本剤が投与された 8 例全例（100%）に副作用が認められた。主な副作用は、血小板数減少 6 例（75.0%）、リンパ球数増加 4 例（50.0%）、肺炎 3 例（37.5%）、好中球数減少 2 例（25.0%）、貧血 2 例（25.0%）、下痢 2 例（25.0%）、関節痛 2 例（25.0%）等であった。

注）フルダラビンリン酸エステル投与の適応とならない患者。

〈再発又は難治性のマントル細胞リンパ腫〉

17.1.5 海外臨床試験成績（第Ⅲ相試験：PCI-32765-MCL3001 試験）

1 レジメン以上の前治療歴を有する再発又は難治性マントル細胞リンパ腫患者を対象とし、テムシロリムス[注)]を対照として本剤 560mg を 1 日 1 回投与した。主要評価項目とされた独立評価委員会判定による無増悪生存期間の中央値は、本剤群で 14.6 ヵ月（95%CI：10.4～NE）、テムシロリムス群で 6.2 ヵ月（95%CI：4.2～7.9）であり、本剤群で統計学的に有意な延長が認められた（ハザード比 0.43（95%CI：0.32～0.58）、p<0.0001（層別 log-rank 検定）、2015 年 4 月 22 日データカットオフ）[19][20]。

本剤が投与された 139 例中 115 例（82.7%）に副作用が認められた。主な副作用は、下痢 27 例（19.4%）、疲労 22 例（15.8%）、血小板減少症 20 例（14.4%）、好中球減少症 18 例（12.9%）、貧血 15 例（10.8%）、発疹 14 例（10.1%）、筋痙縮 14 例（10.1%）等であった。

注）本邦では、テムシロリムスはマントル細胞リンパ腫に関する適応で承認されていない。

17.1.6 国内臨床試験成績（第Ⅱ相試験：PCI-32765-MCL2002 試験）

1 レジメン以上 5 レジメン以下の前治療歴を有する再発又は難治性マントル細胞リンパ腫患者を対象とし、本剤 560mg を 1 日 1 回投与した。奏効率は 87.5%(14/16 例)であった(90%CI: 65.6～97.7%) [20][21]。

本剤が投与された 16 例中 15 例（93.8%）に副作用が認められた。主な副作用は、下痢 5 例（31.3%）、口内炎 4 例（25.0%）、貧血 4 例（25.0%）、血小板減少症 3 例（18.8%）、食欲減退 3 例（18.8%）、発疹 3 例（18.8%）、疲労 3 例（18.8%）等であった。

〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉

17.1.7 海外臨床試験成績（第Ⅰb/Ⅱ相試験：PCYC-1129-CA 試験）

18 歳以上のステロイド依存性又は抵抗性の慢性移植片対宿主病患者を対象とし、本剤 420mg を 1 日 1 回投与した。主要評価項目である NIH Consensus Development Project Criteria（2014）[22] の改訂事項を 2 点反映した NIH Consensus Development Project Criteria（2005）[23] に基づく主要解析時点の全奏効率は 66.7%（28/42 例）であった（95%CI：50.5～80.4%）[24]。

本剤が投与された 42 例中 35 例（83.3%）に副作用が認められた。主な副作用は、疲労 19 例（45.2%）、下痢 11 例（26.2%）、挫傷 11 例（26.2%）、口内炎 7 例（16.7%）、筋痙縮 7 例（16.7%）、上気道感染 6 例（14.3%）等であった。

17.1.8 国内臨床試験成績（第Ⅲ相試験：54179060GVH3001 試験）

12 歳以上のステロイド依存性又は抵抗性の日本人慢性移植片対宿主病患者を対象とし、本剤 420mg を 1 日 1 回投与した。主要評価項目である NIH Consensus Development Project Criteria(2014)に基づく主要解析時点の全奏効率は 73.7%（14/19 例）であった（95%CI：48.8～90.9%）[2)]。
本剤が投与された 19 例中 15 例（78.9%）に副作用が認められた。主な副作用は、肺炎 4 例（21.1%）、口内炎 3 例（15.8%）、挫傷 3 例（15.8%）、上気道感染 2 例（10.5%）、高血圧 2 例（10.5%）、間質性肺疾患 2 例（10.5%）、発疹 2 例（10.5%）等であった。

18. 薬効薬理

18.1 作用機序

ブルトン型チロシンキナーゼ(BTK)は、B 細胞性腫瘍の発症、増殖等に関与する B 細胞受容体（BCR）、及び B 細胞の遊走、接着等に関与するケモカイン受容体の下流に位置するシグナル分子である。イブルチニブは、BTK の活性部位にあるシステイン残基~~(Cys-481)~~と共有結合し、BTK のキナーゼ活性を阻害した。

18.2 抗腫瘍効果

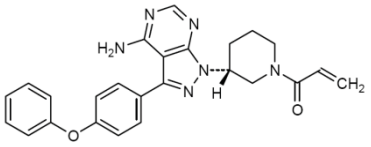
In vitro 試験において、イブルチニブは、慢性リンパ性白血病（CLL）患者由来の CLL 細胞及びヒトマントル細胞リンパ腫（MCL）由来細胞株（Mino、Jeko-1 等）の増殖を抑制した[~~21~~25)、~~22~~26)]。また、CLL 患者由来の CLL 細胞並びにヒト MCL 由来細胞株（Mino 及び Jeko-1）の遊走及び接着を阻害した[~~22~~26)、~~23~~27)]。
In vivo 試験において、イブルチニブは、マウス CLL 由来 TCL1-192 細胞を腹腔内移植した重症複合免疫不全（SCID）マウスにおいて、末梢血中の TCL1-192 細胞の増殖を抑制した[~~21~~25)]。また、Mino 細胞株を静脈内に移植した SCID マウスにおいて、Mino 細胞数を減少させた[~~24~~28)]。

18.3 慢性移植片対宿主病に対する作用

In vivo 試験において、イブルチニブは T 及び B 細胞が発症に関与するマウス慢性移植片対宿主病モデル（LP/J の骨髄細胞を C57BL/6 に移植、又は C57BL/6 の骨髄細胞を B10.BR に移植）での慢性移植片対宿主病症状（強皮症、または肺及び肝の線維化）を改善し、無増悪生存期間を延長した[29)]。

19. 有効成分に関する理化学的知見

一般的名称：イブルチニブ（Ibrutinib）
化学名：1-{(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one
分子式：$C_{25}H_{24}N_6O_2$
分子量：440.50
性状：白色の固体
化学構造式：



融点：149～158 ℃
分配係数：3.97（Log P, 1-オクタノール/pH7 緩衝液）
溶解性：ジメチルスルホキシドに溶けやすく、メタノールにやや溶けやすく、アセトニトリルにやや溶けにくく、水にほとんど溶けない。

20. 取扱い上の注意

小児の手の届かないところに保管すること。

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。
〈再発又は難治性の慢性リンパ性白血病（小リンパ球性リンパ腫を含む）、再発又は難治性のマントル細胞リンパ腫〉
21.2 国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22. 包装

14 カプセル［14 カプセル（PTP）×1］

23. 主要文献

1) 社内資料：イブルチニブの国内第Ⅰ相試験（PCI-32765-JPN-101）（2016 年 3 月 28 日承認、CTD2.7.6.2）
2) 社内資料：イブルチニブの国内第Ⅲ相試験（54179060GVH3001）（2021 年 XX 月 XX 日承認、CTD2.7.6.2）
~~2~~3) 社内資料：イブルチニブのバイオアベイラビリティ及び食事の影響の検討（PCI-32765CLL1011）（2016 年 3 月 28 日承認、CTD2.7.6.9）
~~3~~4) 社内資料：イブルチニブの食事の影響の検討（PCI-32765CLL1001）（2016 年 3 月 28 日承認、CTD2.7.6.7）
~~4~~5) 社内資料：イブルチニブの海外第 Ib/II 相試験（PCYC-1102-CA）（2016 年 3 月 28 日承認、CTD2.7.6.3）
~~5~~6) 社内資料：イブルチニブの血漿蛋白結合率の検討（12-083-Hu-X-PB）（2016 年 3 月 28 日承認、CTD2.7.2.1.1.3）
~~6~~7) 社内資料：ヒト CYP 発現系を用いたイブルチニブの代謝の検討（12-013-Hu-X-MT）（2016 年 3 月 28 日承認、CTD2.6.4.5.1.3）
~~7~~8) 社内資料：ヒト肝ミクロソーム及び CYP 特異的阻害剤を用いたイブルチニブの代謝の検討（12-014-Hu-X-MT）（2016 年 3 月 28 日承認、CTD2.6.4.5.1.3）
~~8~~9) 社内資料：イブルチニブ代謝物の阻害活性の検討（13-047-Hu-X-ENZ）（2016 年 3 月 28 日承認、CTD2.6.2.2.3）
~~9~~10) 社内資料：イブルチニブのマスバランスの検討（PCI-32765CLL1004）（2016 年 3 月 28 日承認、CTD2.7.6.6）
~~10~~11) 社内資料：肝機能障害被験者におけるイブルチニブの薬物動態の検討（PCI-32765CLL1006）（2016 年 3 月 28 日承認、CTD2.7.6.10）
~~11~~12) 社内資料：イブルチニブとケトコナゾールの薬物相互作用の検討（PCI-32765CLL1002）（2016 年 3 月 28 日承認、CTD2.7.6.5）
~~12~~13) 社内資料：イブルチニブとボリコナゾール及びエリスロマイシンの薬物相互作用の検討（PCI-32765LYM1003）
~~13~~14) 社内資料：イブルチニブとリファンピシンの薬物相互作用の検討（PCI-32765CLL1010）（2016 年 3 月 28 日承認、CTD2.7.6.8）
~~14~~15) 社内資料：イブルチニブとオメプラゾールの薬物相互作用の検討（PCI-32765CLL1005）（2018 年 7 月 2 日承認、CTD2.7.6.3）
~~15~~16) 社内資料：生理学的薬物動態モデルによるイブルチニブの薬物相互作用の検討(2016 年 3 月 28 日承認、CTD2.7.2.2）
~~16~~17) Byrd JC, et al.: N Engl J Med. 2014; 371: 213-223
~~17~~18) 社内資料：イブルチニブの海外第Ⅲ相試験（PCYC-1115-CA）（2018 年 7 月 2 日承認、CTD2.7.6.1）
~~18~~19) 社内資料：イブルチニブの国内第Ⅰ相試験（54179060LEU1001）（2018 年 7 月 2 日承認、CTD2.7.6.2）
~~19~~20) 社内資料：イブルチニブの海外第Ⅲ相試験（PCI-32765-MCL3001）（2016 年 12 月 2 日承認、CTD2.7.6.3）
~~20~~21) 社内資料：イブルチニブの国内第Ⅱ相試験（PCI-32765-MCL2002）（2016 年 12 月 2 日承認、CTD2.7.6.1）
22) Lee SJ, Wolff D, Kitko C, et al.: Biol Blood Marrow Transplant. 2015; 21: 984-999
23) Pavletic SZ, Martin P, Lee SJ, et al.: Biol Blood Marrow Transplant. 2006; 12: 252-266
24) 社内資料：イブルチニブの海外第Ⅰb/Ⅱ相試験（PCYC-1129-CA）（2021 年 XX 月 XX 日承認、CTD2.7.6.1）
~~21~~25) Ponader S, et al.: Blood. 2012; 119 :1182-1189
~~22~~26) 社内資料：ヒトマントル細胞リンパ腫由来細胞株に対するイブルチニブの作用（2016 年 12 月 2 日承認、CTD2.6.2.2.1.4）
~~23~~27) de Rooij MFM, et al.: Blood. 2012; 119: 2590-2594
~~24~~28) 社内資料：ヒトマントル細胞リンパ腫由来細胞株の異種移植マウスモデルに対するイブルチニブの作用（2016 年 12 月 2 日承認、CTD2.6.2.2.2.2）
29) Dubovsky JA, Flynn R, Du J, et al.: J Clin Invest. 2014;124(11): 4867-4876

24. 文献請求先及び問い合わせ先

ヤンセンファーマ株式会社　メディカルインフォメーション
コールセンター
〒101-0065　東京都千代田区西神田 3-5-2
フリーダイヤル　0120-183-275
https://www.janssenpro.jp

26. 製造販売業者等

26.1 製造販売元

ヤンセンファーマ株式会社
〒101-0065　東京都千代田区西神田 3-5-2

製造販売元
ヤンセンファーマ株式会社
〒101-0065 東京都千代田区西神田3-5-2

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共同開発
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pharmacyclics
An AbbVie Company

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1.8.1 効能・効果（案），用法・用量（案）及びその設定根拠

1.8.1.1 効能・効果（案）及びその設定根拠

1.8.1.1.1 効能・効果（案）

造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）

1.8.1.1.2 設定根拠

本申請の効能・効果（案）は，ステロイド依存性又は抵抗性の慢性移植片対宿主病（cGVHD）患者を対象とした海外第 Ib/II 相試験（PCYC-1129-CA 試験，以下 1129 試験）及び国内第 III 相試験（54179060GVH3001，以下 GVH3001 試験）の結果に基づいて設定した。

cGVHD は，同種造血幹細胞移植後の合併症として発現する疾患であり，複数の臓器に自己免疫疾患に類似した臨床徴候と症状を示す。全身治療を要する cGVHD に対する一次治療の標準療法はステロイド又はステロイドとカルシニューリン・インヒビターの併用であるが，一次治療による治療効果が不十分で二次治療を必要とする患者に対する標準療法は確立されていない。

1129 試験は，ステロイド依存性又は抵抗性の cGVHD 患者を対象に本剤の有効性及び安全性を検討する非盲検，単群，多施設共同，第 Ib/II 相試験である。主要評価項目である主要解析時点の National Institutes of Health (NIH) Consensus Development Project Criteria（2005）に基づく全奏効率（完全奏功及び部分奏効の割合）は 66.7%［28/42 例，95%信頼区間（CI）：50.5%，80.4%］であり，95% CI の下限が有効性を判断するために事前に設定した閾値の 25%を超え，主要目的を達成した。また，ステロイド必要量の全体的な減量を伴って持続的な奏効が認められた。1129 試験において，本剤の安全性プロファイルは許容可能であり，既承認の B 細胞腫瘍患者で認められた本剤の安全性プロファイル及びステロイドを継続的に投与している cGVHD 患者において予測される安全性プロファイルとおおむね同様であった。

GVH3001 試験は，12 歳以上のステロイド依存性又は抵抗性の日本人 cGVHD 患者を対象に，本剤の有効性，安全性及び薬物動態（PK）を評価する非盲検，単群，多施設共同，第 III 相試験である。主要評価項目である NIH Consensus Development Project Criteria（2014）に基づく全奏効率は 73.7%（14/19 例，95% CI：48.8%，90.9%）であり，95% CI の下限が有効性を判断するために事前に設定した閾値の 25%を超え，主要目的を達成した。また，ステロイド必要量は経時的に減少する傾向が認められ，持続的な奏効も認められた。GVH3001 試験において，本剤の安全性プロファイルは許容可能であり，本剤の既知の安全性プロファイル及びステロイドを継続的に投与している cGVHD 患者で予測される安全性プロファイルとおおむね同様であった。

以上から，本剤の効能・効果（案）を「造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）」とした。

1.8.1.2 用法・用量（案）及びその設定根拠

1.8.1.2.1 用法・用量（案）

通常，成人及び 12 歳以上の小児にはイブルチニブとして 420 mg を 1 日 1 回経口投与する。なお，患者の状態により適宜減量する。

1.8.1.2.2 設定根拠

cGVHD に対する本剤の用法・用量（案）は，18 歳以上のステロイド依存性又は抵抗性の cGVHD 患者を対象とした海外第 Ib/II 相試験（1129 試験），12 歳以上のステロイド依存性又は抵抗性の日本人 cGVHD 患者を対象とした国内第 III 相試験（GVH3001 試験），1～21 歳の cGVHD 患者を対象とした海外第 I/II 相試験（PCYC-1146-IM 試験，以下 1146 試験）の 12 歳以上の被験者，及び 12 歳以上の未治療の cGVHD 患者を対象とした国際共同第 III 相試験（PCYC-1140-IM 試験，以下 1140 試験）のデータを用いて検討した。

cGVHD に対する本剤の投与量は，B 細胞腫瘍に対する本剤の投与量を参考に検討した。海外で承認されている B 細胞腫瘍に対する本剤の推奨用量は，慢性リンパ性白血病（CLL）/小リンパ球性リンパ腫（SLL）及び原発性マクログロブリン血症に対しては 420 mg/日，マントル細胞リンパ腫（MCL）に対しては 560 mg/日である。本剤の主な副作用である消化器症状（下痢，悪心及び嘔吐），感染症，発疹等が cGVHD の病態と重複する可能性があるため，1129 試験の開始用量は保守的に 420 mg/日を選択した。1129 試験の第 Ib 相において用量制限毒性は認められず，第 II 相推奨用量は 420 mg/日に決定された。1129 試験で本剤 420 mg/日を投与したときの曝露量は，同じ推奨用量の CLL/SLL 患者でみられた曝露量より高かったが，1129 試験における本剤 420 mg/日投与の安全性プロファイルは許容可能であり，良好なベネフィット・リスクプロファイルが示された。また，1129 試験において，本剤 420 mg/日投与時の高いブルトン型チロシンキナーゼ占有率及び一定のインターロイキン 2 誘導型 T 細胞キナーゼ占有率が確認された。以上から，海外において cGVHD に対する本剤の推奨用量は 420 mg/日と決定された。

国内で承認されている本剤の推奨用量は， CLL/SLL に対しては 420 mg/日であり，MCL に対しては 560 mg/日である。日本人患者を対象とした GVH3001 試験の本剤の投与量は，海外の cGVHD に対する推奨用量と同じ 420 mg/日を選択した。GVH3001 試験の日本人 cGVHD 患者の曝露量は，1129 試験と同様に CLL/SLL 患者の曝露量よりも高く，また，1129 試験の曝露量より高い傾向を示したが，1129 試験で観測された曝露量の範囲とおおむね一致しており，血漿中からの消失半減期も両試験で同程度であった。GVH3001 試験の本剤の安全性プロファイルは許容可能であり，良好なベネフィット・リスクプロファイルが示された。また，GVH3001 試験においても 1129 試験と同様に高いブルトン型チロシンキナーゼ占有率が確認された。

1129 試験，GVH3001 試験，1146 試験及び 1140 試験の計 162 例の被験者から得られた 1281 測定時点の血漿中イブルチニブ濃度を用いて母集団 PK 解析を行った結果，日本人の曝露量は非日本人と比較して高かった。母集団 PK 解析で構築した最終モデルを用いた推奨用量投与時の曝露量のシミュレーションを行った結果，本剤 420 mg と中程度のチトクローム P450（CYP）3A 阻害薬併用時の日本人で，最高血漿中濃度（C_{max}）及び定常状態における血漿中濃度－時間曲線下面積（AUC_{ss}）の中央値が最も高値を示したが，このときの血漿中イブルチニブ濃度の 90%予測区間を，臨床試験で得られた実測値と比較したところ，臨床試験で得られた実測値の範囲を超えな

かった。また，本剤の注目すべき有害事象（出血事象，心房細動，血球減少症，肝機能異常及び感染症）を安全性指標として，1129 試験，GVH3001 試験及び 1140 試験のデータ（N=146）を用いて曝露量－安全性関係を検討した結果，いずれの安全性の指標についても，曝露量と事象発現との関連はみられなかった。

以上のとおり，日本人において曝露量が高い傾向がみられたものの，安全性への影響は特定されなかった。したがって，日本人においても海外と同様に，cGVHD 患者に対する推奨用量を 420 mg/日と設定した。

青年期患者については，本剤の主要な代謝酵素である CYP3A4 の発現量はおおむね 1 歳頃までに成人と同程度にまで達すること，本剤が消化管及び肝臓の CYP3A により代謝され主要なトランスポーターの基質とはならないこと，並びに成人 B 細胞腫瘍患者の母集団 PK 解析において体重が本剤の PK に意味のある影響を及ぼさないことが示されており，大半の青年期患者は検討された体重範囲に含まれると考えられることから，青年期患者における本剤の PK プロファイルは成人と類似していると考えられた。このため，青年期患者を対象とした臨床試験（1146 試験，GVH3001 試験，1140 試験）では，成人と同じ用法・用量を設定した。1146 試験の 12～19 歳の被験者の定常状態におけるトラフ濃度は，1129 試験で成人 cGVHD 患者に本剤 420 mg/日を投与したときの定常状態におけるトラフ濃度と同程度であった。1129 試験，GVH3001 試験，1146 試験及び 1140 試験のデータを用いた母集団 PK 解析では，年齢及び体重について，曝露量に対する明らかな影響はみられなかった。GVH3001 試験，1146 試験及び 1140 試験において，青年期患者の安全性プロファイルは許容可能であり，本剤の成人患者に対する既知の安全性プロファイルと比較して，青年期患者に特有の安全性シグナルは特定されなかった。したがって，12 歳以上の青年期 cGVHD 患者に対する推奨用量を，成人と同様に 420 mg/日と設定した。

以上より，本剤の用法・用量（案）を「通常，成人及び 12 歳以上の小児にはイブルチニブとして 420 mg を 1 日 1 回経口投与する。なお，患者の状態により適宜減量する。」とした。

1.8.2　使用上の注意（案）及びその設定根拠

使用上の注意（案） 2021年5月改訂（第2版）からの変更箇所 （下線：追記箇所、取消線：削除箇所）	設定根拠
1. 警告 本剤は、緊急時に十分に対応できる医療施設において、造血器悪性腫瘍の治療<u>又は造血幹細胞移植</u>に対して十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。	効能効果（案）との整合性を踏まえ追記した。
5. 効能又は効果に関連する注意 **〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）〉** 5.1 未治療の慢性リンパ性白血病（小リンパ球性リンパ腫を含む）の場合、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。 **〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉** 5.2「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。	既治療のcGVHDに対しては現在承認されている薬剤がないことから，5.1項における「本剤以外の治療の実施についても慎重に検討し」については該当しないため，別項として追記した。
7. 用法及び用量に関連する注意 **〈効能共通〉** 7.1 Grade 3[注)] 以上の副作用が発現した場合には、Grade 1以下に回復するまで本剤を休薬すること。再開する場合には、以下の目安を参考に減量又は中止すること。 注）CTCAE（Common Terminology Criteria for Adverse Events）version 4.0に準じる。	効能共通の注意，効能・効果毎の注意事項を区別する記載に変更した。 7.1：効能・効果（案）及び用法・用量（案）に合わせて追記した。

使用上の注意（案） 2021年5月改訂（第2版）からの変更箇所 （下線：追記箇所、取消線：削除箇所）	設定根拠

用量調節の目安

発現回数	回復後の再開時投与量	
	慢性リンパ性白血病 慢性移植片対宿主病	マントル細胞リンパ腫
1回	1日1回420mg	1日1回560mg
2回	1日1回280mg	1日1回420mg
3回	1日1回140mg	1日1回280mg
4回	投与中止	

7.2 ~~ボリコナゾールと併用する場合には、本剤の血中濃度が上昇するおそれがあるため、イブルチニブとして140mgを1日1回経口投与すること。［10.2、16.7.2参照］~~以下のCYP3A阻害作用を有する薬剤を併用する場合には、本剤の血中濃度が上昇するおそれがあるため、併用薬に応じて次のように投与すること。

CYP3A阻害剤との併用時の用量調節基準

効能又は効果	併用薬	投与方法
慢性リンパ性白血病（小リンパ球性リンパ腫を含む）、再発又は難治性のマントル細胞リンパ腫	ボリコナゾール	イブルチニブとして140mgを1日1回経口投与すること。［10.2、16.7.2参照］
	ポサコナゾール	イブルチニブとして140mgを1日1回経口投与すること。［10.2、16.7.7参照］
造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）	ボリコナゾール	イブルチニブとして280mgを1日1回経口投与すること。［10.2参照］
	ポサコナゾール	イブルチニブとして140mgを1日1回経口投与すること。［10.2、16.7.7参照］

7.2：本剤は主にCYP3Aにより代謝される。cGVHD患者は感染症のリスクが高く，cGVHD症状と感染症管理を持続的に両立させる必要がある。そのため，強力なCYP3A阻害薬のうち高頻度での併用が想定されるボリコナゾール及びポサコナゾールについては，cGVHDの臨床試験及び最新の企業中核データシート（CCDS）に基づき，B細胞腫瘍患者に対する基準とは別に本剤の用量調節基準を設定した。

7.4：cGVHDに対する注意を追加した。

<table>
<tr><th>使用上の注意（案）
2021年5月改訂（第2版）からの変更箇所
（下線：追記箇所、取消線：削除箇所）</th><th>設定根拠</th></tr>
<tr><td><u>〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）、再発又は難治性のマントル細胞リンパ腫〉</u>
7.<u>3</u> 本剤と他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。
<u>〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉</u>
<u>7.4 治療にあたっては経過を十分に観察し、漫然と投与を継続しないこと。</u></td><td></td></tr>
<tr><td>9. 特定の背景を有する患者に関する注意
＜9.1-9.6, 9.8：略＞
9.7 小児等
<u>〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）、再発又は難治性のマントル細胞リンパ腫〉</u>
<u>9.7.1</u> 小児等を対象とした臨床試験は実施していない。
<u>〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉</u>
<u>9.7.2 12歳未満の小児等を対象とした臨床試験は実施していない。</u></td><td>1146試験における12歳以上の患者の薬物動態及び安全性評価に基づき，新記載要領に基づく添付文書等の作成の留意点（Q&A）No.33を踏まえて追記した。</td></tr>
<tr><td>10. 相互作用
本剤は主にCYP3Aにより代謝される。
＜10.1：略＞

10.2 併用注意（併用に注意すること）
<table><tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr><tr><td>CYP3A阻害作用を有する薬剤</td><td>本剤の血中濃度が上昇し、副作用が増強される</td><td></td></tr></table></td><td>10.2：ポサコナゾールについては，B細胞腫瘍患者及びcGVHD患者において得られた臨床試験成績及び生理学的薬物動態モデルによるシミュレーションの結果より，7.2項にある「CYP3A阻害剤との併用時の用量調節基準」に沿って本剤の用量調節をすることで併用可能と評価されたため追記した。</td></tr>
</table>

<table>
<tr><td>使用上の注意（案）
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（下線：追記箇所、取消線：削除箇所）</td><td>設定根拠</td></tr>
<tr><td>
<table>
<tr><td>インジナビル
ネルフィナビル
リトナビル含有製剤
サキナビル
コビシスタット含有製剤
アタザナビル
ダルナビル
ホスアンプレナビル</td><td rowspan="11">おそれがあるので、CYP3A阻害作用のない薬剤への代替を考慮すること。やむを得ず併用する際には、本剤の減量を考慮するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。</td><td rowspan="11">これらの薬剤のCYP3A阻害作用により、本剤の代謝が阻害される。</td></tr>
<tr><td>テラプレビル</td></tr>
<tr><td>ボリコナゾール
［7.2、16.7.2参照］
ポサコナゾール
［7.2、16.7.7参照］
フルコナゾール</td></tr>
<tr><td>エリスロマイシン
［16.7.3参照］
シプロフロキサシン</td></tr>
<tr><td>ジルチアゼム
［16.7.7参照］
ベラパミル
アミオダロン</td></tr>
<tr><td>アプレピタント</td></tr>
<tr><td>＜略＞</td><td>＜略＞</td><td>＜略＞</td></tr>
</table>
</td><td></td></tr>
<tr><td>11. 副作用
次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。
11.1 重大な副作用
11.1.1 出血</td><td>薬生安発0608第1号に基づき，慢性リンパ性白血病（小リンパ球性リンパ腫を含む）及び再発又は難治性のマントル細胞リンパ腫を対象として実施した試験に，cGVHDを対象とする1129試験及びGVH3001試験を加えて併合解析し，発現頻度を算出しなおした。</td></tr>
</table>

使用上の注意（案） 2021年5月改訂（第2版）からの変更箇所 （下線：追記箇所、取消線：削除箇所）	設定根拠
脳出血（0.2%）、消化管出血（0.4%）等の重篤な出血があらわれることがあり、死亡に至った例が報告されている。 **11.1.2 白血球症**（頻度不明） 頭蓋内出血、嗜眠、不安定歩行、頭痛等を伴う白血球症があらわれることがある。 **11.1.3 感染症** 肺炎（8.9%）、敗血症（2.3%）等の重篤な感染症があらわれることがある。また、B型肝炎ウイルス、結核、帯状疱疹等の再活性化があらわれることがある。[8.2、9.1.1参照] **11.1.4 進行性多巣性白質脳症（PML）**（頻度不明） 本剤投与中及び投与終了後は患者の状態を十分に観察すること。意識障害、認知障害、麻痺症状（片麻痺、四肢麻痺）、言語障害等の症状があらわれた場合には、MRIによる画像診断及び脳脊髄液検査を行うとともに、投与を中止するなどの適切な処置を行うこと。 **11.1.5 骨髄抑制** 貧血（9.6%）、好中球減少症（12.5%）、血小板減少症（9.8%）等の重篤な骨髄抑制があらわれることがある。[8.3、9.1.2参照] **11.1.6 不整脈** 心房細動（2.7%）、心房粗動（0.5%）、心室性不整脈（頻度不明）等の重篤な不整脈があらわれることがある。[8.4、9.1.3参照] **11.1.7 腫瘍崩壊症候群**（0.2%） 異常が認められた場合には、直ちに投与を中止し、適切な処置（生理食塩液、高尿酸血症治療剤の投与等）を行うとともに、症状が回復するまで患者の状態を十分に観察すること。なお、重篤な腫瘍崩壊症候群が遅発性にあらわれることがある。[8.5参照] **11.1.8 過敏症**（0.2%）	11.2：破線で示した副作用は、再集計により頻度の列が変更になった事象である。

使用上の注意（案） 2021年5月改訂（第2版）からの変更箇所 （下線：追記箇所、取消線：削除箇所）	設定根拠

アナフィラキシー等の重篤な過敏症があらわれることがある。

11.1.9 皮膚粘膜眼症候群（Stevens-Johnson症候群）（頻度不明）

11.1.10 肝不全、肝機能障害（頻度不明）

肝不全、ALT、AST、ビリルビン等の上昇を伴う肝機能障害があらわれることがある。［8.6参照］

11.1.11 間質性肺疾患（0.5%）

異常が認められた場合には、胸部X線、胸部CT等の検査を実施すること。間質性肺疾患が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。［8.7参照］

11.2 その他の副作用

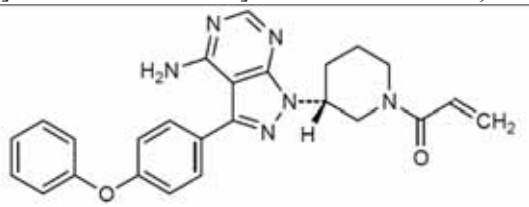
	10%以上	10%未満 5%以上	5%未満	頻度不明
感染症及び寄生虫症		上気道感染	皮膚感染、尿路感染、副鼻腔炎	
良性、悪性及び詳細不明の新生物（嚢胞及びポリープを含む）			扁平上皮癌、基底細胞癌	前立腺癌、悪性黒色腫、リンパ腫、骨髄異形成症候群
血液及びリンパ系障害			白血球増加症、リンパ球増加症、発熱性好中球減少症	
代謝及び栄養障害			食欲減退、高尿酸血症、低カリウム血症、脱水、低ナトリウム血症	

<table>
<tr><th>使用上の注意（案）
2021年5月改訂（第2版）からの変更箇所
（下線：追記箇所、取消線：削除箇所）</th><th>設定根拠</th></tr>
<tr><td>
<table>
<tr><td>神経系障害</td><td></td><td>頭痛</td><td>浮動性めまい、末梢性ニューロパチー</td><td></td></tr>
<tr><td>眼障害注)</td><td></td><td></td><td>霧視、眼乾燥、流涙増加、視力低下、結膜炎</td><td></td></tr>
<tr><td>血管障害</td><td></td><td></td><td>高血圧</td><td></td></tr>
<tr><td>呼吸器、胸郭及び縦隔障害</td><td></td><td></td><td>鼻出血、咳嗽、呼吸困難</td><td></td></tr>
<tr><td>胃腸障害</td><td>下痢（28.5%）、悪心</td><td>口内炎、嘔吐</td><td>便秘、消化不良、腹痛、胃食道逆流性疾患</td><td></td></tr>
<tr><td>皮膚及び皮下組織障害</td><td>発疹、挫傷</td><td>点状出血</td><td>そう痒症、爪破損、紅斑、蕁麻疹、血管浮腫</td><td>脂肪織炎、急性熱性好中球性皮膚症（Sweet症候群）</td></tr>
<tr><td>筋骨格系及び結合組織障害</td><td></td><td>関節痛、筋痙縮、筋骨格痛</td><td></td><td>関節障害</td></tr>
<tr><td>一般・全身障害及び投与部位の状態</td><td>疲労</td><td>発熱</td><td>末梢性浮腫、無力症、硬膜下血腫</td><td></td></tr>
<tr><td>傷害、中毒及び処置合併症</td><td></td><td></td><td>転倒</td><td></td></tr>
</table>
注）眼の異常があらわれた場合には、直ちに眼科的検査を行うなどの適切な処置を行うこと。
</td><td></td></tr>
<tr><td>上記以外の項目</td><td>変更なし</td></tr>
</table>

1.10　毒薬・劇薬等の指定審査資料のまとめ

毒薬・劇薬等の指定審査に係る資料について，【現行】の内容と合わせて，本申請に係る【追加】の内容を次ページより示す。

【現行】

化学名・別名	1-{(3R)-3-[4-アミノ-3-(4-フェノキシフェニル)-1H-ピラゾロ[3,4-d]ピリミジン-1-イル]ピペリジン-1-イル}プロパ-2-エン-1-オン
構造式	
効能・効果	○慢性リンパ性白血病（小リンパ球性リンパ腫を含む） ○再発又は難治性のマントル細胞リンパ腫
用法・用量	〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）〉 通常、成人にはイブルチニブとして 420 mg を 1 日 1 回経口投与する。なお、患者の状態により適宜減量する。 〈再発又は難治性のマントル細胞リンパ腫〉 通常、成人にはイブルチニブとして 560 mg を 1 日 1 回経口投与する。なお、患者の状態により適宜減量する。
劇薬等の指定	原体及び製剤はいずれも劇薬に該当し、生物由来製品及び特定生物由来製品のいずれにも該当しない
市販名及び有効成分・分量	イムブルビカカプセル 140 mg （1 カプセル中イブルチニブ 140 mg を含む）
毒性	**単回投与毒性** **反復投与毒性**

単回投与毒性

動物種	投与経路	概略の致死量（mg/kg）
マウス	経口	♂♀：>2000
ラット	経口	♂：2000, ♀：1000
	静脈内	♀：100（急速静脈内） ♀：>100（30 及び 60 分間の持続静脈内）
イ　ヌ	経口	♂♀：>200
	皮下	♂♀：>40

反復投与毒性

動物種	投与期間 投与経路	性別	投与量 (mg/kg/日)	無毒性量 (mg/kg/日)	主な所見
ラット	4 週間 経口 回復 期間: 28 日間	♂♀	0, 2.5, 40, 150(♀), 300(♂)	♂♀：40	300/150： 死亡(試験 16 日目-♂:1 例) 体重↓(♂), 体重増加量↓(♂), 摂餌量↓(♂), 軟便, 鼻周囲に赤色物質, Alb↓, TP↓, グロブリン↓(♂),下顎リンパ節:腫大, リンパ球過形成, 脾臓:リンパ球枯渇, 胸腺:単細胞壊死(アポトーシス), 前胃:扁平上皮過形成(♂), 皮膚:炎症性変化, 肝臓:肝細胞壊死

反復投与毒性

動物種	投与期間 投与経路	性別	投与量 (mg/kg/日)	無毒性量 (mg/kg/日)	主な所見
ラット	13 週間 経口 回復 期間: 42 日間	♂ ♀	0, 30, 100, 300(♂), 300/175(♀)[a]	♂ ♀ : 30	100≦ : 軟便(♀), 顔面発赤(♀), 鼻周囲に赤色物質(♀), Alb↓, TP↓, グロブリン↓(♀), 骨皮質及び骨梁の減少(♀), 膵臓:腺房萎縮(♂) 300/175 : 死亡又は切迫屠殺(試験 41~79 日目-♂:7 例), 死亡(試験 90 日目-♀:1 例) 体重↓, 体重増加量↓, 摂餌量↓, 軟便(♂), 顔面発赤(♂), 鼻周囲に赤色物質(♂), グロブリン↓(♂), リンパ節:リンパ球枯渇(♀), 脾臓:リンパ球枯渇(♀), 胸腺:リンパ球枯渇(♀), 前胃:潰瘍(♀), 浮腫(♀), 扁平上皮過形成(♀), 扁平上皮萎縮(♀), 腸:潰瘍(♀), 急性炎症(♀), 骨皮質及び骨梁の減少(♂)
ラット	6 カ月間 経口 回復 期間: 1 カ月間	♂ ♀	0, 25, 50, 80(♀), 100(♂)	♂ : 100 ♀ : 50	80 : 死亡(試験 131 日-♀: 1 例)[b] 体重↓(♀), 体重増加量↓(♀)
イ　ヌ	4 週間 経口 回復 期間: 29 日間	♂ ♀	0, 1.5, 24, 150	♂ ♀ : 24	150 : 体重↓, 摂餌量↓(♀), 軟便, 下痢, 便退色, 角膜ジストロフィー, Alb↓, TP↓, A/G 比↓, 腸:炎症性変化
イ　ヌ	13 週間 経口 回復 期間: 91 日間	♂ ♀	0, 30, 80/60[c], 220/120[c]	♂ ♀ : 30	80/60≦ : 体重増加量↓, 摂餌量↓, 軟便, 下痢, 嘔吐, Alb↓, A/G 比↓, パイエル板:リンパ球枯渇 220/120 : 切迫屠殺(試験 31 日目-♂:1 例) 体重↓, 角膜ジストロフィー(♂), 腸:急性炎症(♀), 胃:平滑筋変性(♀)
イ　ヌ	9 カ月間 経口 回復 期間: 1 カ月間	♂ ♀	0, 30, 50, 80	♂ ♀ : 80	特記すべき所見なし

[a] 300 mg/kg/日投与群の雌性で体重減少がみられたことから，試験 8 日に投与量を 175 mg/kg/日に減量して投与終了時まで投与。
[b] 試験 131 日に死亡発見。死因は特定されず。
[c] 80 及び 220 mg/kg/日投与群の雄性各 1 例に有意な体重減少及び健康状態の悪化がみられ，切迫屠殺したことから，試験 42 日に雌雄とも投与量をそれぞれ 60 及び 120 mg/kg/日に減量して投与終了時まで投与。

副作用

副作用発現割合（臨床検査値異常変動を含む）15 例／15 例＝100.0%
［国内第 I 相試験（PCI-32765-JPN-101）］

副作用（臨床検査値異常変動を含む）の種類	例数
好中球減少症	8
貧血	7
血中ビリルビン増加	6
白血球減少症	5

	発疹　5 下痢　5 鼻咽頭炎　4 白血球増加症　4 皮膚乾燥　4 点状出血　4 Ｃ－反応性蛋白増加　4 血小板数減少　4 等 副作用発現割合（臨床検査値異常変動を含む）15 例／16 例＝93.8% ［国内第 II 相試験（PCI-32765MCL2002）］ 副作用（臨床検査値異常変動を含む）の種類　例数 下痢　5 血小板数減少　5 口内炎　4 貧血　4 発疹　3 血小板減少症　3 疲労　3 食欲減退　3 等 副作用発現割合（臨床検査値異常変動を含む）8 例／8 例＝100% ［国内第 I 相試験（54179060LEU1001）］ 副作用（臨床検査値異常変動を含む）の種類　例数 血小板数減少　6 リンパ球数増加　4 下痢　2 肺炎　2 関節痛　2 等
会社	ヤンセンファーマ株式会社　製剤：輸入

【追加】

化学名・別名	
構造式	
効能・効果	○慢性リンパ性白血病（小リンパ球性リンパ腫を含む） ○再発又は難治性のマントル細胞リンパ腫 ○造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合） （下線部追加箇所）
用法・用量	〈慢性リンパ性白血病（小リンパ球性リンパ腫を含む）〉 通常、成人にはイブルチニブとして 420 mg を 1 日 1 回経口投与する。なお、患者の状態により適宜減量する。 〈再発又は難治性のマントル細胞リンパ腫〉 通常、成人にはイブルチニブとして 560 mg を 1 日 1 回経口投与する。なお、患者の状態により適宜減量する。 〈造血幹細胞移植後の慢性移植片対宿主病（ステロイド剤の投与で効果不十分な場合）〉 通常、成人及び 12 歳以上の小児にはイブルチニブとして 420 mg を 1 日 1 回経口投与する。なお、患者の状態により適宜減量する。 （下線部追加箇所）
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	副作用発現割合（臨床検査値異常変動を含む）15 例／15 例＝100.0% ［国内第 I 相試験（PCI-32765-JPN-101）］ 副作用（臨床検査値異常変動を含む）の種類　例数 好中球減少症　8 貧血　7 血中ビリルビン増加　6 白血球減少症　5 発疹　5 下痢　5 鼻咽頭炎　4 白血球増加症　4 皮膚乾燥　4 点状出血　4 Ｃ－反応性蛋白増加　4 血小板数減少　4 等 副作用発現割合（臨床検査値異常変動を含む）15 例／16 例＝93.8% ［国内第 II 相試験（PCI-32765MCL2002）］ 副作用（臨床検査値異常変動を含む）の種類　例数 下痢　5 血小板数減少　5 口内炎　4 貧血　4 発疹　3 血小板減少症　3 疲労　3 食欲減退　3 等

	副作用発現割合（臨床検査値異常変動を含む）8 例／8 例＝100% ［国内第 I 相試験（54179060LEU1001）］ 副作用（臨床検査値異常変動を含む）の種類　例数 血小板数減少　6 リンパ球数増加　4 下痢　2 肺炎　2 関節痛　2 等 副作用発現割合（臨床検査値異常変動を含む）15 例／19 例＝78.9% ［国内第III相試験（54179060GVH3001）］ 副作用（臨床検査値異常変動を含む）の種類　例数 肺炎　4 血小板減少　4 蜂巣炎　3 口内炎　3 細気管支炎　2 上気道感染　2 紫斑　2 高血圧　2 等 （二重下線部追加箇所）
会社	

添付資料番号	タイトル	掲載誌	評価資料 参考資料
4.2 試験報告書			
4.2.1 薬理試験			
4.2.1.1 効力を裏付ける試験			
4.2.1.1.1	Ibrutinib treatment ameliorates murine chronic graft-versus-host disease.	J Clin Invest. 2014;124(11):4867-76	参考資料
4.2.1.1.2	Inhibition of BTK and ITK with Ibrutinib Is Effective in the Prevention of Chronic Graft-versus-Host Disease in Mice.	PloS One. 2015;10(9):e0137641	参考資料
4.2.1.2 副次的薬理試験			
	該当資料なし		
4.2.1.3 安全性薬理試験			
	該当資料なし		
4.2.1.4 薬力学的薬物相互作用試験			
	該当資料なし		
4.2.2 薬物動態試験			
4.2.2.1 分析法及びバリデーション報告書			
	該当資料なし		
4.2.2.2 吸収			
	該当資料なし		
4.2.2.3 分布			
	該当資料なし		
4.2.2.4 代謝			
	該当資料なし		
4.2.2.5 排泄			
	該当資料なし		
4.2.2.6 薬物動態学的薬物相互作用（非臨床）			
	該当資料なし		
4.2.2.7 その他の薬物動態試験			
	該当資料なし		
4.2.3 毒性試験			
4.2.3.1 単回投与毒性試験			
	該当資料なし		
4.2.3.2 反復投与毒性試験			
	該当資料なし		
4.2.3.3 遺伝毒性試験			
4.2.3.3.1 *In Vitro* 試験			
	該当資料なし		
4.2.3.3.2 *In Vivo* 試験			
	該当資料なし		
4.2.3.4 がん原性試験			
4.2.3.4.1 長期がん原性試験			
	該当資料なし		
4.2.3.4.2 短期又は中期がん原性試験			
4.2.3.4.2.1	A 26-week Carcinogenicity Study of Ibrutinib by Oral Gavage in CByB6F1/Tg rasH2 Hemizygous Mice	ヤンセンファーマ社内資料 TOX11482	評価資料
4.2.3.4.3 その他の試験			
	該当資料なし		
4.2.3.5 生殖発生毒性試験			
4.2.3.5.1 受胎能及び着床までの初期胚発生に関する試験			
	該当資料なし		
4.2.3.5.2 胚・胎児発生に関する試験			
	該当資料なし		
4.2.3.5.3 出生前及び出生後の発生並びに母体の機能に関する試験			

添付資料番号	タイトル	掲載誌	評価資料 参考資料
	該当資料なし		
4.2.3.5.4 新生児を用いた試験			
	該当資料なし		
4.2.3.6 局所刺激性試験			
	該当資料なし		
4.2.3.7 その他の毒性試験			
4.2.3.7.1 抗原性試験			
	該当資料なし		
4.2.3.7.2 免疫毒性試験			
	該当資料なし		
4.2.3.7.3 毒性発現の機序に関する試験			
	該当資料なし		
4.2.3.7.4 依存性試験			
	該当資料なし		
4.2.3.7.5 代謝物の毒性試験			
	該当資料なし		
4.2.3.7.6 不純物の毒性試験			
	該当資料なし		
4.2.3.7.7 その他の試験			
	該当資料なし		
4.3 参考文献			
4.3.1	参考文献	参考文献一覧表及び参考文献を添付	参考資料

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子 データ 有無
5.2 全臨床試験一覧表				
5.3 臨床試験報告書				
5.3.1 生物薬剤学試験報告書				
5.3.1.1 バイオアベイラビリティ（BA）試験報告書				
	該当資料なし			－
5.3.1.2 比較BA試験及び生物学的同等性（BE）試験報告書				
	該当資料なし			－
5.3.1.3 In Vitro－In Vivo の関連を検討した試験報告書				
	該当資料なし			－
5.3.1.4 生物学的及び理化学的分析法検討報告書				
5.3.1.4.1	Report for the Partial Validation of Method BTM-2201: Determination ofJNJ-54179060 (Ibrutinib, PCI-32765) and JNJ-54243761 (PCI-45227, dihydrodiol metabolite) in Sodium Heparin Human Plasma by LC-MS/MS (0.500 - 250 ng/mL)	ヤンセンファーマ 社内資料 BA12048	評価資料	無
5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書				
5.3.2.1 血漿蛋白結合試験報告書				
	該当資料なし			－
5.3.2.2 肝代謝及び薬物相互作用試験報告書				
5.3.2.2.1	Physiologically Based Pharmacokinetic Drug-Drug Interaction Simulations of JNJ-54179060 (PCI-32765 or Ibrutinib) and the Strong CYP3A4 Inhibitor Posaconazole in Non-Fasted Healthy Subjects	ヤンセンファーマ 社内資料 FK12024	参考資料	有
5.3.2.3 他のヒト生体試料を用いた試験報告書				
	該当資料なし			－
5.3.3 臨床薬物動態（PK）試験報告書				
5.3.3.1 健康被験者におけるPK及び初期忍容性試験報告書				
	該当資料なし			－
5.3.3.2 患者におけるPK及び初期忍容性試験報告書				
	該当資料なし			－
5.3.3.3 内因性要因を検討したPK試験報告書				
	該当資料なし			－
5.3.3.4 外因性要因を検討したPK試験報告書				
	該当資料なし			－
5.3.3.5 ポピュレーションPK試験報告書				
5.3.3.5.1	Population PK and Exposure-Response Analysis of Ibrutinib for Chronic Graft-Versus-Host Disease	ヤンセンファーマ 社内資料 poppk	評価資料	有
5.3.4 臨床薬力学（PD）試験報告書				
5.3.4.1 健康被験者におけるPD試験及びPK/PD試験報告書				
	該当資料なし			－
5.3.4.2 患者におけるPD試験及びPK/PD試験報告書				

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子 データ 有無
	該当資料なし			―
5.3.5 有効性及び安全性試験報告書				
5.3.5.1 申請する適応症に関する比較対照試験報告書				
5.3.5.1.1	A Randomized, Double-Blind Phase 3 Study of Ibrutinib in Combination With Corticosteroids versus Placebo in Combination With Corticosteroids in Subjects with New Onset Chronic Graft Versus Host Disease (cGVHD)	ヤンセンファーマ 社内資料 試験番号： PCYC-1140-IM	参考資料	有
5.3.5.2 非対照試験報告書				
5.3.5.2.1-1	A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease	ヤンセンファーマ 社内資料 試験番号： PCYC-1129-CA	評価資料	有
5.3.5.2.1-2	A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease_Addendum	ヤンセンファーマ 社内資料 試験番号： PCYC-1129-CA	評価資料	有
5.3.5.2.2	A Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib in Subjects with Steroid Dependent/Refractory Chronic Graft Versus Host Disease (cGVHD)	ヤンセンファーマ 社内資料 試験番号： 54179060GVH3001	評価資料	有
5.3.5.2.3	Phase 1/2 Dose Finding, Safety and Efficacy Study of Ibrutinib in Pediatric Subjects with Chronic Graft Versus Host Disease (cGVHD)	ヤンセンファーマ 社内資料 試験番号： PCYC-1146-IM	評価資料	有
5.3.5.3 複数の試験成績を併せて解析した報告書				
	該当資料なし			―
5.3.5.4 その他の試験報告書				
	該当資料なし			―
5.3.6 市販後の使用経験に関する報告書				
5.3.6.1	Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report 13 November 2017 to 12 November 2018	ヤンセンファーマ 社内資料	参考資料	無
5.3.6.2	Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report 13 November 2018 to 12 November 2019	ヤンセンファーマ 社内資料	参考資料	無
5.3.6.3	市販後に報告された重篤な有害事象一覧	ヤンセンファーマ 社内資料	参考資料	無
5.3.6.4	Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report 13 November 2019 to 12 November 2020	ヤンセンファーマ 社内資料	参考資料	無
5.3.7 患者データ一覧表及び症例記録				
5.3.7.1 用量設定の根拠となった主要な試験及び主要な有効性の検証試験の症例一覧表				
	該当資料なし			―
5.3.7.2 実施された全ての臨床試験において副作用が観察された症例の一覧表				
5.3.7.2.1	副作用一覧表（試験番号：PCYC-1129-CA）	ヤンセンファーマ 社内資料 試験番号： PCYC-1129-CA	評価資料	無
5.3.7.2.2	副作用一覧表（試験番号：54179060GVH3001）	ヤンセンファーマ 社内資料 試験番号： 54179060GVH3001	評価資料	無
5.3.7.2.3	副作用一覧表（試験番号：PCYC-1146-IM）	ヤンセンファーマ 社内資料 試験番号： PCYC-1146-IM	評価資料	無

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子データ有無
5.3.7.3 実施された全ての臨床試験において重篤な有害事象が観察された症例の一覧表				
5.3.7.3.1	重篤な有害事象一覧表（試験番号：PCYC-1129-CA）	ヤンセンファーマ社内資料 試験番号： PCYC-1129-CA	評価資料	無
5.3.7.3.2	重篤な有害事象一覧表（試験番号：54179060GVH3001）	ヤンセンファーマ社内資料 試験番号： 54179060GVH3001	評価資料	無
5.3.7.3.3	重篤な有害事象一覧表（試験番号：PCYC-1146-IM）	ヤンセンファーマ社内資料 試験番号： PCYC-1146-IM	評価資料	無
5.3.7.4 実施された全ての臨床試験において臨床検査値異常変動が観察された症例の一覧表				
5.3.7.4.1	臨床検査値異常変動一覧表（試験番号：PCYC-1129-CA）	ヤンセンファーマ社内資料 試験番号： PCYC-1129-CA	評価資料	無
5.3.7.4.2	臨床検査値異常変動一覧表（試験番号： 54179060GVH3001）	ヤンセンファーマ社内資料 試験番号： 54179060GVH3001	評価資料	無
5.3.7.4.3	臨床検査値異常変動一覧表（試験番号：PCYC-1146-IM）	ヤンセンファーマ社内資料 試験番号： PCYC-1146-IM	評価資料	無
5.3.7.5 実施された全ての臨床試験において観察された臨床検査値の変動を適切に示した図				
	該当資料なし			－
5.4 参考文献				
5.4.1	参考文献	参考文献一覧表及び参考文献を添付	参考資料	無