ウェリレグ錠 40 mg
に関する資料

本資料に記載された情報に係る権利及び内容の責任は MSD 株式会社にあります。当該製品の適正使用の利用目的以外の営業目的に本資料を利用することはできません。

MSD 株式会社

目次

図一覧
1.5　起原又は発見の経緯及び開発の経緯
1.5.1　起原又は発見の経緯
1.5.2　開発の経緯
1.5.2.1　品質・安定性試験の経緯
1.5.2.2　非臨床試験の経緯
1.5.2.3　臨床試験の経緯

図一覧

図 1.5-1　　開発の経緯図

1.5　起原又は発見の経緯及び開発の経緯

1.5.1　　起原又は発見の経緯

当該内容については、＜RCC [2.5.1　項]＞及び＜VHL [2.5.1　項]＞参照。

1.5.2　　開発の経緯

本申請に係る MK-6482の開発の経緯図を[図　1.5-1]に示す。

1.5.2.1　　品質・安定性試験の経緯

原薬の規格及び試験方法の設定については、[2.3.S.4　項]参照。また、原薬の安定性試験成績については、[2.3.S.7　項]参照。

製剤の規格及び試験方法の設定については、[2.3.P.5　項]参照。また、製剤の安定性試験成績については、[2.3.P.8　項]参照。

1.5.2.2　　非臨床試験の経緯

当該内容については、[2.4.1　項]参照。

1.5.2.3　　臨床試験の経緯

当該内容については、＜RCC [2.5.1.4　項]＞及び＜VHL [2.5.1.4　項]＞参照。

図 1.5-1 開発の経緯図

試験項目		内容	
正式な安定性試験	原薬	長期保存試験（25°C/60%RH）	[redacted]
		加速試験（40°C/75%RH）	
	製剤	長期保存試験（25°C/60%RH）	
		加速試験（40°C/75%RH）	
薬理試験		効力を裏付ける試験	
		副次的薬理試験	
		安全性薬理	
薬物動態		吸収・分布・代謝・排泄	
毒性試験		反復投与	
		遺伝毒性	
		がん原性	
		生殖発生	
		局所刺激性試験	
		その他	
臨床試験	第Ⅰ相	海外試験（001試験）	2016年12月～継続中*
		海外試験（002試験）	2018年2月～2018年5月*
		海外試験（006試験）	
		国内試験（007試験）	
		海外試験（008試験）	
		海外試験（009試験）	
		海外試験（014試験）	
		海外試験（019試験）	
		海外試験（020試験）	2022年6月～2024年1月*
		海外試験（021試験）	2022年7月～2024年4月*
		国内試験（025試験）	2022年4月～2022年10月*
	第Ⅱ相	海外試験（004試験）	2018年5月～継続中*
		海外試験（013試験）	2020年9月～継続中*
	第Ⅲ相	国際共同試験（005試験）	2020年2月～継続中*

* 新薬承認情報提供時に置き換え

C Confidential

目次

表一覧
1.6　外国における使用状況等に関する資料
1.6.1　外国における使用状況等
1.6.2　外国の添付文書
1.6.2.1　外国の添付文書の概要（和訳）
1.6.2.1.1　米国添付文書の概要（和訳）
1.6.2.1.2　EU 添付文書の概要（和訳）

表一覧

表 1.6-1　外国における本剤の使用状況
表 1.6-2　副作用に対し推奨される用法・用量の変更
表 1.6-3　LITESPARK-004試験で本剤を投与された患者の10%以上に発現した副作用
表 1.6-4　LITESPARK-004試験で本剤を投与された患者におけるベースラインから悪化した臨床検査値異常（10%以上）
表 1.6-5　LITESPARK-005試験で本剤を投与された進行 RCC 患者における副作用（10%以上）
表 1.6-6　LITESPARK-005試験で本剤を投与された進行 RCC 患者におけるベースラインから悪化した臨床検査値異常（20%以上）
表 1.6-7　推奨される用法・用量の変更
表 1.6-8　ベルズチファンを投与された患者における副作用*

1.6　外国における使用状況等に関する資料

1.6.1　外国における使用状況等

外国における本剤の使用状況は[表 1.6-1]のとおり。

2025年3月1日現在、本剤はフォン・ヒッペル・リンドウ（VHL）病関連の腎細胞癌（RCC）、中枢神経系（CNS）血管芽腫及び膵神経内分泌腫瘍（pNET）に対する治療薬として米国及びEUを含む40以上の国又は地域で承認されている。また、PD-1/L1阻害剤及びVEGF標的療法による前治療歴を有する進行RCCに対する治療薬として、米国及びEUを含む30以上の国又は地域で承認されている。

表 1.6-1 外国における本剤の使用状況

本剤が最初に承認された年月（国、適応症）	2021年8月［米国、VHL病関連のRCC、CNS血管芽腫及びpNET（治療を要するが、即時手術を必要としない）成人患者の治療］
本剤の欧米等6ヵ国（米・英・独・仏・加・豪）の承認状況	全ての国で承認取得済み。

1.6.2　外国の添付文書

1.6.2.1　外国の添付文書の概要（和訳）

1.6.2.1.1　米国添付文書の概要（和訳）

販売名／販売会社名

WELIREG®／Merck Sharp & Dohme LLC

剤型・含量

剤型及び含量

錠剤：40 mg、青色、楕円形、フィルムコーティング、片面に「177」と刻印があり、反対側に刻印はない。

効能・効果

効果・効能及び用法

1)　フォン・ヒッペル・リンドウ（VHL）病

本剤は、VHL 病関連の RCC、CNS 血管芽腫及び pNET（治療を要するが、即時手術を必要としない）成人患者の治療に適応される。

2)　進行腎細胞癌（RCC）

本剤は、プログラム細胞死1（PD-1）／プログラム細胞死リガンド1（PD-L1）阻害剤及び血管内皮増殖因子チロシンキナーゼ阻害剤（VEGF-TKI）投与後の進行 RCC 成人患者の治療に適応される。

用法・用量

用法・用量

1)　推奨用量

本剤の推奨用量は120 mg であり、病勢進行又は許容できない毒性が発現するまで1日1回経口投与する。本剤は毎日同じ時間に服用し、食事の有無は問わない。

錠剤をそのまま飲み込むよう患者に指導する。嚥下前に本剤を噛んだり、砕いたり、割ったりしないこと。

本剤の服用を忘れた場合は、その日のできるだけ早い時間に服用することができる。翌日から本剤の通常の1日1回の服用スケジュールを再開する。飲み忘れた分を補う目的で余分に錠剤を服用しないこと。

本剤服用後に嘔吐が起こった場合は、再服用しないこと。次回は翌日に服用すること。

2)　副作用に対する用法・用量の変更

副作用に対する本剤の用法・用量の変更を表 1.6-2に要約する。

推奨される減量は以下のとおりである。

- 初回の減量：本剤80 mg を1日1回経口投与する。

- 2回目の減量：本剤40 mg を1日1回経口投与する。
- 3回目の減量：投与を中止する。

表 1.6-2 副作用に対し推奨される用法・用量の変更

副作用	重症度	用法・用量の変更
貧血 ［警告及び使用上の注意 1）を参照］	ヘモグロビンが8 g/dL 未満又は輸血が適応となる	• ヘモグロビンが8 g/dL 以上になるまで休薬する。 • 同量又は減量して再開する、又は貧血の重症度に応じて中止する。
	生命を脅かす又は緊急介入が適応となる	• ヘモグロビンが8 g/dL 以上になるまで休薬する。 • 減量して再開する又は投与を中止する。
低酸素症 ［警告及び使用上の注意 2）を参照］	労作時の酸素飽和度の低下（例：パルスオキシメーター88%未満）	• 回復するまで休薬することを検討する。 • 低酸素症の重症度に応じて、同量又は減量して再開する。
	安静時の酸素飽和度の低下（例：パルスオキシメーター88%未満又は PaO_2 55 mmHg 以下）又は緊急介入が適応となる	• 回復するまで休薬する。 • 低酸素症の重症度に応じて、減量して再開する又は中止する。
	生命を脅かす又は再発性の症候性低酸素症	• 投与を中止する。
その他の副作用 ［副作用を参照］	Grade 3	• Grade 2以下に回復するまで休薬する。 • 減量（40 mg 減量）して再開することを検討する。 • Grade 3が再発した場合は投与を中止する。
	Grade 4	• 投与を中止する。

警告

警告：胚・胎児毒性

- 妊娠中の本剤への曝露は、胚・胎児に害を及ぼす可能性がある。
- 本剤の投与開始前に妊娠状況を確認すること。
- これらのリスク及びホルモン薬以外の有効な避妊法の必要性について患者に説明すること。本剤は一部のホルモン避妊薬を無効にすることがある［警告及び使用上の注意 3)、薬物相互作用 2)、特殊集団への投与 1、3）を参照］。

禁忌

なし

使用上の注意

1)　貧血

本剤は、輸血を必要とする重度の貧血を引き起こす可能性がある。

本剤の投与開始前及び投与中は、定期的に貧血を観察する。臨床的に必要であれば輸血を行う。

ヘモグロビンが8 g/dL 未満の患者には、貧血の重症度に応じて、8 g/dL 以上になるまで本剤を休薬し、その後、同量又は減量して再開するか、本剤を中止する。生命を脅かす貧血又は緊急介入が適応となる場合は、ヘモグロビンが8 g/dL 以上になるまで本剤を休薬し、その後減量して再開するか、本剤の投与を中止する［用法・用量 2）を参照］。

VHL 病

LITESPARK-004試験では、患者の93%にヘモグロビン減少が認められ、7%に Grade 3の事象が認められた［副作用 1）を参照］。貧血発現までの期間中央値は31日（範囲：1日～8.4ヵ月）であった。

本剤を投与された VHL 病患者の貧血治療における赤血球造血刺激因子製剤（ESA）の安全性は確立していない。骨髄抑制を起こしやすい化学療法を受けているがん患者を対象とした ESA に関する無作為化比較試験では、ESA は死亡及び重篤な心血管系反応のリスクを増加させ、無増悪生存期間又は全生存期間を減少させることが示されている。詳しい情報については、ESA の処方情報を参照のこと。

進行 RCC

LITESPARK-005試験では、患者の88%にヘモグロビン減少が認められ、29%に Grade 3の事象が認められた［副作用 1）を参照］。貧血が発現するまでの期間の中央値は29日（範囲：1日～16.6ヵ月）であった。貧血が発現した患者のうち、22%は輸血のみ、20%は ESA のみ、12%は輸血と ESA による治療を受けた。

2)　低酸素症

本剤は重度の低酸素症を引き起こすことがあり、投与中止、酸素補給、又は入院が必要となることがある［用法・用量 2）を参照］。

本剤の投与開始前及び投与中は定期的に酸素飽和度を監視する。労作時の酸素飽和度が低下した場合（例：パルスオキシメーター88%未満又は PaO_2 55 mmHg 以下）、労作時のパルスオキシメトリーが88%以上になるまで本剤を休薬し、その後、同量又は減量して再開することを検討する。安静時の酸素飽和度の低下（例：パルスオキシメーター88%未満又は PaO_2 55 mmHg 以下）又は緊急介入が適応となる場合は、回復するまで本剤を休薬し、減量して再開するか中止する。生命を脅かす低酸素症又は再発性の症候性低酸素症の場合は、本剤の投与を中止する［用法・用量 2）を参照］。

低酸素症の徴候及び症状を認めたら、直ちに医療従事者に報告するよう患者に指導する。

VHL 病

LITESPARK-004試験では、患者の1.6%に低酸素症が発現した［副作用 1）を参照］。

進行 RCC

LITESPARK-005試験では、患者の15%に低酸素症が認められ、10%に Grade 3の事象が認められた［副作用 1）を参照］。低酸素症が発現した患者のうち、69%が酸素療法を受けた。低酸素症が

発現するまでの期間の中央値は30.5日（範囲：1日～21.1ヵ月）であった。

3)　胚・胎児毒性

動物試験で得られた知見によると、本剤を妊婦に投与すると胎児に害を及ぼす可能性がある。動物生殖試験において、器官形成期の妊娠ラットにベルズチファンを経口投与したところ、推奨用量である1日120 mg でヒト曝露量（AUC）の0.2倍以上の母体曝露量において、胚・胎児致死、胎児体重減少、及び胎児骨格奇形を引き起こした。

妊婦及び生殖可能な女性に対し、胎児への潜在的リスクについて説明すること。本剤は一部のホルモン避妊薬を無効にする可能性があるため、生殖可能な女性に対して、本剤の投与中及び最終投与後1週間は、ホルモン薬以外の有効な避妊法を使用するよう指導する［薬物相互作用 1）を参照］。生殖可能な女性のパートナーがいる男性患者には、本剤の投与中及び最終投与後1週間は有効な避妊法を使用するよう指導する［特殊集団への投与 1、3）を参照］。

有害事象

副作用

以下の臨床的に重要な副作用については、添付文書の他の箇所に記載する。

- 貧血［警告及び使用上の注意 1）を参照］
- 低酸素症［警告及び使用上の注意 2）を参照］

1)　臨床試験成績

臨床試験は様々な条件下で実施されるため、ある薬剤の臨床試験で認められた副作用の発現割合を他の薬剤の臨床試験での発現割合と直接比較することはできず、臨床現場で認められる発現割合を反映していない可能性がある。

VHL 病

LITESPARK-004試験

本剤の安全性は、腎臓に少なくとも1つの測定可能な固形腫瘍を有する VHL 病患者61例を対象とした非盲検臨床試験（LITESPARK-004試験）で評価された［臨床成績 1）を参照］。患者は本剤120 mg を1日1回経口投与された。本剤の投与期間の中央値は68週（範囲：8.4～104.7週）であった。

重篤な副作用は、貧血、低酸素症、アナフィラキシー反応、網膜剥離、及び網膜中心静脈閉塞（各1例）などであり、本剤を投与された患者の15%に発現した。

副作用による本剤の投与中止は患者の3.3%で行われた。本剤の投与中止に至った副作用は、浮動性めまい及びオピオイド過量投与（各1.6%）であった。

副作用による本剤の休薬は患者の39%で行われた。患者の2%超で休薬を必要とした副作用は、疲労、ヘモグロビン減少、貧血、悪心、腹痛、頭痛、及びインフルエンザ様疾患であった。

副作用による本剤の減量は患者の13%で行われた。最も多く報告された、減量を必要とする副作用は疲労（7%）であった。

本剤を投与された患者に発現した臨床検査値異常を含む主な（25%以上）副作用は、ヘモグロビン減少、疲労、クレアチニン増加、頭痛、浮動性めまい、ブドウ糖増加、及び悪心であった。

LITESPARK-004試験で本剤を投与された患者に報告された副作用の要約を表 1.6-3に示す。

表 1.6-3 LITESPARK-004 試験で本剤を投与された患者の 10%以上に発現した副作用

副作用	本剤 (n=61)	
	すべての Grade * (%)	Grade 3～4 (%)
一般		
疲労†	64	5
神経系障害		
頭痛†	39	0
浮動性めまい†	38	0
胃腸障害		
悪心	31	0
便秘	13	0
腹痛†	13	0
眼障害		
視力障害‡	21	3.3
感染症		
上気道感染†	21	0
呼吸器、胸郭および縦隔障害		
呼吸困難	20	1.6
筋骨格系および結合組織障害		
関節痛	18	0
筋肉痛	16	0
血管障害		
高血圧	13	3.3
代謝および栄養障害		
体重増加	12	1.6

* Grade は NCI CTCAE v4.0に基づく
† 他の関連疾患を含む
‡ 視力障害、霧視、網膜中心静脈閉塞、及び網膜剥離を含む

LITESPARK-004試験の臨床検査値異常の要約を表 1.6-4に示す。

表 1.6-4 LITESPARK-004 試験で本剤を投与された患者におけるベースラインから悪化した臨床検査値異常（10%以上）

臨床検査値異常*	本剤 (n=61)	
	Grade 1～4 %	Grade 3～4 %
血液学		
ヘモグロビン減少	93	7
白血球減少	11	0
血清生化学		

クレアチニン増加	64	0
ブドウ糖増加	34	4.9
ALT 増加	20	0
AST 増加	16	0
（補正）カルシウム減少	10	0
リン酸塩減少	10	1.6

*　発現割合の算出に使用する分母は、安全性解析集団のすべての患者を基にしている。

進行 RCC

LITESPARK-005試験

本剤の安全性は、PD-1又は PD-L1チェックポイント阻害剤投与及び VEGF 受容体標的治療後に進行した進行性 RCC 患者732例を対象とした無作為化実薬対照試験（LITESPARK-005試験）で評価された［臨床成績 2）を参照］。患者には、本剤120 mg（n=372）又はエベロリムス10 mg（n=360）が1日1回経口投与された。本剤の投与期間の中央値は7.6ヵ月（範囲：0.1～28.5ヵ月）であった。

重篤な副作用は本剤を投与された患者の38%に発現した。本剤を投与された患者の2%以上に発現した重篤な副作用は、低酸素症（7%）、貧血（5%）、肺炎（3.5%）、出血（3%）、及び胸水（2.2%）であった。死亡に至った副作用は、敗血症（0.5%）及び出血（0.5%）などで、本剤を投与された患者の3.2%に認められた。

副作用による本剤の投与中止は患者の6%で行われた。本剤の投与中止に至った副作用（0.5%以上）は、低酸素症（1.1%）、貧血（0.5%）、及び出血（0.5%）であった。

副作用による本剤の休薬は患者の39%で行われた。患者の2%以上で休薬を必要とした副作用は、貧血（8%）、低酸素症（5%）、COVID-19（4.3%）、疲労（3.2%）、及び出血（2.2%）であった。

副作用による本剤の減量は患者の13%で行われた。患者の1%以上で減量を必要とした副作用は、低酸素症（5%）及び貧血（3.2%）であった。

本剤を投与された患者に発現した臨床検査値異常を含む主な（25%以上）副作用は、ヘモグロビン減少、疲労、筋骨格痛、クレアチニン増加、リンパ球減少、ALT 増加、ナトリウム減少、カリウム増加、及び AST 増加であった。

LITESPARK-005試験における副作用の要約を表 1.6-5に示す。

表 1.6-5 LITESPARK-005 試験で本剤を投与された進行 RCC 患者における副作用（10%以上）

副作用	本剤 (n=372)		エベロリムス (n=360)	
	すべての Grade * (%)	Grade 3～4 (%)	すべての Grade * (%)	Grade 3～4 (%)
疲労†	43	3.2	41	6
浮腫†	20	0.5	23	0.6
筋骨格系および結合組織障害				
筋骨格痛†	34	1.1	27	2.2

胃腸障害				
悪心	17	0.5	11	0.3
便秘	15	0	8	0
嘔吐	11	0.8	8	0.8
下痢†	11	1.3	19	1.4
腹痛†	10	0.8	8	0.3
呼吸器、胸郭および縦隔障害				
呼吸困難†	16	1.6	16	2.5
低酸素症	15	10	1.4	1.4
代謝および栄養障害				
食欲減退	13	1.1	16	0
神経系障害				
頭痛†	12	0.5	8	0.3
浮動性めまい†	11	0	1.9	0

*　Grade は NCI CTCAE v5.0に基づく
†　他の関連疾患を含む

LITESPARK-005試験において本剤を投与された患者の10%未満に認められた臨床的に重要な副作用は、出血（9%）［頭蓋内出血／脳出血（0.8%）を含む］、発疹（8%）、高血圧（6%）、視力障害［霧視（4%）、視力低下（1.1%）、視力障害（0.5%）、及び網膜剥離（0.3%）を含む］（6%）、及び体重増加（5%）であった。

LITESPARK-005試験における臨床検査値異常の要約を表 1.6-6に示す。

表 1.6-6 LITESPARK-005 試験で本剤を投与された進行 RCC 患者におけるベースラインから悪化した臨床検査値異常（20%以上）

臨床検査*	本剤		エベロリムス	
	すべての Grade † %	Grade 3～4 %	すべての Grade † %	Grade 3～4 %
血液学				
ヘモグロビン減少	88	29	76	17
リンパ球減少	34	8	53	20
血清生化学				
クレアチニン増加	34	4.7	43	5.1
ALT 増加	32	2.2	40	1.1
ナトリウム減少	31	1.6	36	0.8
カリウム増加	29	2.5	20	2.8
AST 増加	27	2.2	38	2
ブドウ糖減少	22	1.1	19	1.1
カルシウム減少	21	1.1	45	3.1

*　各検査の発現割合は、ベースライン及び試験中に少なくとも1回の臨床検査値測定が可能であった本剤（範囲：359～366例）、及びエベロリムス（範囲：351～356例）の患者数に基づいている。
†　Grade は NCI CTCAE v5.0に基づく

薬物相互作用

1)　本剤に対する他の薬剤の影響

UGT2B17阻害剤又は CYP2C19阻害剤

本剤と UGT2B17阻害剤又は CYP2C19阻害剤との併用により、ベルズチファンの血漿中曝露が増加し［臨床薬理 3、5）を参照］、本剤の副作用の発現割合及び重症度が増加する可能性がある。貧血及び低酸素症を監視し、推奨されるように本剤の投与量を減らすこと［用法・用量 2)、警告及び使用上の注意 1、2)、副作用を参照］。

2)　他の薬剤に対する本剤の影響

CYP3A4の基質

本剤と CYP3A4の基質との併用により、CYP3A の基質の濃度が低下し［臨床薬理 3）を参照］、これらの基質の有効性が低下する可能性がある。この低下の程度は、UGT2B17及び CYP2C19の両酵素が poor metabolizer である患者においてより顕著となる可能性がある［臨床薬理 3）を参照］。CYP3A4の基質の濃度低下により治療効果が得られないことがあるため、本剤と CYP3A4の基質との併用は避けること。併用が避けられない場合は、添付文書に従って CYP3A4の基質を増量すること。

ホルモン避妊薬

本剤とホルモン避妊薬との併用は、避妊の失敗又は破綻出血の増加につながる可能性がある［臨床薬理 3)、特殊集団への投与 3）を参照］。

特殊集団への投与

1)　妊娠

リスクの概要

動物試験で得られた知見によると、本剤は妊婦に投与すると胎児に害を及ぼす可能性がある。本剤を妊婦に使用した場合の薬物関連リスクを示すデータは存在しない。動物生殖試験において、器官形成期の妊娠ラットにベルズチファンを経口投与したところ、推奨用量である1日120 mg でヒト曝露量（AUC）の0.2倍以上の母体曝露量において、胚・胎児致死、胎児体重減少、及び胎児骨格奇形を引き起こした（データを参照）。妊婦及び生殖可能な女性に対し、胎児への潜在的リスクについて説明すること。

適応集団における重大な先天異常及び流産の背景リスクは不明である。米国の一般集団では、臨床的に認識された妊娠における重大な先天異常及び流産の背景リスクは、それぞれ2%～4%及び15%～20%と推定される。

データ

動物データ

胚・胎児発生パイロット試験において、器官形成期の妊娠ラットにベルズチファンを6 mg/kg/日、60 mg/kg/日、又は200 mg/kg/日の用量で経口投与した。ベルズチファンは60 mg/kg/日以上の用量で胚・胎児致死を引き起こした（AUC に基づく推奨用量でのヒト曝露量の約1倍）。胎児体重の減少、胎児の肋骨奇形、骨化率の低下は、6 mg/kg/日及び60 mg/kg/日の用量で発生した（AUC に基づく推奨用量におけるヒト曝露量の約0.2倍以上）。

2)　授乳

リスクの概要

ヒト母乳中に存在するベルズチファン又はその代謝物、それらの母乳栄養児又は母乳産生への影響に関するデータは存在しない。母乳栄養児に重篤な副作用が発現する可能性があるため、本剤投与中及び最終投与後1週間は授乳しないよう女性に指導すること。

3)　生殖可能な女性及び男性

本剤を妊婦に投与すると胎児に害を及ぼす可能性がある［特殊集団への投与 1）を参照］。

妊娠検査

本剤の投与を開始する前に、生殖可能な女性の妊娠状況を確認すること。

避妊

女性

本剤の投与中及び最終投与後1週間は、ホルモン薬以外の有効な避妊法を使用するよう、生殖可能な女性に指導すること。本剤は一部のホルモン避妊薬を無効にすることがある［薬物相互作用 2）を参照］。

男性

生殖可能な女性のパートナーがいる男性には、本剤の投与中及び最終投与後1週間は有効な避妊法を使用するよう指導すること。

不妊

動物において得られた知見によると、本剤は生殖可能な男性及び女性の生殖能力を損なう可能性がある［非臨床毒性 1）を参照］。生殖能力への影響の可逆性は不明である。

4)　小児等への投与

本剤の小児患者における安全性及び有効性は確立していない。

5)　高齢者への投与

LITESPARK-004試験において本剤を投与された患者のうち、3.3%が65歳以上であった［臨床成績 1）を参照］。VHL 病患者を対象とした本剤の臨床試験では、65歳以上の患者が若年患者と異なる反応を示すかどうかを判断するのに十分な症例数が組み入られていなかった。

LITESPARK-005試験において本剤を投与された進行 RCC 患者372例のうち、65歳未満の患者は62%、65～74歳の患者は28%、75歳以上の患者は10%であった。全般的に、65歳以上の患者と若年患者の有効性に差は認められなかった。本剤の休薬は65歳以上の患者の48%及び若年患者の34%で行われた。本剤の減量は65歳以上の患者の18%及び若年患者の10%で行われた。

6)　腎機能障害

軽度（MDRD に基づく eGFR 60～89 mL/分/1.73 m^2）及び中等度（eGFR 30～59 mL/分/1.73 m^2）の腎機能障害患者において、本剤の用量調節は推奨されない［臨床薬理 3）を参照］。重度（eGFR 15～29 mL/分/1.73 m^2）の腎機能障害患者を対象とした本剤の試験は実施されていない。

7)　肝機能障害

軽度［総ビリルビン値が基準値上限（ULN）以下、かつ AST 値が ULN を超える、又は総ビリルビン値及び AST 値が ULN の1～1.5倍を超える］の肝機能障害患者において、本剤の用法・用量の変更は推奨されない。中等度又は重度（総ビリルビン値及び AST 値が ULN の1.5倍を超える）の肝機能障害患者を対象とした本剤の試験は実施されていない［臨床薬理 3）を参照］。

8)　UGT2B17及び CYP2C19の両酵素が poor metabolizer である患者

UGT2B17及び CYP2C19の両酵素が poor metabolizer である患者では、ベルズチファンの曝露が増加し、本剤の副作用の発現割合及び重症度が増加する可能性がある。UGT2B17及び CYP2C19の両酵素が poor metabolizer である患者においては、副作用を注意深く監視すること［警告及び使用上の注意、副作用、臨床薬理 5）を参照］。

過量投与

本剤の過量投与に対する特別な処置はない。過量投与が疑われる場合には、本剤を休薬し、支持療法を行う。Grade 3の低酸素症は本剤120 mg を1日2回投与した場合に、Grade 4の血小板減少症は本剤240 mg を1日1回（推奨用量の約2倍）投与した場合に発現した。

1.6.2.1.2　EU 添付文書の概要（和訳）

販売名／販売会社名

WELIREG 40 mg film-coated tablets／Merck Sharp & Dohme B.V.

剤型・含量

フィルムコーティング錠（錠剤）、1錠中にベルズチファン40 mg 含有。青色の楕円形の錠剤、約13 x 8 mm、片面に「177」の刻印。

効能・効果

4.1　効能・効果

腎細胞癌（RCC）

本剤は、PD-(L)1阻害剤及び少なくとも2種類の VEGF 標的治療薬を含む治療を2ライン以上受けた後に進行が認められた進行淡明細胞型腎細胞癌の成人患者の単剤療法に適応される。

フォン・ヒッペル・リンドウ（VHL）病関連の腫瘍

本剤は、フォン・ヒッペル・リンドウ（VHL）病を有し、それに関連する限局性の腎細胞癌（RCC）、中枢神経系（CNS）血管芽腫及び膵神経内分泌腫瘍（pNET）に対する治療を必要とするが、局所治療を行うことが望ましくない成人患者の単剤療法に適応される。

用法・用量

4.2　用法・用量、投与方法

治療は、がん治療経験を有する専門医が主導し、その監視下で行う。

用法・用量

本剤の推奨用量はベルズチファン120 mg（40 mg x 3錠）であり、毎日同じ時間に1日1回投与する。

病勢進行又は許容できない毒性が発現するまで継続して投与する。

飲み忘れ

本剤の服用を忘れた場合は、その日のできるだけ早い時間に服用することができる。翌日から本剤の通常の1日量の服用を再開する。飲み忘れた分を補う目的で余分に錠剤を服用しないこと。

本剤服用後に嘔吐が起こった場合は、再服用しないこと。次回は翌日に服用すること。

用法・用量の変更

副作用に対する本剤の用法・用量の変更を表 1.6-7に要約する。

表 1.6-7 推奨される用法・用量の変更

副作用	重症度*	用法・用量の変更
貧血 （4.4項を参照）	Grade 3 （ヘモグロビンが8 g/dL 未満；4.9 mmol/L 未満；80 g/L 未満；輸血が適応となる）	• Grade 2以下に回復するまで休薬する • 同一用量又は減量して再開する（40 mg ずつ減量）；貧血の重症度及び持続性に応じて中止を検討する

	Grade 4（生命を脅かす又は緊急介入が適応となる）	• Grade 2以下に回復するまで休薬する • 減量して再開する（40 mg ずつ減量）、又は Grade 4が再発した場合は投与を中止する
低酸素症（4.4項を参照）	Grade 3の無症候性［安静時の酸素飽和度の低下（例：パルスオキシメーター88%未満又は PaO_2 55 mmHg 以下）］	• 継続又は Grade 2以下に回復するまで休薬を選択できる • 減量して再開する（40 mg ずつ減量）、又は低酸素症の重症度及び持続性に応じて中止する
	Grade 3の症候性［安静時の酸素飽和度の低下（例：パルスオキシメーター88%未満又は PaO_2 55 mmHg 以下）］	• Grade 2以下に回復するまで休薬する • 減量して再開する（40 mg ずつ減量）、又は低酸素症の重症度及び持続性に応じて中止する
	Grade 4［生命を脅かす気道障害又は緊急介入を要する（例：気管切開や挿管）］	• 投与を中止する
その他の副作用（4.8項を参照）	Grade 3	• Grade 2以下に回復するまで休薬する • 重症度及び持続性に応じて減量して再開する（40 mg ずつ減量）ことを検討する • Grade 3が再発した場合は中止する
	Grade 4	• 投与を中止する

*　米国国立がん研究所の有害事象共通用語規準（NCI CTCAE）v 5.0に基づく

特別な患者集団

高齢者

高齢者において本剤の用法・用量の調整は推奨されない（5.2項を参照）。

腎機能障害

末期腎疾患を含む腎機能障害を有する患者において、本剤の用法・用量の調整は推奨されない（5.2項を参照）。

肝機能障害

軽度の肝機能障害［総ビリルビン値が基準値上限（ULN）以下、かつアスパラギン酸アミノトランスフェラーゼ（AST）値が ULN を超える、又は AST 値を問わず総ビリルビン値が ULN の1倍超～1.5倍以下］、又は中等度の肝機能障害［AST 値を問わず総ビリルビン値が ULN の1.5倍超～3倍以下、又は Child-Pugh 分類 B］患者において、本剤の用法・用量の調整は推奨されない。重度肝機能障害患者を対象としたベルズチファンの試験は実施されていない（5.2項を参照）。

小児集団

18歳未満の小児患者における本剤の安全性及び有効性は確立していない（5.1項を参照）。本集団のデータは得られていない。

投与方法

本剤は経口投与する。

錠剤をそのまま飲み込むよう患者に指導する。食事の有無は問わない。ベルズチファンの吸収に及ぼす影響は不明であるため、錠剤を割ったり、砕いたり、噛んだりしないこと。

禁忌

4.3　　禁忌

- 本剤の有効成分又は6.1項に示す添加物に対し過敏症のある患者。
- 妊娠している VHL 病関連腫瘍を有する患者（4.6項を参照）。

使用上の注意

4.4　　警告及び使用上の注意

貧血

臨床試験においてベルズチファンを投与された患者に貧血が報告されている（4.8項を参照）。ベルズチファンの投与開始前及び投与中は定期的に貧血を監視する。Grade 3の貧血が発現した場合はベルズチファンを休薬し、Grade 2以下に回復するまで赤血球造血刺激因子製剤（ESA）の投与を含め標準的な治療方法に従って患者を治療する（詳しい情報については、ESA の処方情報を参照のこと）。再発性の Grade 3の貧血の場合は、ベルズチファンの投与を中止する。Grade 4の貧血が発現した場合はベルズチファンを休薬し、再発性の Grade 4の貧血の場合は投与を中止する（4.2項を参照）。

低酸素症

臨床試験においてベルズチファンを投与された患者に低酸素症が報告されている（4.8項を参照）。ベルズチファンの投与開始前及び投与中は定期的に酸素飽和度をパルスオキシメトリーにより監視する。Grade 3の無症候性低酸素症が発現した場合は、酸素補給及び投与を継続するか休薬するかを検討する。休薬した場合、減量して再開する。Grade 3の症候性低酸素症が発現した場合、ベルズチファンを休薬し、低酸素症を治療する。ベルズチファンは減量して再開する。再開後に症候性低酸素症が再発した場合は、投与を中止する。Grade 4の低酸素症が発現した場合、投与を中止する（4.2項を参照）。

胚・胎児毒性：妊娠可能な女性

ベルズチファンはヒトにおいて、胎児死亡を含め胚・胎児毒性を引き起こすおそれがある（4.6項及び5.3項を参照）。妊娠可能な女性ではベルズチファンの投与開始前に妊娠状況を確認すること。

胎児に害を及ぼす危険性があることから、妊娠可能な女性の場合、ベルズチファンの投与中及び最終投与後少なくとも1週間は極めて有効な避妊法を使用すること（4.5項及び4.6項を参照）。

VHL 病関連の CNS 血管芽腫（CNS-HB）の患者における CNS 出血

VHL 病関連の CNS-HB 患者において、致死的転帰を伴うものを含め CNS 出血が認められている。ベルズチファン投与中の VHL 病関連の CNS-HB 患者では、CNS 出血の症状及び徴候を注意深く観察すること。

添加物情報

本剤には1錠あたり1 mmol（23 mg）未満のナトリウムが含有されている。つまり、実質的に「ナトリウム不含」である。

薬物相互作用

4.5　　他の医薬品との相互作用及びその他の相互作用

In vitro 及びゲノム薬理試験から、ベルズチファンは UGT2B17及び CYP2C19により代謝されること、またベルズチファンは濃度依存的に CYP3A4を誘導することが示されている。

他の薬剤に対するベルズチファンの影響

ベルズチファンと CYP3A4の基質（ホルモン避妊薬を含む）との併用により、CYP3A4の基質の濃度が低下し、これらの基質の有効性が低下する可能性がある。この低下の程度は、UGT2B17及び CYP2C19の両酵素が poor metabolizer である患者において、より顕著となる可能性がある（5.2項を参照）。わずかな濃度低下により治療効果が得られないことがある CYP3A4の基質とベルズチファンの併用は避けること。併用が避けられない場合は、製品概要に従って CYP3A4の基質を増量すること。

ベルズチファンとホルモン避妊薬との併用は、避妊の失敗（4.4項及び4.6項を参照）又は破綻出血の増加につながる可能性がある。ホルモン避妊薬を使用中の患者には、ベルズチファンの投与中にホルモン避妊薬以外の避妊法を使用するか、又は男性パートナーがコンドームを使用するよう指導すること。

臨床試験においてベルズチファン120 mg を反復投与した際、ミダゾラムの血中濃度曲線下面積（AUC）が40%減少した。この影響は、弱い CYP3A4誘導剤に相当する。ベルズチファンの血漿中濃度が高い患者では、中程度の CYP3A4誘導作用が認められる可能性がある（5.2項を参照）。

In vitro データに基づくと、ベルズチファンの臨床曝露量で MATE-2K が阻害されることが予想され、さらに MATE1の阻害を否定できない。

In vitro においてベルズチファンは CYP2B6及び CYP2C8の誘導剤である。*In vivo* 試験は実施されていない。ベルズチファンとの併用投与により、CYP2B6及び／又は CYP2C8の基質の血漿中濃度は臨床的に意味のある低下を示す可能性がある。

ベルズチファンに対する他の薬剤の影響

ベルズチファンと UGT2B17阻害剤又は CYP2C19阻害剤との併用により、ベルズチファンの血漿中曝露量が増加し、それによりベルズチファンの副作用の発現割合及び重症度が増加する可能性がある。貧血及び低酸素症を監視し、推奨量に従いベルズチファンの投与量を減らすこと。

強力な CYP2C19誘導剤がベルズチファンの曝露量に及ぼす影響は検討されていない。

妊婦及び授乳婦

4.6　　生殖能力、妊娠、授乳

妊娠可能な女性／男性及び女性の避妊

妊娠可能な女性ではベルズチファンの投与開始前に妊娠状況を確認すること。

妊婦に投与されたベルズチファンは、胎児死亡を含め胚・胎児毒性を引き起こす可能性がある（4.4項及び5.3項を参照）。妊娠可能な女性に対し、胎児への潜在的リスクについて説明すること。

妊娠可能な女性は、ベルズチファンの投与中及び最終投与後少なくとも1週間は極めて有効な避妊法を使用すること。ベルズチファンの使用はホルモン避妊薬の有効性を低下させる可能性がある。ホルモン避妊薬を使用中の患者には、ベルズチファンの投与中にはホルモン避妊薬以外の避妊法を使用するか、又は男性パートナーがコンドームを使用するよう指導すること（4.5項を参照）。

妊娠

ベルズチファンを妊婦に使用した場合のデータはほとんど得られていない。動物を用いた試験で生殖毒性が認められている（5.3項を参照）。

腎細胞癌

臨床的に女性の病状がベルズチファンを必要とする場合を除き、妊娠中はベルズチファンを使用してはならない。

フォン・ヒッペル・リンドウ（VHL）病関連の腫瘍

妊娠中のベルズチファンの投与は禁忌である（4.3項を参照）。ベルズチファン投与中に妊娠した場合、投与を中止すること。

授乳

ヒト母乳中に存在するベルズチファン又はその代謝物、それらの母乳栄養児又は母乳産生への影響に関するデータは存在しない。母乳栄養児に重篤な副作用が発現する可能性があるため、ベルズチファン投与中及び最終投与後1週間は授乳しないよう女性に指導すること。

受胎能

動物において得られた知見によると、ベルズチファンは生殖可能な男性及び女性の生殖能力を損なう可能性がある（5.3項を参照）。こうした潜在的リスクを患者に説明する。生殖能力への影響の可逆性は不明である。

運転及び機械作業への影響

4.7　運転及び機械作業への影響

ベルズチファンは運転及び機械操作能力に対してわずかな影響を及ぼす。ベルズチファン投与後には浮動性めまい及び疲労が発現することがある（4.8項を参照）。

ベルズチファンが運転や機械操作能力に影響しないことが合理的に明らかになるまでは、運転や機械操作を行わないように患者に指導する。

副作用

4.8　副作用

安全性プロファイルの要約

臨床試験において進行固形腫瘍及び VHL 病関連腫瘍の患者576例を対象にベルズチファン120 mg を1日1回投与し、ベルズチファンの安全性が評価された。ベルズチファン曝露期間の中央値は9.2ヵ月（範囲：0.1～55.4ヵ月）であった。

ベルズチファン投与下で発現割合が高かった副作用は貧血（84.2%）、疲労（42.7%）、悪心（24.1%）、

呼吸困難（21.4%）、浮動性めまい（17.9%）及び低酸素症（16.3%）であった。

発現割合が高かった Grade 3又は4の副作用は、貧血（28.8%）及び低酸素症（12.2%）であった。発現割合が高かった重篤な副作用は、低酸素症（7.1%）、貧血（4.7%）及び呼吸困難（1.2%）であった。

発現割合が高かったベルズチファンの休薬に至った副作用は、貧血（7.1%）、低酸素症（5.4%）、疲労（2.6%）、悪心（2.4%）、呼吸困難（1.7%）及び浮動性めまい（1.6%）であった。発現割合が高かったベルズチファンの減量に至った副作用は、低酸素症（6.3%）、貧血（3.8%）及び疲労（1.7%）であった。発現割合が最も高かったベルズチファンの投与中止に至った副作用は、低酸素症（1.4%）であった。

副作用の一覧表

ベルズチファンを投与された患者を統合したデータセット（n=576）で報告された、又は製造販売後調査で報告された副作用を、表 1.6-8に示す。これらの副作用は器官別大分類及び発現割合別に示している。発現割合の定義は very common（極めて高い：10%以上）、common（高い：1%以上10%未満）、uncommon（低い：0.1%以上1%未満）、rare（まれ：0.01%以上0.1%未満）及び very rare（極めてまれ：0.01%未満）である。

表 1.6-8 ベルズチファンを投与された患者における副作用*

副作用	すべての Grade	Grade 3～4
血液およびリンパ系障害		
貧血†	Very Common	Very Common
神経系障害		
浮動性めまい	Very Common	-
呼吸器、胸郭および縦隔障害		
呼吸困難	Very Common	Common
低酸素症	Very Common	Very Common
血管障害		
出血‡#	Very Common	Common
胃腸障害		
悪心	Very Common	Uncommon
一般・全身障害および投与部位の状態		
疲労	Very Common	Common
臨床検査		
体重増加	Common	Common

*　表1.6-8に示されている副作用の発現割合には、基礎疾患の影響が含まれている可能性がある。
†　「貧血」には、貧血とヘモグロビン減少が含まれる。
‡　個別に示していない、異なる部位からの異なる出血事象を含む。
ベルズチファンを投与された5例以上の患者に発現した出血は、血尿、喀血、挫傷及び鼻出血（すべての Grade）並びに血尿（Grade 3～4）であった。
#CNS 出血を含む（1例は死亡に至った）（4.4項を参照）。

副作用の説明

貧血（4.4項を参照）

貧血は、ベルズチファンを投与された進行 RCC 患者の83%に発現した。32%には Grade 3の貧

血、0.5%には Grade 4の貧血が発現した。貧血発現までの期間の中央値は29日（範囲：1日～27ヵ月）であった。貧血が発現した患者のうち、22%は輸血のみ、20%は ESA のみ、14%は輸血と ESA による治療を受けた。ESA 投与回数の中央値は、6.5回（範囲：1～87回）であった。ESA の投与は、患者のヘモグロビン値及び医師の判断に基づいて行った（5.1項を参照）。

ベルズチファンを投与された VHL 病関連腫瘍患者の90.2%に貧血が発現し、患者の11.5%には Grade 3の貧血が発現した。Grade を問わない貧血発現までの期間の中央値は、30日（範囲：1日～8ヵ月）であった。貧血が発現した患者のうち、1.8%は輸血のみ、16.4%は ESA のみ、9.1%は輸血と ESA による治療を受けた。ESA 投与回数の中央値は5回（範囲：1～35回）であった。ESA の投与は、患者のヘモグロビン値及び医師の判断に基づいて行った（5.1項を参照）。

ベースラインのヘモグロビン値が12 g/dL 未満の患者における Grade 3の貧血の発現割合は、ベルズチファンの曝露量が高いほど増加した（4.4項を参照）。

低酸素症（4.4項を参照）

低酸素症は、ベルズチファンを投与された進行 RCC 患者の15%に発現した。10%には Grade 3の低酸素症、0.3%には Grade 4の低酸素症が発現した。低酸素症が認められた患者のうち70%は酸素療法による治療を受けた。低酸素症発現までの期間の中央値は31日（範囲：1日～21ヵ月）であった。

ベルズチファンを投与された VHL 病関連腫瘍患者の1.6%に低酸素症（Grade 3）が報告された。低酸素症発現までの期間は56日であった。

副作用が疑われる事象の報告

本剤承認後の副作用が疑われる事象の報告は重要である。この報告により、本剤のベネフィットとリスクのバランスを継続して監視することが可能となる。医療従事者は付録 V の一覧に示した各国の報告システムを用いて、副作用が疑われる事象をすべて報告するよう求められている。

過量投与

4.9　　過量投与

ベルズチファンの過量投与に対する特別な治療はない。過量投与が疑われる場合には、必要に応じてベルズチファンを休薬し、支持療法を行う。臨床試験でのベルズチファンの最高用量は、1日総投与量で240 mg である（120 mg を1日2回又は240 mg を1日1回投与）。Grade 3の低酸素症はベルズチファン120 mg を1日2回投与した場合に発現し、Grade 4の血小板減少症はベルズチファン240 mg を1日1回投与した場合に発現した。

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use WELIREG safely and effectively. See full prescribing information for WELIREG.

WELIREG® (belzutifan) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: EMBRYO-FETAL TOXICITY
See full prescribing information for complete boxed warning.

- **Exposure to WELIREG during pregnancy can cause embryo-fetal harm.**
- **Verify pregnancy status prior to the initiation of WELIREG.**
- **Advise patients of these risks and the need for effective non-hormonal contraception. WELIREG can render some hormonal contraceptives ineffective. (5.3, 7.2, 8.1, 8.3)**

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

Indications and Usage, Advanced Renal Cell Carcinoma (RCC) (1.2) 12/2023
Dosage and Administration, Dosage Modification for Adverse Reactions (2.2) 12/2023
Warnings and Precautions (5.1, 5.2) 12/2023

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

WELIREG is a hypoxia-inducible factor inhibitor indicated:
von Hippel-Lindau (VHL) disease

- for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. (1.1)

Advanced Renal Cell Carcinoma (RCC)

- for treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI). (1.2)

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

The recommended dosage of WELIREG is 120 mg administered orally once daily with or without food. (2.1)

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

Tablets: 40 mg (3)

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

None. (4)

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

- Anemia: Monitor for anemia before initiation of and periodically throughout treatment with WELIREG.(2.2, 5.1)
- Withhold WELIREG until hemoglobin ≥8g/dL, then resume at the same or reduced dose or discontinue. For life threatening anemia, or for anemia requiring urgent intervention, withhold WELIREG until hemoglobin ≥8g/dL and resume at a reduced dose or permanently discontinue WELIREG. (2.2, 5.1)
- Hypoxia: Monitor oxygen saturation before initiation of, and periodically throughout, treatment with WELIREG. For hypoxia at rest, withhold until resolved, resume at reduced dose, or discontinue depending on severity. For life-threatening hypoxia, permanently discontinue WELIREG. (2.2, 5.2)

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

VHL disease: Most common (≥25%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea. (6.1)
Advanced RCC: Most common (≥25%) adverse reactions, including laboratory abnormalities were decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium, and increased aspartate aminotransferase. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

UGT2B17 or CYP2C19 Inhibitors: Monitor for signs and symptoms of anemia and hypoxia and reduce the dosage of WELIREG as recommended. (2.2, 7.1)

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

- Lactation: Advise not to breastfeed. (8.2)
- Infertility: May impair fertility in males and females. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

BOXED WARNING: EMBRYO-FETAL TOXICITY
1 INDICATIONS AND USAGE
1.1 von Hippel-Lindau (VHL) disease
1.2 Advanced Renal Cell Carcinoma (RCC)
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Dosage Modifications for Adverse Reactions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Anemia
5.2 Hypoxia
5.3 Embryo-Fetal Toxicity
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Effects of Other Drugs on WELIREG
7.2 Effect of WELIREG on Other Drugs
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
8.8 Dual UGT2B17 and CYP2C19 Poor Metabolizers
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 von Hippel-Lindau (VHL) disease
14.2 Advanced Renal Cell Carcinoma (RCC)
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

- **Exposure to WELIREG during pregnancy can cause embryo-fetal harm.**
- **Verify pregnancy status prior to the initiation of WELIREG.**
- **Advise patients of these risks and the need for effective non-hormonal contraception. WELIREG can render some hormonal contraceptives ineffective *[see Warnings and Precautions (5.3), Drug Interactions (7.2), Use in Specific Populations (8.1, 8.3)].***

1 INDICATIONS AND USAGE

1.1 von Hippel-Lindau (VHL) disease

WELIREG is indicated for treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

1.2 Advanced Renal Cell Carcinoma (RCC)

WELIREG is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of WELIREG is 120 mg administered orally once daily until disease progression or unacceptable toxicity. WELIREG should be taken at the same time each day and may be taken with or without food.

Advise patients to swallow tablets whole. Do not chew, crush, or split WELIREG prior to swallowing.

If a dose of WELIREG is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for WELIREG the next day. Do not take extra tablets to make up for the missed dose.

If vomiting occurs any time after taking WELIREG, do not retake the dose. Take the next dose on the next day.

2.2 Dosage Modifications for Adverse Reactions

Dosage modifications for WELIREG for adverse reactions are summarized in Table 1.

The recommended dose reductions are:

- First dose reduction: WELIREG 80 mg orally once daily
- Second dose reduction: WELIREG 40 mg orally once daily
- Third dose reduction: Permanently discontinue

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Anemia *[see Warnings and Precautions (5.1)]*	Hemoglobin <8 g/dL or transfusion indicated	• Withhold until hemoglobin ≥8g/dL. • Resume at the same or reduced dose; or discontinue depending on the severity of anemia.
	Life-threatening or urgent intervention indicated	• Withhold until hemoglobin ≥8g/dL. • Resume at a reduced dose or permanently discontinue.
Hypoxia *[see Warnings and Precautions (5.2)]*	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%)	• Consider withholding until resolved. • Resume at the same dose or at a reduced dose depending on the severity of hypoxia.
	Decreased oxygen saturation at rest (e.g., pulse oximeter	• Withhold until resolved. • Resume at reduced dose or discontinue depending on the severity of hypoxia.

	<88% or PaO_2 ≤55 mm Hg) or urgent intervention indicated	
	Life-threatening or recurrent symptomatic hypoxia	• Permanently discontinue.
Other Adverse Reactions *[see Adverse Reactions (6)]*	Grade 3	• Withhold dosing until resolved to ≤ Grade 2. • Consider resuming at a reduced dose (reduce by 40 mg). • Permanently discontinue upon recurrence of Grade 3.
	Grade 4	• Permanently discontinue.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg, blue, oval shaped, film-coated, debossed with “177” on one side and plain on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anemia

WELIREG can cause severe anemia that can require blood transfusion.

Monitor for anemia before initiation of, and periodically throughout, treatment with WELIREG. Transfuse patients as clinically indicated. For patients with hemoglobin <8g/dL, withhold WELIREG until ≥8g/dL, then resume at the same or reduced dose or permanently discontinue WELIREG, depending on the severity of anemia. For life threatening anemia or when urgent intervention is indicated, withhold WELIREG until hemoglobin ≥8g/dL, then resume at a reduced dose or permanently discontinue WELIREG *[see Dosage and Administration (2.2)]*.

von Hippel-Lindau (VHL) disease

In LITESPARK-004, decreased hemoglobin occurred in 93% of patients and 7% had Grade 3 events *[see Adverse Reactions (6.1)]*. Median time to onset of anemia was 31 days (range: 1 day to 8.4 months).

The safety of erythropoiesis stimulating agents (ESAs) for treatment of anemia in patients with VHL disease treated with WELIREG has not been established. Randomized controlled trials in patients with cancer receiving myelosuppressive chemotherapy with ESAs have shown that ESAs increased the risks of death and serious cardiovascular reactions, and decreased progression-free survival and/or overall survival. See the prescribing information for ESAs for more information.

Advanced Renal Cell Carcinoma (RCC)

In LITESPARK-005, decreased hemoglobin occurred in 88% of patients and 29% had Grade 3 events *[see Adverse Reactions (6.1)]*. Median time to onset of anemia was 29 days (range: 1 day to 16.6 months). Of the patients with anemia, 22% received transfusions only, 20% of patients received ESAs only and 12% received both transfusion and ESAs.

5.2 Hypoxia

WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization *[see Dosage and Administration (2.2)].*

Monitor oxygen saturation before initiation of, and periodically throughout, treatment with WELIREG. For decreased oxygen saturation with exercise (e.g., pulse oximeter <88% or P_aO_2 ≤55 mm Hg), consider withholding WELIREG until pulse oximetry with exercise is greater than 88%, then resume at the same

dose or at a reduced dose. For decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 ≤55 mm Hg) or urgent intervention indicated, withhold WELIREG until resolved and resume at a reduced dose or discontinue. For life-threatening hypoxia or for recurrent symptomatic hypoxia, permanently discontinue WELIREG *[see Dosage and Administration (2.2)]*.

Advise patients to report signs and symptoms of hypoxia immediately to a healthcare provider.

von Hippel-Lindau (VHL) disease

In LITESPARK- 004, hypoxia occurred in 1.6% of patients *[see Adverse Reactions (6.1)]*.

Advanced Renal Cell Carcinoma (RCC)

In LITESPARK- 005, hypoxia occurred in 15% of patients and 10% had Grade 3 events *[see Adverse Reactions (6.1)]*. Of the patients with hypoxia, 69% were treated with oxygen therapy. Median time to onset of hypoxia was 30.5 days (range: 1 day to 21.1 months).

5.3 Embryo-Fetal Toxicity

Based on findings in animals, WELIREG can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, oral administration of belzutifan to pregnant rats during the period of organogenesis caused embryo-fetal lethality, reduced fetal body weight, and fetal skeletal malformations at maternal exposures ≥0.2 times the human exposures (AUC) at the recommended dose of 120 mg daily.

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose, since WELIREG can render some hormonal contraceptives ineffective *[see Drug Interactions (7.1)].* Advise male patients with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Anemia *[see Warnings and Precautions (5.1)]*
- Hypoxia *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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

von Hippel-Lindau (VHL) disease

LITESPARK-004

The safety of WELIREG was evaluated in an open-label clinical trial (LITESPARK-004) in 61 patients with VHL disease who had at least one measurable solid tumor localized to the kidney *[see Clinical Studies (14.1)]*. Patients received WELIREG 120 mg orally once daily. The median duration of exposure to WELIREG was 68 weeks (range: 8.4 to 104.7 weeks).

Serious adverse reactions occurred in 15% of patients who received WELIREG, including anemia, hypoxia, anaphylaxis reaction, retinal detachment, and central retinal vein occlusion (1 patient each).

Permanent discontinuation of WELIREG due to adverse reactions occurred in 3.3% of patients. Adverse reactions which resulted in permanent discontinuation of WELIREG were dizziness and opioid overdose (1.6% each).

Dosage interruptions of WELIREG due to an adverse reaction occurred in 39% of patients. Adverse reactions which required dosage interruption in >2% of patients were fatigue, decreased hemoglobin, anemia, nausea, abdominal pain, headache, and influenza-like illness.

Dose reductions of WELIREG due to an adverse reaction occurred in 13% of patients. The most frequently reported adverse reaction which required dose reduction was fatigue (7%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, that occurred in patients who received WELIREG were decreased hemoglobin, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea.

Table 2 summarizes the adverse reactions reported in patients treated with WELIREG in LITESPARK-004.

Table 2: Adverse Reactions Occurring in ≥10% of Patients Who Received WELIREG in LITESPARK-004

Adverse Reaction	WELIREG (n=61)	
	All Grades* (%)	Grade 3-4 (%)
General		
Fatigue†	64	5
Nervous system		
Headache†	39	0
Dizziness†	38	0
Gastrointestinal		
Nausea	31	0
Constipation	13	0
Abdominal pain†	13	0
Eye Disorders		
Visual impairment‡	21	3.3
Infections		
Upper respiratory tract infection †	21	0
Respiratory, Thoracic and Mediastinal		
Dyspnea	20	1.6
Musculoskeletal and Connective Tissue		
Arthralgia	18	0
Myalgia	16	0
Vascular		
Hypertension	13	3.3
Metabolism and Nutrition		
Weight increased	12	1.6

*Graded per NCI CTCAE v4.0
† Includes other related terms
‡Includes visual impairment, vision blurred, central retinal vein occlusion and retinal detachment

Table 3 summarizes the laboratory abnormalities in LITESPARK-004.

Table 3: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients Who Received WELIREG in LITESPARK-004

Laboratory Abnormality*	WELIREG (n=61)	
	Grades 1-4 %	Grades 3-4 %
Hematology		
Decreased hemoglobin	93	7
Decreased leukocytes	11	0
Chemistry		
Increased creatinine	64	0
Increased glucose	34	4.9
Increased ALT	20	0
Increased AST	16	0
Decreased calcium (corrected)	10	0
Decreased phosphate	10	1.6

*The denominator used to calculate the rate is based on all patients in the safety analysis population.

Advanced Renal Cell Carcinoma (RCC)

LITESPARK-005

The safety of WELIREG was evaluated in a randomized, active-controlled study (LITESPARK- 005) in 732 patients with advanced RCC that has progressed after prior PD-1 or PD-L1 checkpoint inhibitor and VEGF receptor targeted therapies *[see Clinical Studies (14.2)]*. Patients received 120 mg WELIREG (n=372) or 10 mg everolimus (n=360) by oral administration once daily. The median duration of exposure to WELIREG was 7.6 months (range 0.1 to 28.5 months).

Serious adverse reactions occurred in 38% of patients who received WELIREG. Serious adverse reactions in ≥2% of patients treated with WELIREG were hypoxia (7%), anemia (5%), pneumonia (3.5%), hemorrhage (3%), and pleural effusion (2.2%). Fatal adverse reactions occurred in 3.2% of patients who received WELIREG, including sepsis (0.5%) and hemorrhage (0.5%).

Permanent discontinuation of WELIREG due to adverse reactions occurred in 6% of patients. Adverse reactions which resulted in permanent discontinuation (≥0.5%) of WELIREG were hypoxia (1.1%), anemia (0.5%), and hemorrhage (0.5%).

Dosage interruptions of WELIREG due to an adverse reaction occurred in 39% of patients. Adverse reactions which required dosage interruption in ≥2% of patients were anemia (8%), hypoxia (5%), COVID-19 (4.3%), fatigue (3.2%), and hemorrhage (2.2%).

Dose reductions of WELIREG due to an adverse reaction occurred in 13% of patients. Adverse reactions which required dose reduction in ≥1% of patients were hypoxia (5%) and anemia (3.2%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, that occurred in patients who received WELIREG were decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium, and increased aspartate aminotransferase.

Table 4 summarizes the adverse reactions in LITESPARK-005.

Table 4: Adverse Reactions (≥10%) in Patients with Advanced RCC Receiving WELIREG in LITESPARK-005

Adverse Reaction	WELIREG (n=372)		Everolimus (n=360)	
	All Grades* (%)	Grade 3-4 (%)	All Grades* (%)	Grade 3-4 (%)
Fatigue†	43	3.2	41	6
Edema†	20	0.5	23	0.6

Musculoskeletal and Connective Tissue				
Musculoskeletal Pain†	34	1.1	27	2.2
Gastrointestinal				
Nausea	17	0.5	11	0.3
Constipation	15	0	8	0
Vomiting	11	0.8	8	0.8
Diarrhea†	11	1.3	19	1.4
Abdominal Pain†	10	0.8	8	0.3
Respiratory, Thoracic, and Mediastinal				
Dyspnea†	16	1.6	16	2.5
Hypoxia	15	10	1.4	1.4
Metabolism and Nutrition				
Decreased Appetite	13	1.1	16	0
Nervous Systems				
Headache†	12	0.5	8	0.3
Dizziness†	11	0	1.9	0

* Graded per NCI CTCAE v5.0
† Includes other related terms

Clinically relevant adverse reactions in <10% of patients who received WELIREG in LITESPARK-005 included hemorrhage (9%) [including intracranial/cerebral hemorrhage (0.8%)], rash (8%), hypertension (6%), visual impairment [including vision blurred (4%), visual acuity decreased (1.1%), visual impairment (0.5%), and retinal detachment (0.3%)] (6%) and increased weight (5%).

Table 5 summarizes the laboratory abnormalities in LITESPARK-005.

Table 5: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline In Patients with Advanced RCC who Received WELIREG in LITESPARK-005

Laboratory Test*	WELIREG		Everolimus	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Decreased hemoglobin	88	29	76	17
Decreased lymphocytes	34	8	53	20
Chemistry				
Increased creatinine	34	4.7	43	5.1
Increased alanine aminotransferase	32	2.2	40	1.1
Decreased sodium	31	1.6	36	0.8
Increased potassium	29	2.5	20	2.8
Increased aspartate aminotransferase	27	2.2	38	2
Decreased glucose	22	1.1	19	1.1
Decreased calcium	21	1.1	45	3.1

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available WELIREG (range: 359 to 366 patients), and everolimus (range: 351 to 356 patients).
† Graded per NCI CTCAE v5.0

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on WELIREG

UGT2B17 or CYP2C19 Inhibitors

Coadministration of WELIREG with inhibitors of UGT2B17 or CYP2C19 increases plasma exposure of belzutifan *[see Clinical Pharmacology (12.3, 12.5)]*, which may increase the incidence and severity of adverse reactions of WELIREG. Monitor for anemia and hypoxia and reduce the dosage of WELIREG as recommended *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2), Adverse Reactions (6)]*.

7.2 Effect of WELIREG on Other Drugs

Sensitive CYP3A4 Substrates

Coadministration of WELIREG with CYP3A4 substrates decreases concentrations of CYP3A substrates *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of these substrates. The magnitude of this decrease may be more pronounced in patients who are dual UGT2B17 and CYP2C19 poor metabolizers *[see Clinical Pharmacology (12.3)].* Avoid coadministration of WELIREG with sensitive CYP3A4 substrates, for which minimal decrease in concentration may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its Prescribing Information.

Hormonal Contraceptives

Coadministration of WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding *[see Clinical Pharmacology (12.3), Use in Specific Populations (8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies, WELIREG can cause fetal harm when administered to a pregnant woman. There are no available data on the use of WELIREG in pregnant women to inform the drug-associated risk. In an animal reproduction study, oral administration of belzutifan to pregnant rats during the period of organogenesis caused embryo-fetal lethality, reduced fetal body weight, and fetal skeletal malformations at maternal exposures ≥0.2 times the human exposure (AUC) at the recommended dose of 120 mg daily (*see Data*). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The 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

In a pilot embryo-fetal development study, pregnant rats received oral doses of 6, 60, or 200 mg/kg/day of belzutifan during the period of organogenesis. Belzutifan caused embryo-fetal lethality at doses ≥60 mg/kg/day (approximately 1 time the human exposure at the recommended dose based on AUC). Reduced fetal body weights, fetal rib malformations, and reduced skeletal ossification occurred at doses of 6 and 60 mg/kg/day (approximately ≥0.2 times the human exposure at the recommended dose based on AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of belzutifan or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with WELIREG and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

WELIREG can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose. WELIREG can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose.

Infertility

Based on findings in animals, WELIREG may impair fertility in males and females of reproductive potential *[see Nonclinical Toxicology (13.1)]*. The reversibility of the effect on fertility is unknown.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the patients who received WELIREG in LITESPARK-004, 3.3% were ≥65 years old *[see Clinical Studies (14.1)]* Clinical trials of WELIREG in patients with VHL did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

Of the 372 patients who received WELIREG for advanced RCC in LITESPARK-005, 62% of patients younger than 65 years, 28% of patients were 65 to 74 years, and 10% were 75 years and over. No overall difference in efficacy was reported between patients who were ≥65 years of age and younger patients. Dose interruptions occurred in 48% of patients ≥65 years of age and in 34% of younger patients. Dose reductions occurred in 18% of patients ≥65 years of age and in 10% of younger patients.

8.6 Renal Impairment

No dosage modification of WELIREG is recommended in patients with mild (eGFR 60-89 mL/min/1.73 m^2 estimated by MDRD) and moderate (eGFR 30-59 mL/min/1.73 m^2) renal impairment *[see Clinical Pharmacology (12.3)].* WELIREG has not been studied in patients with severe (eGFR 15-29 mL/min/1.73 m^2) renal impairment.

8.7 Hepatic Impairment

No dosage modification of WELIREG is recommended in patients with mild [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1 to 1.5 x ULN and any AST] hepatic impairment. WELIREG has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and any AST) *[see Clinical Pharmacology (12.3)]*.

8.8 Dual UGT2B17 and CYP2C19 Poor Metabolizers

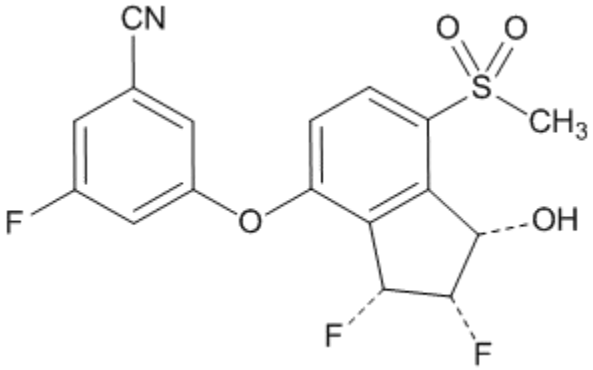
Patients who are dual UGT2B17 and CYP2C19 poor metabolizers have higher belzutifan exposures, which may increase the incidence and severity of adverse reactions of WELIREG. Closely monitor for adverse reactions in patients who are dual UGT2B17 and CYP2C19 poor metabolizers *[see Warnings and Precautions (5), Adverse Reactions (6), Clinical Pharmacology (12.5)]*.

10 OVERDOSAGE

There is no specific treatment for WELIREG overdose. In cases of suspected overdose, withhold WELIREG and institute supportive care. Grade 3 hypoxia occurred at dosages of 120 mg twice a day and Grade 4 thrombocytopenia occurred at dosages of 240 mg once daily (approximately 2 times the recommended dosage).

11 DESCRIPTION

Belzutifan is an inhibitor of hypoxia-inducible factor-2α (HIF-2α). The chemical name of belzutifan is 3-[[(1S,2S,3R)-2,3-Difluoro-2,3-dihydro-1-hydroxy-7-(methylsulfonyl)-1H-inden-4-yl]oxy]-5-fluorobenzonitrile. The molecular formula is $C_{17}H_{12}F_3NO_4S$ and the molecular weight is 383.34 Daltons. The chemical structure is:



Belzutifan is a white to light brown powder that is soluble in acetonitrile, dimethoxyethane, and acetone, sparingly soluble in ethyl acetate, very slightly soluble in isopropanol and toluene, and insoluble in water.

WELIREG is supplied as blue, film-coated tablets for oral use containing 40 mg of belzutifan together with croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide, as inactive ingredients. In addition, the film-coating contains FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2α is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional VHL protein results in stabilization and accumulation of HIF-2α. Upon stabilization, HIF-2α translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1β) to form a transcriptional complex that induces expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumor growth. Belzutifan binds to HIF-2α, and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α-HIF-1β interaction, leading to reduced transcription and expression of HIF-2α target genes. In vivo, belzutifan demonstrated anti-tumor activity in mouse xenograft models of renal cell carcinoma.

12.2 Pharmacodynamics

Reductions in plasma levels of erythropoietin (EPO) were observed to be dose- and exposure-dependent at dosages up to 120 mg once daily. The maximum EPO suppression occurred following 2 weeks of consecutive dosing of WELIREG (mean percent decrease from baseline of approximately 60%). Mean EPO levels gradually returned to baseline values after 12 weeks of treatment.

The incidence of Grade 3 anemia increased with higher belzutifan exposure in patients with baseline hemoglobin levels <12 g/dL *[see Warnings and Precautions (5.1)]*.

Cardiac Electrophysiology

At the recommended dosage, WELIREG does not cause large mean increases (i.e., >20 msec) in the QT interval.

12.3 Pharmacokinetics

The C_{max} and AUC of belzutifan increase proportionally over a dose range of 20 mg to 120 mg WELIREG (0.17 to 1 times the approved recommended dose). The estimated geometric mean steady-state (CV%) C_{max} is 1.5 µg/mL (45%) and AUC_{0-24h} is 20.4 µg•hr/mL (62%) in patients treated with 120 mg WELIREG. Steady state is reached after approximately 3 days.

Absorption

The median T_{max} occurs at 1 to 2 hours after WELIREG administration.

Effect of Food

A high-fat, high-calorie meal (total calories approximately 1000 kcal, 56 g fat, 55 g carbohydrate, and 31 g protein) delayed T_{max} by approximately 2 hours with no clinically meaningful effect on C_{max}, and AUC of belzutifan.

Distribution

The estimated mean (CV%) volume of distribution is 119 L (28%) Plasma protein binding of belzutifan is 45%. The blood-to-plasma concentration ratio of belzutifan is 0.88.

Elimination

The estimated mean (CV%) clearance is 6.0 L/hr (58%) and the mean elimination half-life is 14 hrs.

Metabolism

Belzutifan is primarily metabolized by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4 *[see Clinical Pharmacology (12.5)]*.

Excretion

Following oral administration of radiolabeled belzutifan to healthy subjects, approximately 49.6% of the dose was excreted in urine and 51.7% in feces (primarily as inactive metabolites).

Specific Populations

Patients who are poor metabolizers of UGT2B17 and CYP2C19 had higher belzutifan AUC *[see Clinical Pharmacology (12.5)]*.

There were no clinically significant differences in the pharmacokinetics of belzutifan based on age (19 to 90 years), sex, ethnicity (non-Hispanic, Hispanic), race (White, Black, Asian, Native American, Pacific Islander), body weight (42 to 166 kg), mild to moderate renal impairment (eGFR 30-89 mL/min/1.73 m^2 estimated by MDRD), or mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN or total bilirubin > ULN to 1.5 x ULN with any AST). The effect of severe renal impairment (eGFR 15-29 mL/min/1.73 m^2) and moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST) have not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Belzutifan on CYP3A Substrates: Coadministration of WELIREG 120 mg once daily with midazolam (a sensitive CYP3A4 substrate) decreased the midazolam AUC by 40% and the C_{max} by 34%. Midazolam AUC is predicted to decrease up to 70% in patients with higher belzutifan concentrations (e.g., dual poor metabolizers) *[see Clinical Pharmacology (12.5)]*.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Belzutifan does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

Belzutifan does not induce CYP1A2 or CYP2B6.

Transporter Systems: Belzutifan is a substrate of P-gp, OATP1B1, and OATP1B3, but is not a substrate of BCRP.

Belzutifan inhibits MATE2K. Belzutifan does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or MATE1.

12.5 Pharmacogenomics

Patients who are UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolizers are estimated to have 2.5-, 1.3-, or 3.2-fold higher belzutifan steady state $AUC_{0\text{-}24h}$, respectively compared to patients who are UGT2B17 normal (extensive) metabolizers and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizers *[see Use in Specific Populations (8.7)].*

UGT2B17 poor metabolizers who are homozygous for the UGT2B17*2 allele have no UGT2B17 enzyme activity. CYP2C19 poor metabolizers (such as *2/*2, *3/*3, *2/*3) have significantly reduced or absent CYP2C19 enzyme activity. Approximately 15% of White, 6% of Black or African American, and up to 77% of certain Asian populations are UGT2B17 poor metabolizers. Approximately 2% of White, 5% of Black or African American, and up to 19% of certain Asian populations are CYP2C19 poor metabolizers. Approximately 0.4% of White, 0.3% of Black or African American, and up to 15% of certain Asian populations are dual UGT2B17 and CYP2C19 poor metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with belzutifan.

Belzutifan was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Belzutifan was not clastogenic in either an in vitro micronucleus assay or an in vivo rat bone marrow micronucleus assay.

Fertility studies in animals have not been conducted with belzutifan. In repeat-dose toxicity studies up to 3-month duration, belzutifan-related findings included degeneration/atrophy of testes and hypospermia and cellular debris of the epididymis in rats administered ≥2 mg/kg/day (approximately 0.1 times the human exposure at the recommended dose of 120 mg daily). Findings in testes and epididymis were associated with decreased sperm count and motility and abnormal sperm morphology at ≥6 mg/kg/day (approximately 0.2 times the human exposure at the recommended dose of 120 mg daily) and did not reverse by the end of the recovery period. Belzutifan had no adverse effects on female reproductive organs in repeat-dose toxicity studies up to 3-month duration; however, belzutifan caused embryo-fetal lethality (post-implantation loss) in pregnant rats given oral doses ≥60 mg/kg/day (approximately 1 time the human exposure at the recommended dose based on AUC) during the period of organogenesis *[see Use in Specific Population (8.1)].*

14 CLINICAL STUDIES

14.1 von Hippel-Lindau (VHL) disease

The efficacy of WELIREG was evaluated in LITESPARK-004 (NCT03401788), an open-label clinical trial in 61 patients with VHL-associated RCC diagnosed based on a VHL germline alteration and with at least one measurable solid tumor localized to the kidney as defined by response evaluation criteria in solid tumors (RECIST) v1.1. Enrolled patients had other VHL-associated tumors including CNS hemangioblastomas and pNET. CNS hemangioblastomas and pNET in these patients were diagnosed based on the presence of at least one measurable solid tumor in brain/spine or pancreas, respectively, as defined by RECIST v1.1 and identified by IRC. The study excluded patients with metastatic disease. Patients received WELIREG 120 mg once daily until progression of disease or unacceptable toxicity.

The study population characteristics were: median age 41 years [range 19-66 years], 3.3% age 65 or older; 53% male; 90% were White, 3.3% were Black or African-American, 1.6% were Asian, and 1.6% were Native Hawaiian or other Pacific Islander; 82% had an ECOG PS of 0, 16% had an ECOG PS of 1, and 1.6% had an ECOG PS of 2; and 84% had VHL Type I Disease. The median diameter of RCC target lesions per central independent review committee (IRC) was 2.2 cm (range 1-6.1). Median time from

initial radiographic diagnosis of VHL-associated RCC tumors that led to enrollment on LITESPARK-004 to the time of treatment with WELIREG was 17.9 months (range 2.8-96.7). Seventy-seven percent of patients had prior surgical procedures for RCC.

The major efficacy endpoint for the treatment of VHL-associated RCC was objective response rate (ORR) measured by radiology assessment using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 as assessed by IRC. Additional efficacy endpoints included duration of response (DoR), and time to response (TTR).

Table 6 summarizes the efficacy results for VHL-associated RCC in LITESPARK-004.

Table 6: Efficacy Results (IRC assessment) for LITESPARK-004 for VHL-Associated RCC

Efficacy Outcome Measure	**WELIREG n=61**
Objective Response Rate, % (n) (95% CI)	49% (30)* (36, 62)
Complete response	0%
Partial response	49%
Duration of Response	
Median in months (range)	Not reached (2.8+, 22+)
% (n) with DoR ≥ 12 months	56% (17/30)

* All patients with a response were followed for a minimum of 18 months from the start of treatment.
\+ Denotes ongoing response.

For VHL-associated RCC, median TTR was 8 months (range 2.7, 19).

Table 7 summarizes the efficacy results for VHL-associated pNET or CNS hemangioblastomas in LITESPARK-004.

Table 7. Efficacy Results (IRC assessment) for LITESPARK-004 for VHL-Associated Subgroups with CNS Hemangioblastomas or pNET

Endpoint	**Patients with CNS Hemangioblastomas n=24***	**Patients with pNET n=12***
Objective Response Rate, % (n) (95% CI)	63%, (15) (41, 81)	83% (10) (52, 98)
Complete response	4% (1)	17% (2)
Partial response	58% (14)	67% (8)
Duration of Response		
Median in months (range)	Not reached (3.7+, 22+)	Not reached (11+, 19+)
% (n) with DoR ≥12 months	73% (11/15)	50% (5/10)

* Number of patients with measurable solid lesions, based on IRC assessment.
\+ Denotes ongoing response.

For VHL-associated CNS hemangioblastomas, TTR was 3.1 months (range 2.5, 11). For VHL-associated pNET, median TTR was 8.1 months (range 2.7, 11).
Decreases in size of CNS hemangioblastoma-associated peri-tumoral cysts and syringes were observed.

14.2 Advanced Renal Cell Carcinoma (RCC)

The efficacy of WELIREG was evaluated in LITESPARK-005 (NCT04195750), an open-label, randomized, active-controlled clinical trial in 746 patients with unresectable, locally advanced or metastatic clear cell RCC that progressed following PD-1 or PD-L1 checkpoint inhibitor and VEGF receptor targeted therapies either in sequence or in combination.

Patients could have received up to 3 prior treatment regimens and were required to have measurable disease per RECIST v1.1. Patients were randomized in a 1:1 ratio to receive 120 mg WELIREG or 10 mg everolimus by oral administration once daily. Randomization was stratified by IMDC risk categories (favorable versus intermediate versus poor) and number of prior VEGF receptor targeted therapies (1

versus 2-3). Patients were evaluated radiologically at Week 9 from the date of randomization, then every 8 weeks through Week 49, and every 12 weeks thereafter.

The study population characteristics were: median age 63 years [range 22 to 90 years], 42% age 65 or older; 78% male; 79% White; 12% Asian; 1% Black or African American; 11% Hispanic or Latino; 44% ECOG performance status 0 and 55% ECOG performance status 1. Prior therapies: 13% patients had 1 prior line of therapy, 43% had 2 prior lines of therapy and 43% had 3 prior lines of therapy; 49% received 2 to 3 prior VEGF receptor targeted therapies. Patient distribution by IMDC risk categories was 22% favorable, 66% intermediate, and 12% poor. Common sites of metastasis in patients were 65% lung, 59% lymph nodes, and 49% bone.

The major efficacy endpoints were Progression Free Survival (PFS) measured by BICR using RECIST v1.1 and Overall Survival (OS). Additional efficacy endpoint included objective response rate (ORR) by BICR using RECIST v1.1.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to WELIREG compared with everolimus. Table 8 and Figure 1 summarize the efficacy results for LITESPARK-005.

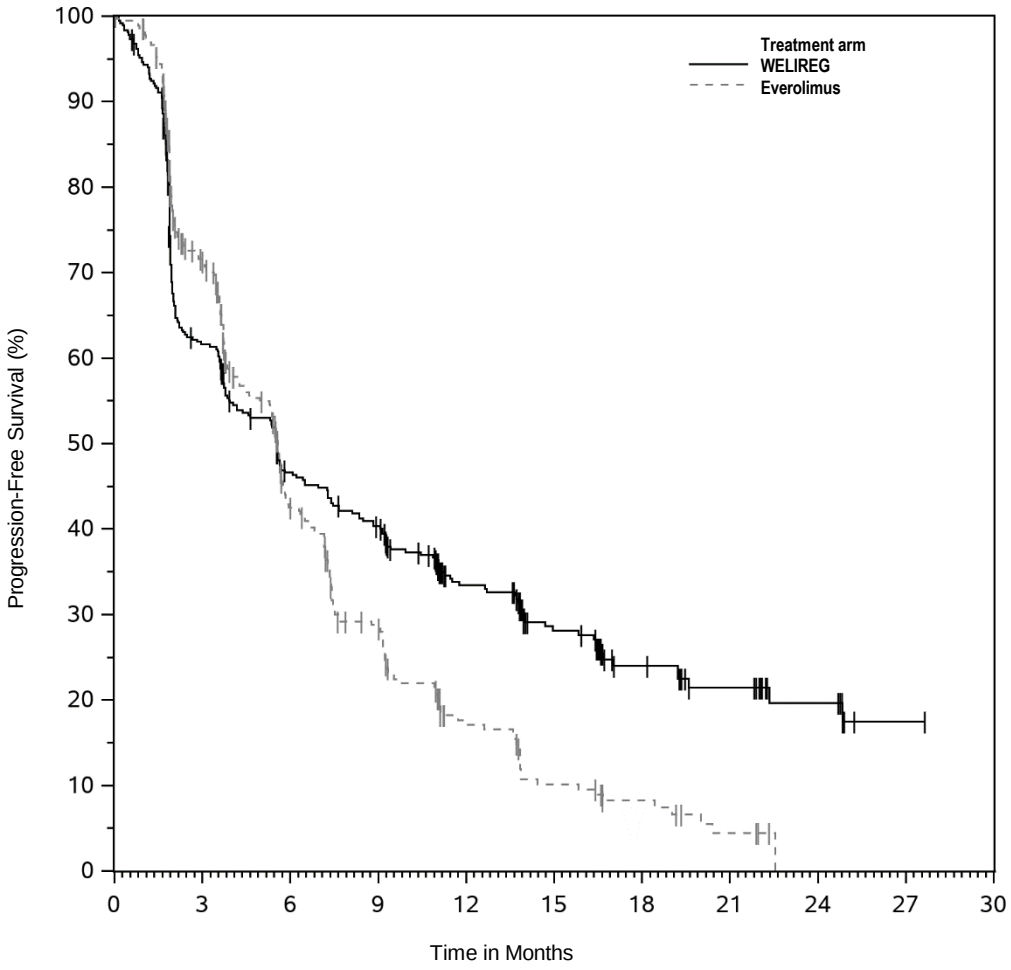
Table 8: Efficacy Results for Advanced RCC (IRC assessment) for LITESPARK-005

Efficacy Outcome Measure	**WELIREG n=374**	**Everolimus n=372**
Progression-Free Survival (PFS)		
Number of events, n (%)	257 (69%)	262 (70%)
Progressive disease	234 (63%)	222 (60%)
Death	23 (6%)	40 (11%)
Median in months (95% CI) *	5.6 (3.9, 7.0)	5.6 (4.8, 5.8)
Hazard ratio † (95% CI)	0.75 (0.63, 0.90)	
p-Value ‡	0.0008	
Confirmed Objective Response Rate		
Number of patients with measurable disease at baseline	373	364
ORR % (n) (95% CI)	22% (82) (18, 27)	4% (13) (2, 6)
Complete response	3% (10)	0% (0)
Partial response	19% (72)	4% (13)
p-Value§	<0.0001	

* From product-limit (Kaplan-Meier) method for censored data
† Based on the stratified Cox proportional hazard model.
‡ One-sided p-Value based on stratified log-rank test compared with the significance boundary of 0.0021.
§ One-sided p-value based on stratified Miettinen and Nurminen (M&N) method.

Among the 82 patients treated with WELIREG who achieved a confirmed response based on BICR per RECIST 1.1, 25 (30%) patients had a duration of response ≥12 months. OS results were immature. At the time of the subsequent pre-specified analysis, 59% of the patients had died in the randomized population.

Figure 1: Kaplan-Meier Curve for Progression-Free Survival in LITESPARK-005



Number at Risk											
WELIREG	374	218	157	134	85	55	32	20	11	1	0
Everolimus	372	226	113	68	31	17	10	4	0	0	0

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

WELIREG tablets are supplied as 40 mg blue, oval shaped, film-coated, debossed with “177” on one side and plain on the other side, available in:

- bottles of 90 tablets with child-resistant closure: NDC 0006-5331-01.

The bottle also contains two desiccant canisters. Do not eat.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Anemia

Inform patients that WELIREG can cause severe anemia that may require blood transfusions and that red blood cell levels will be monitored routinely during treatment. Advise patients to contact their healthcare provider if the patient experiences any symptoms suggestive of anemia *[see Warnings and Precautions (5.1)]*.

Hypoxia

Inform patients that WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization; and that oxygen levels will be monitored routinely during treatment. Advise patients to contact their healthcare provider if the patient experiences any symptoms suggestive of hypoxia *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Population (8.1)]*.
- Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during treatment with WELIREG and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise male and female patients that WELIREG may impair fertility *[see Use in Specific Populations (8.3)]*.

Dosage and Administration

Instruct patients to take their dose of WELIREG at the same time each day (once daily). Advise patients WELIREG can be taken with or without food. Each tablet should be swallowed whole *[see Dosage and Administration (2.1)].*

Manufactured for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

Copyright © 2021-2023 Merck & Co., Inc., Rahway, NJ, USA, and its affiliates.
All rights reserved.

uspi-mk6482-t-2312r002

MEDICATION GUIDE
WELIREG® (Well-ih-reg)
(belzutifan)
tablets

What is the most important information I should know about WELIREG?

WELIREG may cause serious side effects, including:

- **Low red blood cell counts (anemia).** Low red blood cell counts are common with WELIREG and can be severe. You may need a blood transfusion if your red blood cell counts drop too low. Your healthcare provider will do blood tests to check your red blood cell counts before you start and during treatment with WELIREG. Tell your healthcare provider if you get any symptoms of low red blood cell counts, including tiredness, feeling cold, shortness of breath, chest pain, or fast heartbeat.
- **Low oxygen levels in your body.** WELIREG can cause low oxygen levels in your body that can be severe and may require you to stop treatment with WELIREG, receive oxygen therapy, or be hospitalized. Your healthcare provider will monitor your oxygen levels before you start and during treatment with WELIREG. Tell your healthcare provider or get medical help right away if you get symptoms of low oxygen in your body, including shortness of breath or increased heart rate.
- **Harm to your unborn baby.** Treatment with WELIREG during pregnancy can cause harm to your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will do a pregnancy test before you start treatment with WELIREG.
  - You should use an effective form of non-hormonal birth control (contraception) during treatment with WELIREG and **for 1 week** after your last dose.
  - Birth control methods that contain hormones (such as birth control pills, injections, or transdermal system patches) may not work as well during treatment with WELIREG.
  - Talk to your healthcare provider about birth control methods that may be right for you during treatment with WELIREG.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with WELIREG.

  Males with female partners who are able to become pregnant:
  - You should use effective birth control (contraception) during treatment with WELIREG and **for 1 week** after your last dose.
  - Tell your healthcare provider right away if your partner becomes pregnant or thinks she is pregnant while you are taking WELIREG.

See **"What are the possible side effects of WELIREG?"** for more information about side effects.

What is WELIREG?

WELIREG is a prescription medicine used to treat adults with:

- von Hippel-Lindau (VHL) disease who need treatment for a type of kidney cancer called renal cell carcinoma (RCC), tumors in the brain and spinal cord called central nervous system hemangioblastomas (CNS), or a type of pancreatic cancer called pancreatic neuroendocrine tumors (pNET), that do not require surgery right away.
- kidney cancer that has spread (advanced RCC) following treatment with a PD-1 or PD-L1 and VEGF cancer medicines.

It is not known if WELIREG is safe and effective in children.

Before taking WELIREG, tell your healthcare provider about all of your medical conditions, including if you:

- have low red blood cell counts (anemia)
- are pregnant or plan to become pregnant. See **"What is the most important information I should know about WELIREG?"**
- are breastfeeding or plan to breastfeed. It is not known if WELIREG passes into your breast milk. **Do not** breastfeed during treatment with WELIREG and for 1 week after your last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. WELIREG and certain other medicines can affect each other and cause serious side effects.

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

How should I take WELIREG?

- Take WELIREG exactly as your healthcare provider tells you.
- Do not stop taking WELIREG or change your dose without talking to your healthcare provider.
- Take your prescribed dose of WELIREG 1 time a day, at the same time each day.

- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with WELIREG if you have certain side effects.
- Take WELIREG with or without food.
- Swallow WELIREG tablets whole. **Do not** chew, crush, or split WELIREG tablets.
- If you miss a dose of WELIREG, take it as soon as possible on the same day. Then take your next dose of WELIREG at your regular time the next day. **Do not** take extra tablets to make up for the missed dose.
- If you vomit after taking a dose of WELIREG, **do not** take an extra dose. Take your next dose at your regular time the next day.
- If you take too much WELIREG, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of WELIREG?

WELIREG may cause serious side effects, including:

- See **"What is the most important information I should know about WELIREG?"**

The most common side effects of WELIREG in adults with VHL disease include:

- tiredness
- increased creatinine (kidney function test)
- headache
- dizziness
- increased blood sugar (glucose) levels
- nausea

The most common side effects of WELIREG in adults with advanced RCC include:

- tiredness
- decreased white blood cells
- increased creatinine (kidney function test)
- muscle and joint pain
- increased liver function tests
- decreased blood salts (sodium) levels
- increased blood potassium levels

WELIREG may cause fertility problems in males and females, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of WELIREG.

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

How should I store WELIREG?

- Store WELIREG at room temperature between 68°F to 77°F (20°C to 25°C).
- The WELIREG bottle contains 2 desiccant canisters that help keep your medicine dry. **Do not** eat the desiccant canisters.

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

General information about the safe and effective use of WELIREG.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use WELIREG for a condition for which it was not prescribed. Do not give WELIREG to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about WELIREG that is written for health professionals.

What are the ingredients in WELIREG?

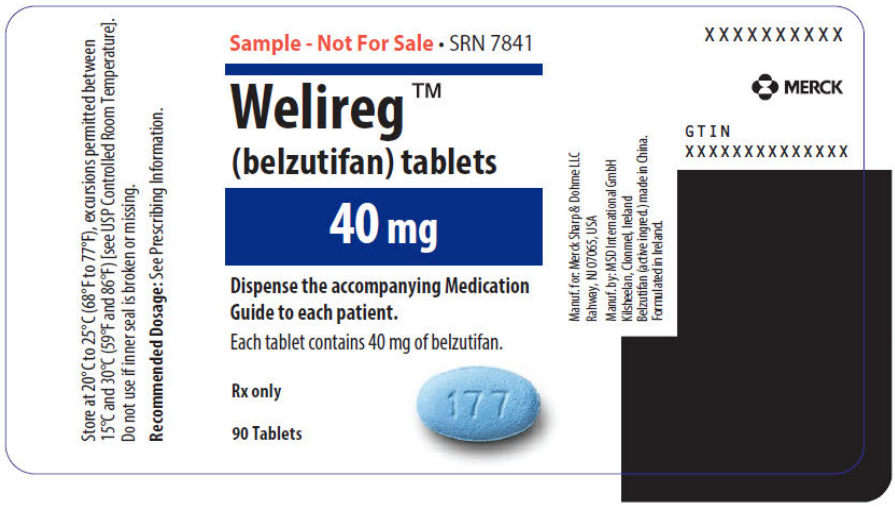
Active ingredient: belzutifan

Inactive ingredients: croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide. The film-coating contains FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA
For patent information: www.msd.com/research/patent
Copyright © 2021-2024 Merck & Co., Inc., Rahway, NJ, USA, and its affiliates.
All rights reserved.
usmg-mk6482-t-2401r003

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 02/2024

Container label for professional sample



Encoding area:
Space reserved for 2D Serialization Barcode, Serial Number, Expiry and Lot

Carton labeling for professional sample



Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 2/26/2024 10:52:20PM
GUID: 502d0913000029f375128b0de8c50020

08JRM4

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg of belzutifan.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Blue, oval tablet, approximately 13 x 8 mm, debossed with markings "177" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal cell carcinoma (RCC)

WELIREG is indicated as monotherapy for the treatment of adult patients with advanced clear cell renal cell carcinoma that progressed following two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies.

von Hippel-Lindau (VHL) disease-associated tumours

WELIREG is indicated as monotherapy for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised renal cell carcinoma (RCC), central nervous system (CNS) haemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable.

4.2 Posology and method of administration

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

Posology

The recommended dose of WELIREG is 120 mg belzutifan (three 40 mg tablets) administered once daily, at the same time every day.

Treatment should continue until disease progression or unacceptable toxicity occurs.

Missed dose
If a dose of WELIREG is missed, it can be taken as soon as possible on the same day. The regular daily dose should be resumed the next day. Extra tablets should not be taken to make up for the missed dose.

If vomiting occurs any time after taking WELIREG, another dose should not be taken. The next dose should be taken the next day.

Dose modifications
Dose modifications for WELIREG for adverse reactions are summarised in Table 1.

Table 1: Recommended dose modifications

Adverse reactions	Severity*	Dose modification
Anaemia *(see section 4.4)*	Grade 3 (haemoglobin < 8 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated)	• Withhold until resolved to ≤ Grade 2 • Resume at the same or reduced dose (reduce by 40 mg); consider discontinuing depending on the severity and persistence of anaemia
	Grade 4 (life-threatening consequences or urgent intervention indicated)	• Withhold until resolved to ≤ Grade 2 • Resume at a reduced dose (reduce by 40 mg) or permanently discontinue upon recurrence of Grade 4
Hypoxia *(see section 4.4)*	Grade 3 asymptomatic (decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or Pa O_2 ≤ 55 mm Hg))	• Option to continue or withhold until resolved to ≤ Grade 2 • Resume at reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of hypoxia
	Grade 3 symptomatic (decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or Pa O_2 ≤ 55 mm Hg))	• Withhold until resolved to ≤ Grade 2 • Resume at reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of hypoxia
	Grade 4 (life-threatening airway compromise; urgent intervention needed (e.g., tracheotomy or intubation))	• Permanently discontinue
Other adverse reactions *(see section 4.8)*	Grade 3	• Withhold dosing until resolved to ≤ Grade 2 • Consider resuming at a reduced dose (reduce by 40 mg) depending on the severity and persistence

Adverse reactions	Severity*	Dose modification
		• Permanently discontinue upon recurrence of Grade 3
	Grade 4	• Permanently discontinue

*Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0

Special populations

Elderly
No dose adjustment is recommended in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is recommended in patients with renal impairment including end-stage renal disease (see section 5.2).

Hepatic impairment
No dose adjustment is recommended in patients with mild (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1 to 1.5 x ULN and any AST) or moderate (total bilirubin within range of > 1.5 x ULN and ≤ 3 x ULN and any AST or Child-Pugh B) hepatic impairment. Belzutifan has not been studied in patients with severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy in children less than 18 years of age have not been established (see section 5.1). No data are available.

Method of administration

WELIREG is for oral use.

The tablets should be swallowed whole and may be taken with or without food. Tablets should not be split, crushed or chewed, as it is not known whether this impacts absorption of belzutifan.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy in patients with VHL disease-associated tumours (see section 4.6).

4.4 Special warnings and precautions for use

Anaemia

Anaemia has been reported in patients receiving belzutifan in clinical studies (see section 4.8). Patients should be monitored for anaemia before initiation of and periodically throughout treatment with belzutifan. For patients who develop Grade 3 anaemia, belzutifan should be withheld and patients should be treated according to standard medical practice, including erythropoiesis-stimulating agent (ESA) administration until resolved to ≤ Grade 2 (see the prescribing information for ESAs for more information). For recurrent Grade 3 anaemia, belzutifan should be discontinued. For patients who develop Grade 4 anaemia, belzutifan should be withheld and permanently discontinued for recurrent Grade 4 anaemia (see section 4.2).

Hypoxia

Hypoxia has been reported in patients receiving belzutifan in clinical studies (see section 4.8).

Patients should be monitored for oxygen saturation with pulse oximetry before initiation of and periodically throughout treatment with belzutifan. For Grade 3 asymptomatic hypoxia, providing supplemental oxygen and continuing or withholding treatment should be considered. If withheld, belzutifan should be resumed at a reduced dose. For patients who have Grade 3 symptomatic hypoxia, belzutifan should be withheld, hypoxia should be treated, and belzutifan should be resumed at a reduced dose. If symptomatic hypoxia continues to recur, treatment should be discontinued. For Grade 4 hypoxia, treatment should be permanently discontinued (see section 4.2).

Embryo-foetal toxicity: Women of childbearing potential

Belzutifan may cause embryo-foetal harm, including foetal loss, in humans (see sections 4.6 and 5.3). The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with belzutifan.

Women of childbearing potential have to use highly effective contraceptive methods during treatment with belzutifan and for at least 1 week after the last dose due to the potential risk to the foetus (see sections 4.5 and 4.6).

CNS haemorrhage in patients with VHL disease-associated CNS-haemangioblastomas (CNS-HB)

CNS haemorrhage, including with fatal outcome, has been observed in patients with VHL disease-associated CNS-HB. Physicians should be cautious of symptoms or signs of CNS haemorrhage in patients with VHL disease-associated CNS-HB being treated with belzutifan.

Information about excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro and pharmacogenomic studies indicate that belzutifan is metabolised by UGT2B17 and by CYP2C19, and that belzutifan induces CYP3A4 in a concentration dependent manner.

Effects of belzutifan on other medicinal products

Coadministration of belzutifan with CYP3A4 substrates, including hormonal contraceptives, decreases concentrations of CYP3A4 substrates, which may reduce the efficacy of these substrates. The magnitude of this decrease may be more pronounced in patients who are dual UGT2B17 and CYP2C19 poor metabolisers (see section 5.2). Coadministration of belzutifan with sensitive CYP3A4 substrates, for which minimal decrease in concentration may lead to therapeutic failures of the substrate should be avoided. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dose in accordance with its summary of product characteristics.

Coadministration of belzutifan with hormonal contraceptives may lead to contraceptive failure (see sections 4.4 and 4.6) or an increase in breakthrough bleeding. Patients using hormonal contraceptives should be advised to use an alternative non-hormonal contraceptive method or have their male partner use a condom during treatment with belzutifan.

In a clinical study, repeat administration of belzutifan 120 mg daily resulted in a 40% reduction in midazolam area under the curve (AUC), an effect consistent with a weak CYP3A4 inducer. Belzutifan may exhibit moderate CYP3A4 induction in patients who have higher belzutifan plasma exposures (see section 5.2).

Based on *in vitro* data, MATE- 2K inhibition by belzutifan is expected at clinically relevant exposures, and inhibition of MATE1 cannot be excluded.

Belzutifan is a CYP2B6 and CYP2C8 inducer *in vitro. In vivo* investigations have not been performed. Co-administration with belzutifan may result in a clinically relevant decrease in the plasma concentration of sensitive CYP2B6 and/or CYP2C8 substrates.

Effects of other medicinal products on belzutifan

Coadministration of belzutifan with inhibitors of UGT2B17 or CYP2C19 increases plasma exposures of belzutifan, which may increase the incidence and severity of adverse reactions of belzutifan. Patients should be monitored for anaemia and hypoxia and the dose of belzutifan should be reduced as recommended.

Effects of strong CYP2C19 inducers on belzutifan exposure have not yet been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with belzutifan.

Belzutifan may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman (see sections 4.4 and 5.3). Women of childbearing potential should be informed of the potential risk to a foetus.

Women of childbearing potential have to use highly effective contraception during treatment with belzutifan and for at least 1 week after the last dose. Use of belzutifan may reduce the efficacy of hormonal contraceptives. Patients using hormonal contraceptives should be advised to use an alternative non-hormonal contraceptive method or have their male partner use a condom during treatment with belzutifan (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of belzutifan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Renal cell carcinoma
Belzutifan should not be used during pregnancy unless the clinical condition of the woman requires treatment with belzutifan.

von Hippel-Lindau (VHL) disease-associated tumours
Belzutifan is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during treatment with belzutifan, treatment should be discontinued.

Breast-feeding

There are no data on the presence of belzutifan or its metabolites in human milk, their effects on the breast-fed child, or on milk production. Because of the potential for serious adverse reactions in breast-fed children, advise women not to breast-feed during treatment with belzutifan and for 1 week after the last dose.

Fertility

Based on findings in animals, belzutifan may impair fertility in males and females of reproductive potential (see section 5.3). Patients should be advised of this potential risk. The reversibility of the effect on fertility is unknown.

4.7 Effects on ability to drive and use machines

Belzutifan has minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of belzutifan (see section 4.8).

Patients should be advised not to drive and use machines, until they are reasonably certain belzutifan therapy does not affect them adversely.

4.8 Undesirable effects

Summary of the safety profile

The safety of belzutifan has been evaluated in 576 patients with advanced solid tumours and VHL disease-associated localised tumours treated with 120 mg belzutifan once daily in clinical studies. The median duration of exposure to belzutifan was 9.2 months (range: 0.1 to 55.4 months).

The most common adverse reactions under treatment with belzutifan were anaemia (84.2%), fatigue (42.7%), nausea (24.1%), dyspnoea (21.4%), dizziness (17.9%) and hypoxia (16.3%).

The most common Grade 3 or 4 adverse reactions were anaemia (28.8%) and hypoxia (12.2%). The most common serious adverse reactions were hypoxia (7.1%), anaemia (4.7%) and dyspnoea (1.2%).

The most common adverse reactions resulting in dose interruption of belzutifan were anaemia (7.1%), hypoxia (5.4%), fatigue (2.6%), nausea (2.4%), dyspnoea (1.7%) and dizziness (1.6%). The most common adverse reactions resulting in dose reduction of belzutifan were hypoxia (6.3%), anaemia (3.8%) and fatigue (1.7%). The most common adverse reaction resulting in discontinuation of belzutifan was hypoxia (1.4%).

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with belzutifan (n=576) or reported from post-marketing use are listed in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: 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); and very rare (< 1/10 000).

Table 2: Adverse reactions in patients treated with belzutifan*

Adverse drug reaction	All Grades	Grade 3 – 4
Blood and lymphatic system disorders		
Anaemia†	Very common	Very common
Nervous system disorders		
Dizziness	Very common	-
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Very common	Common
Hypoxia	Very common	Very common
Vascular disorders		
Haemorrhage‡#	Very common	Common
Gastrointestinal disorders		
Nausea	Very common	Uncommon
General disorders and administration site conditions		
Fatigue	Very common	Common
Investigations		
Weight increased	Common	Common

*Adverse reaction frequencies presented in Table 2 may contain contributions from the underlying disease.
†Anaemia includes anaemia and haemoglobin decreased.
‡ Includes different bleeding events from different sites not listed individually.
Haemorrhage terms that occurred in 5 or more patients treated with belzutifan were: haematuria, haemoptysis, contusion and epistaxis (any grade); and haematuria (grades 3-4).
#Includes CNS haemorrhage (a fatal case was observed) (see section 4.4).

Description of selected adverse reactions

Anaemia (see section 4.4)
Anaemia occurred in 83% of patients with advanced RCC receiving belzutifan, 32% had Grade 3 and 0.5% had Grade 4 anaemia. Median time to onset of anaemia was 29 days (range: 1 day to 27 months). Of the patients with anaemia, 22% received transfusions only, 20% of patients received ESAs only and 14% received both transfusion and ESAs. The median number of ESA doses administered to patients was 6.5 (range: 1-87). Patients received an ESA based on haemoglobin levels and physician discretion (see section 5.1).

Anaemia occurred in 90.2% of patients with VHL disease-associated tumours receiving belzutifan, 11.5% of patients had Grade 3 anaemia. Median time to onset of all Grade anaemia events was 30 days (range: 1 day to 8 months). Of the patients with anaemia, 1.8% received transfusions only, 16.4% received ESAs only and 9.1% of patients received both transfusion and ESAs. The median number of ESA doses administered to patients was 5 (range: 1- 35). Patients received an ESA based on haemoglobin levels and physician discretion (see section 5.1).

The incidence of Grade 3 anaemia increased with higher belzutifan exposure in patients with baseline haemoglobin levels < 12 g/dL (see section 4.4).

Hypoxia (see section 4.4)
Hypoxia occurred in 15% of patients with advanced RCC receiving belzutifan and 10% of patients had Grade 3 hypoxia and 0.3% patients had Grade 4 hypoxia. Of the patients with hypoxia, 70% were treated with oxygen therapy. Median time to onset of hypoxia was 31 days (range: 1 day to 21 months).

Hypoxia (Grade 3) was reported in 1.6% of patients with VHL disease-associated tumours receiving belzutifan. Time to onset of hypoxia was 56 days.

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 is no specific treatment for belzutifan overdose. In cases of suspected overdose, if necessary, withhold belzutifan and institute supportive care. The highest dose of belzutifan studied clinically was 240 mg total daily dose (120 mg twice a day or 240 mg once a day). Grade 3 hypoxia occurred at 120 mg twice a day and Grade 4 thrombocytopenia occurred at 240 mg once daily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, other antineoplastic agents. ATC code: L01XX74

Mechanism of action

Belzutifan is an inhibitor of the transcription factor hypoxia-inducible factor 2 alpha (HIF-2α). Under normal oxygen levels, HIF-2α is targeted for degradation by VHL protein. Impairment of VHL protein function results in accumulation of HIF-2α. Consequently, HIF-2α translocates into the nucleus and regulates expression genes, associated with cellular proliferation, angiogenesis, and tumour growth. Belzutifan binds to HIF-2α, and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α-HIF-1β interaction, leading to reduced transcription and expression of HIF-2α target genes.

Pharmacodynamic effects

Circulating plasma levels of erythropoietin (EPO) were monitored in patients as a pharmacodynamic marker of HIF-2α inhibition. Reductions in EPO were observed to be dose/exposure dependent and showed a plateauing effect on reduction at exposures achieved with doses above 120 mg once daily. The maximum EPO suppression occurred following 2 weeks of consecutive dosing of belzutifan (mean percent decrease from baseline of approximately 60%). Mean EPO levels gradually returned to baseline values after 12 weeks of treatment.

At the recommended dose (120 mg once daily) for belzutifan, there were no clinically relevant effects on the QTc interval.

Clinical efficacy

Clinical study in adult patients with advanced renal cell carcinoma (RCC)
The efficacy of belzutifan was evaluated in LITESPARK-005, an open-label, randomised, active-controlled Phase 3 clinical study comparing belzutifan with everolimus in 746 patients with unresectable, locally advanced or metastatic clear cell RCC that has progressed following PD-1/L1 checkpoint inhibitors and VEGF receptor targeted therapies either in sequence or in combination. Patients could have received up to 3 prior treatment regimens and must have measurable disease per RECIST v1.1. The study excluded patients with hypoxia, active CNS metastases and clinically significant cardiac disease. Patients were randomised in a 1:1 ratio to receive 120 mg belzutifan or 10 mg everolimus by oral administration once daily. Randomisation was stratified by International

Metastatic RCC Database Consortium (IMDC) risk categories (favourable versus intermediate versus poor) and number of prior VEGF receptor targeted therapies (1 versus 2- 3).

Patients were evaluated radiologically at Week 9 from the date of randomisation, then every 8 weeks through Week 49, and every 12 weeks thereafter.

Among the 746 patients in LITESPARK-005, 369 patients received two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies. The baseline characteristics of those patients were: median age 63 years (range: 33 to 82 years), 40 % age 65 or older; 11 % age 75 or older; 79 % male; 78 % White; 12 % Asian; 1 % Black or African American; 42 % ECOG performance status 0 and 56 % ECOG performance status 1. Prior lines of therapies: 17 % of patients had 2 , 81 % had 3 and 2 % had 4 prior lines of therapies. Patient distribution by IMDC risk categories was 22 % favourable, 66 % intermediate, and 12 % poor.

The primary efficacy outcome measures were progression-free survival (PFS) measured by BICR using RECIST v1.1, and overall survival (OS). Secondary efficacy outcome measures included objective response rate (ORR) and duration of response (DOR) by BICR using RECIST v1.1.
In the overall population, the study demonstrated statistically significant improvements of PFS (HR: 0.75 [95% CI 0.63, 0.90], p-Value 0.00077) and ORR (21.9% versus 3.5%, p-Value < 0.00001) for patients randomised to belzutifan compared with everolimus at a pre-specified interim analysis (median follow-up time of 13.5 months [range: 0.2 to 31.8 months]).

Table 3 summarises key efficacy measures in the subgroup of patients that received two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies in LITESPARK-005. The KM curves for PFS and OS are shown in Figures 1 and 2.

Table 3: Efficacy results (BICR assessment) in LITESPARK-005 for patients that received two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies

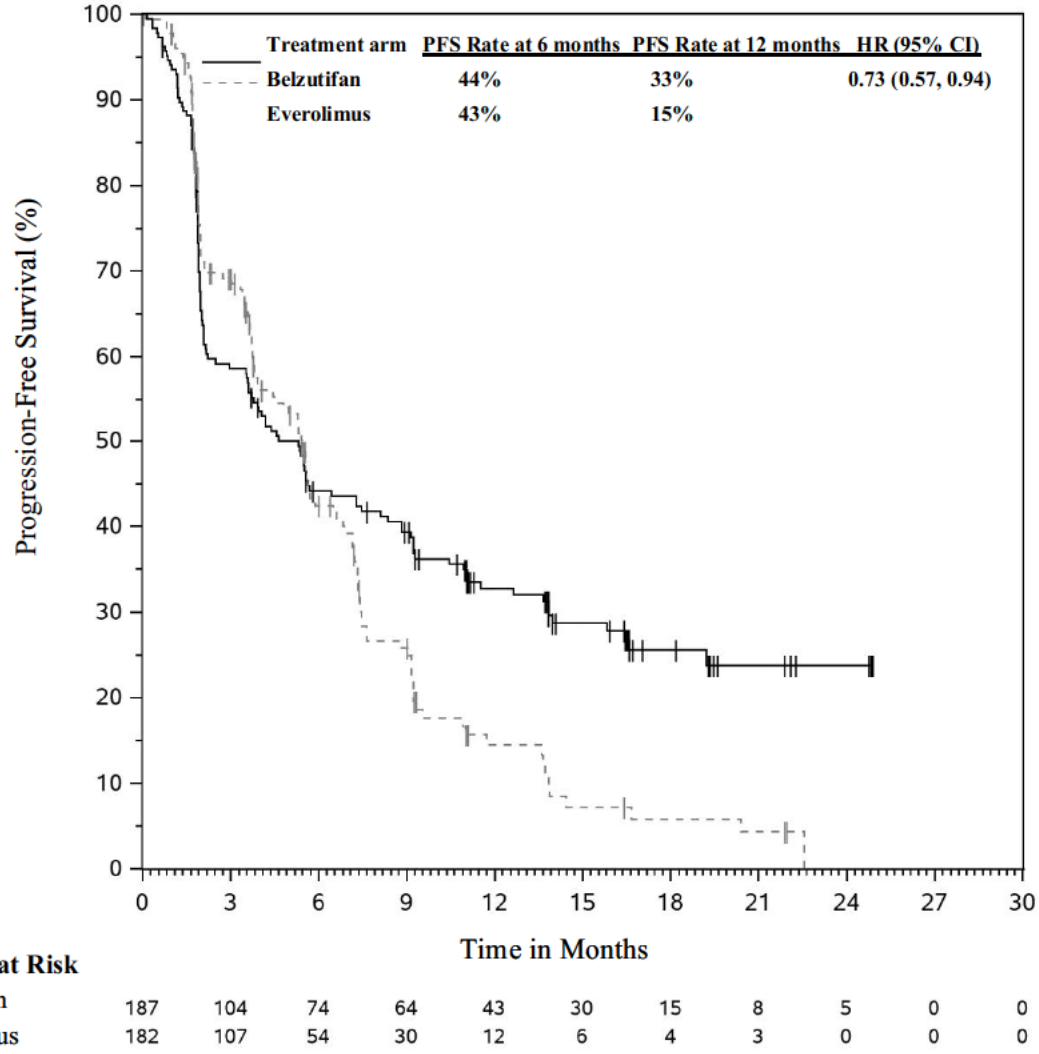
Endpoint	**Belzutifan n=187**	**Everolimus n=182**
PFS[*]		
Number of events, n (%)	127 (67.9%)	130 (71.4%)
Median[†] PFS in months (95% CI)	4.6 (3.5, 7.3)	5.4 (3.8, 6.5)
Hazard ratio[‡] (95% CI)	0.73 (0.57, 0.94)	
OS[¶]		
Number of events, n (%)	128 (68.1%)	125 (68.7%)
Median[†] OS in months (95% CI)	21.8 (17.4, 25.8)	18.1 (14.2, 23.9)
Hazard ratio[‡] (95% CI)	0.94 (0.74, 1.21)	
ORR[*] **%** (95% CI)	24.1% (18.1, 30.8)	3.3% (1.2, 7.0)
Complete response, n (%)	5 (2.7%)	0 (0%)
Partial response, n (%)	40 (21.4%)	6 (3.3%)
Response duration[*]		
Median in months (range)	NR (1.9+, 23.1+)	17.2 (3.8, 17.2)

[*] Based on first pre-specified interim analysis (median follow-up time of 13.5 months)
[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Based on Cox regression model
[¶] Based on final analysis (median follow-up time of 19.6 months)
+ Denotes ongoing response
NR = Not reached

The median time to response (TTR) was 3.7 months (range: 1.7- 16.6) in the belzutifan arm and 3.0 months (range: 1.8- 5.4) in the everolimus arm (median follow-up time of 13.5 months), in the subgroup of patients that received two or more lines of therapy that included a PD-L(1) inhibitor and

at least two VEGF-targeted therapies in LITESPARK-005.

Figure 1: Kaplan-Meier curve for progression-free survival by treatment arm in LITESPARK- 005 for patients that received two or more lines of therapy that included a PD- (L)1 inhibitor and at least two VEGF-targeted therapies*

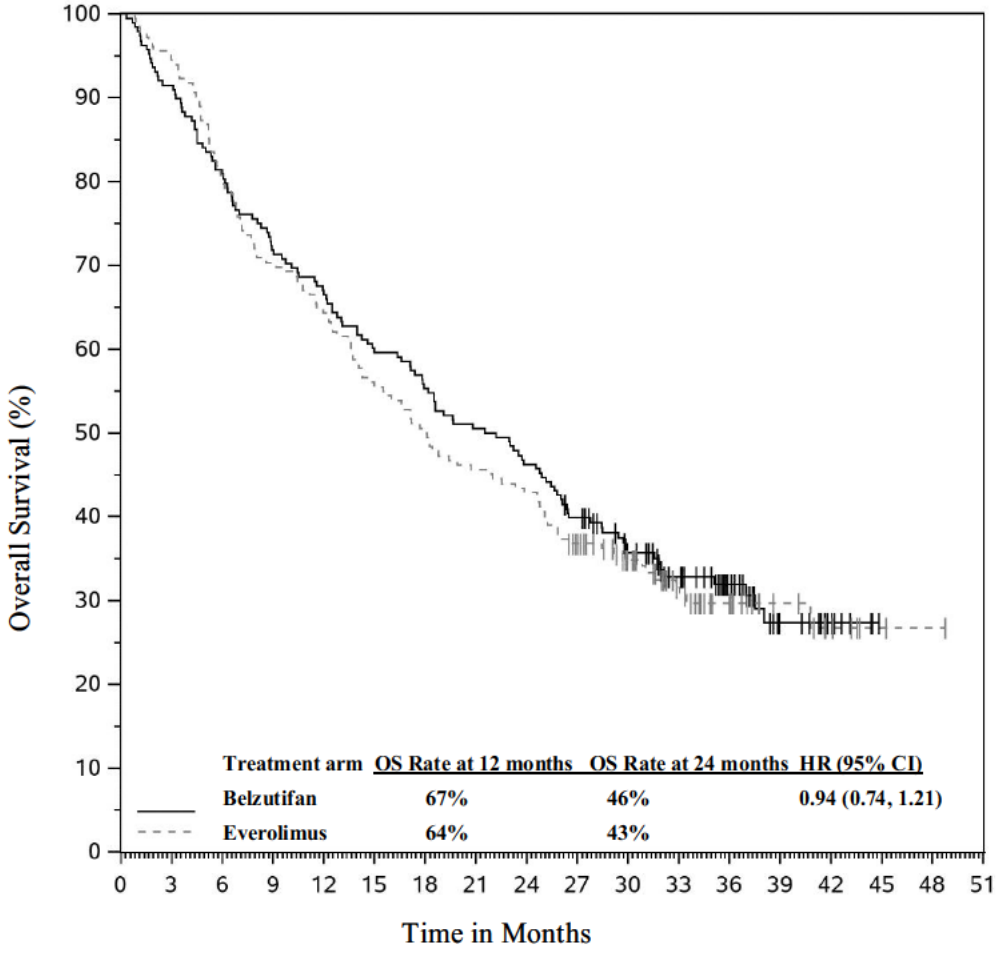


Number at Risk

Belzutifan	187	104	74	64	43	30	15	8	5	0	0
Everolimus	182	107	54	30	12	6	4	3	0	0	0

* Median follow-up time of 13.5 months

Figure 2: Kaplan-Meier curve for overall survival by treatment arm in LITESPARK-005 for patients that received two or more lines of therapy that included a PD- (L)1 inhibitor and at least two VEGF-targeted therapies*



Number at Risk																	
Belzutifan	188	172	152	135	125	112	104	95	87	73	57	43	28	13	7	0	0	0
Everolimus	182	172	146	128	117	101	92	83	78	64	49	34	22	12	6	2	1	0

* Median follow-up time of 19.6 months

Clinical study in adult patients with von Hippel-Lindau (VHL) disease-associated tumours
The efficacy of belzutifan was investigated in LITESPARK-004, an open-label Phase 2 clinical study in 61 patients with VHL disease who had at least one measurable solid tumour (as defined by RECIST v1.1) localised to the kidney and who did not require immediate surgery. Patients could also have other VHL disease-associated tumours, such as CNS haemangioblastomas and pNET. Patients received belzutifan at a dose of 120 mg once daily. Patients were evaluated radiologically approximately 12 weeks after initiation of treatment and every 12 weeks thereafter. Treatment was continued until progression of disease or unacceptable toxicity. Patients were required to have an ECOG PS of 0 or 1. The study excluded patients who had any evidence of metastatic disease, either RCC or other VHL disease-associated tumours, an immediate need for surgical intervention for tumour treatment, any major surgical procedure completed within 4 weeks prior to study enrolment, any major cardiovascular event within 6 months prior to study drug administration, or prior systemic treatments for VHL disease-associated RCC.

Among the 61 patients enrolled in LITESPARK-004, the population characteristics were: median age of 41 years, 3.3% age 65 or older; 52.5% male; 90.2% White; and 82.0% had an ECOG PS of 0 and 16.4% had an ECOG PS of 1. Seventy-seven percent of patients had prior RCC surgical procedures. Other VHL disease-associated tumours in patients included pancreatic lesions (100.0%) of which 36.1% were pancreatic neuroendocrine tumours, CNS haemangioblastomas (82.0%), and retinal angiomas (19.7%).

The primary efficacy endpoint for the treatment of VHL disease-associated RCC was ORR measured by radiology assessment using RECIST v1.1 as assessed by a central independent review committee (IRC). Additional efficacy endpoints included DOR and TTR. ORR and DOR in other VHL disease-associated tumours were assessed as secondary efficacy endpoints.

Table 4 summarises the efficacy results for VHL disease-associated RCC tumours in LITESPARK-004, based on an interim analysis with a median follow-up time of 49.7 months.

Table 4: Efficacy results in VHL disease-associated RCC tumours in LITESPARK-004

Endpoint	**Belzutifan n=61**
ORR* % (95% CI)	67.2% (54.0, 78.7)
Complete response	11.5%
Partial response	55.7%
Response duration†	
Median in months (range)	NR (8.6+, 44.4+)
% with duration ≥ 12 months	100.0%
Time to response	
Median in months (range)	11.1 (2.7, 41.2)

Efficacy data with a median follow-up of 49.7 months (cut-off date 3 Apr 2023)
* Response: Best objective response as confirmed complete response or partial response
† Based on Kaplan-Meier estimates
+ Denotes ongoing response
NR = Not reached

Efficacy endpoints for the treatment of other VHL disease-associated tumours included ORR and DOR, as assessed by IRC using RECIST v1.1. These results are shown in Table 5.

Table 5: Efficacy results for belzutifan for other VHL disease-associated tumours

	Belzutifan n=61	
Endpoint	**Patients with evaluable CNS haemangioblastomas n=50**	**Patients with evaluable pancreatic neuroendocrine tumours n=22**
ORR* % (95% CI)	48% (33.7, 62.6)	90.9% (70.8, 98.9)
Complete response	8.0%	50.0%
Partial response	40.0%	40.9%
Response duration†		
Median in months (range)	NR (0.0+, 47.5+)	NR (11.0+, 48.3+)
% with duration ≥ 12 months	95.5%	100.0%

Efficacy data with a median follow-up of 49.7 months (cut-off date 3 Apr 2023)
* Response: Best objective response as confirmed complete response or partial response
† Based on Kaplan-Meier estimates
+ Denotes ongoing response
NR = Not reached

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with belzutifan in all subsets of the paediatric population in renal neoplasms and VHL disease (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of belzutifan are similar in healthy subjects and patients with solid tumours including advanced RCC. Based on population PK analysis, the simulated geometric mean steady-state (CV%) C_{max} is 1.5 mcg/mL (46%) and AUC_{0-24hr} is 20.8 mcg•hr/mL (64%) in patients treated with 120 mg belzutifan. Steady state is reached after approximately 3 days.

Absorption

Following single-dose oral administration of 120 mg of belzutifan, peak plasma concentrations (median T_{max}) of belzutifan occurred at 1 to 2 hours post dose.

Effect of food
A high-fat, high-calorie meal delayed peak belzutifan concentration by approximately 2 hours but, had no effect on exposure (AUC). There was a modest decrease of C_{max} by 24% following consumption of a high-fat, high-calorie meal, but this was not clinically meaningful. Therefore, belzutifan can be taken without regard to food.

Distribution

Based on the population PK analysis, the mean (CV%) volume of distribution is 120 L (28.5%). Plasma protein binding of belzutifan is 45%. The blood-to-plasma concentration ratio of belzutifan is 0.88.

Biotransformation

Belzutifan is primarily metabolised by UGT2B17 and CYP2C19 and to lesser extent by CYP3A4. Both UGT2B17 and CYP2C19 display genetic polymorphisms (see 'Special populations - *Dual UGT2B17 and CYP2C19 Poor Metabolisers'*).

In vitro assessment of drug interactions
Belzutifan is a substrate of UGT2B17, CYP2C19 and CYP3A4. Active transport is not an important determinant of belzutifan disposition. Belzutifan is not an inhibitor of CYP enzymes, UGT enzymes, or transporters with the exception of MATE-2K, and potentially MATE1. Belzutifan does not induce CYP1A2, however, belzutifan induces CYP2B6, CYP2C8 and CYP3A4 in a concentration dependent manner (see section 4.5).

Elimination

Based on the population PK analysis, the mean (CV%) clearance is 5.89 L/hr (60.6%) and the mean elimination half-life is approximately 14 hrs.

Following oral administration of radiolabelled belzutifan to healthy subjects, approximately 49.6% of the dose was excreted in urine and 51.7% in faeces (primarily as inactive metabolites). Approximately 6% of the dose was recovered as parent drug in urine.

Linearity

The plasma C_{max} and AUC increased proportionally over a dose range of 40 mg to 120 mg.

Special populations

Renal impairment
Based on a population pharmacokinetic analysis of belzutifan in healthy subjects and patients with cancer, no clinically significant differences in the mean belzutifan exposure were observed between subjects with normal renal function and those with mild and moderate renal impairment (as evaluated by estimated glomerular filtration rate (eGFR)). In a dedicated pharmacokinetic study, belzutifan exposure ($AUC_{0\text{-}INF}$) decreased by 6% and increased by 14% in patients with end-stage renal disease before and after haemodialysis, respectively (see section 4.2).

Hepatic impairment
Based on a population pharmacokinetic analysis of belzutifan in healthy subjects and patients with cancer, no clinically significant differences in the mean belzutifan exposure were observed between subjects with normal liver function (total bilirubin and AST ≤ ULN), and those with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 x ULN and any AST). In a dedicated pharmacokinetic study, belzutifan exposure ($AUC_{0\text{-}INF}$) increased by 52% in patients with moderate hepatic impairment (Child-Pugh B). Patients with severe hepatic impairment have not been studied (see section 4.2).

Dual UGT2B17 and CYP2C19 Poor Metabolisers
Patients who are dual UGT2B17 and CYP2C19 poor metabolisers have higher belzutifan exposures, which may increase the incidence and severity of adverse reactions of belzutifan and should be closely monitored (see sections 4.4 and 4.8).

Belzutifan is primarily metabolised by UGT2B17 and CYP2C19. The activity of these enzymes varies among individuals who carry different genetic variants, which may impact belzutifan concentrations. Poor metabolisers are individuals who are considered to have no enzyme activity. In patients who are dual UGT2B17 and CYP2C19 poor metabolisers, CYP3A4 may be a major elimination pathway. Approximately 15% of Caucasians, 11% of Latinos, 6% of African Americans, 38% of South Asians, and 70% of East Asians are UGT2B17 poor metabolisers. Approximately 2% of Caucasians, 1% of Latinos, 5% of African Americans, 8% of South Asians, and 13% of East Asians are CYP2C19 poor metabolisers. Approximately 0.3% of Caucasians, 0.1% of Latinos, 0.3% of African Americans, 3% of South Asians, and 9% of East Asians are dual UGT2B17 and CYP2C19 poor metabolisers. Expected frequencies in the Japanese population for the UGT2B17, CYP2C19, and dual UGT2B17 and CYP2C19 poor metabolisers are approximately 77%, 19%, and 15%, respectively. Expected frequencies in the United States population for the UGT2B17, CYP2C19, and dual UGT2B17 and CYP2C19 poor metabolisers are approximately 16%, 3%, and 0.5%, respectively based on the reported proportion of the US population represented by major racial/ethnic groups.

The impact of CYP2C19 and UGT2B17 poor metabolisers on belzutifan exposure was assessed in a population PK analysis. Based on the population PK model, patients who are CYP2C19, UGT2B17, or dual UGT2B17 and CYP2C19 poor metabolisers, are projected to have 1.3-, 2.7- or 3.3 -fold the exposures (steady-state $AUC_{0\text{-}24hr}$), respectively, compared to a typical reference patient (UGT2B17 extensive metaboliser, CYP2C19 extensive/intermediate metaboliser) for the recommended dose. No dose adjustment is recommended based on exposure-response analyses for efficacy and safety and the risk-benefit profile.

Effects of age, gender, ethnicity, race, and body weight
Based on a population pharmacokinetic analysis, age (range: 19 to 90 years), gender, ethnicity, race, and body weight (range: 42.1 to 166 kg) do not have a clinically meaningful effect on the

pharmacokinetics of belzutifan. Potential differences in exposure across races are possible due to different frequencies of metabolising enzymes (see 'Special populations - *Dual UGT2B17 and CYP2C19 Poor Metabolisers'*).

5.3 Preclinical safety data

Repeat dose toxicity

Repeat-dose oral toxicity studies in rats and dogs for up to 3 months duration revealed anaemia at all doses including at exposure levels lower than the human exposure levels. Although the anaemia was reversible, this is relevant to humans.

Carcinogenesis

A 26-week transgenic rasH2 mouse carcinogenicity study has been conducted with belzutifan at doses up to 600 mg/kg/day, corresponding to exposures up to 28-fold the human exposure at the approved dose. No belzutifan-related neoplastic findings were observed at any dose level and no carcinogenic risk was identified in the study.

Mutagenesis

Belzutifan was not genotoxic in *in vitro* bacterial mutagenesis and micronucleus assays, and an *in vivo* rat micronucleus assay at 1.7-fold human exposure.

Reproductive toxicity

Fertility studies with belzutifan have not been conducted. In the 3-month repeat-dose toxicity study in rats, irreversible testicular atrophy/degeneration and oligospermia was observed at exposures lower than the human exposure at the recommended dose of 120 mg daily. No testicular toxicity was observed in dogs up to an exposure similar to the human exposure. There were no findings in female reproductive organs in either rat or dog 3-month toxicity studies, but HIF-2α has a functional role in the uterus during embryo implantation and establishment of pregnancy in mice. HIF-2α inhibition by exposure to belzutifan has the potential to interfere with embryo implantation, leading to impairment of female fertility.
In a rat embryo-foetal development study, administration of belzutifan during organogenesis caused embryo-foetal lethality up to 100%, reduced foetal body weight, and foetal skeletal abnormalities at exposures similar to or below the human exposure at the recommended dose of 120 mg daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose acetate succinate
Cellulose microcrystalline (E460)
Mannitol (E421)
Croscarmellose sodium (E468)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Film-coating

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol (E1521)

Talc (E553b)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blisters.

Pack containing 30 film-coated tablets.
Multipack containing 90 (3 packs of 30) film-coated tablets.

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1893/001
EU/1/24/1893/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) 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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

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 Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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.

- **Additional risk minimisation measures**

Prior to the launch of WELIREG in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the guide for health care professionals, including communication media, distribution modalities, and any other aspects of the safety advice tool, with the National Competent Authority. The patient card is included in the pack.

The safety advice tools are aimed at informing about appropriate contraceptive measures to prevent pregnancies in female patients treated with belzutifan.

The MAH shall ensure that in each Member State where WELIREG is marketed, all healthcare professionals and female patients of childbearing potential who are expected to prescribe or use WELIREG, respectively, have access to/are provided with the following educational package:

- Guide for healthcare professionals
- Patient card

Educational material for healthcare professionals:

- The Summary of Product Characteristics
- Guide for healthcare professionals

Guide for healthcare professionals:

- Belzutifan may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman.
- Belzutifan is contraindicated in pregnant women treated for von Hippel-Lindau (VHL) disease-associated tumours.
- Belzutifan should not be used during pregnancy in women treated for renal cell carcinoma unless the clinical condition requires treatment with belzutifan.
- Details on how to reduce the potential risk of exposure during pregnancy for women of childbearing potential based on the following:
    - o A pregnancy test should be performed before start of treatment with belzutifan.
    - o Women of childbearing potential have to use highly effective contraception method during treatment with belzutifan and up to at least 1 week after the last dose.
    - o Explain to patient that belzutifan may reduce the efficacy of hormonal contraceptives. Therefore, a non-hormonal contraceptive method should be used or have their male partner use a condom.
    - o The female patients of childbearing potential should be informed about the potential risk of embryo-foetal harm and appropriate contraceptive measures before start of treatment with belzutifan.
- Need to discontinue treatment with belzutifan if a pregnancy is planned or a pregnancy is detected.
- A patient card is included in the pack. Healthcare professionals should inform each female patient of childbearing potential prior to the start of treatment about the purpose of the patient card.

Patient card:

- Belzutifan should not be used by pregnant women because the use of belzutifan can cause foetal harm, including foetal loss, when used during pregnancy.
- Language describing how to reduce the potential risk of exposure during pregnancy based on the following:
    - o A pregnancy test should be performed before start of treatment with belzutifan.
    - o Women of childbearing potential have to use highly effective contraception method during treatment with belzutifan and up to at least 1 week after the last dose.
    - o Belzutifan may reduce the efficacy of hormonal contraceptives. Therefore, a non-hormonal contraceptive method should be used or have their male partner use a condom.
    - o If a pregnancy occurs during treatment with belzutifan contact your treating physician immediately.
- Contact details of the belzutifan prescriber.
- Women of childbearing potential should be instructed to talk to their healthcare professional about contraception while taking belzutifan.
- Instruct patient to refer to PIL for additional information about the safety of belzutifan.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of belzutifan as monotherapy for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised renal cell carcinoma (RCC), central nervous system (CNS) haemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable, the MAH should submit the final results of the ongoing study MK-6482-004, an open-label Phase II single-arm study to further investigate the long-term efficacy and safety of belzutifan for the treatment of von Hippel-Lindau disease-associated Renal Cell Carcinoma.	Q1 2027
In order to confirm the efficacy and safety of belzutifan as monotherapy for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised RCC, CNS haemangioblastomas, or pNET, and for whom localised procedures are unsuitable, the MAH should submit efficacy and safety data from at least 64 patients with at least 24 months follow-up of cohort B1 for the ongoing study MK-6482-015, an uncontrolled Phase II study to evaluate the efficacy and safety of belzutifan in patients with von Hippel Lindau disease-associated tumours who have at least 1 measurable RCC, pNET, or pheochromocytoma/paraganglioma (PPGL) tumour.	Q1 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg film-coated tablets
belzutifan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg belzutifan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1893/001 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

WELIREG 40 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 OUTER PACKAGING
OUTER CARTON OF MULTIPACK – INCLUDING BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg film-coated tablets
belzutifan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg belzutifan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
Multipack: 90 (3 packs of 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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1893/002 Multipack: 90 (3 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

WELIREG 40 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 OUTER PACKAGING

INNER CARTON OF MULTIPACK – WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg film-coated tablets
belzutifan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg belzutifan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets
Component of a multipack, can't be sold separately.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1893/002 Multipack: 90 (3 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

WELIREG 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg tablets
belzutifan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PATIENT CARD

Welireg ▼ (belzutifan)

- Do not take WELIREG for von Hippel-Lindau disease if you are pregnant.
- If you are pregnant and need treatment for Renal Cell Carcinoma (RCC), talk to your doctor about the use of WELIREG.
- WELIREG may harm the baby and may cause a miscarriage. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Your doctor will do a pregnancy test before you start taking WELIREG.
- You should not become pregnant while taking WELIREG.

Birth control (contraception)

•If you are a woman who could get pregnant:

- Birth control methods that contain hormones-such as birth control pills, injections, or transdermal patches-may not work as well while you are taking WELIREG.
- While you are taking WELIREG and for at least 1 week after your last dose you should:
  - Use an effective form of non-hormonal birth control (contraception) or
  - Have your male partner use a condom.

• Talk to your doctor or pharmacist about birth control methods that may be right for you while you are taking WELIREG.

• Tell your doctor immediately if you become pregnant or think you might have become pregnant during treatment.

For more information, consult the Package Leaflet for WELIREG containing information for the patient.

Important Contact Information

Name of Doctor _____
Office Phone _____
After-hours Phone_____
My Name _____

[MSD logo]

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

WELIREG 40 mg film-coated tablets
belzutifan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 or pharmacist.
- The pack also contains a patient card intended for women who could get pregnant. Please read it as it contains important safety information you need to be aware of before and during your treatment with WELIREG.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What WELIREG is and what it is used for
2. What you need to know before you take WELIREG
3. How to take WELIREG
4. Possible side effects
5. How to store WELIREG
6. Contents of the pack and other information

1. What WELIREG is and what it is used for

WELIREG is a cancer medicine that contains the active substance belzutifan.
WELIREG is used to treat adults with:
- renal cell carcinoma (RCC) with a clear cell component, a type of kidney cancer. It is used when the cancer is advanced (has spread) following treatments that target the immune system (PD-1 or PD-L1 inhibitor) and cancer blood vessels (VEGF-targeted therapy).
- von Hippel-Lindau (VHL) disease (a genetic condition that causes tumours and cysts to grow in certain parts of the body) who need treatment for renal cell carcinoma (RCC), tumours in the brain and spinal cord called central nervous system haemangioblastomas, or a type of pancreatic cancer called pancreatic neuroendocrine tumour, and for whom surgery or other local procedures are unsuitable.

The active substance in WELIREG, belzutifan, blocks a protein called hypoxia-inducible factor 2 alpha (HIF-2α). This protein helps control how cells and blood vessels grow, which can play a role in the development and spread of tumours in the body.

2. What you need to know before you take WELIREG

Do not take WELIREG
- if you are allergic to belzutifan or any of the other ingredients of this medicine (listed in section 6). Talk to your doctor or pharmacist if you are not sure.
- if you are pregnant and need to be treated for von Hippel-Lindau disease (see section 'Pregnancy').

Warnings and precautions
Talk to your doctor or pharmacist before taking WELIREG:
- if you have breathing problems
- if you have low levels of red blood cells (anaemia)
- if you have von Hippel-Lindau disease and tumours in the brain and spinal cord

Low levels of red blood cells (anaemia)

Treatment with WELIREG can cause anaemia (low levels of red blood cells). Tell your doctor if you develop any of the following symptoms:
- shortness of breath
- feeling tired (fatigue)
- dizziness
- pale skin

Your doctor will monitor you for anaemia before you start treatment with WELIREG and during treatment. If you develop severe anaemia your doctor may begin treatment with medicines known to stimulate the production of red blood cells (erythropoiesis-stimulating agents) and/or blood transfusion and stop treatment with WELIREG until the anaemia resolves or they may permanently stop treatment with WELIREG.

Lower oxygen levels in your blood (hypoxia)

Treatment with WELIREG can cause hypoxia. Tell your doctor immediately if you develop any of the following symptoms:
- shortness of breath
- fast heartbeat
- rapid breathing
- bluish discolouration of the skin around your mouth
- inability to speak in full sentences without catching your breath
- unusual tiredness
- confusion

Your doctor will monitor you for hypoxia before you start treatment with WELIREG and during treatment. If you develop severe hypoxia, your doctor may begin treatment with oxygen therapy or stop treatment with WELIREG. Treatment with WELIREG will be restarted at a lower dose. If it recurs, your doctor will discontinue treatment with WELIREG.
In some cases, if you develop hypoxia that is very severe, your doctor may permanently discontinue treatment with WELIREG.

Bleeding in your brain and spinal cord (central nervous system haemorrhage)

Treatment with WELIREG for von Hippel-Lindau disease may cause bleeding in your brain and spinal cord if you have tumours in the brain and/or spinal cord. Tell your doctor immediately if you develop any of the following symptoms:
- severe headache
- vision problems
- severe sleepiness
- severe weakness on one side of your body
- uncoordinated muscle movements
- severe pain in the neck or back
- loss of sensation of pain, temperature and touch

Children and adolescents
WELIREG is not recommended for children and adolescents under 18 years of age. It is unknown if WELIREG is safe and effective for use in these patients.

Other medicines and WELIREG
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because WELIREG can affect the way some other medicines work. Also, some other medicines can affect the way WELIREG works.
WELIREG may affect the way hormonal contraceptives work. While you are taking WELIREG and for at least 1 week after your last dose you should:
- use an effective form of non-hormonal birth control (contraception) or
- have your male partner use a condom.

Pregnancy
Do not take WELIREG for von Hippel-Lindau disease if you are pregnant.
If you are pregnant and need treatment for RCC, talk to you doctor about the use of WELIREG.
WELIREG may harm the baby and may cause a miscarriage. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Your doctor will do a pregnancy test before you start taking WELIREG.
You should not become pregnant while taking WELIREG.

If you are a woman who could get pregnant:
- birth control methods that contain hormones - such as birth control pills, injections, or transdermal patches - may not work as well while you are taking WELIREG.
- while you are taking WELIREG and for at least 1 week after your last dose you should
    - use an effective form of non-hormonal birth control (contraception) or
    - have your male partner use a condom.

Talk to your doctor or pharmacist about birth control methods that may be right for you while you are taking WELIREG.

Fertility
WELIREG may cause fertility problems in men and women, which may affect your ability to have children. Talk to your doctor or pharmacist if this is a concern for you.

Breast-feeding
Tell your doctor or pharmacist if you are breast-feeding or plan to breast-feed.
It is unknown if WELIREG passes into your breast milk. Taking this medicine when you are breast-feeding may harm your baby. You and your doctor should decide together if you will take WELIREG or if you will breast-feed. Do not do both at the same time. If you want to start breast-feeding, wait at least 1 week after your last dose of WELIREG.

Driving and using machines
You may feel dizzy or tired while taking WELIREG. If this happens, do not drive or use machines until you no longer feel dizzy or tired.

WELIREG contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

3. How to take WELIREG

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- The recommended dose is 120 mg once daily. Take three 40 mg tablets once a day, at about the same time every day.
- Your doctor may lower your dose or stop treatment, either for a short time or permanently if you experience certain side effects while you are taking WELIREG (see section 4).

How to take
Swallow the tablets whole – do not break them up. It is not known if this medicine works if the tablets are not whole.
You can take WELIREG with or without food.

If you take more WELIREG than you should
If you take too many tablets, contact a doctor or hospital for advice.

If you forget to take WELIREG
If you miss a dose of WELIREG, take the missed dose as soon as possible on the same day. Take your regular dose of WELIREG the next day.

If you vomit after taking WELIREG, do not take another dose. Take your regular dose of WELIREG the next day.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

WELIREG may cause the following side effects, which may be serious (see section 2):
- reduced levels of red blood cells (anaemia) (very common, may affect more than 1 in 10 people)
- lower oxygen levels in your blood (hypoxia) (very common, may affect more than 1 in 10 people)
- have difficulty breathing (dyspnoea) (very common, may affect more than 1 in 10 people)

Tell your doctor if you feel any of the following symptoms:
- feeling tired (fatigue)
- pale skin
- shortness of breath
- trouble breathing
- chest pain
- a fast heartbeat
- or dizziness

You may need a blood transfusion if your red blood cell counts are too low. You may need supplemental oxygen if your blood oxygen levels are too low.

Your doctor will do blood tests to check your red blood cell counts and measure blood oxygen level before and during your treatment with WELIREG.

Other side effects that may occur:

Very common (may affect more than 1 in 10 people):
- feeling tired (fatigue)
- feeling dizzy
- feeling sick (nausea)
- bleeding (haemorrhage) (including bleeding in your brain and spinal cord if you have von Hippel-Lindau disease associated-central nervous system haemangioblastomas)

Common (may affect up to 1 in 10 people):
- weight gain

Tell your doctor or pharmacist if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 WELIREG

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 blister foil and 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 use this medicine if the packaging is damaged or shows signs of tampering.

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 WELIREG contains
* The active substance is belzutifan. Each film-coated tablet contains 40 mg of belzutifan.
* The other ingredients are croscarmellose sodium (E468) (see "WELIREG contains sodium" in section 2), hypromellose acetate succinate, magnesium stearate (E470b), mannitol (E421), cellulose microcrystalline (E460), and colloidal anhydrous silica (E551). The film-coat contains indigo carmine aluminium lake (E132), macrogol (E1521), polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171).

What WELIREG looks like and contents of the pack
WELIREG is a blue, oval film-coated tablet, debossed with 177 on one side and plain on the other side. WELIREG is available in aluminium/ aluminium blisters. Each pack contains 30 film-coated tablets. Each multipack contains 90 (three packs of 30) film-coated tablets. Not all pack sizes may be available in your country.

Marketing Authorisation Holder and Manufacturer
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Lietuva
UAB Merck Sharp & Dohme
Tel. + 370 5 278 02 47
dpoc_lithuania@msd.com

България
Мерк Шарп и Доум България ЕООД
Тел.: +359 2 819 3737
info-msdbg@merck.com

Česká republika
Merck Sharp & Dohme s.r.o.
Tel: +420 233 010 111
dpoc_czechslovak@merck.com

Danmark
MSD Danmark ApS
Tlf.: + 45 4482 4000
dkmail@msd.com

Deutschland
MSD Sharp & Dohme GmbH
Tel: +49 (0) 89 20 300 4500
medinfo@msd.de

Eesti
Merck Sharp & Dohme OÜ
Tel: +372 6144 200
dpoc.estonia@msd.com

Ελλάδα
MSD Α.Φ.Ε.Ε
Τηλ: +30 210 98 97 300
dpoc_greece@merck.com

España
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@merck.com

France
MSD France
Tél: + 33 (0) 1 80 46 40 40

Hrvatska
Merck Sharp & Dohme d.o.o.
Tel: + 385 1 6611 333
croatia_info@merck.com

Ireland
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@msd.com

Luxembourg/Luxemburg
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Magyarország
MSD Pharma Hungary Kft.
Tel.: +36 1 888 5300
hungary_msd@merck.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
malta_info@merck.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800 9999000
(+31 23 5153153)
medicalinfo.nl@merck.com

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
medinfo.norway@msd.com

Österreich
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
dpoc_austria@merck.com

Polska
MSD Polska Sp. z o.o.
Tel: +48 22 549 51 00
msdpolska@merck.com

Portugal
Merck Sharp & Dohme, Lda
Tel: +351 21 4465700
inform_pt@merck.com

România
Merck Sharp & Dohme Romania S.R.L.
Tel: +40 21 529 29 00
msdromania@merck.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: +386 1 5204 201
msd.slovenia@merck.com

Ísland
Vistor hf.
Sími: + 354 535 7000

Italia
MSD Italia S.r.l.
Tel: 800 23 99 89 (+39 06 361911)
dpoc.italy@msd.com

Κύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ.: 800 00 673 (+357 22866700)
cyprus_info@merck.com

Latvija
SIA Merck Sharp & Dohme Latvija
Tel.: + 371 67025300
dpoc.latvia@msd.com

Slovenská republika
Merck Sharp & Dohme, s. r. o.
Tel: +421 2 58282010
dpoc_czechslovak@merck.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: +358 (0)9 804 650
info@msd.fi

Sverige
Merck Sharp & Dohme (Sweden) AB
Tel: +46 77 5700488
medicinskinfo@msd.com

This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.