

Claims

1. An isolated antibody, or an antigen binding fragment thereof, that binds to the antigenic loop region of HBsAg and neutralizes infection with hepatitis B virus and hepatitis delta virus.
2. The antibody according to claim 1, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment promotes clearance of HBsAg and HBV.
3. The antibody according to claim 1 or 2, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment comprises an Fc moiety.
4. The antibody according to any of claims 1 – 3, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to at least 6, preferably to at least 8, more preferably to all 10 of the HBsAg genotypes A, B, C, D, E, F, G, H, I, and J.
5. The antibody according to any of claims 1 – 4, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to at least 12, preferably to at least 15, more preferably to all 18 of the HBsAg mutants having mutations in the antigenic loop region: HBsAg Y100C/P120T, HBsAg P120T, HBsAg P120T/S143L, HBsAg C121S, HBsAg R122D, HBsAg R122I, HBsAg T123N, HBsAg Q129H, HBsAg Q129L, HBsAg M133H, HBsAg M133L, HBsAg M133T, HBsAg K141E, HBsAg P142S, HBsAg S143K, HBsAg D144A, HBsAg G145R and HBsAg N146A.
6. The antibody according to any of claims 1 – 5, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an epitope comprising at least one, preferably at least two, more preferably at least three, even more preferably at least four amino acids of the antigenic loop region of HBsAg, wherein the at least one, preferably the at least two, more preferably the at least three, even more preferably the at least four amino acids are selected from amino acids 115 – 133 of the S domain of HBsAg, preferably from amino acids 120 – 133 of the S domain of HBsAg, more preferably from amino acids 120 – 130 of the S domain of HBsAg.
7. The antibody according to claim 6, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an epitope comprising at least two, preferably at least three, more preferably at least four amino acids of the antigenic loop

region of HBsAg, wherein the at least two, preferably the at least three, more preferably the at least four amino acids are selected from amino acids 120 – 133, preferably from amino acids 120 – 130, of the S domain of HBsAg and wherein the at least two, preferably the at least three, more preferably the at least four amino acids are located in adjacent positions.

8. The antibody according to claim 6 or 7, or an antigen binding fragment thereof, wherein the epitope is a conformational epitope.
9. The antibody according to any of claims 6 – 8, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an epitope comprising at least two, preferably at least three, more preferably at least four amino acids of the antigenic loop region of HBsAg, wherein the at least two, preferably the at least three, more preferably the at least four amino acids are selected from amino acids 120 – 133, preferably from amino acids 120 – 130, of the S domain of HBsAg and wherein at least two, preferably at least three, of the at least two, preferably the at least three, more preferably the at least four amino acids are not located in adjacent positions.
10. The antibody according to claim 9, or an antigen binding fragment thereof, wherein at least one, preferably at least two, more preferably at least three, even more preferably at least four, most preferably at least five amino acids are located between the at least two, preferably at least three, amino acids, which are comprised by the epitope and which are not located in adjacent positions.
11. The antibody according to any of claims 6 – 10, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an epitope comprising at least amino acids P120, C121, R122 and C124 of the S domain of HBsAg.
12. The antibody according to any of claims 6 – 11, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an epitope comprising an amino acid sequence according to SEQ ID NO: 88:
PCRXC

wherein X is any amino acid or no amino acid; preferably X is any amino acid; more preferably X is T, Y, R, S, or F; even more preferably X is T, Y or R; most preferably X is T or R.

13. The antibody according to any of claims 6 – 12, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an epitope comprising an amino acid sequence according to SEQ ID NO: 80:
TGPCRTC
or an amino acid sequence sharing at least 80%, preferably at least 90%, more preferably at least 95% sequence identity with SEQ ID NO: 80.
14. The antibody according to any of claims 6 – 13, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an epitope comprising an amino acid sequence according to SEQ ID NO: 85:
STTSTGPCRTC
or an amino acid sequence sharing at least 80%, preferably at least 90%, more preferably at least 95% sequence identity with SEQ ID NO: 85.
15. The antibody according to any of claims 6 – 14, or an antigen binding fragment thereof, wherein the epitope further comprises an amino acid sequence comprising at least amino acids 145 – 151 of the S domain of HBsAg (SEQ ID NO: 81).
16. The antibody according to any of claims 6 – 15, or an antigen binding fragment thereof, wherein the epitope comprises an amino acid sequence according to SEQ ID NO: 80 and an amino acid sequence according to SEQ ID NO: 81.
17. The antibody according to any of claims 6 – 16, or an antigen binding fragment thereof, wherein the epitope comprises an amino acid sequence according to SEQ ID NO: 85 and an amino acid sequence according to SEQ ID NO: 87.
18. The antibody according to any of the previous claims, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an epitope in the antigenic loop of HBsAg formed by an amino acid sequence according to SEQ ID NO: 1:
X₁ X₂ X₃ TC X₄ X₅ X₆A X₇G

wherein X₁, X₂, X₃, X₄, X₅, X₆ and X₇ may be any amino acid.

19. The antibody according to claim 18, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an epitope in the antigenic loop of HBsAg formed by an amino acid sequence according to SEQ ID NO: 2:

X₁ X₂ X₃ TC X₄ X₅ X₆A X₇G

wherein

X ₁	is P, T or S,
X ₂	is C or S,
X ₃	is R, K, D or I,
X ₄	is M or T,
X ₅	is T, A or I,
X ₆	is T, P or L, and
X ₇	is Q, H or L.

20. The antibody according to claim 19, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to an antigenic loop region of the S domain of HBsAg having an amino acid sequence selected from SEQ ID NO's 5 – 33 or to a sequence variant thereof.
21. The antibody according to any of the previous claims, or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment is a monoclonal antibody or monoclonal antigen binding fragment thereof and/or a human antibody or human antigen binding fragment thereof.
22. The antibody according to any of the previous claims, or an antigen binding fragment thereof, characterized in that the antibody, or the antigen binding fragment thereof, is of the IgG type, preferably of the IgG1 type.
23. The antibody, or the antigen binding fragment thereof, according to any of claims 1 - 22, characterized in that the antibody or the antigen binding fragment comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with each of SEQ ID NOs: 34 – 38 and 40, respectively; or (ii) sharing at least

80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with each of SEQ ID NOs: 34 – 37, 39 and 40, respectively; or (iii) sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with each of SEQ ID NOs: 34 – 38 and 58, respectively; or (iv) sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with each of SEQ ID NOs: 34 – 37, 39 and 58, respectively; or (v) sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with each of SEQ ID NOs: 34, 66, 36 – 38, and 40, respectively; or (vi) sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with each of SEQ ID NOs: 34, 66, 36 – 37, 39, and 40, respectively; or (vii) sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with each of SEQ ID NOs: 34, 66, 36 – 38, and 58, respectively; or (viii) sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with each of SEQ ID NOs: 34, 66, 36 – 37, 39, and 58, respectively.

24. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 22, characterized in that the antibody or the antigen binding fragment comprises CDRH1, CDRH2, and CDRH3 amino acid sequences and CDRL1, CDRL2, and CDRL3 amino acid sequences (i) according to SEQ ID NOs: 34 – 38 and 40, respectively; or (ii) according to SEQ ID NOs: 34 – 37, 39 and 40, respectively; or (iii) according to SEQ ID NOs: 34 – 38 and 58, respectively; or (iv) according to SEQ ID NOs: 34 – 37, 39 and 58, respectively; or (v) according to SEQ ID NOs: 34, 66, 36 – 38, and 40, respectively; or (vi) according to SEQ ID NOs: 34, 66, 36 – 37, 39, and 40, respectively; or (vii) according to SEQ ID NOs: 34, 66, 36 – 38, and 58, respectively; or (viii) according to SEQ ID NOs: 34, 66, 36 – 37, 39, and 58, respectively.
25. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 24, characterized in that the antibody or the antigen binding fragment comprises (i) a heavy

chain variable region (VH) amino acid sequence sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with SEQ ID NO: 41 or 67; and (ii) a light chain variable region (VL) amino acid sequence sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with SEQ ID NO: 42, 59 or 65.

26. The antibody, or the antigen binding fragment thereof, according to any of claims 1 – 25, characterized in that the antibody or the antigen binding fragment comprises a heavy chain variable region (VH) amino acid sequence according to SEQ ID NO: 41 or 67 and a light chain variable region (VL) amino acid sequence according to SEQ ID NO: 42, 59 or 67.
27. The antibody, or the antigen binding fragment thereof, according to any of the previous claims, characterized in that the antibody, or the antigen binding fragment thereof, is a purified antibody, a single chain antibody, Fab, Fab', F(ab')₂, Fv or scFv.
28. The antibody, or the antigen binding fragment thereof, according to any of the previous claims, for use as a medicament.
29. A nucleic acid molecule comprising a polynucleotide encoding the antibody, or the antigen binding fragment thereof, according to any of the previous claims.
30. The nucleic acid molecule according to claim 29, wherein the polynucleotide sequence comprises or consists of a nucleic acid sequence sharing at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95% and particularly preferably at least 98% or 99% sequence identity with any of SEQ ID NOs: 43 – 51, 60 – 64 and 68 – 78.
31. The nucleic acid molecule according to claim 29 or 30, wherein the polynucleotide sequence comprises or consists of a nucleic acid sequence according to any one of SEQ ID NOs: 43 – 51, 60 – 64 and 68 – 78.
32. A vector comprising the nucleic acid molecule according to any of claims 29 – 31.

33. A cell expressing the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 27; or comprising the vector according to claim 32.
34. A pharmaceutical composition comprising the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 27, the nucleic acid according to claims 29 – 31, the vector according to claim 32 and/or the cell according to claim 33.
35. The pharmaceutical composition according to claim 34 comprising a pharmaceutically acceptable excipient, diluent or carrier.
36. Use of the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 27, the nucleic acid according to claims 29 – 31, the vector according to claim 32, the cell according to claim 33 or the pharmaceutical composition according to claim 34 or 35 in the manufacture of a medicament for the prophylaxis, treatment or attenuation of hepatitis B and/or hepatitis D.
37. The use according to claim 36, wherein the medicament is to be used for the treatment or attenuation of chronic hepatitis B.
38. The use according to claim 36, wherein the medicament is to be used for the prevention of hepatitis B (re-)infection after liver transplantation in particular for hepatitis B induced liver failure.
39. The use according to claim 36, wherein the medicament is to be used for the prevention/prophylaxis of hepatitis B in non-immunized subjects.
40. The use according to claim 36, wherein the medicament is to be used for the prophylaxis of hepatitis B in haemodialysed patients.
41. The use according to claim 36, wherein the medicament is to be used for the prevention of hepatitis B in the newborn.

- 42. The use according to claim 36, wherein the medicament is to be used for the treatment or attenuation of hepatitis D, preferably of hepatitis B and hepatitis D.
- 43. The use according to claim 36 or 37, wherein the medicament is to be administered in combination with a polymerase inhibitor, an interferon and/or a checkpoint inhibitor.
- 44. The use according to claim 43, wherein the polymerase inhibitor is lamivudine.
- 45. A combination of
 - (i) the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 27, the nucleic acid according to claims 29 – 31, the vector according to claim 32, the cell according to claim 33 or the pharmaceutical composition according to claim 34 or 35; and
 - (ii) a polymerase inhibitor, an interferon and/or a checkpoint inhibitor.
- 46. Use of the combination of claim 45 in the manufacture of a medicament for the prophylaxis, treatment or attenuation of hepatitis B and/or hepatitis D, in particular for the treatment or attenuation of chronic hepatitis B and/or chronic hepatitis D.
- 47. The use according to claim 46, wherein the combination is to be used in HBV mono-infected patients or in HBV/HDV co-infected patients.
- 48. The combination according to claim 45 or the use according to claim 46 or 47, wherein the combination accelerates HBsAg clearance.
- 49. A kit comprising
 - (i) the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 27, the nucleic acid according to claims 29 – 31, the vector according to claim 32, the cell according to claim 33 or the pharmaceutical composition according to claim 34 or 35; and
 - (ii) a polymerase inhibitor, an interferon and/or a checkpoint inhibitor.
- 50. Use of the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 27, the nucleic acid according to claims 29 – 31, the vector according to claim 32, the

cell according to claim 33 or the pharmaceutical composition according to claim 34 or 35 for monitoring the quality of anti-hepatitis-B or anti-hepatitis-D vaccines by checking that the antigen of said vaccine contains the specific epitope in the correct conformation.

51. Use of the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 27, the nucleic acid according to claims 29 – 31, the vector according to claim 32, the cell according to claim 33 or the pharmaceutical composition according to claim 34 or 35 in diagnosis of hepatitis B and/or hepatitis D.
52. Use of the antibody, or the antigen binding fragment thereof, according to any of claims 1 to 27, the nucleic acid according to claims 29 – 31, the vector according to claim 32, the cell according to claim 33 or the pharmaceutical composition according to claim 34 or 35 in determining whether an isolated blood sample is infected with hepatitis B virus and/or hepatitis delta virus.