Alymsys®
(bevacizumab-maly)

Proven Similarity with Avastin®[1,2]

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Alymsys® Meets All FDA Requirements for Similarity[1-3]

Alymsys® **is similar** to Avastin® based on a totality of evidence, with **no clinically meaningful differences in efficacy, safety, and immunogenicity** compared with Avastin®.[1,2,4-7]

Requirements for Biosimilar Approval[8]

Reference Product (RP), Avastin®[9,10]	Alymsys®[1,2,4-7]
✓ Full CMC package	✓ Full CMC package + In vitro similarity
✓ Pharmacological assessment	✓ Pharmacological comparability in healthy volunteers
✓ Clinical studies:	✓ Comparative clinical studies:
✓ Efficacy	✓ Efficacy
✓ Safety	✓ Safety
✓ Immunogenicity	✓ Immunogenicity
✓ Risk management plan	✓ Risk management plan

CMC = Chemistry Manufacturing and Control

Alymsys® robust evidence proved similarity with Avastin®[1,2,4-7]

Alymsys® similarity program, including comparative clinical studies, was designed based on EMA and FDA guidance[2-8,12]

Alymsys® (bevacizumab-maly)

RP = Reference Product; PD = pharmacodynamic; PK = pharmacokinetic; EMA: European Medicines Agency; FDA: United States Food and Drug Administration

Alymsys® Robust Evidence[1,2,4-7]

Multiple *in vitro* analytical similarity studies[1] using state-of-the-art orthogonal analytical methods demonstrated similarity between Alymsys® and Avastin® in key features such as: primary structure, molecular conformation, glycosylation, charge variants, protein content, purity and biological activity.[1]

Comparative stability studies between Alymsys® and Avastin® under accelerated and forced degradation conditions have demonstrated similar behavior and degradation pathways for the two products.[1]

Alymsys® clinical comparability includes data from more than 1000 subjects evaluated in different clinical trials:[2,4-7]

1. Strong comparability PK package in HV clinical trials: In Caucasian and Japanese populations showed the PK similarity of both products.[5,6]

- Statistical analysis of the PK parameters demonstrated similarity between Alymsys® and Avastin® (EU + US).[5]
- Alymsys® was generally well tolerated by healthy subjects and the safety and immunogenicity profile of Alymsys® and Avastin® (EU + US) was determined to be similar.[5]

2. Comparative clinical trial in a relevant and approved indication:[2,4,7]

- A randomized clinical comparability phase III study, the Stella study was conducted in the Non Squamous non-small Cell Lung Cancer (NSCLC).[2,4]
  - The Stella study, confirmed the clinical similarity in terms of efficacy, safety and immunogenicity of Alymsys® and Avastin®, supporting the clinical safety and efficacy of Alymsys® treatment. Alymsys® was well tolerated with manageable adverse events (AEs) in patients with stage IIIB/IV NSCLC.[2,4]

- A supportive comparative clinical trial conducted in Metastatic Colorectal Cancer (mCRC).[7]
  - Has shown similar safety results in both Alymsys® and Avastin® groups, with no relevant differences in the nature, severity, or frequency of AEs.[2,7]

Analytical, preclinical and clinical studies have demonstrated Alymsys® is similar to Avastin®[1,2,4-7]

Alymsys® ~ Avastin®

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The FDA has Approved Alymsys® for Many Avastin® Indications Through Extrapolation[7,10,13]

Extrapolation for the biosimilar is supported by **similarity analyses. It is the extension of the efficacy and safety data** from a therapeutic indication for which the biosimilar has been tested to another indication approved for the Reference Product (RP)[8]. There is over **10 years experience** in the use of approved biosimilars for extrapolated indications in Europe[8] and more than **5 years** in the United States.

Alymsys® (bevacizumab-maly) has been approved by the FDA based on the totality of evidence and scientific justification for the extrapolation.[2,8]

Alymsys® Dosage and Administration* [10,13]

Indication	Dosage (per kilogram of body weight)
Metastatic Colorectal Cancer (mCRC) in combination with fluorouracil-based chemotherapy for first line treatment, and in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy for second-line treatment.	5 mg/kg or 10 mg/kg every 2 weeks. 5 mg/kg every 2 weeks or 7.5 mg/kg once every 3 weeks.
First-Line Non-Squamous Non-small Cell Lung Cancer (NSCLC) in combination with carboplatin and paclitaxel.	15 mg/kg every 3 weeks.
Recurrent Glioblastoma (GBM)	10 mg/kg every 2 weeks.
Metastatic Renal Cell Cancer (mRCC) in combination with interferon.	10 mg/kg every 2 weeks.
Persistent, Recurrent, or Metastatic Cervical Cancer in combination with paclitaxel and cisplatin or paclitaxel and topotecan.	15 mg/kg every 3 weeks.
Platinum-resistant Recurrent Epithelial Ovarian, Fallopian tube, or Primary Peritoneal Cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan.	10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks.

Limitations of Use:

Alymsys is not indicated for adjuvant treatment of colon cancer.

Important Administration Information

Withhold for at least 28 days prior to elective surgery. Do not administer Alymsys® until at least 28 days following major surgery and until adequate wound healing.[12]

Alymsys® (bevacizumab-maly)

This is an abbreviated summary of the approved indications.
Regarding patent restriction, please see Alymsys® full Prescribing Information.


Alymsys® is the unique biosimilar to Avastin® with 2 clinical studies with safety results in 2 of the indications[2,4,7]
Please see accompanying full Prescribing Information.
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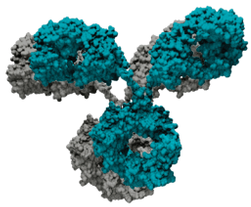
Proven Similarity with Avastin® [1,2]



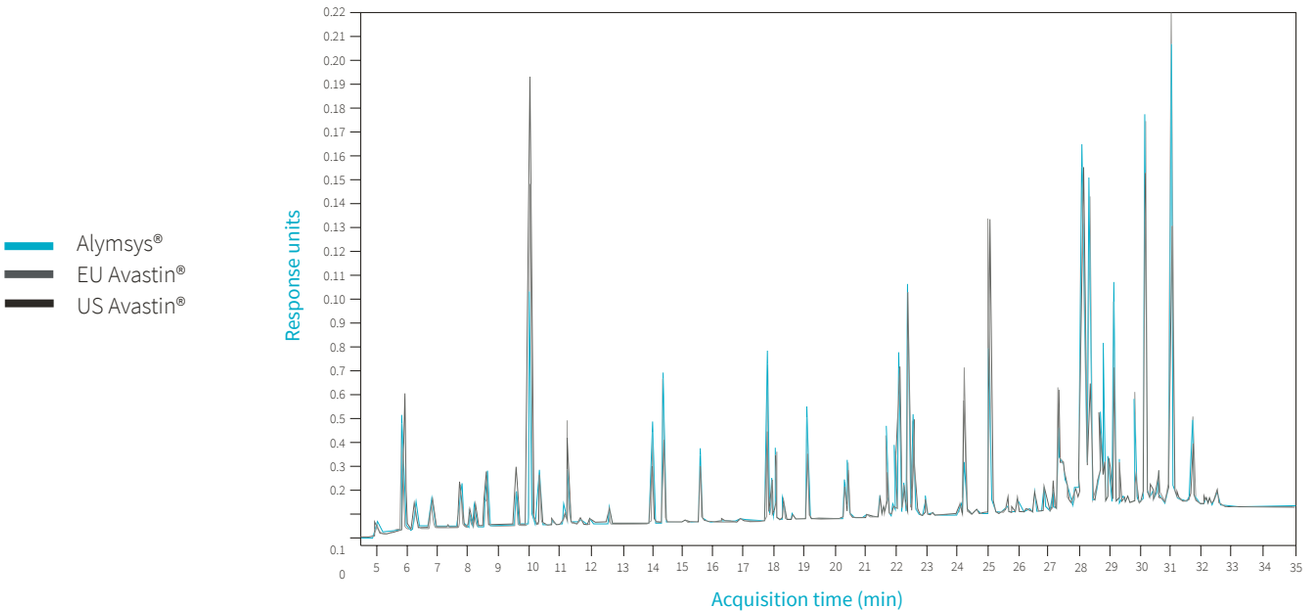
Alymsys® is a biosimilar to bevacizumab which has been developed in comparison with Avastin® as the Reference Product (RP).[1,2]

Over 50 analytical methods were applied to evaluate > 90 quality attributes and confirm analytical similarity between Alymsys® and Avastin®:[1,2]

Primary Structure

The same amino acid composition is confirmed in Alymsys® and Avastin®.[1,2]

Reduced peptide mapping



Molecular Conformation

Similarity of Alymsys® and Avastin® in terms of molecular conformation was demonstrated.[1,2]

Glycosylation Profile

Similar glycoforms profile with the same main glycoforms. Few minor quantitative differences were shown to be not clinically meaningful based on bevacizumab mechanism of action which doesn't involve Fc-related activity.[1,2]

Charge Variants

The post-translational modification analyses demonstrated a similar relative content of acidic and basic forms between both proteins.[1,2]

Protein Content and Purity

Similar protein content and high purity of Alymsys® and Avastin® with slightly less aggregates in Alymsys.®[1,2]

Comparative Stability

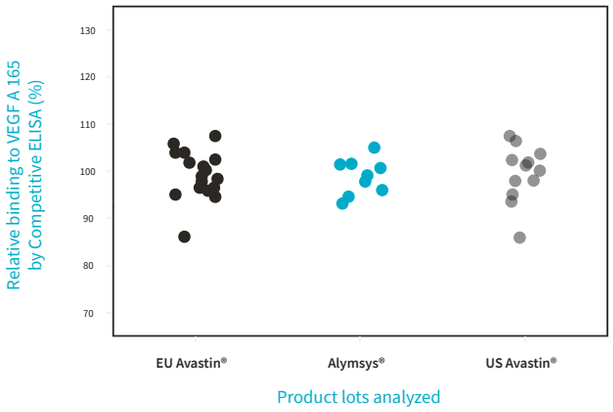
Comparative accelerated and forced degradation studies have shown a similar behavior and degradation profile of Alymsys® and Avastin.®[1,2]

Alymsys®
(bevacizumab-maly)

Biological Activity

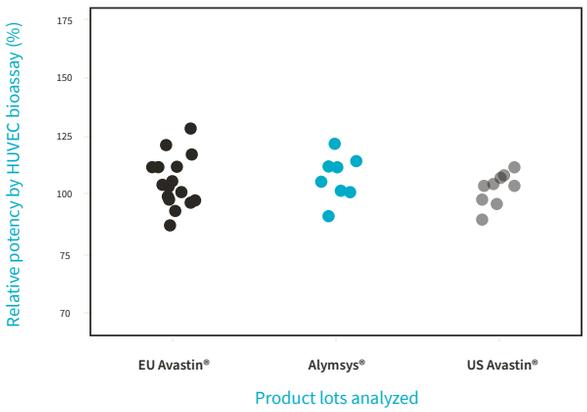
Multiple state-of-the-art orthogonal methods demonstrated the similarity of Alymsys® to its RP Avastin® regarding biological activity; highly similar binding of Alymsys® and Avastin® to VEGF 165 and other main VEGF A variants is shown. Several bioassays confirmed similar VEGF neutralization activity of the 2 molecules[1,2]. Similar binding of Alymsys® and Avastin® to FcRn is predictive of the similar PK.[1,2]

Figure 1[1]



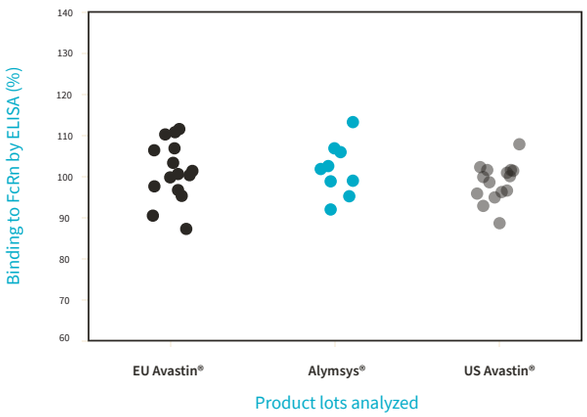
Similar binding to VEGF A 165 (figure 1), the main VEGF A variant as well as other variants (121, 189, 206) was demonstrated for Alymsys® and Avastin®.[1,2]

Figure 2[1]



A cell-based antiproliferation bioassay using human umbilical vein endothelial cells (HUVEC) as a model showed similar potency for Alymsys® and the RP (figure 2).[1,2]

Figure 3[1]



Binding to FcRn*, which is indicative of monoclonal antibodies PK, was similar for Alymsys® and the RP (figure 3).[1,2]

Please see accompanying full Prescribing Information.

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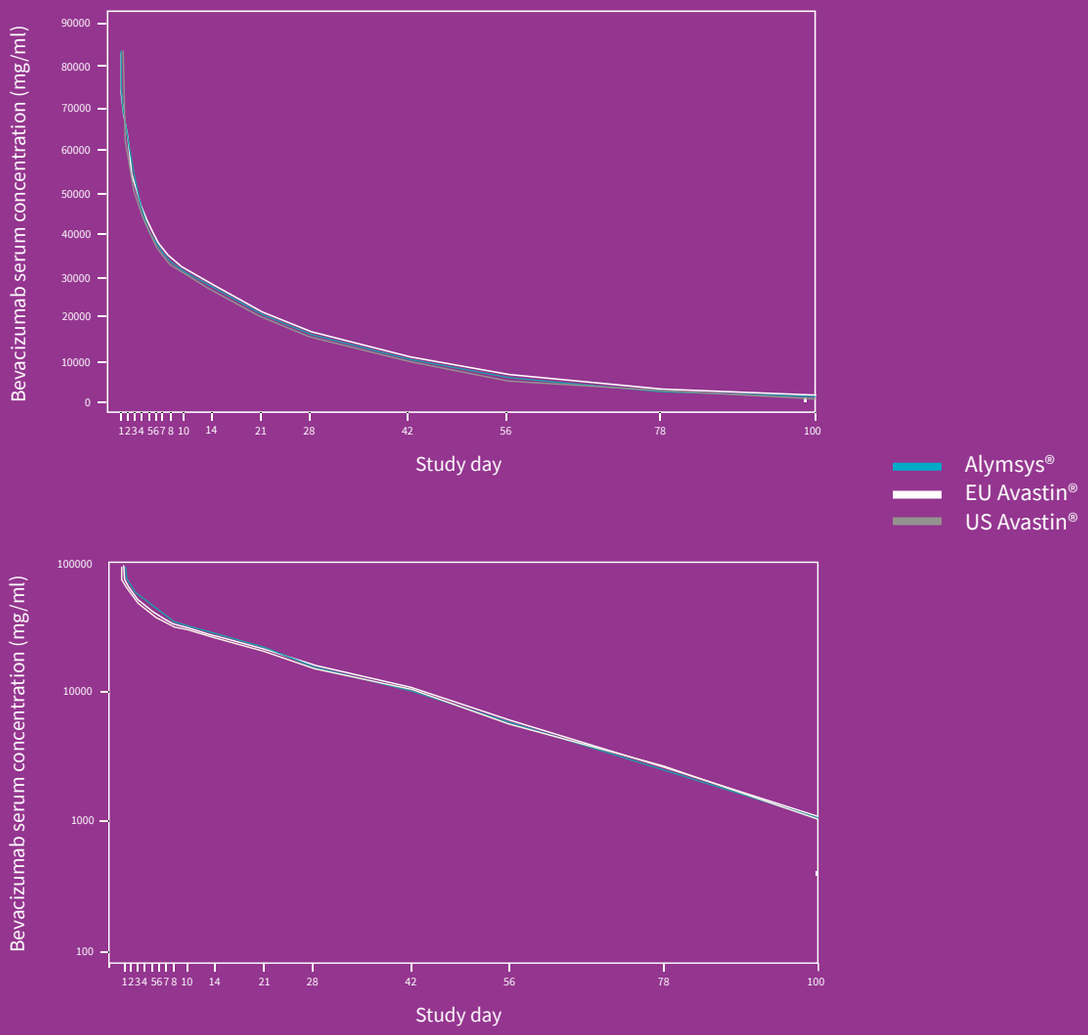
Pharmacokinetics Demonstrate Bioequivalence to Avastin® [2-4]

A phase I, double-blind, randomized, parallel-group, single dose 3-treatment arms healthy male volunteers study was conducted to investigate and compare the PK profiles of Alymsys® and Avastin® (EU + US) and confirmed bioequivalence among the 3 treatments:[2,5]



Serum concentration profiles of bevacizumab (across all days). Pharmacokinetic population.[5]

It is statistically confirmed that comparisons of Alymsys® versus Avastin® (EU + US) were similar for the primary parameters AUC (0-∞) and Cmax, as the 90% CI were fully contained within the pre-defined bioequivalence limits of 0.80 - 1.25.[2,5]

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Please see accompanying full Prescribing Information.

Stella Study Design[4]

Key Eligibility Criteria

- Newly diagnosed or recurrent stage IIIb/IV non-squamous NSCLC
- Patients must have at least 1 measurable lesion per RECIST
- ECOG/PS ≤ 1 at screening

Randomize

Alymsys® Combo (n=300)

Alymsys®:
15 mg/kg IV on D1 q3w until week 18

Paclitaxel:
200 mg/m², IV over 3h on D1 until wk18

Carboplatin:
AUC6 IV infusion over 15-60 min on D1 until wk18

Avastin® Combo (n=300)

Avastin®:
15 mg/kg IV on D1 q3w until week 18

Paclitaxel:
200 mg/m², IV over 3h on D1 until wk18

Carboplatin:
AUC6 IV infusion over 15-60 min on D1 until wk18

Primary Endpoint

Alymsys® Monotherapy

Alymsys®:
15 mg/kg IV on D1 q3w until PD/Week 52

Avastin® Monotherapy

Avastin®:
15 mg/kg IV on D1 q3w until PD/Week 52

Treatment duration: 18 weeks

Up to week 52/PD from first dose

Primary Endpoint

- ORR (Week 18)

Secondary Endpoints

- PFS (Weeks 18 & 52)
- OS (Weeks 18 & 52)
- DOR, OT and TOR
- Safety profile
- Immunogenicity

Stratification Factors

- Gender (male/female)
- Smoking status (smoker/non-smoker)
- Disease diagnosis (newly diagnosed/recurrent disease)
- Stage of disease (IIIB/IV)

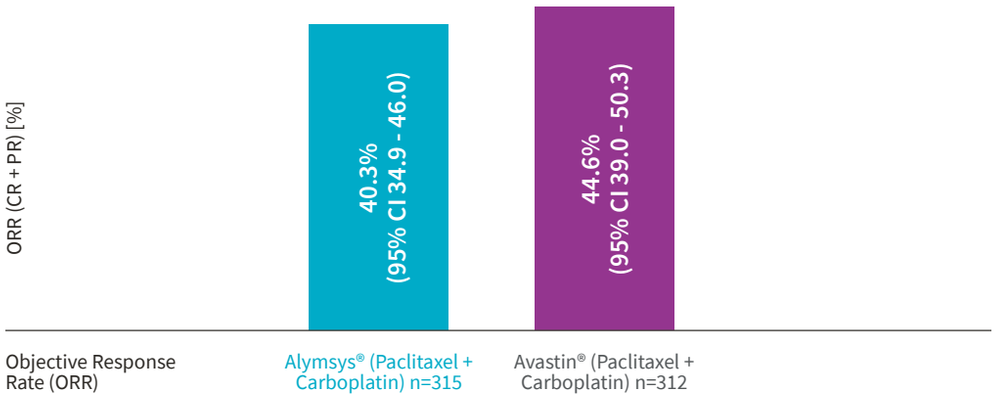
Abbreviations: AUC, Area Under the time-concentration Curve; D1, Day 1; eco, Eastern Cooperative Oncology Group; FD, first dose; IV, intravenous; h, hour; min, minutes; NSCLC, non-small cell lung cancer; OS, Overall Survival; PD, Progressive Disease; PFS, Progression-Free Survival; PS, Performance Status; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; wk, week. DOR, Duration of Response; OT, Observation Time; TOR, Time to Overall Response. ORR, Objective Response Rate.

Similar Efficacy Showed with Avastin® [2-4]

Stella - A randomized, multicenter, multinational, double-blind study in combination with carboplatin and paclitaxel for the treatment of subjects with stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC) was conducted to assess the efficacy and safety of Alymsys® versus Avastin®.[4]

The primary objective was achieved for the clinical similarity of Alymsys® versus Avastin® at week 18 and confirmed at week 52. **The Objective Response Rate (ORR)** to measure the clinical efficacy was comparable and demonstrated in both arms:[4]

ORR at Week 18 (ITT Population)[4]



ORR = Objective Response Rate; CR = Complete Response; PR = Partial Response; CI = Confidence Interval; ITT = Intention-To-Treat

In addition to Key efficacy results for the Stella study, further sensitive secondary endpoints to detect differences in the clinical setting base were included, such as Progression Free Survival (PFS) and Overall Survival (OS) supporting the similarity between the 2 treatment groups.[2,4]

Warnings and Precautions

Alymsys® Important Safety Information includes warnings and precautions on severe and fatal hemorrhage; arterial and venous thromboembolic events; hypertension, hypertensive crisis, and hypertensive encephalopathy; renal injury, proteinuria, and nephrotic syndrome; posterior reversible encephalopathy syndrome; embryo-fetal toxicity; ovarian failure; congestive heart failure; gastrointestinal perforations and fistula; surgery and wound healing complications, and infusion-related reactions.

Please see accompanying full Prescribing Information →

Alymsys® (bevacizumab-maly)

Similar Safety and Immunogenicity to Avastin® Demonstrated[2,4-7]

- Alymsys® demonstrated similar safety and immunogenicity to Avastin.®[2,4-7]
- There were no new or unexpected safety signals for Alymsys® compared with Avastin.®[2,4-7]

Summary of Global Adverse Events of Special Interest (AESI) Grade 3 - 4[4]

Adverse events of interest grade	Alymsys® (n=311)	Avastin® (n= 310)
At least 1 AESI Grade 3 - 4	**49 (15.8)**	**55 (17.7)**
Neutropenia	16 (5.1)	21 (6.8)
Hypertension	7 (2.3)	7 (2.3)
Deep vein thrombosis	1 (0.3)	1 (0.3)
Embolism	2 (0.6)	0
Pulmonary haemorrhage	0	0
Pulmonary embolism	6 (1.9)	3 (1.0)
Haemoptysis	0	1 (0.3)
Epistaxis	0	1 (0.3)
Proteinuria	1 (0.3)	4 (1.3)
Diverticular perforation	0	1 (0.3)
Intestinal perforation	1 (0.3)	0
Gastric ulcer perforation	0	1 (0.3)
Left ventricular dysfunction	1 (0.3)	0
Myocardial infraction	0	1 (0.3)
Ischaemic stroke	0	1 (0.3)
Purpura	1 (0.3)	0
Infusion related reaction	0	0

- The immunogenicity data showed a comparable incidence between treatment groups supporting the similarity between Alymsys® and Avastin®, with no apparent impact on evaluated efficacy or safety concern.[2,4-6]
- Subjects with ADAs positive were not associated with serious infusion-related reactions or anaphylactic reactions.[2,4-6]

Over 60,000 patients have been treated with Alymsys® with no new findings related to safety found from post-marketing and clinical development phase data.[13]**

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**Based on the available data up to April 2022 in approved countries. PSUR data. ADA= Anti Drug Antibody.

Alymsys® Product Characteristics[13]

Alymsys® 25 mg/mL concentrate for solution for infusion is available in the same pack sizes as Avastin®.[13]

Extended shelf life up to 30 months of Alymsys® vs 24 months of Avastin.® [2,13] *

In-use stability of diluted solutions of Alymsys® has been demonstrated up to 12 hours when stored at 2°C to 8°C (36°F to 46°F), versus 8 hours reported for diluted Avastin® solutions.[13]

Unit of Sale NDC	Inner NDC	Dosage Strength	Pack Size
70121-1754-1	70121-1754-1	100 mg/4 mL (25 mg/mL)	1 Vial
70121-1754-7	70121-1754-1	100 mg/4 mL (25 mg/mL)	10 Vials
70121-1755-1	70121-1755-1	400 mg/16 mL (25 mg/mL)	1 Vial
70121-1755-7	70121-1755-1	400 mg/16 mL (25 mg/mL)	10 Vials
HCPCS Code	**Descriptor**		
C9142	Injection, bevacizumab-maly, biosimilar, (ALYMSYS), 10 mg (effective 10/1-12/31/2022)		

Amneal PATHways® Patient Support Program offering services such as:

- Benefits investigation
- Prior authorization support
- Affordability options
- Claims assistance

Amneal PATHways® Patient Access To Health

*Last revision: July 2022.

References:

1. Ruppen I, Beydon ME, Solís C, Sacristán D, et al. Similarity demonstrated between isolated charge variants of MB02, a biosimilar of bevacizumab, and Avastin® following extended physicochemical and functional characterization. Biologicals. 2021 Sep;73:41-56. doi: 10.1016/j.biologicals.2021.09.001
2. FDA Summary Basis of Approval of Alymsys (SBoA). April 2022. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761231Orig1s000TOC.cfm.
3. Food and Drug Administration, FDA. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry, 2015.
4. Trukhin D, Poddubskaya E, Andric Z, et al.. Efficacy, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar) versus Reference Bevacizumab in Advanced Non-Small Cell Lung Cancer: A Randomized, Double-Blind, Phase III Study (STELLA). BioDrugs. 2021 Jul;35(4):429-444. doi: 10.1007/s40259-021-00483-w
5. Sinn, A, García-Alvarado, F, Gonzalez, V, Huerga, C, Bullo, F. A randomized, double blind, single dose, comparative study of the pharmacokinetics, safety and immunogenicity of MB02 (bevacizumab biosimilar) and reference bevacizumab in healthy male volunteers. Br J Clin Pharmacol. 2022; 88(3): 1063- 1073. doi:10.1111/bcp.15032
6. Eto T, Karasuyama Y, González V, Del Campo García A. A randomized, single-dose, pharmacokinetic equivalence study comparing MB02 (proposed biosimilar) and reference bevacizumab in healthy Japanese male volunteers. Cancer Chemother Pharmacol. 2021;88(4):713-722. doi:10.1007/s00280-021-04324-z
7. Romera, A. et al. Bevacizumab biosimilar BEVZ92 versus reference bevacizumab in combination with FOLFOX or FOLFIRI as first-line treatment for metastatic colorectal cancer: a multicentre, open-label, randomised controlled trial. The Lancet Gastroenterology and Hepatology, volume 3, issue 12. 2018.
8. Biosimilars in the EU. Information guide for healthcare professionals. Prepared jointly by the European Medicines Agency and the European Commission. 2019.
9. Avastin® SBoA (FDA) and EPAR (EMA) – Scientific Discussion.
10. Avastin® full Prescribing Information
11. CDER/CBER, May 2019. Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations; Draft Guidance for Industry.
12. Alymsys® full Prescribing Information.
13. Periodic Safety Update Report (PSUR) For Alymsys® (Bevacizumab-maly), 22 April 2022

See accompanying full prescribing information.

Alymsys® (bevacizumab-maly)

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