IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVEO PHARMACEUTICALS, INC. *Plaintiff*, v. HETERO USA INC., HETERO LABS LIMITED UNIT-V, and HETERO LABS LIMITED, *Defendants*.	C.A. No. 25-639-MN

HETERO'S ANSWER, SEPARATE DEFENSES, AND COUNTERCLAIMS

Defendants Hetero USA, Inc., Hetero Labs Limited Unit-V ("Hetero Unit-V"), and Hetero Labs Limited (collectively, "Hetero"), by and through the undersigned attorneys, hereby answer the Complaint of Plaintiff AVEO Pharmaceuticals, Inc. ("Plaintiff") as follows. Every allegation not expressly admitted herein is denied.

RESPONSE TO "NATURE OF ACTION"

1. This is an action for infringement of United States Patent No. 11,504,365 ("the '365 Patent" or "the Patent-in-Suit") in relation to Hetero's Abbreviated New Drug Application ("ANDA") No. 220437 (the "Hetero ANDA"), which seeks approval from the U.S. Food & Drug Administration ("FDA") to make a generic version of AVEO's FOTIVDA® (tivozanib) product.

ANSWER: Paragraph 1 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Plaintiff's Complaint purports to state a claim for alleged infringement of United States Patent No. 11,504,365 ("the '365 patent"). Hetero further admits that this action purports to relate to Hetero Unit-V's Abbreviated New Drug Application ("ANDA") No. 220437 to the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture, use, sell, or import tivozanib capsules, 0.89 mg and 1.34 mg, before the

expiration of the '365 patent. Hetero further admits that the reference listed drug ("RLD") identified in Hetero Unit-V's ANDA No. 220437 is FOTIVDA® (tivozanib) Capsules, 0.89 mg and 1.34 mg. Hetero denies any and all remaining allegations of Paragraph 1.

2. AVEO also seeks a declaratory judgment under the Patent Laws of the United States, 35 U.S.C. § 100 *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. § 2201 *et seq.*, that Hetero's commercial manufacture, use, offer for sale, sale, and/or importation into the United States of its ANDA No. 220437 would directly and indirectly infringe the '365 Patent.

ANSWER: Paragraph 2 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Plaintiff's Complaint purports to state a claim for declaratory judgment of infringement under 28 U.S.C. §§ 2201 and 2202. Hetero denies any and all remaining allegations of Paragraph 2.

RESPONSE TO "PARTIES"

3. Plaintiff AVEO is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at One Marina Park Drive, 12th Floor, Boston, Massachusetts 02210. AVEO develops, manufactures, and markets pharmaceutical products in the United States. AVEO is the owner of the '365 Patent.

ANSWER: Paragraph 3 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero lacks knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 3 and therefore denies them.

4. On information and belief, Defendant Hetero USA is a corporation organized under the laws of the State of Delaware, having a principal place of business at 1035 Centennial Ave, Piscataway, New Jersey 08854-4125. On information and belief, Hetero USA has a registered agent for service of process, W/K Incorporating Services, Inc., located at 3500 S. Dupont HWY, Dover, Delaware 19901. On information and belief, Hetero USA is in the business of, among other things, manufacturing and selling generic versions of branded pharmaceutical products for the United States market, including in this judicial district. On information and belief, Hetero USA is the U.S. Regulatory Agent for Hetero Labs and Hetero Limited. On information and belief, Hetero USA is a wholly owned subsidiary of Hetero Limited.

ANSWER: Paragraph 4 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero USA, Inc. is a corporation organized

and existing under the laws of the State of Delaware, having a principal place of business at 1035 Centennial Ave, Piscataway, NJ 08854. Hetero further admits that Hetero USA, Inc. is the United States regulatory agent for Hetero Unit-V for ANDA No. 220437. Hetero further admits that Hetero Labs Limited is a parent corporation of Hetero USA, Inc. Hetero denies any and all remaining allegations of Paragraph 4.

5. On information and belief, Defendant Hetero Labs is a corporation organized under the laws of India, having corporate headquarters at 439, 440, 441, & 458, TSIIC Formulation SEZ, Polepally Village, Mahabubnagar, Telangana, 509301, India. On information and belief, Hetero Labs is in the business of, among other things, manufacturing and selling generic versions of branded pharmaceutical products for the United States market, including in this judicial district. On information and belief, Hetero Labs is a division of and a wholly owned subsidiary of Hetero Limited. On information and belief, Hetero Labs has and will manufacture the product described in ANDA No. 220437.

ANSWER: Paragraph 5 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero states that Hetero Unit-V is a corporation organized and existing under the laws of India, having a principal place of business at Surv. No. 439-441, 458 TSIIC-Foundation SEZ, Polepally Village, Jadcherla Mandal, Mahabubnager, Telangana 509 301, India. Hetero further admits that Hetero Unit-V is a division of Hetero Labs Limited. Hetero denies any and all remaining allegations of Paragraph 5.

6. On information and belief, Defendant Hetero Limited is a corporation organized and existing under the laws of India, having corporate headquarters at 7-2-A2, Hetero Corporate, Industrial Estate, Sanath Nagar, Hyderabad, Telangana 500018 India. On information and belief, Hetero Limited is in the business of, among other things, manufacturing and selling generic versions of branded pharmaceutical products for the United States market, including in this judicial district, directly and through its affiliates. On information and belief, Hetero Limited owns ANDA No. 220437.

ANSWER: Paragraph 6 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero states that Hetero Labs Limited is a corporation organized and existing under the laws of India, having a principal place of business at Floor 9-11, Tower 30,

RMZ Nexity, Sy. No. 83/1, Knowledge City, Raidurg, Hyderabad, Telangana-500081, India. Hetero denies any and all remaining allegations of Paragraph 6.

7. On information and belief, Defendants hold themselves out as affiliated entities within the same corporate family for purposes of manufacturing, marketing, selling, and distributing generic drug products through the United States, including in this judicial district.

ANSWER: Paragraph 7 contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

8. On information and belief, Defendants acted in concert to prepare and submit ANDA No. 220437 to the FDA.

ANSWER: Paragraph 8 contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

9. On information and belief, upon FDA approval, Defendants will work in concert with one another to make, use, offer to sell, and/or sell the drug products that are the subject of ANDA No. 220437 throughout the United States, and/or import such drug products into the United States, including in this judicial district.

ANSWER: Paragraph 9 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Unit-V's ANDA No. 220437 seeks approval to manufacture, use, sell, or import tivozanib capsules, 0.89 mg and 1.34 mg. Hetero denies any and all remaining allegations of Paragraph 9.

10. On information and belief, Defendants will each derive significant financial benefit resulting from the FDA's approval of ANDA No. 220437 and subsequent marketing and use of Hetero's ANDA product throughout the United States, including in this judicial district.

ANSWER: Paragraph 10 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Unit-V's ANDA No. 220437 seeks approval to manufacture, use, sell, or import tivozanib capsules, 0.89 mg and 1.34 mg. Hetero denies any and all remaining allegations of Paragraph 10.

RESPONSE TO "JURISDICTION AND VENUE"

11. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

ANSWER: Paragraph 11 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that subject matter jurisdiction is proper solely for claims alleging infringement the '365 patent under 35 U.S.C. § 271(e)(2)(A). Hetero denies any and all remaining allegations of Paragraph 11.

12. This Court has personal jurisdiction over Hetero USA because, on information and belief, it is a Delaware corporation. On information and belief, Hetero USA maintains pervasive, continuous, and systematic contacts with the State of Delaware through the marketing, distribution, and sale of generic versions of branded pharmaceutical products in the State of Delaware and by deriving substantial revenue from the importation and sale of its products in the State of Delaware.

ANSWER: Paragraph 12 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero USA, Inc. is a corporation organized and existing under the laws of the State of Delaware. Answering further, Hetero does not contest personal jurisdiction in the District of Delaware solely for the limited purpose of this action only. Hetero denies any and all remaining allegations of Paragraph 12.

13. This Court has personal jurisdiction over Hetero Labs because, on information and belief, it maintains pervasive, continuous, and systematic contacts with the State of Delaware through the marketing, distribution, and sale of generic versions of branded pharmaceutical products in the State of Delaware, directly and through its affiliates, and by deriving substantial revenue from the importation and sale of its products in the State of Delaware.

ANSWER: Paragraph 13 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero does not contest personal jurisdiction in the District of Delaware solely for the limited purpose of this action only. Hetero denies any and all remaining allegations of Paragraph 13.

14. Alternatively, this Court may also exercise jurisdiction over Hetero Labs pursuant to Fed. R. Civ. P. 4(k)(2) to the extent that Hetero Labs, as a foreign defendant, is not subject to personal jurisdiction in any state's court of general jurisdiction, based on Hetero Labs's contacts with the United States as a whole, including without limitation through the manufacture, importation, distribution, and sales of its pharmaceutical products throughout the United States, including in this judicial district.

ANSWER: Paragraph 14 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Unit-V is a corporation organized and existing under the laws of India. Answering further, Hetero does not contest personal jurisdiction in the District of Delaware solely for the limited purpose of this action only. Hetero denies any and all remaining allegations of Paragraph 14.

15. This Court has personal jurisdiction over Hetero Limited because, on information and belief, it maintains pervasive, continuous, and systematic contacts with the State of Delaware through the marketing, distribution, and sale of generic versions of branded pharmaceutical products in the State of Delaware, directly and through its affiliates, and by deriving substantial revenue from the importation and sale of its products in the State of Delaware.

ANSWER: Paragraph 15 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero does not contest personal jurisdiction in the District of Delaware solely for the limited purpose of this action only. Hetero denies any and all remaining allegations of Paragraph 15.

16. Alternatively, this Court may also exercise jurisdiction over Hetero Limited pursuant to Fed. R. Civ. P. 4(k)(2) to the extent that Hetero Limited, as a foreign defendant, is not subject to personal jurisdiction in any state's court of general jurisdiction, based on Hetero Limited's contacts with the United States as a whole, including without limitation through the manufacture, importation, distribution, and sales of its pharmaceutical products throughout the United States, including in this judicial district.

ANSWER: Paragraph 16 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Labs Limited is a corporation organized and existing under the laws of India. Answering further, Hetero does not contest personal

jurisdiction in the District of Delaware solely for the limited purpose of this action only. Hetero denies any and all remaining allegations of Paragraph 16.

17. Venue is proper in this district as to Hetero USA, pursuant to 28 U.S.C. §§ 1391 and 1400(b), because Hetero USA is incorporated in the State of Delaware and thus resides in this judicial district.

ANSWER: Paragraph 17 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero USA, Inc. is a corporation organized and existing under the laws of the State of Delaware. Answering further, Hetero does not contest venue in the District of Delaware solely for the limited purpose of this action only. Hetero denies any and all remaining allegations of Paragraph 17.

18. Venue is proper as to Hetero Labs, pursuant to 28 U.S.C. § 1391(c)(3), because Hetero Labs is a foreign corporation not residing in any judicial district and may be sued in any judicial district that has personal jurisdiction, including this judicial district.

ANSWER: Paragraph 18 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Unit-V is a corporation organized and existing under the laws of India. Answering further, Hetero does not contest venue in the District of Delaware solely for the limited purpose of this action only. Hetero denies any and all remaining allegations of Paragraph 18.

19. Venue is proper as to Hetero Limited, pursuant to 28 U.S.C. § 1391(c)(3), because Hetero Limited is a foreign corporation not residing in any judicial district and may be sued in any judicial district that has personal jurisdiction, including this judicial district.

ANSWER: Paragraph 19 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Labs Limited is a corporation organized and existing under the laws of India. Answering further, Hetero does not contest venue in the District of Delaware solely for the limited purpose of this action only. Hetero denies any and all remaining allegations of Paragraph 19.

RESPONSE TO "THE DRUG APPROVAL PROCESS"

20. A company seeking to market a new pharmaceutical drug in the United States must first obtain approval from the FDA, typically through the filing of a New Drug Application ("NDA"). *See* 21 U.S.C. § 355(a). The sponsor of the NDA is required to submit to FDA information on all patents claiming the drug that is the subject of the NDA, or a method of using that drug, and FDA then lists the patent information in its publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is referred to as the "Orange Book." *See* 21 U.S.C. § 355(b)(1) and (c)(2).

ANSWER: Paragraph 20 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that 21 U.S.C. § 355(b)(1) states, in part:

> (A) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as part of the application—
>
> > (viii) the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that—
> >
> > > (I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or
> >
> > > (II) claims a method of using such drug for which approval is sought or has been granted in the application.

See 21 U.S.C. § 355(b)(1)(A)(viii)(I-II). Hetero further admits that 21 U.S.C. § 355(c)(2) states, in part, that "[u]pon the submission of patent information under this subsection, the Secretary shall publish it." Hetero further admits that FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly is referred to as the "Orange Book." Hetero denies any and all remaining allegations of Paragraph 20.

21. Alternatively, a company seeking to market a generic version of a previously approved drug is not required to submit a full NDA. Instead, it may file an Abbreviated New Drug Application ("ANDA"). *See* 21 U.S.C. § 355(j). The generic drug approval process is considered "abbreviated" because the generic manufacturer may piggyback on the innovator company's data and FDA's prior finding of safety and efficacy by demonstrating, among other things, that the generic product is bioequivalent to the previously approved drug (the "reference listed drug" or "branded drug").

ANSWER: Paragraph 21 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that 21 U.S.C. § 355 states, *inter alia*:

> (j) Abbreviated new drug applications
>
> (4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds—
>
> (F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

See 21 U.S.C. § 355(j)(4)(F). Hetero denies any and all remaining allegations of Paragraph 21.

22. In conjunction with this "abbreviated" application process, Congress has put in place a process for resolving patent disputes relating to generic drugs, pursuant to which an ANDA filer must provide certifications addressing each of the patents listed in the Orange Book for the branded drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12). An ANDA filer may certify, for instance, that it believes a patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV); *see also* 21 C.F.R. § 314.94(a)(12)(i)(A)(4). This is known as a "Paragraph IV Certification."

ANSWER: Paragraph 22 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that 21 U.S.C. § 355 states, *inter alia*:

> (j) Abbreviated new drug applications
>
> (2)
>
> (A) An abbreviated application for a new drug shall contain—
>
> (vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and

> for which information is required to be filed under subsection (b) or (c)—
>
> (I) that such patent information has not been filed,
>
> (II) that such patent has expired,
>
> (III) of the date on which such patent will expire, or
>
> (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted;

See 21 U.S.C. § 355(j)(2)(A)(vii)(I-IV). Hetero denies any and all remaining allegations of Paragraph 22.

23. The filer of an ANDA with a Paragraph IV Certification must also provide notice to both the owner of the listed patents and the holder of the NDA for the referenced listed drug. This "Paragraph IV Notice" must include a detailed statement of the factual and legal bases for the applicant's belief that the challenged patent is invalid or not infringed by the proposed generic product. *See* 21 U.S.C. § 355(j)(2)(B); 21 C.F.R. § 314.95.

ANSWER: Paragraph 23 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that 21 U.S.C. § 355 states, *inter alia*:

> (j) Abbreviated new drug applications
>
> (2)
>
> (B) Notice of opinion that patent is invalid or will not be infringed.—
>
> (iv) Contents of notice.—A notice required under this subparagraph shall—
>
> (I) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and
>
> (II) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

See 21 U.S.C. § 355(j)(2)(B)(iv)(I-II). Hetero denies any and all remaining allegations of Paragraph 23.

24. If the patentee or NDA holder files a patent infringement action within 45 days of receiving a Paragraph IV Notice from an ANDA filer, final approval of the ANDA is subject to a litigation stay. *See* 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(b)(3). When the NDA holder is awarded New Chemical Entity ("NCE") exclusivity, the litigation stay runs to the later of 30 months from receipt of the notice letter or seven-and-a-half years from the approval date of the NDA. 21 U.S.C. §§ 355(c)(3)(E)(ii), (j)(5)(F)(ii). The stay provides an innovator company with the opportunity to resolve any patent dispute before the generic product enters the market. *See* 21 U.S.C. 355(j)(5)(B)(iii).

ANSWER: Paragraph 24 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that 21 U.S.C. § 355 states, *inter alia*:

> (j) Abbreviated new drug applications
>
> (5)
>
> (B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined by applying the following to each certification made under paragraph (2)(A)(vii):
>
> (iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in paragraph (2)(B) is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—
>
> (I) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination

> that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—
>
> (aa) the date on which the court enters judgment reflecting the decision; or
>
> (bb) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;
>
> * * *
>
> (F)
>
> (ii) If an application submitted under subsection (b) for a drug, no active moiety (as defined by the Secretary in section 314.3 of title 21, Code of Federal Regulations (or any successor regulations)) of which has been approved in any other application under subsection (b), is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b), except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

See 21 U.S.C. §§ 355(j)(5)(B)(iii), (j)(5)(F)(ii). Hetero denies any and all remaining allegations of Paragraph 24.

RESPONSE TO "FACTUAL BACKGROUND"

Response to "The Patent-in-Suit"

25. On November 22, 2022, the United States Patent and Trademark Office ("USPTO") duly and legally issued the '365 Patent, entitled "Use of Tivozanib to Treat Subjects with Refractory Cancer," to AVEO as the assignee. A true and correct copy of the '365 Patent is attached as Exhibit A.

ANSWER: Paragraph 25 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that a purported copy of the '365 patent is attached to the Complaint as Exhibit A; that the '365 patent is titled "Use of Tivozanib to Treat Subjects with Refractory Cancer"; and that it bears an issuance date of November 22, 2022. Hetero further admits that the online records of the USPTO lists the current assignee for the '365 patent as AVEO Pharmaceuticals, Inc. Hetero denies any and all remaining allegations of Paragraph 25.

26. AVEO owns the '365 Patent and has all substantial rights in and to the '365 Patent, including the right to assert any claims for past, present, and future infringement of the '365 Patent.

ANSWER: Paragraph 26 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the online records of the USPTO list the current assignee for the '365 patent as AVEO Pharmaceuticals, Inc. Hetero denies any and all remaining allegations of Paragraph 26.

27. The claims of the '365 Patent are generally directed to methods of treating patients with refractory advanced renal cell carcinoma ("RCC") having previously received at least two anti-cancer therapies, at least one of which included a tyrosine kinase inhibitor ("TKI").

ANSWER: Paragraph 27 contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

Response to "FOTIVDA®"

28. AVEO is the holder of NDA No. 212904, including all supplements thereto, for FOTIVDA.

ANSWER: Paragraph 28 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that, according to FDA's online records, "AVEO PHARMACEUTICALS INC" is the holder of NDA No. 212904 for FOTIVDA (tivozanib hydrochloride), capsules; oral, EQ 0.89 mg Base and EQ 1.34 mg Base. Hetero denies any and all remaining allegations of Paragraph 28.

29. On March 31, 2020, AVEO submitted NDA No. 212904, under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), seeking FDA approval for an oral tivozanib hydrochloride product for the treatment of patients with relapsed or refractory RCC. On March 10, 2021, the FDA approved NDA No. 212904. NDA No. 212904 was also awarded NCE exclusivity, which expires March 10, 2026.

ANSWER: Paragraph 29 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that, according to FDA's online records, FDA approved NDA No. 212904 for FOTIVDA (tivozanib hydrochloride), capsules; oral, EQ 0.89 mg Base and EQ 1.34 mg Base, on or about March 10, 2021. Answering further, Hetero states that, according to the approved label for FOTIVDA (tivozanib hydrochloride), Capsules, 0.89 mg and 1.34 mg, currently available from the online records of FDA:

> **1 INDICATIONS AND USAGE**
>
> FOTIVDA is indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

Answering further, Hetero states that the online records of the FDA provide the following "Exclusivity Data" for NDA No. 212904:

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
001	NCE	03/10/2026

Hetero denies any and all remaining allegations of Paragraph 29.

30. AVEO timely submitted information regarding the '365 Patent for listing in FDA's Orange Book with respect to FOTIVDA, for strengths EQ 0.89MG BASE (Product 001), and EQ 1.34MG Base (Product 002), pursuant to 21 U.S.C. §§ 355(b)(1) and (c)(2). The FDA thereafter listed the '365 Patent in the Orange Book with respect to those products, pursuant to 21 C.F.R. § 314.53(e).

ANSWER: Paragraph 30 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the Orange Book identifies "AVEO PHARMACEUTICALS INC" as the holder of NDA No. 212904 for FOTIVDA; lists the '365 patent in connection with NDA No. 212904; and lists the "Submission Date" for the '365 patent as "12/01/2022." Hetero denies any and all remaining allegations of Paragraph 30.

31. AVEO timely submitted information regarding U.S. Patent No. 6,821,987 (the "'987 patent") in the Orange Book with respect to FOTIVDA, for strengths EQ 0.89MG BASE (Product 001), and EQ 1.34MG Base (Product 002), pursuant to 21 U.S.C. §§ 355(b)(1) and (c)(2). The FDA thereafter listed the '987 Patent in the Orange Book with respect to those products, pursuant to 21 C.F.R. § 314.53(e).

ANSWER: Paragraph 31 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the Orange Book identifies "AVEO PHARMACEUTICALS INC" as the holder of NDA No. 212904 for FOTIVDA; lists the '987 patent in connection with NDA No. 212904; and lists the "Submission Date" for the '987 patent as "04/06/2021." Hetero denies any and all remaining allegations of Paragraph 31.

32. AVEO timely submitted information regarding U.S. Patent No. 7,166,722 (the "'722 patent") in the Orange Book with respect to FOTIVDA, for strengths EQ 0.89MG BASE (Product 001), and EQ 1.34MG Base (Product 002), pursuant to 21 U.S.C. §§ 355(b)(1) and (c)(2). The FDA thereafter listed the '722 Patent in the Orange Book with respect to those products, pursuant to 21 C.F.R. § 314.53(e).

ANSWER: Paragraph 32 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the Orange Book identifies "AVEO PHARMACEUTICALS INC" as the holder of NDA No. 212904 for FOTIVDA; lists the '722

patent in connection with NDA No. 212904; and lists the "Submission Date" for the '722 patent as "04/06/2021." Hetero denies any and all remaining allegations of Paragraph 32.

33. The FDA-approved label for FOTIVDA, among other things, provides information and instructions for the safe and effective use of FOTIVDA by healthcare providers and patients. A true and correct copy of the FOTIVDA label is attached as Exhibit B.

ANSWER: Paragraph 33 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that what purports to be a true and correct copy of the current approved label for FOTIVDA is attached to Plaintiff's Complaint as Exhibit B. Hetero denies any and all remaining allegations of Paragraph 33.

34. The FOTIVDA label states that "FOTIVDA is indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies." Ex. B § 1, Indications and Usage.

ANSWER: Paragraph 34 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states in part:

> **1 INDICATIONS AND USAGE**
>
> FOTIVDA is indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

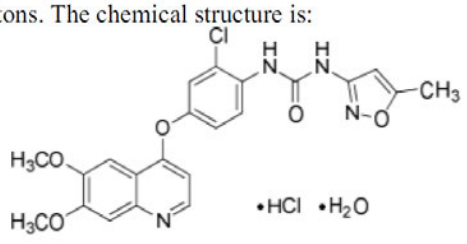
Hetero denies any and all remaining allegations of Paragraph 34.

35. According to the FOTIVDA label, the active ingredient in FOTIVDA is tivozanib hydrochloride. *Id.* § 11, Description.

ANSWER: Paragraph 35 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states in part:

11 DESCRIPTION

Tivozanib is a kinase inhibitor. Tivozanib hydrochloride, the active ingredient, has the chemical name 1-{2-chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-3-(5-methylisoxazol-3-yl)urea hydrochloride hydrate. The molecular formula is $C_{22}H_{19}ClN_4O_5 \cdot HCl \cdot H_2O$ and the molecular weight is 509.34 Daltons. The chemical structure is:



Hetero denies any and all remaining allegations of Paragraph 35.

36. Tivozanib hydrochloride is a tyrosine kinase inhibitor ("TKI") targeting specific proteins that tumors rely on to grow new blood vessels, namely vascular endothelial growth factor receptor ("VEGFR")-1, VEGFR-2, and VEGFR-3. *See* Ex. B § 12.1, Mechanism of Action. This growth of new blood vessels, known as angiogenesis, supplies tumors with the oxygen and nutrients they need to grow and spread. *Id.* By inhibiting angiogenesis, tivozanib acts to slow the growth of a tumor or cause it to shrink. *Id.* Tivozanib exhibits high selectively for these proteins, which means it interferes less with other cellular functions, and can reduce side effects compared to broader systemic treatments.

ANSWER: Paragraph 36 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states in part:

12.1 Mechanism of Action

Tivozanib is a tyrosine kinase inhibitor. In vitro cellular kinase assays demonstrated that tivozanib inhibits phosphorylation of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2 and VEGFR-3 and inhibits other kinases including c-kit and PDGFR β at clinically relevant concentrations. In tumor xenograft models in mice and rats, tivozanib inhibited angiogenesis, vascular permeability, and tumor growth of various tumor cell types including human renal cell carcinoma.

Hetero denies any and all remaining allegations of Paragraph 36.

37. Hepatic impairment refers to the reduction in liver function due to liver disease or damage. It affects the liver's ability to metabolize drugs and can lead to increased bioavailability of orally administered drugs. Among the patients with RCC who are treated with tivozanib hydrochloride are those who have hepatic impairment or develop hepatic impairment during the treatment cycle.

ANSWER: Paragraph 37 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero lacks knowledge and information sufficient to form a belief as to the truth of the remaining allegations of Paragraph 37 and therefore denies them.

38. The "recommended dosage of FOTIVDA is 1.34 mg taken orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle." Ex. B § 2.1, Recommended Dosing. The label states that the "1.34 mg capsule contains 1.5 mg of tivozanib hydrochloride (equivalent to 1.34 mg tivozanib)." *Id.* § 11, Description.

ANSWER: Paragraph 38 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states in part:

> **2.1 Recommended Dosing**
>
> The recommended dosage of FOTIVDA is 1.34 mg taken orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle.
>
> Continue treatment until disease progression or until unacceptable toxicity occurs.
>
> Take FOTIVDA with or without food. Swallow the FOTIVDA capsule whole with a glass of water. Do not open the capsule.
>
> If a dose is missed, the next dose should be taken at the next scheduled time. Do **not** take two doses at the same time.

* * *

> FOTIVDA 1.34 mg capsule contains 1.5 mg of tivozanib hydrochloride (equivalent to 1.34 mg tivozanib) with inactive ingredients: mannitol and magnesium stearate. Capsule composition: gelatin, titanium dioxide, FDA yellow iron oxide, and Blue SB-6018 (ink).

Hetero denies any and all remaining allegations of Paragraph 38.

39. The FOTIVDA label provides further instructions for "use in specific populations," including patients with moderate hepatic impairment. Ex. B, Highlights of Prescribing Information. Specifically, the FOTIVDA label instructs monitoring patients for hepatic impairment and making certain dose modifications for patients exhibiting moderate hepatic impairment. *Id.* § 2.3 Dosage Modifications for Moderate Hepatic Impairment; § 8.7 Hepatic Impairment. For such patients, the "recommended dosage of FOTIVDA [is a] 0.89 mg capsule taken orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle." *Id.* § 2.3. The Dosage and Administration section from the Highlights of Prescribing Information portion of the label also instructs healthcare providers and patients to "reduce the dose to 0.89 mg" for patients with moderate hepatic impairment. *Id.*, Highlights of Prescribing Information. The label states that the "0.89 mg capsule contains 1.0 mg of tivozanib hydrochloride (equivalent to 0.89 mg tivozanib)." *Id.* § 11, Description.

ANSWER: Paragraph 39 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states in part: "Hepatic Impairment: Adjust dosage in patients with moderate hepatic impairment. Avoid use in patients with severe hepatic impairment." Hetero further admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states, *inter alia*: "Reduce the recommended dosage of FOTIVDA to 0.89 mg capsule taken orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle for patients with moderate hepatic impairment." Hetero further admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states, *inter alia*: "Reduce the dosage when administering FOTIVDA in patients with moderate (total bilirubin greater than 1.5 to 3 times ULN with any AST) hepatic impairment [ ]. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) hepatic impairment. The recommended dosage of FOTIVDA in patients with severe (total bilirubin greater than 3 to 10 times ULN with any AST) hepatic impairment has not been established [ ]." Hetero denies any and all remaining allegations of Paragraph 39.

40. The FOTIVDA label also provides that "the safety of FOTIVDA was evaluated in TIVO-3, a randomized, open-label trial in 350 patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments *[see CLINICAL STUDIES (14)]*," and directs the reader to the clinical studies section of the label. Ex. B. § 6.1, Clinical Trial Experience. The clinical studies section states that the "efficacy of FOTIVDA was evaluated in TIVO-3 (NCT02627963), a randomized (1:1), open label, multicenter trial of FOTIVDA versus sorafenib in patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments including at least one VEGFR kinase inhibitor other than sorafenib or tivozanib. " *Id.* § 14 Clinical Studies. Further, the FOTIVDA label, sets forth a summary of the patient demographics for the clinical trial, stating that "[p]rior therapy included two KIs (45%), a KI plus an immune checkpoint inhibitor (26%), and a KI plus another systemi c agent (29%)." *Id.* Thus, all patients in the TIVO-3 trial described in the FOTIVDA label received a TKI prior to treatment with tivozanib as a monotherapy. *See id.* § 6.1 Clinical Trial Experience and § 14 Clinical Studies.

ANSWER: Paragraph 40 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states, *inter alia*: "The safety of FOTIVDA was evaluated in TIVO-3, a randomized, open-label trial in 350 patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments [ ]. Patients were randomized (1:1) to receive FOTIVDA 1.34 mg orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle, or to receive sorafenib 400 mg orally twice a day continuously until disease progression or unacceptable toxicity. Among patients who received FOTIVDA, 53% were exposed for 6 months or longer and 31% were exposed for greater than one year." Hetero further admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states, *inter alia*: "The median age was 63 years (range: 30 to 90 years), 73% were male, 95% were Caucasian, ECOG performance status was 0 in 48% and 1 in 49% of patients (respectively), and 98% of patients had clear cell or clear cell component histology. Prior therapy included two KIs (45%), a KI plus an immune checkpoint inhibitor (26%), and a KI plus another systemic agent (29%). At the time of study entry, 20% of patients had favorable, 61% intermediate, and 19% poor IMDC prognoses." Hetero denies any and all remaining allegations of Paragraph 40.

41. The FOTIVDA label reports the efficacy results of the TIVO-3 clinical trial, providing, among other things, that the median duration of progression free survival in patients receiving FOTIVDA is 5.6 months. Ex. B § 14, Table 4, Efficacy Results in TIVO-3 (ITT).

ANSWER: Paragraph 41 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states, *inter alia*: "The safety of FOTIVDA was evaluated in TIVO-3, a randomized, open-label trial in 350 patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments [ ]. Patients were randomized (1:1) to receive FOTIVDA

1.34 mg orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle, or to receive sorafenib 400 mg orally twice a day continuously until disease progression or unacceptable toxicity. Among patients who received FOTIVDA, 53% were exposed for 6 months or longer and 31% were exposed for greater than one year." Hetero further admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states, *inter alia*, that the "main efficacy outcome measure was progression-free survival (PFS) assessed by a blinded independent radiology review committee." Hetero denies any and all remaining allegations of Paragraph 41.

Response to "Hetero's Infringing Tivozanib Hydrochloride Products"

42. On information and belief, on or before April 22, 2025, Hetero USA, Hetero Labs, and Hetero Limited, submitted ANDA No. 220437 pursuant to 21 U.S.C. § 355(j), seeking FDA approval to engage in the commercial manufacture, importation, use, marketing, and sale of proposed generic tivozanib hydrochloride (eq. 1.34 mg and 0.89 mg base), referencing AVEO's FOTIVDA product as the reference listed drug (the "Proposed ANDA Product").

ANSWER: Paragraph 42 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Unit-V's ANDA No. 220437 was submitted to the FDA pursuant to 21 U.S.C. § 355(j) and that Hetero Unit-V's ANDA contains a certification pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act for the '365 patent. Hetero further admits that the RLD identified in Hetero Unit-V's ANDA No. 220437 is FOTIVDA® (tivozanib) Capsules, 0.89 mg and 1.34 mg. Hetero denies any and all remaining allegations of Paragraph 42.

43. Hetero USA, Hetero Labs, and Hetero Limited sent AVEO a notice letter, dated April 22, 2025, stating that Hetero had submitted the Hetero ANDA seeking approval to manufacture, import, use, market, and/or sell the Proposed ANDA Product prior to the expiration of the '365 Patent (the "Paragraph IV Notice Letter").

ANSWER: Paragraph 43 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Unit-V's ANDA No. 220437 was

submitted to the FDA pursuant to 21 U.S.C. § 355(j) and that Hetero Unit-V's ANDA contains a certification pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act for the '365 patent. Hetero further admits that it sent a letter on April 22, 2025 via Federal Express to AVEO Pharmaceuticals, Inc pursuant to 21 U.S.C. § 355(j)(2)(B) ("Hetero's Notice Letter"), which provided written notification of the paragraph IV certification for the '365 patent. Hetero denies any and all remaining allegations of Paragraph 43.

44. AVEO received the Notice Letter on April 23, 2025.

ANSWER: Paragraph 44 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that it sent Hetero's Notice Letter on April 22, 2025 via Federal Express to AVEO Pharmaceuticals, Inc. Hetero denies any and all remaining allegations of Paragraph 44.

45. The Paragraph IV Notice Letter asserts that the '365 Patent is invalid and not infringed by the Proposed ANDA Product but makes no such assertions with respect to the '987 and '722 Patents.

ANSWER: Paragraph 45 contains legal conclusions and allegations to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Unit-V's ANDA contains a certification pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act for the '365 patent. Hetero denies any and all remaining allegations of Paragraph 45.

46. The Paragraph IV Notice Letter included an offer of confidential access to the Hetero ANDA pursuant to 21 U.S.C. § 355(j)(5)(C). The offer only committed to provide unspecified information from Hetero's ANDA and was subject to unreasonably restrictive confidentiality provisions.

ANSWER: Paragraph 46 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero states that the Offer of Confidential Access ("OCA") to Application sent with Hetero's Notice Letter complied with all statutory and regulatory

requirements. Hetero further states that Plaintiff did not make a good faith request for any information from Hetero Unit-V's ANDA No. 220437. Hetero denies any and all remaining allegations of Paragraph 46.

47. Hetero's submission of the Hetero ANDA to the FDA, including any amendments or supplements thereto, and any commercial manufacture or sale by Hetero of the Proposed ANDA Product, constitutes infringement of the '365 Patent, as detailed below.

ANSWER: Denied.

48. This action is being commenced before the expiration of forty-five days from the date AVEO received Hetero's Paragraph IV Notice Letter.

ANSWER: Paragraph 48 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that it sent Hetero's Notice Letter on April 22, 2025 via Federal Express to AVEO Pharmaceuticals, Inc. Hetero denies any and all remaining allegations of Paragraph 48.

RESPONSE TO "COUNT I INFRINGEMENT OF THE '365 PATENT"

49. AVEO incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Hetero restates and incorporates each of its responses to the preceding Paragraphs 1-48 as if fully set forth herein.

50. The submission of the Hetero ANDA to the FDA, including the Paragraph IV Certification submitted therewith, which seeks approval to engage in the commercial manufacture, use, marketing, offer for sale, sale, and/or importation of the Proposed ANDA Product prior to the expiration of the '365 Patent, constitutes infringement by Hetero of the '365 Patent under 35 U.S.C. § 271(e)(2)(A).

ANSWER: Denied.

51. The commercial manufacture, use, marketing, offer for sale, sale, and/or importation into the United States of the Proposed ANDA Product by Hetero before the expiration of the '365 Patent would instruct, direct, recommend, encourage, and/or promote direct infringement, contributory infringement, and/or active inducement of infringement of the '365 Patent under 35 U.S.C. §§ 271(a)-(c).

ANSWER: Denied.

52. On information and belief, and subject to AVEO's ongoing investigation and discovery efforts, if Hetero's Proposed ANDA Product is approved, Hetero will make, offer for sale, sell, or import Hetero's ANDA Product in a manner that, when used in accordance with its proposed labeling would infringe at least, by way of example, independent claims 1 and 7 of the '365 Patent, which recite as follows:

> **1. A method of treating a human subject with refractory advanced renal cell carcinoma (RCC) having previously received at least two anti-cancer therapies, at least one of which included a tyrosine kinase inhibitor (TKI), the method comprising:**
>
> > **administering to the subject treatment cycles consisting essentially of:**
> >
> > **orally administering a pharmaceutical composition comprising an active agent consisting essentially of 1.5 mg tivozanib hydrochloride daily for 21 days followed by 7 days without administration of tivozanib hydrochloride until the subject experiences moderate hepatic impairment, upon which the amount of tivozanib hydrochloride in each treatment cycle is reduced from 1.5 mg to 1.0 mg,**
> >
> > **thereby to achieve a progression free survival in the subject of at least 5 months.**
>
> **7. A method of treating a human subject with refractory advanced renal cell carcinoma (RCC) having previously received at least two anti -cancer therapies, at least one of which included a tyrosine kinase inhibitor (TKI), and experiencing moderate hepatic impairment, the method comprising:**
>
> > **administering to the subject one or more treatment cycles consisting essentially of:**
> >
> > **orally administering a pharmaceutical composition comprising an active agent consisting essentially of 1.0 mg tivozanib hydrochloride daily for 21 days followed by 7 days without administration of tivozanib hydrochloride thereby to treat RCC.**

ANSWER: Paragraph 52 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that claims 1 and 7 of the '365 patent recite:

> 1. A method of treating a human subject with refractory advanced renal cell carcinoma (RCC) having previously received at least two anti-cancer therapies, at least one of which included a tyrosine kinase inhibitor (TKI), the method comprising:
>
> administering to the subject treatment cycles consisting essentially of:
>
> orally administering a pharmaceutical composition comprising an active agent consisting essentially of 1.5 mg tivozanib hydrochloride daily for 21 days followed by
>
> 7 days without administration of tivozanib hydrochloride until the subject experiences moderate hepatic impairment, upon which the amount of tivozanib hydrochloride in each treatment cycle is reduced from 1.5 mg to 1.0 mg,
>
> thereby to achieve a progression free survival in the subject of at least 5 months.

* * *

> 7. A method of treating a human subject with refractory advanced renal cell carcinoma (RCC) having previously received at least two anti-cancer therapies, at least one of which included a tyrosine kinase inhibitor (TKI), and experiencing moderate hepatic impairment, the method comprising:
>
> administering to the subject one or more treatment cycles consisting essentially of:
>
> orally administering a pharmaceutical composition comprising an active agent consisting essentially of 1.0 mg tivozanib hydrochloride daily for 21 days followed by 7 days without administration of tivozanib hydrochloride,
>
> thereby to treat the RCC.

Hetero denies any and all remaining allegations of Paragraph 52.

53. On information and belief, Hetero's Proposed ANDA Product will substantively copy the FOTIVDA label. *See* 21 C.F.R. § 314.94(a)(8)(iv). Accordingly, on information and belief and subject to AVEO's ongoing investigation and discovery efforts, by virtue of Hetero's submission of the proposed product label and other conduct, Hetero proposes to instruct, direct, recommend, encourage, and/or promote direct infringement of at least claims 1 and 7 of the '365 Patent by patients, physicians, prescribers or other healthcare providers.

ANSWER: Denied.

54. Hetero's Proposed ANDA Product is indicated for the treatment of adult patients with relapsed or refractory advanced RCC following two or more prior systemic therapies.

ANSWER: Denied.

55. On information and belief, the label for Hetero's Proposed ANDA Product, including its indication for patients with refractory advanced RCC would actively direct, instruct, recommend, encourage, and/or promote that physicians, prescribers, and/or patients administer tivozanib hydrochloride to patients with refractory advanced RCC.

ANSWER: Denied.

56. On information and belief, many patients with relapsed or refractory advanced RCC who have had two or more prior systemic therapies would have received at least one TKI prior to treatment with tivozanib hydrochloride.

ANSWER: Paragraph 56 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero lacks knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 56 and therefore denies them.

57. On information and belief, the label for Hetero's Proposed ANDA Product, including its description of the TIVO-3 study conducted on patients who all received a TKI prior to receiving tivozanib hydrochloride, would actively direct, instruct, recommend, encourage, and/or promote that physicians, prescribers, and/or patients administer tivozanib hydrochloride to patients with refractory advanced RCC who have had two or more prior systemic therapies including at least one TKI.

ANSWER: Denied.

58. The recommended dosage of Hetero's Proposed ANDA Product is 1.34 mg once daily for 21 days on treatment followed by 7 days off treatment. On information and belief, the 1.34 mg dosage form of Hetero's Proposed ANDA Product contains 1.5 mg of tivozanib hydrochloride.

ANSWER: Paragraph 58 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states in part:

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

- Recommended Dose: 1.34 mg once daily with or without food for 21 days on treatment followed by 7 days off treatment (28-day cycle) until disease progression or unacceptable toxicity. (2.1)
- Dose interruptions and/or dose reduction may be needed to manage adverse reactions. (2.2)
- For patients with moderate hepatic impairment, reduce the dose to 0.89 mg for 21 days on treatment followed by 7 days off treatment (28-day cycle). (2.3)

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

Capsules: 1.34 mg and 0.89 mg (3)

Answering further, Hetero states that Hetero Unit-V's ANDA meets all statutory and regulatory requirements. Hetero denies any and all remaining allegations of Paragraph 58.

59. On information and belief, among the patients who are administered Hetero's Proposed ANDA Product according to the instructions in its label are those who will have moderate hepatic impairment at the onset of treatment or develop moderate hepatic impairment during treatment.

ANSWER: Paragraph 59 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero lacks knowledge or information sufficient to form a belief as to the truth of the allegations of Paragraph 59 and therefore denies them.

60. Hetero's Proposed ANDA Product label includes instructions to reduce the dose of tivozanib for patients with moderate hepatic impairment. On information and belief, based on these label instructions, physicians or healthcare providers will assess the patients' liver function for hepatic impairment before and during treatment.

ANSWER: Paragraph 60 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that the FOTIVDA label attached as Exhibit B to Plaintiff's Complaint states in part:

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

- Recommended Dose: 1.34 mg once daily with or without food for 21 days on treatment followed by 7 days off treatment (28-day cycle) until disease progression or unacceptable toxicity. (2.1)
- Dose interruptions and/or dose reduction may be needed to manage adverse reactions. (2.2)
- For patients with moderate hepatic impairment, reduce the dose to 0.89 mg for 21 days on treatment followed by 7 days off treatment (28-day cycle). (2.3)

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

Capsules: 1.34 mg and 0.89 mg (3)

Answering further, Hetero states that Hetero Unit-V's ANDA meets all statutory and regulatory requirements. Hetero denies any and all remaining allegations of Paragraph 60.

61. On information and belief, physicians or healthcare providers will consult and follow the instructions of Hetero's Proposed ANDA Product label and adjust the dose of tivozanib hydrochloride from 1.5 mg to 1.0 mg for patients with moderate hepatic impairment. On information and belief, the 0.89 mg dosage form of Hetero's Proposed ANDA Product contains 1.0 mg of tivozanib hydrochloride. Accordingly, Hetero's Proposed ANDA Product label would actively direct, instruct, recommend, encourage, and/or promote, that physicians, prescribers, and/or patients reduce the dose of tivozanib hydrochloride from 1.5 mg to 1.0 mg for patients with moderate hepatic impairment.

ANSWER: Denied.

62. Hetero's Proposed ANDA Product label provides instructions and safety information regarding the use and administration of tivozanib as a monotherapy. Accordingly, Hetero's Proposed ANDA Product label would actively direct, instruct, recommend, encourage, and/or promote that physicians, prescribers, and/or patients administer or take tivozanib hydrochloride as a monotherapy.

ANSWER: Denied.

63. Hetero's Proposed ANDA Product label reports the efficacy results of clinical trials involving the treatment of RCC patients with tivozanib, where the median duration of progression free survival in patients receiving tivozanib is 5.6 months. Accordingly, Hetero's Proposed ANDA Product label would actively direct, instruct, recommend, encourage, and/or promote that physicians, prescribers, and/or patients to administer or take tivozanib hydrochloride to achieve a progression free survival in the subject of at least 5 months.

ANSWER: Denied.

64. On information and belief, and subject to AVEO's ongoing investigation and discovery efforts, the manufacture, use (including as directed in Hetero's proposed labeling for Hetero's Proposed ANDA Product), offer for sale, sale, marketing, distribution, and/or importation of Hetero's Proposed ANDA Product will satisfy each of the recited elements of the methods recited in at least claims 1 and 7, either literally or under the doctrine of equivalents.

ANSWER: Denied.

65. On information and belief, if the FDA were to approve the Hetero ANDA, Hetero's commercial manufacture, use, marketing, offer for sale, sale, and/or importation into the United States of the Proposed ANDA Product, including administration of Hetero's Proposed ANDA Product according to the foregoing label instructions, would necessarily or inevitably cause patients, physicians, prescribers, or other healthcare providers to directly infringe at least claims 1 and 7. Hetero would actively induce and contribute to such direct infringement.

ANSWER: Denied.

66. Hetero has knowledge of the claims of the '365 Patent. Despite this knowledge, Hetero has continued to assert its intent to engage in the manufacture, use, offer for sale, sale, marketing (including marketing Hetero's Proposed ANDA Product as a generic substitute for FOTIVDA to be used and administered in the same manner as FOTIVDA) , distribution, and/or importation of Hetero's Proposed ANDA Product with the proposed labeling to be included for the Proposed ANDA Product, immediately and imminently upon approval of ANDA No. 220437. On information and belief, and subject to AVEO's ongoing investigation and discovery efforts, by engaging in the forgoing activities, Hetero specifically intends to infringe the '365 Patent.

ANSWER: Denied.

67. On information and belief, Hetero's specific intent to actively induce and/or contribute to infringement of at least claims 1 and 7 of the '365 Patent includes Hetero's decision to proceed with its plan to engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Hetero's Proposed ANDA Product, despite being aware that the proposed labeling to be included for the Proposed ANDA Product instructs, directs, recommends, encourages, and/or promotes direct infringement of at least claims 1 and 7 of the '365 Patent.

ANSWER: Denied.

68. On information and belief, and with full knowledge of the '365 Patent, Hetero intends to and will actively induce infringement of the '365 Patent when Hetero's Proposed ANDA is approved and will do so immediately and imminently upon approval.

ANSWER: Denied.

69. FOTIVDA and any corresponding generic tivozanib hydrochloride product is not a staple article of commerce and has no substantial approved uses that do not infringe at least claims 1 and 7 of the '365 Patent. On information and belief, Hetero's Proposed ANDA Product is not a staple article of commerce and has no substantial uses that do not infringe at least claims 1 and 7 of the '365 Patent. Upon information and belief, and subject to AVEO's ongoing investigation and discovery efforts, Hetero, with full knowledge of the '365 Patent, knows that its Proposed ANDA Products are especially adapted for use in a manner that infringes the '365 Patent, are not a staple article of commerce, and have no substantial uses that do not infringe at least claims 1 and 7 of the '365 Patent.

ANSWER: Denied.

70. Any launch by Hetero of the Proposed ANDA Product before expiration of the '365 Patent would cause AVEO to suffer immediate and irreparable harm.

ANSWER: Denied.

71. Unless Hetero is enjoined from infringing the '365 Patent, actively inducing infringement of the '365 Patent, and contributing to the infringement of others of the '365 Patent, AVEO will suffer irreparable injury. AVEO has no adequate remedy at law.

ANSWER: Denied.

72. Hetero's infringement of the '365 Patent is willful.

ANSWER: Denied.

RESPONSE TO "COUNT II DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '365 PATENT"

73. AVEO incorporates each of the preceding paragraphs as if fully set forth herein.

ANSWER: Hetero restates and incorporates each of its responses to the preceding Paragraphs 1-72 as if fully set forth herein.

74. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

ANSWER: Paragraph 74 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Plaintiff's Complaint purports to state a claim

for declaratory judgment of infringement under 28 U.S.C. §§ 2201 and 2202. Hetero denies any and all remaining allegations of Paragraph 74.

75. For the reasons explained in Count I above, if the FDA were to approve the Hetero ANDA, Hetero's commercial manufacture, use, marketing, offer for sale, sale, and/or importation into the United States of the Proposed ANDA Product would instruct, direct, recommend, encourage, and/or promote direct infringement, contributory infringement, and/or active inducement of infringement of at least, by way of example, claims 1 and 7 of the '365 Patent under 35 U.S.C. §§ 271(a)-(c).

ANSWER: Denied.

76. With full knowledge of the '365 Patent, Hetero submitted ANDA No. 220437 to obtain approval under the FDCA to engage in the commercial manufacture, use, offer for sale, and/or sale of Hetero's ANDA Product with its proposed labeling prior to expiration of the '365 Patent.

ANSWER: Paragraph 76 contains legal conclusions to which no answer is required. To the extent an answer is required, Hetero admits that Hetero Unit-V's ANDA contains a certification pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act for the '365 patent. Hetero denies any and all remaining allegations of Paragraph 76.

77. Any launch by Hetero of the Proposed ANDA Product before expiration of the '365 Patent would cause AVEO to suffer immediate and irreparable harm.

ANSWER: Denied.

78. Hetero's infringement of the '365 Patent would be willful.

ANSWER: Denied.

79. A definite and concrete controversy exists between AVEO and Hetero as to whether Hetero's commercial manufacture, use, marketing, offer for sale, sale, and/or importation into the United States of the Proposed ANDA Product prior to the expiration of the '365 Patent would infringe the '365 Patent. Accordingly, AVEO is entitled to a declaratory judgment that it would.

ANSWER: Paragraph 79 contains legal conclusions to which no answer is required. To the extent an answer is required, denied.

* * *

Hetero denies any and all allegations not expressly admitted herein. Hetero further denies that Plaintiff is entitled to any of the relief requested or to any relief whatsoever. Hetero respectfully requests that the Court: (a) dismiss this action with prejudice; (b) enter judgment in favor of Hetero; (c) award Hetero its reasonable attorneys' fees and costs incurred in defending this action pursuant to 35 U.S.C. § 285; and (d) award Hetero such further relief as the Court deems just and appropriate.

DEFENSES

Without prejudice to the denials set forth in its Answer, without admitting allegations of the Complaint not otherwise admitted (and, for purposes of clarity, those allegations not specifically admitted are denied), and without undertaking any of the burdens imposed by law on Plaintiff, Hetero asserts the following defenses to the Complaint:

First Defense

The Complaint fails to state a claim upon which relief can be granted.

Second Defense

The proposed manufacture, use, sale, offer for sale, importation, and/or marketing of the tivozanib capsules, 0.89 mg and 1.34 mg, products described in Hetero Unit-V's ANDA No. 220437 ("Hetero Unit-V's ANDA Products") has not infringed, does not infringe, and will not—if made, used, sold, offered for sale, imported, or marketed—infringe either directly or indirectly, any valid and/or enforceable claim of the '365 patent.

Third Defense

Hetero has not induced, does not induce, and will not induce infringement of any valid and/or enforceable claim of the '365 patent.

Fourth Defense

Hetero has not contributed, does not contribute, and will not contribute to infringement of any valid and/or enforceable claim of the '365 patent.

Fifth Defense

The claims of the '365 patent are invalid for failure to comply with one or more of the requirements in 35 U.S.C. §§ 101, 102, 103, and/or 112, and/or for obviousness-type double patenting.

Sixth Defense

The Court lacks subject matter jurisdiction over any and all claims asserted under 35 U.S.C. § 271(a), (b), and/or (c).

Seventh Defense

The Complaint fails to state a claim for willful infringement and/or exceptional case.

Eighth Defense

Any additional defenses or counterclaims that discovery may reveal.

* * *

COUNTERCLAIMS

Defendants/Counterclaim-Plaintiffs Hetero USA, Inc., Hetero Labs Limited Unit-V ("Hetero Unit-V"), and Hetero Labs Limited (collectively, "Hetero") for their Counterclaims against Plaintiff/Counterclaim-Defendant AVEO Pharmaceuticals, Inc. ("Plaintiff"), allege as follows:

THE PARTIES

1. Hetero USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1035 Centennial Ave, Piscataway, NJ 08854.

2. Hetero Unit-V is a corporation organized and existing under the laws of India, having a principal place of business at Surv. No. 439-441, 458 TSIIC-Foundation SEZ, Polepally Village, Jadcherla Mandal, Mahabubnager, Telangana 509 301, India.

3. Hetero Labs Limited is a corporation organized and existing under the laws of India, having a principal place of business at Floor 9-11, Tower 30, RMZ Nexity, Sy. No. 83/1, Knowledge City, Raidurg, Hyderabad, Telangana-500081, India.

4. On information and belief, and according to Plaintiff's Complaint, AVEO Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at One Marina Park Drive, 12th Floor, Boston, Massachusetts 02210. (Complaint at ¶ 3).

JURISDICTION

5. These Counterclaims arise under the Patent Law of the United States, 35 U.S.C. § 1 *et seq.*; the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202; and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) ("MMA") (21 U.S.C. § 355(j) and 35 U.S.C. § 271(e)(5)).

6. This Court has original jurisdiction over the subject matter of these Counterclaims under 28 U.S.C. §§ 1331 and 1338(a); under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202; and under the MMA (21 U.S.C. § 355(j) and 35 U.S.C. § 271(e)(5)).

7. This Court has personal jurisdiction over Plaintiff because: (i) Plaintiff has availed itself of the rights and privileges—and subjected themselves to the jurisdiction—of this forum by suing Hetero in this District; (ii) Plaintiff is organized and existing under the laws of the State of Delaware; and/or (iii) Plaintiff conducts substantial business in, and have regular and systematic contact with, this District.

FACTUAL BACKGROUND

FOTIVDA® (tivozanib hydrochloride)

8. AVEO Pharmaceuticals, Inc. purports to be the holder of approved New Drug Application ("NDA") No. 212904, under which the United States Food and Drug Administration ("FDA") granted approval for tivozanib hydrochloride, 0.89 mg and 1.34 mg, capsules marketed in the United States under the trade name FOTIVDA®.

9. At the time the Complaint was filed, the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), which is published by FDA, listed U.S. Patent No. 11,504,365 ("the '365 patent"), *inter alia*, in connection with NDA No. 212904.

Patent-in-Suit

10. The '365 patent issued on or about November 22, 2022, from U.S. Patent Application Serial No. 17/720,619 ("the '619 application"), filed on April 14, 2022, as a purported continuation of U.S. Patent Application Serial No. 17/289,913 ("the '913 application"), filed as International Application No. PCT/US2019/059904 ("PCT '904") on November 5, 2019. What purports to be a true and correct copy of the '365 patent is attached to Plaintiff's Complaint as Exhibit A.

11. The '365 patent is titled "Use of Tivozanib to Treat Subjects with Refractory Cancer."

12. The face of the '365 patent identifies Michael P. Bailey and Michael N. Needle as the purported inventors.

13. AVEO Pharmaceuticals, Inc. is listed as "assignee" of the '365 patent on the face of the '365 patent.

14. AVEO Pharmaceuticals, Inc. purports and claims to be the owner of the '365 patent.

15. On information and belief, AVEO Pharmaceuticals, Inc. claims and purports to have the right to enforce the '365 patent.

16. On information and belief, and according to Plaintiff's Complaint, Plaintiff submitted information regarding the '365 patent in the Orange Book with respect to FOTIVDA®, for strengths EQ 0.89MG BASE (Product 001), and EQ 1.34MG BASE (Product 002). (Complaint at ¶ 30).

17. By listing the '365 patent in the Orange Book, Plaintiff maintains that an infringement suit can reasonably be asserted against any generic Abbreviated New Drug Application ("ANDA") applicant—including Hetero Unit-V—that attempts to seek approval for, and market, a generic version of FOTIVDA® before the expiration of the '365 patent.

Hetero Unit-V's ANDA Products

18. Hetero Unit-V has filed ANDA No. 220437 ("Hetero Unit-V's ANDA") with the FDA.

19. Because Hetero Unit-V's ANDA seeks FDA approval to engage in the commercial manufacture, use or sale of Tivozanib Capsules, 0.89 mg and 1.34 mg ("Hetero Unit-V's ANDA Products") prior to the expiration of the '365 patent, Hetero Unit-V's ANDA includes a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) to the '365 patent.

20. On May 23, 2025, Plaintiff filed the above-captioned action against Hetero asserting infringement of the '365 patent.

COUNT I
Declaration of Non-Infringement of the '365 Patent

21. Hetero realleges and incorporates by reference the allegations in the preceding paragraphs as if fully set forth herein.

22. A present, genuine, and justiciable controversy exists between Plaintiff and Hetero regarding, *inter alia*, whether the manufacture, use, offer for sale, sale, or importation of Hetero Unit-V's ANDA Products would infringe any valid and enforceable claim of the '365 patent.

23. The manufacture, use, offer for sale, sale, or importation of Hetero Unit-V's ANDA Products would not directly or indirectly infringe any valid and enforceable claim of the '365 patent, either literally or under the doctrine of equivalents.

24. Hetero is entitled to a declaration that the manufacture, use, offer for sale, sale, or importation of Hetero Unit-V's ANDA Products would not infringe any valid and enforceable claim of the '365 patent.

COUNT II
Declaration of Invalidity of the '365 Patent

25. Hetero realleges and incorporates by reference the allegations in the preceding paragraphs as if fully set forth herein.

26. A present, genuine, and justiciable controversy exists between Plaintiff and Hetero regarding, *inter alia*, the invalidity of the '365 patent.

27. The claims of the '365 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, including, but not limited to, 35 U.S.C. §§ 101, 102, 103, 112, and/or for obviousness-type double patenting, the bases for which include, at the very least, one or more of the following:

a. The alleged invention of the '365 patent does no more than combine familiar elements according to known methods to yield predictable results. Any alleged improvement set forth in the '365 patent over the prior art is no more than the predictable use of prior art elements according to their established functions. A person of ordinary skill in the art would have been motivated to combine the

teachings of the prior art to achieve the alleged invention of the '365 patent and would have had a reasonable expectation of success in doing so.

b. The subject matter claimed in the '365 patent fails to comply with, *inter alia*, 35 U.S.C. §§ 102 and/or 103 at least in that the claimed subject matter as a whole was anticipated by the prior art and/or any differences between the subject matter claimed in the patent and the prior art are such that the claimed invention as a whole would have been obvious at the time the alleged invention was made, and/or before the effective filing date of the claimed invention, would have been obvious before the effective filing date of the claimed invention to a person having knowledge of such prior art and having ordinary skill in the art to which the claimed invention pertains. Non-limiting examples of prior art rendering each of the claims of the '365 patent invalid under, at least, 35 U.S.C. §§ 102 and/or 103, include, but are expressly not limited to, one or more (or a combination of one or more) of the references and/or products set forth, and discussed, in Hetero's Notice Letter. Such references and products include, but are not limited to: 2017 European Medicines Agency (EMEA) label for Fotivda; Brian I. Rini et al., Meeting Abstract: 2017 ASCO Annual Meeting, *Tivo-3: A phase 3, randomized, controlled, multi-center, open-label study to compare tivozanib hydrochloride to sorafenib in subjects with refractory advanced renal cell carcinoma (RCC)*, J. CLINICAL ONCOLOGY, Vol. 35, Issue 15, Suppl. (May 30, 2017); Brian I. Rini et al., poster entitled: *TIVO-3: A phase 3, randomized, controlled, multi-center, open-label study to compare tivozanib hydrochloride to sorafenib in patients with refractory advanced renal cell carcinoma (RCC)*, presented at the ASCO Annual Meeting, June 2-6, 2017,

Chicago, IL, USA; European Medicines Agency, Public Assessment Report for Fotivda (published June 22, 2017).

28. Hetero is entitled to a declaration that the claims of the '365 patent are invalid for failure to satisfy one or more of the conditions for patentability in Title 35 of the United States Code, and/or for obviousness-type double patenting.

PRAYER FOR RELIEF

WHEREFORE, Hetero respectfully requests that this Court enter a Judgment and Order in its favor and against Plaintiff/Counterclaim-Defendant as follows:

(a) Declaring that the manufacture, sale, offer for sale, use, or importation of Hetero Unit-V's ANDA Products do not and will not infringe (either literally or under the doctrine of equivalents), directly or indirectly (either by inducement or contributorily), any valid and enforceable claim of the '365 patent;

(b) Declaring that the claims of the '365 patent are invalid;

(c) Ordering that Plaintiff's Complaint be dismissed with prejudice and judgment entered in favor of Hetero;

(d) Declaring that this is an exceptional case under 35 U.S.C. § 285 and awarding Hetero its attorneys' fees, costs, and expenses in this action; and

(e) Awarding Hetero any further and additional relief as the Court deems just and proper.

DEMAND FOR JURY TRIAL

Hetero hereby demands a jury trial on all issues so triable.

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Dated: August 12, 2025

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