ACP 116-5

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Vergaderstuk Adviescommissie Pakket

Datum	3 mei 2024
Betreft	Sluisgeneesmiddel etranacogene dezaparvovec (Hemgenix®)

Onze referentie
ACP 116-5

Contactpersoon	Mevr. M.J.S. de Vries, *Secretaris Wetenschappelijke Adviesraad Commissie Geneesmiddelen (WAR-CG)* (MdeVries@zinl.nl)
Onderwerp	Etranacogene dezaparvovec (Hemgenix®) voor de behandeling van ernstige en matig ernstige hemofilie B (congenitale factor IX-deficiëntie) bij volwassen patiënten zonder voorgeschiedenis van factor IX-remmers.
Type interventie	Geneesmiddel (gentherapie)
Besprekingshistorie en doel van huidige bespreking	☐ Eerste bespreking in de WAR-CG op 4 december 2023 ☐ Klokstop van 3 maanden aangevraagd door de registratiehouder op 12 december 2023 ☐ Tweede bespreking in de WAR-CG op 2 april 2024 ☐ Afronding rapporten wetenschappelijke weging april 2024 ☑ Bespreking ACP op 3 mei 2024: maatschappelijke weging. Doel: formuleren advies aan de RvB over het wel of niet vergoeden van etranacogene dezaparvovec (Hemgenix®)
Standpunt/advies in het kader van	Specialistische geneesmiddelen
Aanleiding	Verzoek van Ministerie van VWS in het kader van de sluisprocedure. Deze beoordeling maakt deel uit van een gezamenlijke evaluatie in het kader van het **Beneluxa Initiatief** project. Het farmacotherapeutische rapport en de budgetimpactanalyse worden zowel door het Zorginstituut en de Belgische commissie voor de vergoeding van geneesmiddelen (*Commission*

Reimbursement of Medicines: CRM) gebruikt. Alle beoordelingsprocedures lopen parallel volgens de nationale wetgeving.

Achtergrond

Indicatie waarvoor vergoeding wordt aangevraagd

Etranacogene dezaparvovec (hierna: ED) is geïndiceerd voor de behandeling van ernstige en matig ernstige hemofilie B (congenitale stollingsfactor IX-deficiëntie) bij volwassen patiënten zonder voorgeschiedenis van stollingsfactor IX-remmers. Er wordt vergoeding aangevraagd voor deze patiënten met een ernstige uiting van de ziekte (waarbij spontane bloedingen voorkomen), en een gelijke waarde geclaimd met (huidige) profylaxebehandeling van stollingsfactor IX-concentraten.

Korte beschrijving ziektebeeld

Hemofilie B is een zeldzame X-chromosoom-gebonden genetische ziekte. Het is een bloedingsstoornis die wordt veroorzaakt door een mutatie in het gen dat codeert voor stollingsfactor IX. Hierdoor wordt minder of geen stollingsfactor IX aangemaakt. Stollingsfactoren zijn essentieel voor een goede stolling van het bloed. Als gevolg van het gedeeltelijk of volledig tekort aan het essentiële stollingsfactor IX wordt de ziekte gekenmerkt door een verhoogde kans op bloedingen.

De ernst van de ziekte bij hemofilie hangt af van de grootte van het tekort aan stollingsfactor IX. De ernst van de ziekte wordt als volgt geclassificeerd en is gebaseerd op de resterende stollingsfactor IX-spiegels in het bloed.

- Ernstige vorm: stollingsfactor IX-spiegels <1% van normaal
- Matige vorm: stollingsfactor IX-spiegels 1-5% van normaal
- Milde vorm: stollingsfactor IX-spiegels >5 en <40% van normaal

De aandoening komt vooral bij mannen voor. Vrouwen zijn doorgaans dragers van de ziekte maar hebben een milde of geen uiting van de ziekte.

Symptomen en ernst

Patiënten met ernstige hemofilie B hebben altijd een ernstige uiting van de ziekte. Dit houdt in dat spontane bloedingen kunnen optreden. Dit zijn bloedingen die optreden zonder specifieke reden, in tegenstelling tot bijvoorbeeld een blauwe plek of bloeduitstorting in de huid na het stoten van deze plek. Patiënten met de milde en matige vorm van hemofilie ervaren zelden spontane bloedingen. Bij hen treden bloedingen vooral op na verwondingen en bij invasieve operaties. Toch kan de uiting van de ziekte verschillen bij patiënten met eenzelfde vorm van hemofilie B, met name bij een milde of matige vorm. Zo heeft een klein deel van de patiënten met een matige vorm van hemofilie een ernstige uiting van de ziekte, waarbij spontane bloedingen voorkomen. Deze vorm worden als 'matig ernstig' beschreven.

Patiënten met de ernstige en matig ernstige vorm van hemofilie B krijgen regelmatig spontane bloedingen, vaak in gewrichten, spieren of zachte weefsels, zonder enige duidelijke oorzaak. Bloedingen in de gewrichten kunnen zorgen voor schade, met pijn, blijvend letsel (hemofiele artropathie, chronische gewrichtsklachten als gevolg van bloedingen) en verminderde mobiliteit tot

gevolg. Dit heeft gevolgen voor de kwaliteit van leven van de patiënt. De schade kan uiteindelijk zo ernstig zijn dat gewrichtsvervanging nodig is. Naast bloedingen in de gewrichten en spieren kunnen in de rest van het lichaam ook bloedingen optreden. Deze kunnen ook levensbedreigend zijn, zoals bloedingen in de hersenen. Bij een milde vorm van hemofilie B zijn spontane bloedingen zeldzaam en vinden ernstige bloedingen met name plaats bij chirurgische ingrepen of zware verwondingen. Sinds de beschikbaarheid van profylactische behandeling met stollingsfactor IX concentraat, is de levensverwachting van patiënten met hemofilie B vrijwel vergelijkbaar met die van de gemiddelde bevolking.[1]

Prevalentie en incidentie
Bij HemoNED (het Nederlandse register van personen met hemofilie en aanverwante aandoeningen) waren er in 2022 in totaal 204 patiënten met hemofilie B geregistreerd in Nederland. Uit de berekeningen van de budgetimpactanalyse (BIA) blijkt dat er op dit moment in Nederland ongeveer 78 volwassen patiënten met ernstige of matig ernstige hemofilie B zijn. Deze worden profylactisch behandeld met stollingsfactor IX-concentraten. De incidentie is geschat op 2 patiënten.

Huidige behandeling en plaatsbepaling
De huidige behandeling van patiënten met ernstige of matig ernstige hemofilie B bestaat uit het (intraveneus) toedienen van stollingsfactor IX-concentraten. Deze worden fabrieksmatig bereid via DNA-recombinanttechniek of kunnen gemaakt worden uit het plasma van bloeddonoren. Na het toedienen van stollingsfactor IX-concentraten worden de stollingsfactor IX-bloedspiegels hersteld. Hierdoor kan de bloedstolling op een normale wijze plaatsvinden zodat spontane en langdurige bloedingen voorkomen worden.

Behandeling met stollingsfactor IX-concentraten kan bestaan uit profylaxe (uit voorzorg) en/of acute behandeling bij bloedingen (*on demand*). De Nederlandse beroepsgroep behandelt patiënten met profylaxe op basis van de ernst van de uiting van de ziekte, ofwel hoeveel een patiënt (spontaan) bloedt, en niet op de stollingsfactor IX-spiegels. Profylaxe is de standaardbehandeling voor mensen met een ernstige of matig ernstige vorm van hemofilie B. Deze patiënten worden behandeld door stollingsfactor IX-concentraten levenslang toe te dienen om de bloedspiegels normaal te houden. De patiënt dient de stollingsfactor IX-concentraten zelf toe via een infuus. Bij het optreden van een bloeding ondanks profylactische behandeling kan er ook nog '*on demand'* behandeld worden.

In eerste instantie bestond profylaxe alleen uit kortwerkende (*standard half life* (SHL)) stollingsfactor IX-concentraten die enkele keren per week toegediend moesten worden. Later zijn langwerkende (*extended half life* (EHL)) stollingsfactor IX-concentraten op de markt gekomen. Deze werken langer waardoor maar een keer per week of twee weken toediening nodig is. Om deze laatste reden hebben EHL stollingsfactor IX-concentraten de voorkeur bij profylaxe.

De Nederlandse beroepsgroep ziet plaats voor behandeling met ED voor patiënten die op dit moment behandeld worden met profylaxe. Volgens de beroepsgroep zal niet iedere patiënt over willen gaan op behandeling met ED omdat een deel van de patiënten afwachtend is naar meer langetermijn bewijs bij een gentherapie. Ook heeft een deel van de patiënten die enthousiast waren over de behandeling de behandeling, door bijvoorbeeld de eenmalige toediening t.o.v. de chronische

intraveneuze toedieningen bij hun huidige behandeling, al gehad in studieverband. Door de behandelaren wordt verwacht dat ongeveer 50% van de patiënten die op dit moment in aanmerking komen gebruik gaat maken van ED. Verder komen er andere (gen)therapieën aan voor de behandeling van ernstige en matig ernstige hemofilie B, welke momenteel in onder andere in fase 3 onderzoek onderzocht worden. Mogelijk wachten patiënten deze andere behandelopties om indien mogelijk de betere optie te kiezen.

Werking van etranacogene dezaparvovec (ED)
ED is een gentherapie, wat middels een Adeno Associated Virus (AAV) in de levercellen wordt gebracht. Op die manier wordt een werkende kopie van het gen voor stollingsfactor IX in de levercellen geïmplementeerd. Dit stelt de levercellen in staat om zelf stollingsfactor IX te produceren en verhoogt zo de lichaamseigen (endogene) stollingsfactor IX in het bloed. Dit helpt het bloed om op een normale manier te stollen en voorkomt of vermindert bloedingen.[2] Omdat patiënten zelf weer stollingsfactor aanmaken is profylactische behandeling met stollingsfactor IX-concentraten niet meer nodig. Behandeling met ED is eenmalig en kan volgens de SmPC niet herhaald worden. De reden waardoor herbehandeling niet mogelijk zou zijn is dat de patiënt anti-AAV-antilichamen zal hebben ontwikkeld.

Wetenschappelijke weging

Ziektelast
Aangezien er sprake is van een gelijke waarde claim ten opzichte van profylactische behandeling met stollingsfactor IX-concentraten, is er geen farmaco-economische beoordeling uitgevoerd. Hierdoor is de ziektelast voor deze indicatie niet berekend. Voor een beschrijving van de ernst van de ziekte wordt verwezen naar de informatie hierboven.

Stand van Wetenschap en Praktijk

Effectiviteitsargumenten
ED werd onderzocht in de HOPE-B trial. Dit is een enkelarmige, open-label, fase 3-studie, waarin 54 patiënten van 18 tot 75 jaar (gemiddelde leeftijd 41,5 jaar) aan hebben deelgenomen. Er namen 12 Nederlandse patiënten deel aan HOPE-B, wat overeenkomt met 22% van de totale studiepopulatie. Op basis van de testresultaten heeft EMA voorwaardelijke toelating verleend. De definitieve resultaten van HOPE-B, met een follow-up van 5 jaar, dienen aangeleverd te worden voor bevestiging van effectiviteit en veiligheid. Naar verwachting zal de afronding van de studie plaatsvinden in 2025. Momenteel zijn er data tot 24 maanden na de behandeling beschikbaar. Voordat de patiënten de infusie met ED kregen, kregen ze gedurende een inlooptijd van minstens 6 maanden profylactische behandeling met stollingsfactor IX-concentraten. Deze inlooptijd werd gebruikt als de controle voor de intrapatiënt vergelijking. Vanwege de enkelarmige opzet van de studie en de relatief korte follow-up tijd voor een eenmalige behandeling die potentieel levenslang aanhoudt, wordt de kwaliteit van het bewijs gezien als zeer laag.

Na 24 maanden follow-up resulteerde ED in een klinisch relevante vermindering in het aantal jaarlijkse bloedingen ten opzichte van profylactische behandeling met stollingsfactor IX-concentraten (intrapatiënt vergelijking) (rate ratio 0,36 [95% BI: 0,21 - 0,63; $p < 0,001$]).

Van de patiënten die ED toegediend kregen in de studie, moesten 2/54 (3,7%) patiënten profylactische behandeling met stollingsfactor IX-concentraten alsnog voortzetten. Bij deze twee patiënten sloeg de behandeling niet aan omdat ED niet goed of volledig in het lichaam opgenomen kon worden. Eén van patiënt kreeg niet de volledige dosering toegediend omdat er een overgevoeligheidsreactie optrad. De andere patiënt had hoge waardes van antilichamen tegen het AAV, ofwel het virusdeeltje waarin ED verwerkt zit. Omdat ED niet goed in de levercellen opgenomen kon worden is de aanmaak van het stollingsfactor IX in deze patiënten niet voldoende toegenomen. Dit betekent dat de behandeling met ED niet het beoogde effect, waarbij geen profylaxe met stollingsfactor IX-concentraten meer nodig is, heeft gehad.

De belangrijkste surrogaatuitkomstmaat voor bloedingen is de endogene stollingsfactor IX-spiegel. Gemiddeld genomen steeg deze tot 39,0% in maand 6 na toediening van ED, waarna het langzaam begon af te nemen. In maand 24 bedroeg de gemiddelde en mediane endogene stollingsfactor IX-spiegel respectievelijk 36,7% en 33,9% van normaal. Eén patiënt had een endogene stollingsfactor IX-spiegel die onder de grens van 5% (4,7%) gedaald was in maand 24. Hoewel deze patiënt op dat tijdstip nog niet teruggegaan was op profylaxe, valt het te verwachten dat dit de nabije toekomst zal gebeuren.
Er zijn geen gegevens bekend over de cruciale uitkomstmaat hemofilie artropathie. De gewrichtsbloedingen en de gewrichtsgezondheidsscores verbeterden statistisch significant in de periode na de behandeling (7-24 maanden) vergeleken met de inloopperiode met profylactische behandeling met stollingsfactor IX-concentraten.

ED toonde na een follow-up van 12 maanden een statistisch significante, maar niet klinisch relevante verbetering van de kwaliteit van leven op basis van de ziektespecifieke *Hemofilie Quality of Life Questionnaire for Adults* (Hem-A-QoL). De kwaliteit van bewijs is zeer laag. Er werden geen significante verschillen waargenomen in de generieke EQ-5D-5L VAS-scores.
Er vonden geen interventiegerelateerde ernstige ongunstige effecten plaats tijdens de gehele follow-up (inloopperiode en na toediening van ED). Lange termijn onderzoek is nodig om mogelijke zeldzame bijwerkingen vast te leggen en om het potentiële risico op maligniteiten te onderzoeken. Dat laatste is een risico voor alle AAV gentherapieën en niet specifiek voor ED. In HOPE-B stierf één patiënt ongeveer 15 maanden na de behandeling aan een cardiogene shock die volgens de onderzoekers niet gerelateerd was aan de behandeling.

Tabel 2. Resultaten cruciale uitkomstmaten

Cruciale uitkomst	**Effect**			**GRADE score**
	Absoluut	**Relatief**	**Klinische relevantiegrens**	
ABR	FIX-profylaxe (inloopperiode): 4,19 (3,22 tot 5,45) ED: 1,51 (0,83 tot 2,76)	rate ratio: 0,36 (95% BI: 0,210 tot 0,643; p < 0,001)	<0,75 of >1,25	laag
Percentage patiënten die FIX-profylaxe moest voortzetten of hervatten	FIX-profylaxe (inloopperiode): 54/54 (100%) ED: 2/54 (3,7%)	RR 0,037 (0,01 tot 0,14)	<0,75 of >1,25	laag
Hemofiele artropathie	Er zijn geen gegevens over de lange termijn preventie van hemofiele artropathie			
Kwaliteit van leven (Hem-A-QoL)	FIX-profylaxe (lead-in period): Ls mean score 25,6 ED: Ls mean score 20,1 (maand 12)	Verandering in Ls mean score: 5,5 punt reductie (7,4 lager tot 3,6 lager)	7-punt reductie	zeer laag
Interventie-gerelateerde ernstige ongunstige effecten	In beide armen vonden geen interventie-gerelateerde ernstige ongunstige effecten plaats		<0,75 of >1,25	laag

ABR: annual bleeding rate; BI: betrouwbaarheidsinterval; ED: etranacogene dezaparvovec; FIX: stollingsfactor IX; RR: risk ratio

Passend onderzoek argumenten
De studieopzet van de HOPE-B-studie, waarbij personen als hun eigen vergelijking (intra-patiënt) fungeren, is besproken met en geaccepteerd door de FDA en EMA. Omdat het onderzoek een intra-patiëntcontrole omvat, wordt de onderzoeksopzet door het Beneluxa assessment team bruikbaar geacht voor beoordeling van de effectiviteit. Wel resulteert deze studieopzet in een lage kwaliteit van bewijs.

De relatief korte follow-up duur van 2 jaar zorgt voor beperkte gegevens wat betreft de duur van het effect en de lange termijn veiligheid voor een eenmalige gentherapie. Zeker gezien het feit dat de endogene stollingsfactor IX-spiegels tijdens de duur van de studie langzaam begon af te nemen.

Medische argumenten
- Voor deze populatie bestaat een effectieve andere behandeloptie (profylactische behandeling met stollingsfactor IX-concentraten).
- Wel kunnen stollingsfactor IX-spiegels schommelen tijdens behandeling met stollingsfactor IX-concentraten en heeft het levenslang intraveneus toedienen ervan impact op de kwaliteit van leven.

- Ook bij profylactische behandeling met stollingsfactor IX-concentraten treden er bloedingen op (gemiddeld 4,19 per jaar in controlearm van HOPE-B). Op de lange termijn hebben gewrichtsbloedingen een ernstig negatief effect op de mobiliteit en kwaliteit van leven.

Evidence naar conclusie Stand van de Wetenschap en Praktijk
Op basis van de beschikbare gegevens kan geconcludeerd worden dat ED met oog op de cruciale uitkomstmaten minstens even effectief is als profylactische behandeling met stollingsfactor IX-concentraten zonder een toename in ongunstige effecten. Het voldoet daarmee aan de Stand van Wetenschap en Praktijk (SWP). Daarentegen bestaat door de relatief korte follow-up een grote mate van onzekerheid over de duur van het effect en zijn lange termijn veiligheidsgegevens onbekend.
Om de duur van het effect van ED in te schatten is met name de endogene stollingsfactor IX-spiegel en de daling ervan kritisch bekeken. Indien endogene stollingsfactor IX-spiegels dermate gedaald zijn en spontane bloedingen weer optreden, zal de profylactische behandeling met stollingsfactor IX-concentraten weer hervat moeten worden. Wanneer endogene stollingsfactor IX-spiegels boven 5% blijven zal er doorgaans geen profylaxe nodig zijn. Hoewel de gemiddelde endogene stollingsfactor IX-spiegel van de populatie in de studie zich ver boven deze grens begeeft in de huidige data, bestaat er variabiliteit in het effect op patiënt niveau. Zo zijn de spiegels van één patiënt onder deze grens gezakt na maand 24. Naar verwachting zal deze patiënt in de nabije toekomst profylaxe moeten hervatten. Dit geeft onzekerheid over de duurzaamheid van de behandeling. Verder hebben twee andere patiënten profylaxe met stollingsfactor IX-concentraten moeten voortzetten na toediening van ED omdat de behandeling niet aansloeg. In totaal zou bij 3/54 (5,6%) ED geen succesvolle/langdurige effect hebben gehad.
Op basis van de 2-jaarsfollow-up, in overleg met de WAR-CG, heeft het Zorginstituut voldoende vertrouwen in de duur van het effect tot 4 tot 5 jaar. Er is te veel onzekerheid om iets over de duur het effect van de behandeling te concluderen voorbij 4 tot 5 jaar na infusie.

<u>Budgetimpact</u>
Het Zorginstituut schat in dat gedurende de eerste drie jaar na opname in het pakket er in totaal 26 patiënten behandeld zullen worden met ED in Nederland. De vraagprijs van ED bedraagt €2,8 miljoen per patiënt. Op dit moment bedragen de kosten van profylactische behandeling €150,488 tot €350,526 per patiënt per jaar, wat gesubstitueerd zal worden. De budgetimpact komt vervolgens uit op €36,5 tot €39,6 miljoen in jaar 1 en €-1,2 tot €4,3 miljoen in jaar 3.

<u>Kosteneffectiviteit en verantwoording van de vraagprijs</u>
Aangezien er sprake is van een gelijke waarde, is de kosteneffectiviteit van ED niet beoordeeld door het Beneluxa assessment team.
De registratiehouder geeft aan dat de vraagprijs gebaseerd is op de kosten van 10 jaar profylactische behandeling. Hierin is de registratiehouder uitgegaan van de lijstprijzen van de stollingsfactor IX-concentraten. Het Zorginstituut laat in de budgetimpactanalyse zien wat de kosten van de concentraten zijn bij verschillende tijdshorizons, op basis van de lijstprijzen en op basis van een schatting van de onderhandelde prijzen. Zorgverzekeraars en ziekenhuizen voeren prijsonderhandelingen uit bij deze middelen. Op basis van gegevens van de GIPdatabank is een schatting gemaakt van de onderhandelde prijzen (zie de

budgetimpactanalyse voor meer informatie). Wanneer wordt uitgegaan van een tijdshorizon van 4-5 jaar (zoals geadviseerd door de WAR), dan zou, uitgaande van de lijstprijzen van de stollingsfactor IX-concentraten, de maximale prijs van ED €1,4 tot 1,8 miljoen zijn. Wanneer bij dezelfde tijdhorizon wordt uitgegaan van geschatte onderhandelde prijzen van de stollingsfactor IX-concentraten, dan zou de maximale prijs van ED €604,574 tot €757,302 zijn. Hierbij wordt uitgegaan van het principe dat bij een gelijke waarde, de kosten in de nieuwe situatie niet hoger zijn dan in de huidige situatie.

Betalingsvoorstel registratiehouder
De registratiehouder heeft een betalingsvoorstel gedaan waarbij over een periode van 10 jaar per jaar per patiënt een betaling wordt gedaan, mits de patiënt nog steeds profylaxe-vrij is. De hoogte van deze jaarlijkse betaling is gebaseerd op de kosten van profylactische behandeling met stollingsfactor IX concentraat (lijstprijzen). Het Beneluxa assessment team heeft in de budgetimpact analyse - in een alternatieve benadering - inzichtelijk gemaakt hoeveel kosten er per jaar gemoeid zijn met de behandeling met stollingsfactor IX-concentraten en hoe zich dit verhoudt tot de algemene benadering van een gelijke waarde en gelijke prijs.

Conclusie Beneluxa assessment team wetenschappelijke weging
ED bij de behandeling van volwassen patiënten met ernstige en matig ernstige hemofilie B (congenitale stollingsfactor IX-deficiëntie) met een ernstig bloedingsfenotype zonder voorgeschiedenis van stollingsfactorfactor IX-remmers voldoet aan de stand van wetenschap en praktijk op basis van de huidige gegevens. Daarentegen blijft er een substantieel niveau van onzekerheid bestaan over de duur van de effectiviteit en het veiligheidsprofiel.

Overige argumenten/overwegingen/informatie van belang bij de vraag om etranacogene dezaparvovec (ED) wel/niet te vergoeden. We hebben deze onderverdeeld in drie domeinen: onzekerheid, solidariteit/rechtvaardigheid en het competitieve landschap/redelijkheid van de vraagprijs.

Onzekerheden:
- Het is onzeker hoe lang het effect van ED aanhoudt. De registratiehouder suggereert dat het effect tenminste 10 jaar aanhoudt. Op basis van de beschikbare informatie heeft het Zorginstituut, in overleg met de WAR-CG, geconcludeerd dat er voldoende vertrouwen is in een duur van effectiviteit van tot 4 tot 5 jaar. Daarentegen zijn, door de relatief korte follow-up van 2 jaar, veel onzekerheden. Er kunnen daarom geen conclusies getrokken worden over de effectiviteit voorbij een periode van 4 tot 5 jaar. Overigens heeft ED een voorwaardelijke markttoelating en zullen aanvullende gegevens aangeleverd moeten worden. Naar verwachting wordt de HOPE-B studie in 2025 afgerond.
- Er is veel onzekerheid omtrent de budgetimpact. Dit komt met name doordat het lastig is in te schatten hoe veel patiënten er daadwerkelijk gebruik willen gaan maken van ED.
- De vraagprijs van ED is gebaseerd op een tijdshorizon van 10 jaar. Het is echter onzeker hoe het behandellandschap er de komende 10 jaar uit komt te zien: mogelijk dalen de prijzen van stollingsfactor IX-concentraten nog verder en er worden op relatief korte termijn nog andere nieuwe geneesmiddelen op de markt verwacht (zie kopje competitief landschap).

Solidariteit/rechtvaardigheid

- Patiënten worden in de huidige situatie bij voorkeur profylactisch met stollingsfactor IX-concentraten behandeld. Dit is een behandeling die al heel wat jaren bestaat. Sinds 2014 zijn de eerste langwerkende varianten (EHL) van stollingsfactorfactor IX-concentraten op de markt en het grootste deel van de patiënten is inmiddels hierop overgestapt. De langwerkende variant gaat gepaard met een lagere toedieningsfrequentie.
- De vraagprijs van ED is hoog, namelijk €2,8 miljoen per patiënt. Het is hiermee een van de duurste geneesmiddelen ooit. Eerdere gentherapieën die door het Zorginstituut zijn beoordeeld hebben een lijstprijs van:
  - €690.000: voretigene neparvovec (Luxturna®) voor de behandeling van visusverlies (gezichtsvermogen) door erfelijke retinale dystrofie.
  - €1,6 miljoen: betibeglogene autotemcel (Zynteglo®) voor de behandeling van ernstige bèta-thalassemie, een vorm van erfelijke bloedarmoede
  - €2,9 miljoen: atidarsagene autotemcel (Libmeldy®) voor de behandeling van kinderen met de zeldzame, erfelijke stofwisselingsziekte metachromatische leukodystrofie (MLD).
  - €1,9 miljoen: onasemnogene abeparvovec (Zolgensma®) bij de behandeling van spinale musculaire atrofie (SMA).
- Door inzet van ED worden de kosten van profylactische behandeling met stollingsfactor IX-concentraten voor een aantal jaren gesubstitueerd. Hoe lang deze periode zal zijn is lastig in te schatten. De registratiehouder neemt een periode van 10 jaar aan.
- De kosteneffectiviteit van profylactisch gebruik van stollingsfactor IX-concentraten is niet in Nederland onderzocht of beoordeeld.

Competitieve landschap/redelijkheid van de prijs

- ED is een innovatief geneesmiddel voor hemofilie B. Hierbij wordt gebruik gemaakt van AAV-technologie. Deze technologie vormt de basis van meerdere gentherapieën die ontwikkeld zijn.
  Daarnaast is er gebruik gemaakt van een ontwikkeling van een onderzoeker (dr. Simioni) van de Universiteit van Padua. UniQure, een gentherapieontwikkelaar, is een samenwerking met Dr. Simioni aangegaan en de patenten zijn in handen van UniQure. UniQure heeft de ontwikkeling t/m de fase 3 studie uitgevoerd. Vervolgens is er een overeenkomst met CSL Behring gesloten waarbij de productie en levering van ED de verantwoordelijkheid van CSL Behring is.[3] Wel wordt ED nog geproduceerd door UniQure in Lexington, Massachusetts.
- CSL Behring is ook registratiehouder van Idelvion®, een van de langwerkende stollingsfactor IX-concentraten. Idelvion® wordt sinds 2022 niet meer in Nederland gebruikt (reden onbekend) maar in België wordt het bijvoorbeeld nog wel veel ingezet.
- Voor zo ver bekend hebben Frankrijk, Canada en Oostenrijk ED toegelaten tot het basispakket, na het maken van prijsafspraken. NICE heeft ED negatief beoordeeld op basis van twijfels over de lange-termijn gegevens.
- In 2023 zijn de eerste patiënten ter wereld behandeld met ED. Het is onbekend hoeveel geld dit CSL Behring tot nu toe heeft opgeleverd.
- De vergelijkende behandeling, bestaande uit Alprolix® en Refixia® hebben nog een geldend patent. Het patent van Alprolix® verloopt in 2029; het patent van Refixia® verloopt in 2027.

- Zoals beschreven onder het kopje 'kosteneffectiviteit/verantwoording prijs' heeft de registratiehouder de vraagprijs van ED gebaseerd op de kosten van 10 jaar profylactische behandeling met stollingsfactor IX-concentraten. Het Zorginstituut is van mening dat deze tijdshorizon te lang is en daarnaast liggen de werkelijk betaalde (onderhandelde) prijzen voor stollingsfactor IX-concentraten flink onder de lijstprijzen. Dit blijkt uit openbare data van de GIPdatabank (zie uitleg in de bijgevoegde budgetimpactanalyse) en interne vertrouwelijke declaratiedata.
- Op basis van de horizonscan en clinicaltrials.gov kunnen de volgende nieuwe middelen voor hemofilie B worden verwacht:
  - Pfizer en Spark hebben ook een gentherapie ontwikkeld, namelijk fidanacogene elaparvovec. De resultaten lijken positief en het ligt momenteel ter beoordeling bij de EMA.[4] (NCT03861273) Deze behandeling is aangemerkt als sluiskandidaat. Deze behandeling is aangemerkt als sluiskandidaat.[5]
  - Freeline Therapeutics is ook bezig geweest met de ontwikkeling van een gentherapie voor hemofilie B (FLT180a, verbrinacogene setparvovec). Resultaten van de fase 1-2 studie zijn gepubliceerd.[6] Op clinicaltrials.gov is echter terug te lezen dat de ontwikkeling van dit geneesmiddel gepauzeerd is. (NCT03641703)
  - Concizumab: dit is echter bedoeld voor patiënten met inhibitors. Het hebben (of gehad hebben) van inhibitors is een exclusiecriterium voor gebruik van ED dus het betreft hier net een andere subgroep patiënten.
  - Marstacimab: voor profylaxe om bloedingen te voorkomen bij patiënten met hemofilie A of hemofilie B. De registratieprocedure loopt en het is aangemerkt als sluiskandidaat.[5]
  - Fitusiran: een synthetisch RNA-molecuul dat de aanmaak van antitrombine blokkeert. Het wordt subcutaan toegediend, als profylactische behandeling. Resultaten van de fase 3 studie zijn gepubliceerd en lijken positief (bij zowel hemofilie A als hemofilie B).[7]
- Er wordt door de zorgverzekeraars en ziekenhuizen onderhandeld met de fabrikanten over de prijzen van stollingsfactor IX-concentraten. Hierdoor liggen de gedeclareerde prijzen van deze middelen ver onder de lijstprijzen. Wanneer naar de GIPdatabank gekeken wordt dan is te zien dat de gemiddelde kosten per patiënt per jaar van Alprolix (een langwerkende variant van stollingsfactor IX-concentraat) van €585.831 in 2018 naar €251.443 in 2022 zijn gedaald. Het Zorginstituut concludeert op basis van vertrouwelijke declaratiegegevens dat deze daling met name door prijsonderhandelingen is veroorzaakt.

Vraag/vragen aan de commissie

1 Heeft u alle argumenten om de pakketcriteria te wegen?
2 Wat is uw weging van deze argumenten?
3 Tot welk advies komt de commissie op basis van deze argumenten?

Te raadplegen partijen

- Registratiehouder: CSL Behring
- Beroepsgroep: Nederlandse Vereniging van Hemofiliebehandelaars (NVHB)

- Patiëntenvereniging: Nederlandse Vereniging van Hemofilie-Patiënten (NVHP)
- Zorgverzekeraars Nederland (ZN)/ Vereniging Artsen Volksgezondheid (VAV)

Bijlage(n)

I Ingekomen brief patiëntenorganisatie NVHP
II Farmacotherapeutisch rapport
III Budgetimpactanalyse

Referenties

1. Hassan S, Monahan RC, Mauser-Bunschoten EP, et al. Mortality, life expectancy, and causes of death of persons with hemophilia in the Netherlands 2001-2018. J Thromb Haemost 2021; 19: 645-53.
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Zienswijze van de NVHP (Nederlandse Vereniging van Hemofilie-Patiënten) ten aanzien van Hemgenix®

Inhoud:

1. Standpunt NVHP t.a.v. Hemgenix®

De resultaten van de studies naar Etranacogene dezaparvovec (Hemgenix®), hierna te noemen Hemgenix®, zijn veelbelovend. Hemgenix® is het gentherapieproduct voor patiënten met hemofilie B, ontwikkeld door CSL Behring en UniQure.

De NVHP heeft het standpunt dat patiënten die, volgens de geregistreerde indicatie hiervoor in aanmerking komen, de optie moeten hebben voor behandeling met Hemgenix®. Bij dit standpunt speelt een bepalende rol dat de huidige behandeling voor hemofilie B evidente nadelen heeft, zie onder 3, en dat de afweging van voor- en nadelen en de onzekerheden rond gentherapie sterk kunnen afhangen van iemands persoonlijke levensfase en -doelen.

Om al dan niet de keuze voor gentherapie te kunnen maken moet er complete en begrijpelijke informatie voor patiënten beschikbaar zijn. In het gesprek met de behandelend arts moeten de effecten, onzekerheden, bijwerkingen en mogelijke risico's van gentherapie duidelijk naar voren komen.

Er is monitoring van de effectiviteit en bijwerkingen op de lange termijn vereist. Hierbij is het van belang dat 'kwaliteit van leven' en patient reported outcomes (PROs) als uitkomstmaat worden meegenomen in de bepaling van de effectiviteit, in vergelijking met andere behandelopties. Hiervoor zijn verschillende instrumenten beschikbaar en er is een internationale set gedefinieerd [i].
Gezien de sterk individuele afweging, is het belangrijk dat de aspecten die hemofiliepatiënten ervaren en definiëren, hierin worden opgenomen.

In de benadering van de patiënt moet sprake zijn van centrale regie en eenheid in benadering. De behandeling moet voor patiënten beschikbaar zijn ongeacht de woonplaats en het centrum waar men tot dan toe in behandeling is. De patiënt moet ervan op aan kunnen dat de behandeling en de follow-up voldoen aan uniforme kwaliteitseisen. Het is van belang dat de behandelaren landelijk afstemmen over de behandeling en hun ervaringen delen.

2. Impact van de ziekte hemofilie B

Hemofilie B is een zeldzame, erfelijke X-gebonden stoornis van de bloedstolling (hemostase) als gevolg van de afwezigheid of deficiëntie van stollingsfactor, factor IX. Door het X-gebonden overervingspatroon komt hemofilie vaker bij mannen voor dan bij vrouwen. Vrouwen zijn draagster en kunnen ook een lage stollingswaarde hebben, waardoor zij klachten hebben.
Bij patiënten met ernstige en matig ernstige hemofilie ontstaan gemakkelijk bloeduitstortingen en (inwendige) bloedingen spontaan of na een triviaal trauma. Deze bloedingen zijn meestal gelokaliseerd in de grote gewrichten (heup, elleboog, pols, schouder, knie en enkel) of spieren. Bloedingen in de hersenen of andere vitale organen kunnen gemakkelijk fataal zijn. Patiënten herkennen bloedingen aan het voelen van tintelingen ('aura'), pijn, zwelling, warmte en het moeilijker bewegen van de ledematen. Gewrichtsbloedingen kunnen, doordat het aanwezige bloed kraakbeenbeschadiging veroorzaakt, uiteindelijk leiden tot chronische gewrichtsschade (hemofilie-artropathie), die gepaard gaat met chronische pijn, mobiliteitsbeperking en een verminderde kwaliteit van leven. Bovendien is er kans op een vicieuze cirkel van verzwakking van een gewricht of spier die leidt tot recidive en verdere verzwakking/beschadiging. Als de ziekte niet behandeld zou worden is de levensverwachting veel korter.
Patiënten met ernstige hemofilie ervaren over het algemeen beperkingen op diverse terreinen, zoals de keuze voor, en de actieve deelname aan werk en vrijetijdsbesteding.
Ook ervaren veel patiënten impact op het psychosociale vlak, zoals een gevoel van afhankelijkheid van therapie en zorgen voor de toekomst [ii], [iii], [iv].

3. Huidige behandeling van hemofilie B

Huidige behandeling
De standaardbehandeling van patiënten met ernstige hemofilie B bestaat uit routineuze intraveneuze toediening van Extended Half Life en/of Standard Half Life stollingsfactoren FIX. Ca. 10% van de patiënten kiest om diverse redenen om geen routineprofylaxe te gebruiken. Het hoofddoel van de behandeling is om in het dagelijks leven bloedingen te voorkomen en gewrichtsschade te vermijden en gezonde gewrichten te behouden. Dit resulteert in minder orthopedische ingrepen, een verhoogde kwaliteit van leven en betere sociale participatie.

Nadelen huidige behandeling
De huidige therapie biedt geen genezing voor patiënten met hemofilie. Dit betekent dat ze afhankelijk zijn van levenslang 1 tot 4 maal per week een infusie met stollingsfactoren. Hiermee wordt ook geen normalisatie van de hemostase bereikt, maar een minimaal basisniveau door een 'zaagtand' patroon van regelmatige dosering en afbraak.
Voor hemofilie B-patiënten is geen alternatief voor intraveneuze stollingsfactoren beschikbaar, zoals de non-factortherapie emicizumab voor patiënten met hemofilie A, die eens in de 1 tot 4 weken subcutaan toegediend kan worden.
Voor veel patiënten zijn de frequente injecties belastend, soms in die mate dat patiënten alleen bij bloeding worden behandeld (on demand).
Bij kinderen is intraveneuze toediening vaak moeilijk en kan ook prikangst een probleem zijn.

Ook bij ouderen kunnen vaten moeilijk te prikken zijn (slechte vaten door ouderdom of slechter zicht) en kan telkens profylaxe spuiten tot beschadiging van de vaten leiden.
Bovendien is organisatie van de thuisbehandeling voor steeds meer ouderen een probleem: combinatie van intraveneuze stollingsfactoren met andere medicijnen, onbekendheid van hulpverleners in de ouderenzorg en de logistieke organisatie van het regelmatig thuis geleverd krijgen van ziekenhuismedicatie en toebehoren zijn een puzzel voor patiënt en naasten.
Reguliere profylaxe kan ook onvoldoende effectief zijn. Zo is er een grote variatie in bloedingsneiging, waardoor sommigen ook met routinebehandeling niet bloedingsvrij te krijgen zijn, is het behaalde minimumniveau vaak onvoldoende voor mensen die een actieve levensstijl hebben of een fysiek zwaar beroep uitoefenen, en hebben patiënten problemen met therapietrouw of zelfmanagement. Naar schatting neemt de helft van de patiënten de medicatie volgens voorschrift [v]. De rest mist wel eens een van de 104 à 208 injecties in een jaar met direct kans op een bloeding tot gevolg. Hierdoor treden, ondanks de injecties, bloedingen nog steeds op waardoor een risico op de gevolgen blijft bestaan. Op lange termijn treedt bij een groot gedeelte van de patiënten tóch gewrichtsschade op met chronische pijn en beperkingen tot gevolg [vi].
Behandeling kan leiden tot complicaties. Er kunnen remmers tegen FIX (anti-drug antibody) optreden. De behandeling werkt dan niet meer en is er risico op bloedingen. Het is dan noodzakelijk om te stoppen met de therapie omdat er kans is op het nefrotisch syndroom[1]. Bij de generatie oudere patiënten kan comorbiditeit[2] aanwezig zijn.
Oudere patiënten hebben te maken gehad met producten bereid uit bloedplasma die niet geheel veilig waren en hebben in grote aantallen hepatitis C en HIV-infecties opgelopen. Door chronische hepatitis infecties is de gezondheid van de lever soms een punt van aandacht.
Tenslotte is er het kostenaspect. Hoewel proactieve profylaxe véél betere resultaten oplevert [vii] voor beperkte meerkosten in vergelijking met reactief behandelen, blijft het een langdurige kostbare behandeling. Hoewel éénmalig kostbaar, kan een langdurige en constante bescherming via gentherapie uiteindelijk zelfs kostenbesparend uitpakken [viii].

4. Gentherapie voor hemofilie B

4.1. Resultaten van studie

Studie Hemgenix® (AMT 61, Factor IX Padua variant)
Een internationale fase 3-studie waaraan 54 patiënten deelnamen, leverde de volgende resultaten op: Proefpersonen bereikten een gemiddelde Factor IX-activiteitsniveaus van 39% (± 18,7), 41,5% (± 21,7), 36,9% (±21,4) en 36,7 (± 19,0) van normaal, respectievelijk op 6, 12, 18 en 24 maanden.
De gemiddelde jaarlijks aantal bloeding (7 tot 18 maanden na behandeling met Hemgenix®) was 1,51 bloedingen/jaar met een betrouwbaarheid van 95% interval (BI) van (0,81; 2,82), vergeleken met een gemiddelde van 4,1 [95% BI: 3,2; 5,4] tijdens de aanloopperiode. Cruciaal is dat 52 van de 54 deelnemers een toename van FIX niveaus zagen, en na 24 maanden niet hoefden terug te keren naar FIX profylaxe. Het aantal proefpersonen zonder bloeding bedroeg (7 tot 18 maanden na de behandeling) 34. Dit is 63% van het totale aantal proefpersonen.

[1] Nefrotisch syndroom: beschadiging van de nieren door immuuncomplexen.
[2] Comorbiditeit: aanwezigheid van één of meerdere aandoeningen naast de hoofddiagnose.

4.2. Betekenis van gentherapie voor de kwaliteit van leven

Door een continue hoge bescherming bij gentherapie treden er vrijwel geen spontane bloedingen meer op [ix] en heeft een flink aantal mensen ook geen traumatische bloedingen meer. Dit heeft grote impact op de kwaliteit van leven. Voor patiënten is de betekenis veel breder en meer omvattend dan klinische uitkomsten als het percentage FIX of alleen het aantal bloedingen.
De verwachting is dat patiënten minder angst voor bloedingen, en minder bezorgdheid en meer vrijheid ervaren. Hoewel de huidige kwaliteit-van-leven uitkomsten voor hemofiliepatiënten al goed zijn, is er namelijk ook sprake van een adaptatie aan de mogelijkheden die de huidige behandeling biedt [x].
Door de levenslange chronische conditie is er sprake van een 'niet weten wat je mist' of 'ik weet niet beter' effect. Met betere bescherming is een actievere leefstijl mogelijk met meer keuzemogelijkheden wat betreft werk, vrijetijdsbesteding, sport en reizen, die eerder niet eens overwogen werden. Reizen naar het buitenland is mogelijk zonder medicatie of een behandelcentrum in de nabijheid van het vakantieadres. Zo is het bijvoorbeeld mogelijk om te reizen naar of werken in landen zonder goede medische voorzieningen. Dit is effect dat hun leven verandert.
Gentherapie maakt dat patiënten minder afhankelijk worden van behandeling [xi].
Wat betreft de toediening van de gentherapie ervaren patiënten aanzienlijk minder behandellast dan bij de huidige behandeling. Na de toediening van de gentherapie volgt echter wel een intensieve follow-up in de eerste drie maanden, zie onder monitoring.

4.3. Aandachtspunten en vragen m.b.t. gentherapie voor hemofilie B

Genezing
Na de behandeling met gentherapie hebben patiënten genetisch nog steeds hemofilie en is de ziekte nog overdraagbaar op kinderen. Uitgaande van de volgende definitie van genezing, die internationale consultatie van belanghebbenden heeft opgeleverd, ervaart een deel van de patiënten toch dat ze genezen zijn omdat ze tot nu toe geen verdere behandeling nodig hebben.
Volledige correctie van eerdere bloedingsneiging met genormaliseerde stollingsfactorniveaus 5 jaar na curatieve behandeling, waarvoor geen verdere behandeling nodig is (met stollingsfactor of andere behandelingen), zelfs niet voor chirurgie of bloeding. Genezing is fenotypisch bedoeld en omvat niet: het elimineren van overdracht van hemofilie op kinderen of het volledig terugdraaien van vastgestelde schade [xii].

Onzekerheid
Voornaamste zorgenpunt bij gentherapie is de onzekerheid op verscheidene onderdelen: er is de onzekere lange-termijn veiligheid van genomische integratie van de vector, onzekerheid over de uiteindelijke duur van het effect en onzekerheid over de te behalen opbrengst.
Dat betekent dat de bereidheid om aan gentherapie mee te doen afhangt van hoe iemand met deze onzekerheden om kan gaan. Met name voor de opbrengst hangt dit af van de persoonlijke doelen en verwachtingen: hoewel alle succesvolle deelnemers aan de pivotal trial langdurig zonder profylactische behandeling blijven, is het beschermingsniveau na gentherapie zéér verschillend. Patiënten aan de bovenkant van het behaalde bereik hebben een eigenlijk volledig genormaliseerde hemostase, met alle voordelen daarvan.

Diegenen aan de onderkant halen slechts het oude minimale basisniveau – maar dan zonder de regelmatige 'pieken' van het zaagtand-patroon.
Hierdoor zou er dus zelfs minder bescherming tijdens bijvoorbeeld sportactiviteiten kunnen zijn. De huidige gentherapie is dus betrouwbaar effectief in het beperken van de behandellast, en levert een goede káns op aanzienlijk betere bescherming (die door de variatie in opbrengst helaas vooralsnog totaal onvoorspelbaar lijkt).

Informatievoorziening en ondersteuning keuzeproces
Aan het besluit van de patiënt om al dan niet voor gentherapie te kiezen moet een intensief keuzeproces voorafgaan waarbij de verwachtingen van de patiënt over effectiviteit en te behalen doelen dus een belangrijke rol spelen. Voor de afweging van de patiënt moet voor alle beslismomenten volledige, uniforme, goed begrijpelijke en liefst visuele informatie beschikbaar zijn die op landelijk niveau wordt samengesteld. Bij dit proces is ondersteuning door het behandelteam en afstemming met de naasten van de patiënt van groot belang. Deze noodzakelijk persoonlijke benadering maakt het moeilijk om vooraf te voorspellen voor welke patiënten precies gentherapie de beste behandeling is.
In het EHC Guidebook (2022) wordt het belang van Shared Decision Making (Samen Beslissen) benadrukt. Hierbij speelt niet alleen de informatievoorziening een rol, maar ook het aanbod van adequate psychosociale hulpverlening. Deze moet beschikbaar zijn in alle fases van het proces: tijdens het keuzeproces, de behandeling en de follow-up. Ook het belang van ondersteuning door medepatiënten wordt benadrukt.

Eenmalige toediening AAV-gentherapie
De AAV-gentherapie kan éénmalig worden toegediend. Er is geen tweede behandeling met AAV-gentherapie mogelijk. In combinatie met de onzekere duurzaamheid betekent dit dat de timing van de therapie ten opzichte van de levensfase en -plannen van een patiënt van belang zijn, zodat de opbrengst het hoogst is op een moment in het leven dat de patiënt hier ook het meeste baat bij heeft. Ook kan dit betekenen dat patiënten de afweging maken om te wachten met gentherapie totdat er in de toekomst wellicht verbeterde therapieën beschikbaar zijn. Het is belangrijk dat patiënten goed worden begeleid bij de afweging om nu te kiezen voor gentherapie, of juist te wachten.

Overige aspecten
Informatie over de volgende aspecten is eveneens van belang om tot een goed afgewogen keuze te komen.

- Gentherapie is niet geregistreerd voor kinderen tot 18 jaar.
- Hoewel de reguliere behandeling na gentherapie niet meer nodig is, is er bij ingrepen of traumatische bloeding waarschijnlijk wel nog behandeling met factor IX nodig.
- Gentherapie voor hemofilie wordt niet geacht bij te dragen aan een risico op kanker, maar dit zal wel langdurig zorgvuldig bewaakt moeten worden. De aangetoonde toevallige integratie van de vector in het genoom levert namelijk wel een theoretisch risico op.
- De conditie van de lever speelt een rol bij het keuzeproces. Bij patiënten met gevorderde leverfibrose of levercirrose is gentherapie niet geïndiceerd.
- Na de behandeling is langdurige monitoring van de leverfunctie door bloedonderzoeken noodzakelijk. Tot een jaar na de gentherapie-behandeling moet zwangerschap vermeden worden omdat de werkzame stof in Hemgenix® uitgescheiden wordt in het sperma (dit proces wordt shedding genoemd). Voor mensen met een kinderwens heeft dit dus gevolgen voor de korte

termijn. In verband met de uitscheiding van het AAV-virus is ook de veiligheid voor huisgenoten/partners een aspect dat goede voorlichting nodig heeft.

- De verwachting is dat als er schade is aan gewrichten en spieren, deze niet herstelt.
- Variabiliteit in uitkomst stollingsfactor niveau en daarmee beschermingsniveau.

  Vraag: Zijn er personen die minder dan 5% opbrengst hebben?

  Vraag: Zijn er personen die supernormaal opbrengst hebben?

  Vraag: waren er personen met spontane bloedingen? Of waren de bloedingen die optraden alleen traumatische bloedingen?
- De behandeling vereist een periode van intensieve controle en een minderheid van patiënten moet immuunsuppressie gaan gebruiken. Dit heeft allerlei bijwerkingen en ook psychische effecten. Hoe tolereren mensen dit en weegt dit op tegen het beschermingsniveau en de wetenschap dat je beschermd bent?
- Voor verschillende leeftijdsgroepen kan de keuze anders uitpakken. Zo maakt het uit of patiënten al redelijk veel of juist nauwelijks schade ten gevolge van hemofilie hebben. Ook speelt de mate van activiteit en zelfredzaamheid een rol.

Aantal patiënten dat kiest voor gentherapie

In Nederland zijn ongeveer 400 patiënten met hemofilie B. Dit zijn hoofdzakelijk mannen. Vooralsnog komen de volgende patiënten voor gentherapie in aanmerking; patiënten met matig ernstige of ernstige hemofilie B die volwassen zijn, patiënten die nu of in het verleden geen remmende antistoffen tegen factor IX hebben gehad of nu hebben. In de studie voor Hemgenix® is de aanwezigheid van AAV-antistoffen geen exclusiecriterium geweest. Dit is anders bij de huidige gentherapie voor hemofilie A, Roctavian.

Het Nederlands Patiëntenregister HemoNED laat zien dat er ongeveer 120 patiënten met ernstige of matig ernstige hemofilie B geïncludeerd zijn in het register. Een aantal van hen is al in studieverband behandeld. Wij vinden het moeilijk om een voorspelling te doen van het aantal patiënten dat graag met Hemgenix® behandeld wil worden[xiii].

Onze inschatting is dat met name twee groepen patiënten behoefte zullen hebben aan gentherapie. Het betreft jonge actieve mensen (ook in verband met mogelijke problemen met therapietrouw) en ouder wordende patiënten (in verband met mogelijke problemen met zelfmanagement en/of therapietrouw).

5. Monitoring

In de eerste 3 tot 6 maanden na de gentherapie is intensieve controle met wekelijks bloedprikken noodzakelijk om de effecten en mogelijke bijwerkingen te monitoren en om behandeling in te zetten in het geval dat verlies van expressie van het transgen dreigt. Gedurende de eerste twee jaar blijft de monitoring redelijk intensief en zijn er veel bloedafnames nodig.

Voor de effectiviteit en de risico's op de lange termijn bestaat nog onzekerheid. Daarom is lange termijn-monitoring nodig op alle mogelijke bijwerkingen maar ook op de duurzaamheid van de factor IX productie. De European Medicines Agency (EMA) adviseert 15 jaar monitoring. De World Federation of Hemophilia (WFH)-registratie is gericht op levenslange monitoring. De NVHP is voorstander van levenslange monitoring om mogelijke effecten op de lange termijn, zoals het voorkómen van kanker, in beeld te brengen. Het is van belang dat patiënten worden gestimuleerd om hieraan mee te doen.

6. Registratie

HemoNED gaat als landelijk register (en in samenwerking tussen patiënten en behandelaren) data leveren aan het WFH gentherapie register. Hiervoor is een goede afstemming tussen beide in gang gezet. Data betreffen bloedingen, jaarlijks FVIII/FIX gehalte etc. De NVHP zal het belang van deze dataverzameling uitdragen en patiënten stimuleren om hieraan deel te nemen. Wij pleiten voor een adequate en duurzame bekostiging van deze datacollectie en bepleiten dat fabrikanten zo veel mogelijk gevraagd worden om mee te werken aan deze centrale dataverzameling, zodat de langdurige monitoringsdata beschikbaar is voor een brede groep onderzoekers en vergelijkbare datasets oplevert. Wij hopen ook dat fabrikanten ervoor zullen kiezen om samen met HemoNED fase IV-studies uit te voeren.

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Referenties

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[xiii] Hemoned Rapportage 2021

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Nijkerk, 16 februari 2024
Betreft: Conceptbeoordeling etranacogene dezaparvovec (Hemgenix®)

Geachte mevrouw Hoets,

Graag willen we u bedanken voor het toezenden van het conceptrapport en de budget impact analyse voor de beoordeling van etranacogene dezaparvovec (Hemgenix®).

Reactie op Farmacotherapeutische rapport

Wij zijn het eens met de conclusie van het farmacotherapeutisch rapport dat etranacogene dezaparvovec (Hemgenix®) aan de stand van wetenschap en praktijk voldoet, bij de behandeling van volwassen patiënten met ernstige en matige hemofilie B met een ernstig bloedingsfenotype zonder voorgeschiedenis van factor-IX remmers. Dit past bij ons beeld van deze nieuwe therapie. Zoals in onze zienswijze aangegeven, is Hemgenix een zeer welkome aanvulling op de bestaande behandeling voor hemofilie B, vanwege de eenmalige behandeling, de over het algemeen goede FIX opbrengst en langdurige bescherming tegen bloedingen.

Naar ons inzicht is de werkzaamheid van de behandeling met Hemgenix minstens zo goed en in veel gevallen beter als met FIX profylaxe. Een vergelijking van het aantal patiënten zonder bloedingen op Hemgenix of FIX profylaxe, laat zien dat Hemgenix juist op deze uitkomstmaat het potentieel heeft om een aanzienlijke verbetering tot stand te brengen. Toenemend inzicht in lange-termijn gewrichtsschade, zelfs tijdens profylaxe, (niet gerapporteerde) subklinische bloedingen en de lange-termijn uitkomsten en ziektelast leidden ondertussen tot verbeterde behandelprotocollen. Daarbij wordt steeds duidelijker dat er, zeker voor gewrichtsbloedingen, eigenlijk geen ‘acceptabel aantal’ is en gaat het streven naar het volledig voorkomen van bloedingen bij dagelijkse activiteiten.

Uw conclusie dat er een aanzienlijke mate van onzekerheid bestaat over de werkzaamheid en het veiligheidsprofiel op de lange termijn delen wij. Het is ook mede om deze redenen dat de EMA een voorwaardelijke handelsvergunning heeft toegekend. De evaluatietermijn van 15 jaar geeft ook al aan dat ook de EMA niet op korte termijn verwacht hier definitieve antwoorden over te hebben – aangezien risico's als tumorvorming en lange-termijn uitkomsten als gewrichtsschade nu eenmaal niet snel zijn vast te stellen.

Toch is het op basis van de huidige resultaten wel te verwachten dat Hemgenix in de meeste gevallen zeker meer dan 10 jaar werkzaamheid zal hebben, omdat de FIX activiteit stabiel blijft en dit ook in andere studies met dezelfde techniek het geval is (https://doi.org/10.1089/hum.2022.169).

De resultaten van de behandeling met gentherapie Hemgenix zijn goed maar zeer wisselend. De bereikte FIX activiteit van ongeveer 35% levert een goede continue bescherming tegen bloedingen. Veel hogere uitkomsten zijn mogelijk, die dichtbij volledige genezing komen, maar ook aanzienlijk lagere die overeenkomen met standaard profylaxe. De NVHP vindt dat patiënten waarvoor gentherapie geschikt is, de mogelijkheid moeten hebben om voor deze behandeling te kiezen op basis van hun individuele ziektebeeld en behandelvoorkeuren. Daarmee hebben we ook bezwaar tegen de vrij lichtvaardige suggestie dat een *gerandomiseerde* trial zomaar mogelijk zou zijn. De onomkeerbaarheid, eenmaligheid en grote onzekerheid rond gentherapie vereist een zorgvuldig informatietraject en gezamenlijke besluitvorming tussen patiënt en arts, waar willekeurige toewijzing vanuit ethisch oogpunt niet zomaar in past.

Wij willen graag de werkzaamheid en veiligheid van Hemgenix in de praktijk monitoren en zullen ons inzetten om ervoor te zorgen dat patiënten die behandeld zijn met deze gentherapie het belang van monitoring inzien en meewerken aan deze monitoring in het patiëntenregister HemoNED.

Reactie op de Budget Impact Analyse

U heeft ons een tweetal vragen gesteld over de BIA.

- *Kunt een reflectie geven op de aangenomen marktpenetratie en daarmee het geschatte aantal patiënten wat per jaar etranacogene dezaparvovec zal krijgen?*

Ons valt op dat er in de BIA geen rekening is gehouden met bestaande seropositiviteit voor de AAV vector. De SmPC stelt niet voor niets expliciet om vooraf hierop te testen. Hoewel beperkte seropositiviteit niet onoverkomelijk lijkt, is de data beperkt. Seropositiviteit heeft een negatief effect op de uitkomst en een titer boven 1:678 geeft wel degelijk een hoog risico op falen van de therapie. Op basis van AAV5 seropositiviteit, onderzocht in ernstige hemofilie A patiënten (https://doi.org/10.1089/hum.2021.287), zal een extra 5% van de patiënten niet in aanmerking komen door hoge seropositiviteit of door een te hoge onzekerheid over het nog te behalen effect van de gentherapie.

Het is moeilijk om een gegronde inschatting te maken over de te verwachten marktpenetratie. Dit is een terugkerend probleem: in een situatie waar er keus is tussen verschillende effectieve therapieën kunnen patiënten zich pas een gedegen mening vormen wanneer zij bekend zijn met de voor- en nadelen van een nieuwe therapie. Het in detail informeren over een therapie is voor hen pas relevant wanneer deze goedgekeurd en (spoedig) beschikbaar is.

Gezien de penetratie in de eerste 3 jaar van eerdere recombinante factor producten van ongeveer 30% en de inzet van Hemlibra naar 50% penetratie in 3 jaar (https://hemoned.nl/publicaties/jaarrapportages/) - beide aanzienlijk minder ingrijpende therapeutische alternatieven - is een totale verwachting van 50% *van de patiëntenpopulatie* waarschijnlijk realistisch als worst-case scenario. Daarbij moet u er rekening mee houden dat juist de meest 'enthousiaste' patiënten diegenen zijn die al in de trials meegedaan hebben. In uw berekening wordt dit aantal vooraf van de geïndiceerde patiëntengroep afgetrokken, alsof er geen bias zou zijn tussen de trial-deelnemers en 'overige patiënten' in waarschijnlijke interesse voor gentherapie. Daarmee zal u dus waarschijnlijk de aantallen overschatten.

Een derde punt is het verloop van de adoptie. Gezien de noodzaak tot het ontwikkelen van zorgpad, protocollen, faciliteiten en capaciteit in de behandelcentra, de bekostiging en de tijdsduur die gedegen screening en de geïnformeerde besluitvorming vereist, en het gebrek aan een acute noodzaak door beschikbare alternatieven, verwachten wij eerder een trage start met toenemende aantallen over de eerste jaren dan de aflopende aantallen die u beschrijft.

- *Kunt u een reflectie geven op de berekeningen en doseringen van profylactische FIX? Wat is volgens u een juiste schatting van het gemiddelde aantal IE FIX per patiënt per jaar?*

U geeft aan dat u HemoNED gevraagd heeft om gegevens aan te leveren om deze vraag te beantwoorden. De meest accurate data die wij kennen wat betreft gebruik van eenheden factor, zijn die uit de WFH Global Survey (https://wfh.org/research-and-data-collection/annual-global-survey/):

Deze gegevens voor Nederland worden door de NVHP verzameld in samenwerking met HemoNED en de inkoopgegevens van IZAAZ.

Country	Factor IX total IU	Factor IX plasma derived	Factor IX recombinant	Factor IX recombinant, extended half life	Total percent plasma derived	Total percent recombinant	Total percent extended half life	Factor IX humanitarian aid total	Factor IX WFH humanitarian aid – standard half life*	Factor IX WFH humanitarian aid – extended half life	Factor IX per capita	Factor IX per capital without humanitarian aid
Netherlands	17,987,350	45,600	5,326,250	12,615,500	0	30	70				1.016	1.016

Feit is dat de Nederlandse behandelpraktijk vanuit kostenefficiëntie internationaal gezien lage profylaxe doses gebruikt en dit op individuele basis aanpast, reactief aan de hand van het optreden van doorbraakbloedingen of proactief met PK modellen (https://doi.org/10.1182/blood-2012-12-470898). Dit maakt de SmPC dosering beperkt relevant en hierdoor is het ook moeilijk om een generiek behandelschema te beschrijven. Wel kan op basis van bovenstaande gebruiksgegevens een gemiddeld gebruik van 165.000 IU/patiënt/jaar worden geschat – wat bij lijstprijzen overeenkomt met ongeveer € 330.000 /patiënt/jaar.

U benoemt de grote discrepantie tussen het model met lijstprijzen en met gedeclareerde tarieven. Dit is ons niet onbekend: het huidige prijsmodel is soms ondoorgrondelijk, met totaal verschillende (vaak geheime) prijzen op verschillende plekken in de zorgketen. Om te weten welke prijs de juiste is, is het nodig goed te kijken wat het budget is waar u de impact op wilt berekenen en welke kosten daar uit betaald worden. Zo wordt bij sommige behandelcentra de inkoopkorting op medicijnen ingezet voor

financiering van de logistiek rondom de thuisbehandeling of instandhouding van multidisciplinaire poliklinieken. Een besparing op het geneesmiddelenbudget kan dus makkelijk een 'waterbed-effect' op andere zorgbudgetten veroorzaken. Een mogelijke verklaring in uw situatie is dat niet alleen de ziekenhuizen kortingen bij de fabrikanten bedingen, maar dat de zorgverzekeraars ook kortingen op de lijstprijs hanteren richting de ziekenhuizen – en zo al een deel van de inkoopkorting verzilveren.

Aanvullend op bovenstaande vragen

Graag willen we nog de volgende overwegingen toevoegen;

Opmerkelijk is dat er geen rekening wordt gehouden met de voorgestelde betaling-per-jaar zolang er effect is. Dit lijkt vanuit budgetimpact oogpunt wel degelijk relevant, aangezien de jaarbetaling directe vervanging is van de herhalende kosten voor profylaxe. Deze zal dus per jaar gematigd zijn in tegenstelling tot de nu gepresenteerde afschrijving. Dit zou juist voor de eerste 3 jaar een veel beperktere budgetimpact betekenen dan nu wordt voorgespiegeld. Bovendien voorziet deze betaling-per-jaar in een dekking van het risico dat patiënten niet of slechts beperkt profylaxe-vrij worden na behandeling – een van de grote onzekerheden benoemd in uw analyse.

Tevens is er in het scenario geen rekening gehouden met de redelijke kans dat een deel van de patiënten langer dan de 'beprijsde' 10 jaar baat zal hebben van de therapie. Het allereerste cohort dat met vergelijkbare techniek is behandeld heeft een follow-up van 10 jaar met nog steeds effectiviteit (https://doi.org/10.1182/blood-2023-186891); vergelijkbare positieve resultaten zijn er na 6 jaar follow-up van AMT-060, precursor van etranacogene dezaparvovec (presentatie EAHAD 2024). Hoewel hier de nodige onzekerheid speelt, zal dit een aanzienlijk effect op de levenslange kosten hebben. Het is op z'n minst opmerkelijk om een 10-jaar-tot-levenslang durende therapie te beoordelen op de kosten in de eerste 3 jaar.

Daarnaast wordt aangegeven dat in de BIA voor Nederland alleen wordt gerekend met de kosten van geneesmiddelen. Het eventueel (gedeeltelijk) wegvallen van andere zorgkosten voor bijvoorbeeld fysiotherapie, medische hulpmiddelen, kosten gerelateerd aan een ziekenhuisopname (na een bloeding, of een langere opname vanwege de stollingsafwijking bij een 'reguliere' behandeling) wordt hiermee niet meegenomen. Vanuit perspectief van de patiënt is de impact meer dan het geneesmiddel en zou dit bij beoordeling op z'n minst benoemd moeten worden.

Breder gezien willen we u ook waarschuwen dat er in de hemofiliezorg een stroom aan nieuwe behandelingen in de pijplijn zit, die allen een hoge kwaliteit van leven beloven. Voor hemofilie A is de eerste gentherapie reeds geregistreerd, voor hemofilie B ligt een alternatieve gentherapie ter beoordeling bij de EMA. Ook zijn er nieuwe antilichaam-gebaseerde en replacement therapieën in verschillende beoordelingsfases. Uit oogpunt van efficiëntie valt af te vragen of een individuele beoordeling op kostenefficiëntie wenselijk is wanneer de kosten per patiënt per jaar binnen een (ruime) onzekerheidsmarge vallen en de keuze voor 'de beste' therapie sterk bepaald zal worden door de context (levensfase, activiteiten, bloedingsneiging) van een individuele patiënt. Zoals ook bij deze gentherapie valt te zien is een algemene positionering dan moeilijk vast te stellen, zeker wanneer deze opzichzelfstaand bekeken wordt en niet in de context van het volledige landschap van behandelopties.

Mocht u nog vragen hebben, dan staan wij natuurlijk tot uw beschikking.

Hoogachtend,

namens de NVHP (in 1971 opgericht als de Nederlandse Vereniging van Hemofilie-Patiënten)

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Annex:

Opmerkingen NVHP op Farmacotherapeutisch rapport

Annex to letter NVHP - Comments on FT report

P7 line 5 twice Etranacogene dezaparvovec

P7 line 40 **Favourable effects (value versus alternatives)**
In HOPE-B one patient died approximately 15 months after treatment from cardiogenic shock that was considered by the investigators to be unrelated to treatment.

Q: Why is this placed under heading favourable effects?

P8 line 3 the level of endogenous FIX determines the risk of bleeding.

A level of FIX between 50 - 150 % is considered normal. So, the higher the better since better protection. However supranormal levels will increase risk of thrombosis.

See this publication of FLT180 another GT for hemophilia B:
https://pubmed.ncbi.nlm.nih.gov/35857660/

P8 line 20 hemophilic arthropathy This is a long-term effect of bleeds. A proxy measure is the number of joint bleeds. Annual Joint Bleed Rate is being used.

P8 line 47 After the first 3 months of administration, hepatic and FIX monitoring is needed... this is a mistake: During the first months of administration, weekly monitoring is needed. SmPC 4.4.

P9 line 8 Monitoring of the FIX activity is recommended post-dose to follow the patient's response to etranacogene dezaparvovec.

Monitoring FIX activity is required to monitor the cytotoxic T cell response of the immune system. If FiX levels drop, a course of immunosuppression needs to be started ASAP to maintain the FIX production in the transduced hepatocytes. So, this is a marker for immune reaction and thus more a safety marker to maintain efficacy by timely administration of immune suppressants.

P12 line 20 Mild is 6% - 40% and not 5

P12 line 23 Please see novel Classification of women of SSC of ISTH It distinguishes five clinically relevant Hemophilia Carrier categories: women/girls with mild, moderate, or severe hemophilia (FVIII/IX >0.05 and <0.40 IU/ml, 0.01-0.05 IU/ml, and <0.01 IU/ml, respectively), symptomatic and asymptomatic HC (FVIII/IX ≥0.40 IU/ml with and without a bleeding phenotype, respectively).
https://pubmed.ncbi.nlm.nih.gov/34327828/

P12 line 39 pain **and reduced mobility of the joint.**

P12 line 51 This is not correct. Moderate hemophilia still has spontaneous bleeds.

P12 55-57 This text is not correct! Text should be amended.
Moderate form: FIX level 1-5% of normal is called moderate severe.

P13 line 25
Patients who are classified as 'moderate' and 25 who present with a severe bleeding phenotype, are classified as patients with moderately severe hemophilia B.
This is not correct! Please check with clinicians!!

P15 in the outcomes of the PICO How about Joint Bleeds as a subcategory that causes irreversible damage in the joint leading to hemophilia arthropathy? We miss this outcome!

P20 line 29 Typo please remove use after FIX inhibitor.

P23 Line 1-5
Study CT-AMT-061-01 *(ref. EPAR,* 21*)* is an open-label, single-arm study. The average FIX activity at 26 weeks was 47 IU/dL (SD: 33,2 – 57,0). No proper dose finding study for etranacogene dezaparvovec has been done. After one year of follow-up, mean FIX activity levels remained in the near-normal range.

> ***Our comment:***
> FIX Wild Type cDNA was swapped with FIX Padua Variant that has a higher (estimated seven-fold) FIX activity. Three patients were treated in a bridging study. A kind of bioequivalence study that will normally be performed in case of production changes a filed as a variation to MA. So, a new dose finding study was not necessary! Please can you nuance this remark?

P24 line 23 We do not understand your remark about treatment optimalisation?

Treatment optimalisation to stable endogenous levels with troughs of 39%??? YES! If that was possible! Because of the short half-life, amount of injection and amount of factor it is not feasible to achieve steady state levels of 39% of Factor IX with existing recombinant factor. Please explain or consider rewording this sentence?

P24 line 27 This is not a trough but steady state level because of continuous production of factor in the liver cells.

P25 line 10 Expert opinion is that because of high levels of anti-AAV antibodies no re-administration is possible not even of other subtypes.

P29 Line 21 About monitoring of adverse events. The evaluation of adverse events of etranacogene dezaparvovec **compared to EHL FIX prophylaxis** is challenging due to a number of aspects.

Please look at EUHASS the European Safety Surveillance system for hemophilia for context on safety events. https://web.euhass.org/

EMA has defined adverse events of special interest (AESI) in 2018 Report of Registries Workshop: https://www.ema.europa.eu/en/documents/report/report-haemophilia-registries-workshop_en.pdf

P50 Treatments under development: missing is Serpin C:
https://www.sciencedirect.com/science/article/abs/pii/S0006497123092212

P51 Rixubus is Short acting so Standard Half-life. SHL. Please, correct?

Pharmacotherapeutic Report

Etranacogene dezaparvovec (Hemgenix®) for the treatment of severe and moderately severe Haemophilia B (congenital factor IX-deficiency) in adult patients without a history of factor IX inhibitors.

Date April 16, 2024
Status Day 90 Definitive

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Abbreviations

Abbreviation	Description
AAV5	Adeno-associated viral vector of serotype 5
ABR	Annualized Bleeding Rate
CAT	Committee for Advanced Therapies
CI	Confidence Interval
CHMP	Committee for Medicinal Products for Human Use
CRM	Commission for Reimbursement of Medicines (Belgium)
CSR	Clinical Study Report
EHL	Extended Half-Life
EMA	European Medicine Agency
EPAR	European public assessment report
EQ-5D-5L	EuroQol-5 dimensions-5 levels
FIX	Factor IX
FU	Follow up
Gc	Genome copies
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Haem-A-QoL	Haemophilia Quality of Life Questionnaire
HR	Hazard ratio
MCID	Minimal Clinically Important Difference
NVHB	Nederlandse Vereniging van Hemofiliebehandelaars
QoL	Quality of Life
RCT	Randomised clinical trial
RR	Relative risk (risk ratio)
SAE	Serious adverse event
SHL	Standard Half-Life
SMD	Standardized mean difference
SmPC	Summary of Product Characteristics
ZIN	Zorginstituut Nederland

Samenvatting

In dit relatieve effectiviteitsrapport beschrijft het Beneluxa-beoordelingsteam, bestaande uit *Zorginstituut Nederland (ZIN: het Zorginstituut*) en de Belgische Commissie voor de Terugbetaling van Geneesmiddelen (CTG), de inhoudelijke beoordeling van de therapeutische waarde van etranacogen dezaparvovec (Hemgenix®) voor de behandeling van ernstige en matig ernstige hemofilie B met een ernstig fenotype (aangeboren factor IX (FIX)-deficiëntie) bij volwassen patiënten zonder voorgeschiedenis van FIX-remmers.

Etranacogen dezaparvovec is vergeleken met extended half-life (EHL) FIX profylaxe op volgende criteria: gunstige effecten, ongunstige effecten, ervaring, toepasbaarheid en gebruiksvriendelijkheid. Het Beneluxa beoordelingsteam wordt hierin geadviseerd door de Nederlandse *Wetenschappelijke adviesraad* (WAR) en door de CTG. De evaluatie maakt deel uit van een gemeenschappelijke evaluatie in het kader van het Beneluxa Initiative-project. Dit rapport, evenals de budgetimpactanalyse, zal zowel door ZIN als door CTG worden gebruikt. Alle beoordelingsprocedures lopen parallel volgens de nationale wetgeving.

Etranacogen dezaparvovec is een gentherapieproduct, toegediend als éénmalige intraveneuze infusie, dat is ontworpen om een kopie van de FIX-coderende DNA-sequentie (Padua-gen) in hepatocyten te introduceren om de oorzaak van de ziekte aan te pakken. Het gen is ingekapseld in een niet-replicerende recombinante adeno-geassocieerde virale vector van serotype 5 (AAV5).

Het klinische ontwikkelingsprogramma van etranacogen dezaparvovec omvat één fase 3 klinische studie, HOPE-B, een niet-gerandomiseerde, ongecontroleerde, multicenter, open-label, éénarmige studie. De studie is nog lopende.
Er was een inloopperiode (lead-in) van minimaal 6 maanden, waarin patiënten werden behandeld met FIX-profylaxe. Na de inloopperiode werd één infuus met etranacogen dezaparvovec 2 x 10^{13} gc/kg toegediend aan de proefpersonen. Initiële follow-up gebeurde 18 maanden na behandeling, waarbij de werkzaamheid en veiligheid werden geëvalueerd. Later werden de post-hoc analyses op 24 maanden toegevoegd, op basis van het klinisch studierapport en de publicatie. Een langere termijn follow-upperiode tot 5 jaar na toediening is voorzien. De inloopperiode wordt gebruikt als controle-arm.

De kwaliteit van bewijs is laag tot zeer laag door de beperkte opzet van de studie: een éénarmige studie, een beperkt aantal patiënten en een korte follow-up periode voor een potentieel levenslange behandeling. De vergunning voor het in de handel brengen werd voorwaardelijk afgeleverd door EMA.
Het beoordelingsteam van Beneluxa is van mening dat een RCT mogelijk was geweest.
Etranacogen dezaparvovec is een gentherapie die slechts één keer kan worden toegediend. Dit betekent dat de effecten onomkeerbaar zijn. Daarom is een follow-up van minimaal 10 tot 15 jaar nodig om de langetermijneffecten van de gentherapie te evalueren.

Therapeutische waarde ten opzichte van alternatieven

Etranacogen dezaparvovec resulteert mogelijk in een klinisch relevante verlaging van de jaarlijkse bloedingsfrequentie (annualized bleeding rate, ABR) in vergelijking met FIX-profylaxe: de ABR verminderde van 4,19 (95% BI: 3,22 tot 5,45) tijdens de inloopperiode tot 1,51 (95% BI: 0,83 tot 2,76) gedurende maand 7 tot en met 24 na behandeling. De afname resulteerde in een ABR-frequentieratio van 0,36 (95% BI: 0,21 tot 0,63; p<0,001). De rate ratio en 95% BI liggen onder de klinische relevantiegrens van 0,75.

Het aantal bloedingen was gebaseerd op zelfrapportage door de patiënt, wat als subjectief kan worden beschouwd. Anderzijds vertoonde de belangrijkste surrogaatuitkomstmaat voor bloedingen, endogene FIX, een significante toename na toediening van etranocagen dezaparvovec. Deze toename hield aan tot en met maand 12 (kleinste kwadraten gemiddelde (least-square mean, LSM) toename ten opzichte van baseline: 38,8 procentpunten - 95% BI, 34,0 tot 43,6; p<0,001) en daalde licht tot maand 24 (LSM stijging ten opzichte van baseline: 34,1 procentpunten - 95% BI: 29,6 tot 38,7; p<0,001). Het is onduidelijk of deze daling van endogene FIX-niveaus in de loop van de tijd zal aanhouden, verminderen of vergroten.

Etranacogen dezaparvovec resulteert mogelijk in een klinisch relevante vermindering van het percentage patiënten dat FIX-profylaxe moet voortzetten of hervatten. Alle patiënten die de inloopperiode voltooiden, zetten hun FIX-profylaxe tijdens de inloopperiode voort. 96% (52/54) stopte met FIX-profylaxe na de behandeling met etranacogen dezaparvovec en hervatte deze niet tijdens de onderzoeksperiode. Dit resulteerde in een RR van 0,04 (95% BI: 0,01 tot 0,14). Twee patiënten stopten niet met de FIX-profylaxe tijdens de volledige follow-up periode. Bij deze twee studie deelnemers was de FIX-activiteit minder dan 5% in maand 18. Aanvullend had een andere patiënt een FIX-activiteit van <5% (4,7%) op maand 24, wat de onzekerheid over de duurzaamheid van het effect van etranacogene dezaparvovec vergroot.

Er zijn te weinig gegevens met betrekking tot de cruciale uitkomstmaat hemofiele artropathie om conclusies te kunnen trekken. Anderzijds verbeterden gewrichtsbloedingen, alsook de Joint Health Score scores tijdens de post-behandeling periode (7-24 maanden) ten opzichte van baseline.

Etranacogen dezaparvovec heeft een statistisch significante verbetering van de kwaliteit van leven laten zien op de ziektespecifieke hemofilie Quality of Life Questionnaire for Adults (Hem-A-QoL).
De LSM totaalscore was 25,6 tijdens de inloopperiode en daalde met 21,5%, tot 20,1 in maand 12 (LSM verandering in score -5,5; 95% BI: -7,4 tot -3,6). De klinische relevantie van het effect is onzeker.
Er werden geen significante verschillen waargenomen in de VAS-scores van het generieke instrument EQ-5D-5L tussen de aanloopperiode en maand 12 na de behandeling.

Ongunstige effecten

Er werden geen behandelingsgerelateerde ernstige bijwerkingen gemeld gedurende

de gehele follow-up periode (inloopperiode en periode na toediening van etranacogen dezaparvovec). Zorgvuldige postmarketingsurveillance is van het grootste belang om potentiële zeldzame bijwerkingen op te sporen en het potentiële risico op maligniteit als gevolg van vectorintegratie te onderzoeken.

In HOPE-B stierf één patiënt ongeveer 15 maanden na de behandeling door cardiogene shock, die door de onderzoekers werd beschouwd als niet gerelateerd aan de behandeling.

Toepasbaarheid

Etranacogen dezaparvovec-specifieke contra-indicaties zijn actieve infecties, zowel acute als chronische die niet onder controle zijn, en bekende gevorderde leverfibrose of -cirrose.

Voorafgaand aan de behandeling moeten de volgende onderzoeken worden uitgevoerd: titer van reeds bestaande neutraliserende anti-AAV5-antilichamen, levertransaminasen, echografie van de lever en elastografie. Etranacogen dezaparvovec mag alleen worden toegediend aan patiënten bij wie is aangetoond dat zij geen FIX-remmers hebben.

Tijdens of kort na toediening van de behandeling zijn infusiegerelateerde reacties mogelijk.
Na de toediening van etranacogene dezaparvovec, is wekelijkse lever- en FIX-monitoring nodig tijdens de eerste drie maanden om verhogingen van ALT te detecteren. Dit zou kunnen wijzen op de noodzaak om een behandeling met corticosteroiden op te starten. Na de eerste drie maanden, blijven lever- en FIX-monitoring aangeraden om routinematig de gezondheidsstatus van de lever en het bloedingsrisico op te volgen.
De momenteel beschikbare informatie wijst erop dat er een levenslang risico op insertionele mutagenese met daaropvolgende carcinogenese kan bestaan.
Na toediening van etranacogen dezaparvovec moeten patiënten die kinderen willen verwekken en hun vrouwelijke partners die kinderen kunnen krijgen, gedurende 12 maanden een zwangerschap voorkomen of uitstellen met een barrièremethode.
Mannen die met etranacogen dezaparvovec worden behandeld, mogen geen sperma doneren.

Gebruiksvriendelijkheid

De intraveneuze infusie met een enkelvoudige dosis moet worden toegediend onder toezicht van een arts die ervaring heeft met de behandeling van hemofilie en/of bloedingsstoornissen.
Hemostatische ondersteuning met exogene humane FIX kan nodig zijn tijdens de eerste weken na infusie van etranacogen dezaparvovec.
Wekelijkse lever- en FIX monitoring zijn nodig in de eerste drie maanden post-dosis.
Na de eerste drie maanden zijn routine lever- en FIX monitoring aanbevolen.

Onzekerheden en problemen

	Onzekerheden	Problemen
Klinische gegevens	Extrapolatie van AMT-060 naar etranacogen dezaparvovec (AMT-061) Geen gegevens over optimalisatie van de behandeling voor/tijdens de inloopperiode	Lage kwaliteit van bewijs en risico op bias - Weinig gegevens, door klein aantal patiënten - Geen controle-arm - Verschil in duur tussen inloopperiode en follow-up periode - Zeldzame bijwerkingen niet gedetecteerd Therapietrouw gedurende de lead-in periode (‘treatment exposure’ in vergelijking met de totale hoeveelheid FIX die de patiënten verondersteld werden te krijgen) werd niet gemeten.
Dagelijkse praktijk	Werkzaamheid op lange termijn, met risico op noodzaak om terug te keren naar FIX profylaxe Veiligheid op lange termijn: - Levenslang risico op maligniteit als gevolg van vectorintegratie - Impact van neutraliserende anti-AAV5-antilichamen op werkzaamheid en veiligheid - Vectorverspreiding op lange termijn via lichaamsvloeistoffen - Risico op trombo-embolische voorvallen Risico op ontwikkeling van FIX-remmers Therapietrouw aan FIX-profylaxe kan in de dagelijkse praktijk lager zijn dan in de HOPE-B studie Aantal patiënten die behandeld zullen worden met etranacogene dezaparvovec	Geen gegevens over hemofiliele artropathie (korte termijn data over gewrichtsbloedingen zijn beschikbaar) Zeer beperkte lange termijn gegevens Geen gegevens bij kinderen Geen aanwijzing dat herhalen van etranacogene dezaparvovec of een andere gentherapie (gebaseerd op dezelfde of een andere vector) mogelijk is, in geval van falen van werkzaamheid van etranacogene dezaparvovec. Het is onwaarschijnlijk dat dit mogelijk zal zijn.

Op basis van de momenteel beschikbare gegevens, concludeert het Beneluxa-

beoordelingsteam (de Belgische CTG en het Zorginstituut Nederland) dat etranacogen dezaparvovec (Hemgenix®) voor de behandeling van volwassen patiënten met ernstige en matig ernstige hemofilie B (congenitale FIX-deficiëntie) met een ernstig bloedingsfenotype, zonder voorgeschiedenis van FIX-remmers, voldoet aan de huidige stand van wetenschap en praktijk. Er blijft echter een aanzienlijke mate van onzekerheid bestaan over de duurzaamheid van de werkzaamheid en het veiligheidsprofiel van etranacogen dezaparvovec.

De bespreking van het concept van dit relatieve effectiviteitsrapport vond plaats in de vergadering van de Wetenschappelijke Adviesraad – Commissie Geneesmiddelen van Zorginstituut Nederland op 8 april 2024, en in de vergadering van de Belgische Commissie Vergoeding van Geneesmiddelen op 16 april 2024.

Summary

In this relative effectiveness report, the Beneluxa assessment team, including *Zorginstituut Nederland* (ZIN: the National Healthcare Institute) and the Belgian Commission for Reimbursement of Medicines (CRM), describes the substantive assessment of the benefit of etranacogene dezaparvovec (Hemgenix®) for the treatment of severe and moderately severe haemophilia B with a severe phenotype (congenital factor IX (FIX)-deficiency) in adult patients without a history of FIX inhibitors.

Etranacogene dezaparvovec has been compared to prophylaxis with EHL FIX on the criteria favourable effects, unfavourable effects, experience, applicability, and usability. The Beneluxa assessment team has been advised in this regard by its Dutch Scientific Advisory Board (*Wetenschappelijke adviesraad*: WAR) and by the Belgian Commission Reimbursement of Medicines (CRM). The evaluation is part of a common evaluation in the context of the Beneluxa Initiative project. This report, as well as the budget impact analysis, will be used both by ZIN and CRM. All assessment procedures are running in parallel according to the national legislations. Etranacogene dezaparvovec is a single-dose intravenous infusion of a gene therapy product designed to introduce a copy of the FIX coding DNA sequence (Padua gene) into hepatocytes to address the root cause of the disease. The gene is encapsulated in a non-replicating recombinant adeno-associated viral vector of serotype 5 (AAV5).

The clinical development program of etranacogene dezaparvovec includes one phase 3 clinical trial, HOPE-B, a non-randomized, uncontrolled, multicentre, open-label and single-arm trial. There was a lead-in period of minimum 6 months, in which patients were treated with FIX prophylaxis. After the lead-in period, one infusion of etranacogene dezaparvovec 2 x 10^{13} gc/kg was administered to the study subjects. Initial follow-up was 18 months after treatment for evaluation of efficacy and safety. Later, 24-month post-hoc efficacy and safety data were added, based on the Clinical Study Report (CSR) and the publication. A longer-term follow-up period extends through 5 years after dosing and is still ongoing. The lead-in arm serves as a control arm.

The quality of the evidence is low to very low due to the limited set-up of the trial: a single-arm trial, a limited number of patients and a short follow-up period for a potentially lifelong treatment. The marketing authorisation is delivered on a conditional basis. The Beneluxa assessment team believes an RCT could have been possible. Etranacogene dezaparvovec is a gene therapy that can be administered only once. This means its effects are irreversible. Therefore, a minimum of 10 to 15 years follow-up is needed to evaluate the long-term effects of the gene therapy.

Favourable effects (value versus alternatives)

Etranacogene dezaparvovec may result in a clinically relevant reduction of the annualized bleeding rate (ABR) compared to FIX prophylaxis: decrease in ABR from 4,19 (95% CI: 3,22 to 5,45) during the lead-in period to 1,51 (95% CI: 0,83 to 2,76) during months 7 through 24 after treatment, resulting in an ABR rate ratio of 0,36 (95% CI: 0,21 to 0,63; p<0,001). The rate ratio and 95% CI are below the clinical relevance boundary of 0,75.

The number of bleeds were based on patient-reporting, which may be considered as subjective. On the other hand, the major surrogate outcome measure for bleeding, endogenous FIX, showed a significant increase after etranocagene dezaparvovec administration. This increase was sustained through month 12 (least-squares mean increase from baseline: 38,8 percentage points - 95% CI, 34,0 to 43,6; p<0,001) and slightly decreased until month 24 (least-squares mean increase from baseline: 34,1 percentage points (95% CI: 29,6 to 38,7; p<0,001). It is unclear if this decline in endogenous FIX levels will be sustained, lessened, or enhanced over time.

Etranacogene dezaparvovec may result in a clinically relevant reduction of the percentage of patients who are required to continue or resume FIX prophylaxis. Of all patients completing the lead-in period, of which 100% continued FIX prophylaxis during the lead-in period, 96% (52/54) discontinued FIX prophylaxis post-treatment with etranacogene dezaparvovec and did not resume it during the study period. This resulted in a RR of 0,04 (95% CI: 0,01 to 0,14). The two participants, whose FIX activity was less than 5% at month 18, did not discontinue FIX prophylaxis throughout the entire follow-up. An additional patient had a FIX activity of <5% (4,7%) at month 24, which increases the uncertainties of the durability of etranacogene dezaparvovec.

There are insufficient data related to the crucial outcome measure haemophilic arthropathy to be able to draw conclusions. However, joint bleeds and the joint health score scores improved in the post-treatment period (7-24 months) compared to the lead-in period.

Etranacogene dezaparvovec has shown a statistically significant improvement of quality of life on the disease-specific Haemophilia Quality of Life Questionnaire for Adults (Hem-A-QoL). At month 12 after treatment, the mean total score has decreased by 21,5% as compared with the lead-in period (least-square mean change in score -5,5; 95% CI: -7,4 to -3,6), from a least-square mean score of 25,6 at lead-in to 20,1 at month 12. The clinical relevance of the effect is uncertain. No significant differences were observed in the generic instrument EQ-5D-5L VAS scores between the lead-in period and month 12 after treatment.

Unfavourable effects
No treatment-related serious adverse events were reported during the entire follow-up period (lead-in and after etranacogene dezaparvovec administration). Diligent post-marketing surveillance is of utmost importance to detect potential rare adverse events and to investigate the potential risk of malignancy, due to vector integration.

In HOPE-B, one patient died approximately 15 months after treatment from cardiogenic shock that was considered by the investigators to be unrelated to treatment.

Applicability
Etranacogene dezaparvovec-specific contra-indications are active infections, either acute or uncontrolled chronic, and known advanced hepatic fibrosis or cirrhosis.
Prior to treatment, following investigations must be performed: titre of pre-existing neutralising anti-AAV5 antibodies, liver transaminases, liver ultrasound and elastography. Etranacogene dezaparvovec should only be administered to patients who have demonstrated absence of FIX inhibitors.
During of shortly after treatment administration, infusion-related reactions are possible.
After administration, weekly hepatic and FIX monitoring is needed in the first 3

months to detect increases in ALT that may indicate the need to initiate corticosteroid treatment. After the first 3 months, hepatic and FIX monitoring is recommended to routinely assess liver health and bleeding risk, respectively.
The currently available information suggests that there might be a lifelong risk of insertional mutagenesis and subsequently carcinogenesis.
For 12 months after administration of etranacogene dezaparvovec treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using barrier contraception. Males treated with etranacogene dezaparvovec must not donate semen.

Usability
The single-dose intravenous infusion must be administered under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Haemostatic support with exogenous human FIX may be needed during the first weeks after etranacogene dezaparvovec infusion. Weekly hepatic and FIX monitoring is needed in the first 3 months post-dose. After the first 3 months, routine hepatic and FIX monitoring is recommended.

Uncertainties and problems

	Uncertainties	Problems
Clinical data	Extrapolation AMT-060 to etranacogene dezaparvovec (AMT-061) No data on optimalisation of treatment before/during the lead-in period	Low quality of evidence and risk of bias due to: - Limited available data, due to small sample size - Lack of control arm - Difference in duration between lead-in period and follow-up period - Uncommon adverse events not captured Treatment compliance during the lead-in period (treatment exposure compared to the total amount of FIX the patients were supposed to receive) not captured
Daily practice	Durability and need to return to factor replacement Long-term safety: - Lifelong risk of malignancy as a result of vector integration - Impact of neutralizing anti-AAV5 antibodies on efficacy and safety - Long-term vector shedding via body fluids - Risk of thromboembolic events Risk of development of FIX inhibitors	No data on haemophilic arthropathy (short-term data on joint bleeds are available) Very limited long-term data No data in children No indication that repetition of etranacogene dezaparvovec or another gene therapy (based on the same or another vector) will be possible, in case of failure of etranacogene dezaparvovec to show sustainable efficiency. It is unlikely that it will be possible.

	Compliance to FIX prophylaxis may be lower in daily practice Number of patients that will be treated with etranacogene dezaparvovec	

The Beneluxa assessment team (the Belgian CRM and Zorginstituut Nederland) concludes that etranacogene dezaparvovec (Hemgenix®) for adult patients with severe and moderately severe haemophilia B (congenital FIX-deficiency) with a severe bleeding phenotype, without a history of FIX inhibitors, meets the current state of science and practice based on the currently available data. However, a substantial level of uncertainty remains related to the durability of effectiveness and the safety profile of etranacogene dezaparvovec.

The discussion of the concept of this relative effectiveness report by the Scientific Advisory Board of Zorginstituut Nederland took place at its meeting on April 8th, 2024, and by the Belgian Commission Reimbursement of Medicines at its meeting on April 16th, 2024.

1 Introduction

1.1 Subject of the submission

In this report, Beneluxa assesses the value of etranacogene dezaparvovec in severe and moderately severe haemophilia B (congenital FIX-deficiency) with a severe bleeding phenotype in adult patients without a history of FIX inhibitors, compared to standard of care therapy. In severe and moderately severe haemophilia B, patients present with a severe bleeding phenotype.

Etranacogene dezaparvovec (Hemgenix®) intravenous infusion (ref. SmPC)
Registered indication: Treatment of severe and moderately severe Haemophilia B (congenital FIX deficiency) in adult patients without a history of FIX inhibitors.
Claim of the registration holder: Etranacogene dezaparvovec is non-inferior to FIX prophylaxis in severe and moderately severe haemophilia B (congenital FIX-deficiency) with a severe bleeding phenotype in adult patients without a history of FIX inhibitors.[1]
Posology: A single dose of 2 x 10^{13} gc/kg body weight corresponding to 2 mL/kg body weight, administered as an intravenous infusion after dilution with sodium chloride 9 mg/mL (0,9%) solution for injection. Etranacogene dezaparvovec can be administered only once.
Composition: 1 x 10^{13} genome copies/mL concentrate for solution for infusion. Each vial contains an extractable volume of 10mL of concentrate for solution for infusion, containing a total of 1 x 10^{14} genome copies.
Mode of action: Etranacogene dezaparvovec is a gene therapy product designed to introduce a copy of the human FIX coding DNA sequence into hepatocytes to address the root cause of the Haemophilia B disease. It consists of a codon-optimised coding DNA sequence of the gain-of-function Padua variant of the human FIX (hFIXco-Padua), under control of the liver-specific LP1 promoter, encapsulated in a non-replicating recombinant adeno-associated viral vector of serotype 5 (AAV5). Following single intravenous infusion, etranacogene dezaparvovec preferentially targets liver cells, where the vector DNA resides almost exclusively in episomal form. After transduction, etranacogene dezaparvovec directs long-term liver-specific expression of FIX-Padua protein. As a result, etranacogene dezaparvovec partially or completely ameliorates the deficiency of circulating FIX procoagulant activity in patients with Haemophilia B.
Comments: Etranacogene dezaparvovec is an orphan drug. It has received a conditional marketing authorisation by EMA on February 20th, 2023. The Pharmacotherapeutic Group : Blood coagulation factors ATC code: B02BD16. *(website EMA, accessed February 2024)*

[1] The registration holder suggested to amend the claim by adding an upper limit of anti-AAV5 antibody titres (<1:678), excluding patients with titres beyond this limit. After consultation with the Dutch clinical experts, the Beneluxa assessment team did not agree with the suggested claim amendment. The clinical experts are of the opinion that more data is needed to validate such, at the moment arbitrary, value. The assessment was therefore performed based on the initial claim as stated above.

In the Netherlands, etranacogene dezaparvovec (Hemgenix®) has been placed in the *'Sluis voor Dure Geneesmiddelen'* on February 9, 2023. *(website Zorginstituut Nederland, accessed November 2023)*

1.2 Background

1.2.1 Disease

Haemophilia B is an orphan disease, an X-linked, recessive bleeding disorder caused by a mutation in the gene encoding coagulation factor IX (FIX). The FIX gene is produced by the liver. Etranacogene dezaparvovec contains the human coagulation FIX variant R338L gene, also called the FIX-Padua gene.

Haemophilia B is less frequent than haemophilia A and accounts for 15-20% of all congenital haemophilia cases.

The disease is characterised by an increased bleeding tendency due to either a partial or complete deficiency in the activity of the essential blood coagulation FIX. The disease severity in haemophilia generally correlates with the degree of the coagulation factor FIX deficiency. The classification is based on the residual FIX activity level.

- Severe form: FIX level <1% of normal
- Moderate form: FIX level 1-5% of normal
- Mild form: FIX level >5 and <40%

Because haemophilia B is an X-linked, recessive condition, it occurs primarily in males. Females are typically carriers with a mild or absent bleeding phenotype.

Haemophilia should be suspected in individuals presenting with a history of easy bruising, spontaneous bleeding particularly in the joints, muscles and soft tissue and excessive bleeding following surgery or trauma; a family history suspicious of haemophilia and/or an isolated prolonged aPTT with no explanation. If haemophilia is suspected, the clinician should obtain a family history to assess patterns of inheritance. The diagnosis is established by identification of decreased FIX clotting activity. One-stage clotting based on aPTT is the most commonly used technique.

References[1, 2, 3, 4, 5, 6]

1.2.2 Symptoms and severity

Patients with severe haemophilia frequently develop haemorrhages, often into joints, muscles, or soft tissues without any apparent cause.
Intra-articular and intramuscular bleeding most commonly occurs in the knees, elbows, and ankles, with pain and reduced mobility of the joint as a result. Unless appropriately managed, even subclinical hemarthrosis can cause synovial proliferation and inflammation, called haemophilic synovitis, and lead to haemophilic arthropathy. The latter is a disabling, multifactorial condition, with changes occurring in the synovium, bone, cartilage, and blood vessels. Haemophilic arthropathy causes pain and limitation of motion, severely affecting patients' quality of life (QoL). It eventually requires joint replacement. Other musculoskeletal complications include compartment syndrome and pseudotumors. Bleeding episodes can also be life-threatening, such as intracranial haemorrhages.

The severity of bleeding manifestations generally correlates with the degree of the clotting factor deficiency. Patients with severe haemophilia B always have a severe bleeding phenotype. Severe forms become apparent early in life. In patients with mild and moderate factor IX deficiency spontaneous haemorrhages are more rare,

and excessive bleeding mainly occurs following trauma or in association with invasive procedures. However, heterogeneous bleeding phenotypes among individuals with the same factor levels can occur.
A small proportion of patients with moderately deficient FIX levels also have a clinically severe bleeding phenotype and musculoskeletal complications.

A severe phenotype is defined by EMA as:
- Current of historical repeated spontaneous bleeding episodes, which may include joint or life-threatening haemorrhage
- And/or joint damage due to hemarthrosis
- And/or current use of FIX continuous prophylaxis

Without treatment, patients die at a young age (13 years of age at the beginning of the 20th century). As a result of the recent progress made in the field of haemophilia therapy, the life span of people with haemophilia has gradually become similar to that of males in the general population, at least in more developed countries. However, haemorrhage remains a leading cause of death.
An observational cohort study in the Netherlands showed that survival in 1066 patients with haemophilia has improved over time, but it is still lower than in the general population. A study in the Netherlands showed that the number of deaths because of an intracranial bleeding is 12,8 times higher than in the general male population.

(Ref.[7, 8 ,9 ,10 ,11, 12, 13, 14]; EPAR; website Beneluxa, accessed February 2024)

1.2.3 Prevalence and incidence

The prevalence of haemophilia B across all severity levels is estimated to be 5,0 cases per 100,000 males[15]. All patients with severe haemophilia B are considered to have a severe bleeding phenotype. Patients who are classified as 'moderate' and who present with a severe bleeding phenotype, are classified as patients with moderately severe haemophilia B in accordance with the Dutch and Belgian clinical experts.

There are 182 patients with haemophilia B registered in the Netherlands[16]. A total of 86 patients has severe haemophilia B. Another 13 patients have moderate haemophilia B and are using FIX prophylaxis (considered moderately severe). Precise prevalence data for the Belgian patient populations are unavailable. Belgian clinical experts estimate the number of prevalent adult patients with severe or moderately severe haemophilia B in Belgium at 75 to 85.

Dutch and Belgian clinical experts estimate the incidence number to be 2 to 3 and 3 in the Netherlands and Belgium respectively.

1.2.4 Current Standard of Care

Haemophilia B management needs a multidisciplinary approach, with prevention of bleeding and joint damage amongst the most important treatment goals. The Dutch national guidelines[17] are in line with the World Federation of Haemophilia (WFH) recommendations *(Srivastasa et al. 2020)*. As there are no national guidelines in Belgium, a treatment approach consistent with the WFH recommendations is applied by clinicians.

Treatment of haemophilia B mainly relies on **FIX replacement therapy**, which restores haemostasis by replacing the missing natural clotting protein, FIX, with clotting FIX concentrates. Dutch and Belgian experts state they treat patients based on bleeding phenotype rather than on genotype.

Prophylaxis or regular replacement therapy is the standard of care for people with a severe bleeding phenotype. Replacement therapy must be tailored to the patient and the situation, for example around surgery. **Episodic replacement therapy or on-demand therapy** is defined as the administration of clotting factor concentrate only at the time of a bleed.

Extended half-life (EHL) FIX concentrates allow for wider intervals between treatment, once every 7 to 14 days, compared to **standard half-life (SHL) FIX concentrates**. EHL is standard of care for prophylaxis in both countries and exclusively used in Belgium. In the Netherlands, a small proportion of patients is still using SHL for various reasons. The transition from SHL to EHL is ongoing in the Netherlands.

There is a risk of developing neutralizing antibodies against the administered FIX, neutralizing the function of FIX clotting concentrate. Treatment of haemophilia is becoming increasingly difficult in presence of **FIX inhibitors**. The bypassing agent, activated recombinant factor VII, can be used for the treatment of bleeding in presence of FIX inhibitors. rFVIIa promotes coagulation via binding to tissue factor to activate FX and FIX, allowing the coagulation cascade to resume.

Positioning of etranacogene dezaparvovec according to haemophilia professional organisations

Belgian and Dutch clinical experts position etranacogene dezaparvovec in adult patients with haemophilia B, who are treated or should be treated prophylactically with FIX concentrate according to the current guidelines.
The company summarized the eligible population for etranacogene dezaparvovec in everyday life as illustrated in figure 1.

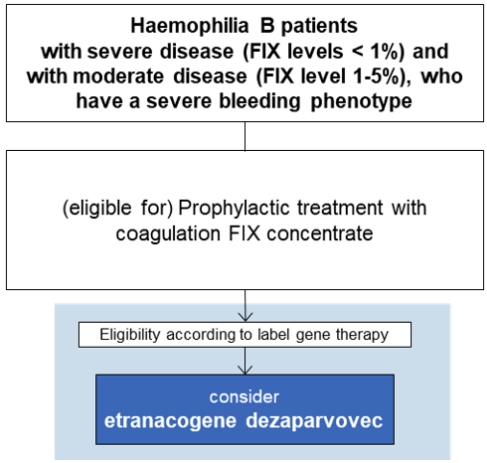


Figure 1. Positioning of etranacogene dezaparvovec treatment within haemophilia B.

2 Methodology systematic literature search

2.1 Scope of the report

Is etranacogene dezaparvovec (AMT-061 or Hemgenix®) a non-inferior treatment option and alternative compared to routine EHL FIX prophylaxis, in adult patients with severe and moderate haemophilia B (congenital FIX deficiency) with a severe bleeding phenotype, without a history of FIX inhibitors?

2.1.1 PICO

Tabel 1. PICO

Patient population	Adult patients with severe and moderate haemophilia B (congenital FIX deficiency) with a severe bleeding phenotype, without a history of FIX inhibitors*
Intervention	Etranacogene dezaparvovec (AMT-061) as a single dose administration via intravenous infusion
Controls	Prophylactic treatment with EHL FIX concentrate
Outcome measures	**Bleeding outcomes:** Annualised Bleeding Rate (ABR), all bleeds **Exogenous FIX use:** percentage of patients who did resume FIX prophylaxis after treatment with etranacogene dezaparvovec **Quality of life** - Generic instruments: o EuroQol-5 dimensions-5 levels (EQ-5D-5L) Visual Analogue Scale - Disease-specific instrument: Haemophilia Quality of Life Questionnaire for Adults (Hem-A-QoL) questionnaire **Long-term outcome:** prevention of haemophilic arthropathy **Incidence of serious adverse events (SAEs)**
Relevant follow-up period	**<u>Short-term follow-up</u>** As the transgene needs several months to become active, a follow-up of 3 to 5 years would be needed to evaluate the magnitude of the effect. This is in line with advice from clinical experts. **<u>Long-term follow-up</u>** Etranacogene dezaparvovec is a gene therapy that can be administered only once. This means its effects are irreversible. Therefore, a minimum of 10 to 15 years follow-up is needed to evaluate the long-term effects of the gene therapy.

Study design	The **optimal** study design would be a long-term, prospective, double-blind, randomized, controlled trial versus standard-of-care, FIX prophylaxis. **Feasibility** A randomized controlled trial comparing etranacogene dezaparvovec with standard of care, FIX prophylaxis, could be possible. Blinding is difficult, because: - Frequent IV infusions are needed with FIX prophylaxis. Frequent infusions with placebo would not be ethical. - Blinding of the reviewers would be difficult because patients are used to control their body for bleeds at home. Haemophilia B is an orphan indication. Therefore, only a limited number of patients can be included in a clinical trial. Nevertheless, because there is a total of between 150 and 200 severe or moderately severe haemophilia B patients combined in the Netherlands and Belgium alone, the Beneluxa assessment team believes an RCT may be conceivable. A potential hurdle for patients to enrolling in such a trial, may be the fact that it concerns a highly experimental and irreversible gene therapy. A very long-term clinical trial with two arms would be difficult, because patients on FIX therapy should have the opportunity to receive etranacogene dezaparvovec, if they decide this, for example at commercialisation. **Optimal and feasible design** An open label, parallel, randomized controlled trial versus SoC (FIX prophylaxis) with a single-arm long-term follow-up, including patients having received etranacogene dezaparvovec, as well as 'cross-over patients' having been enrolled in the FIX prophylaxis arm and receiving etranacogene dezaparvovec at the end of the parallel phase, would be the optimal and feasible design. The design of the HOPE-B trial, in which persons serve as their own comparators, has been discussed with and accepted by FDA and EMA. As the study does include an intra-patient control, the study design is deemed usable for assessment of effectiveness by the Beneluxa assessment team.

** For Belgium, the company added a reimbursement limitation as follows: 'AAV5-antibody titre lower than 1:678, as shown by an appropriately validated cell-based test'. However, CRM decided to follow EMA and recommendations by the Dutch Clinical Expert group, and decided not to include a limitation based on AAV5-*

antibody titre (see also 3.3.1).

2.1.2 Outcome measures and clinical relevance limits

Crucial outcome measures were established in a scoping meeting between RIZIV-INAMI and the National Healthcare institute with Belgian and Dutch clinical experts and patient organisations (Dutch Association for Haemophilia-Patients and Belgian Association of Haemophilia, Von Willebrand and Other Coagulation Disorders).

Survival of haemophilia B patients has improved over the years and, although still lower, has become close to survival in the general population *(Ref.[18], Hassan et al. 2020).* The amount of data and duration of follow-up to be able to show a difference between etranacogene dezaparvovec and FIX prophylaxis would need to be too extensive to be feasible. For these reasons and based on the input in the scoping meeting, survival and mortality has not been retained as a crucial outcome measure.

Annualized Bleeding Rate (ABR)
Bleeding is the main symptom of haemophilia B. The aim of prophylactic treatment is to prevent bleeding and thus haemophilic arthropathy in the long term.

ABR is the estimated annual number of bleedings, calculated by extrapolating the number of bleedings during the study duration to one year. It is considered a crucial outcome measure because the goal of prophylactic treatment is prevention of bleeding. ABR is a degree of lack of treatment efficiency compared to the ideal, which would be no bleeds.
ABR is generally based on self-reporting (e-diary) because patients often already feel bleeding, with tingling, pain, 'aura'…, before it is visible on the outside. Confirmation by a physician is not practically feasible as bleeding may occur at all times.

Percentage of patients who are required to continue or resume FIX prophylaxis
The goal of gene therapy is to avoid bleeds without the need for FIX prophylaxis. Each patient that is required to continue or to resume FIX prophylaxis, with the associated treatment burden of frequent IV infusions, is a measure of treatment failure. Therefore, the percentage of patients who are required to continue or resume FIX prophylaxis is considered a crucial outcome measure.

In HOPE-B, continuous routine prophylaxis was defined as the intent of treating with an a priori defined frequency of infusions (e.g., twice weekly, once every two weeks, etc.) as documented in the medical records. *(Ref. CSR)*

Quality of life
Quality of life is considered a crucial outcome measure. Both generic and disease-specific measuring instruments are relevant for measuring quality of life (QoL).
A commonly used generic instrument is the EuroQol 5-Dimension 5-Level (EQ-5D-5L) visual analogue scale (VAS). EQ-ED-5L scores range from 0 to 100, with higher scores indicating better health. For the clinical evaluation, disease-specific questionnaires are preferred if available.
The validated Haem-A-QoL questionnaire has been developed for haemophilia patients. In this questionnaire physical and emotional limitations are questioned. The scale ranges from 0 to 100, with higher numbers indicating deterioration. Responders are defined as an improvement (i.e., a reduction) of 7 points on the total score and 10 points on the physical health domain. A minimal clinically important improvement was identified as a 10-point reduction in the 'Physical Health' and 'Sports & Leisure' domains, and a 7-point reduction in 'Total Score' for

the Hem-A-QoL in by Wyrwich et al, 2015[19].

Long-term outcome: prevention of haemophilic arthropathy
Prevention of haemophilic arthropathy is a crucial outcome measure, because haemophilic arthropathy is a very disabling long-term consequence of frequent joint bleeds. It is a measure of lack of treatment efficiency compared to the ideal, which would be no haemophilic arthropathy and no bleeds. In the short-term, a decrease of the number of joint bleeds may be used as a surrogate for prevention of haemophilic arthropathy.

Serious adverse events
The incidence of intervention-related serious adverse events (treatment-related serious adverse events) is considered a crucial outcome measure. In addition, an overview is provided of the most frequently occurring (serious) adverse effects.

For the outcome measures for which there are no published or professionally established and supported **minimal important differences** (MIDs), the following values are taken as a starting point for determining clinical relevance: for dichotomous outcome measures a relative risk (RR) of 0,75 or 1,25 and for continuous outcomes a standardized mean difference (SMD) of 0,5. These values reflect a moderate to reasonable effect.

2.2 Search Strategy

To extract relevant data from scientific studies, a literature search in PubMed was conducted for publications on etranacogene dezaparvovec in haemophilia B.

Furthermore, the Summary of Product Characteristics (SmPC) of the registration dossier and the European Public Assessment Report (EPAR) of the European Medicines Agency (EMA) were used in the assessment.

2.3 Selection criteria

In- and exclusion of the literature found happened based on the abstracts. If the publications could not be excluded on the basis of the abstract, the whole publication has been evaluated.

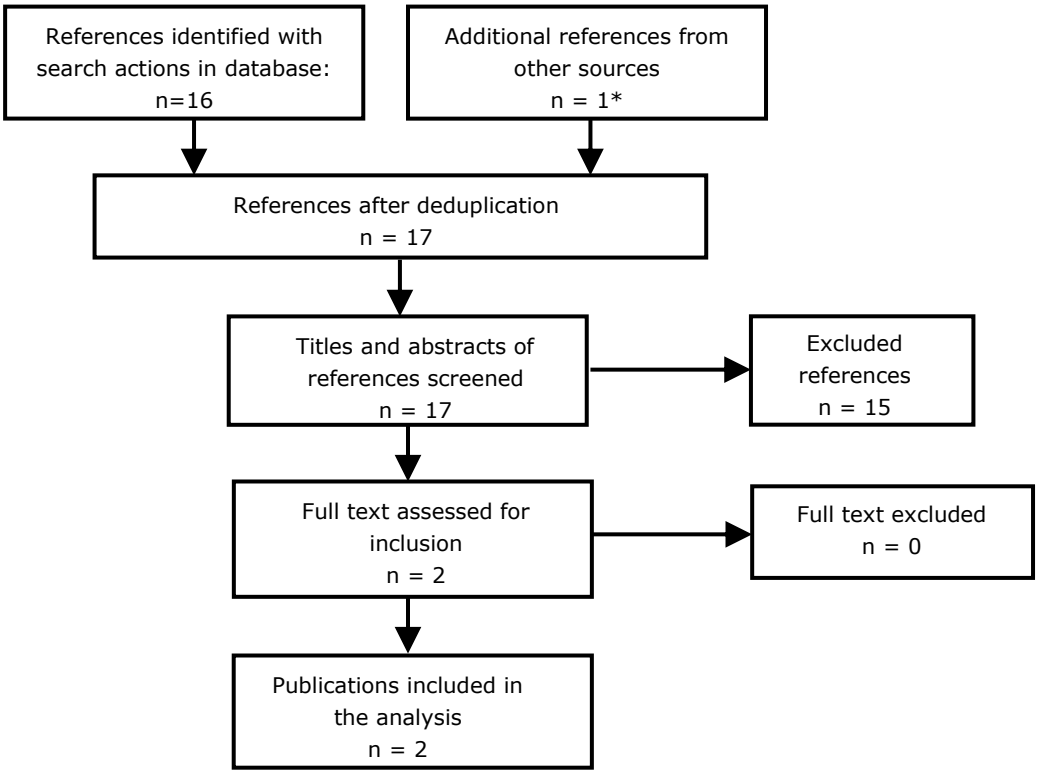
The following inclusion criterion was used:
- Clinical trials

The following exclusion criteria were used in the literature search:
- Preclinical and modelling studies
- Phase 1 and 2 studies
- Review articles and abstracts.

3 Results

3.1 Results literature search

Besides the SmPC, the literature search resulted in 16 references, of which 1 published study met the inclusion criteria. The following PRISMA flowchart shows the selection process.



*The EPAR Assessment report of etranacogene dezaparvovec was included as an additional reference.

The search strategy is detailed in Appendix 1. The characteristics of the selected study are presented in Appendix 2. The excluded studies are presented in Appendix 3. The included guidelines and other sources are set out in Appendix 4.

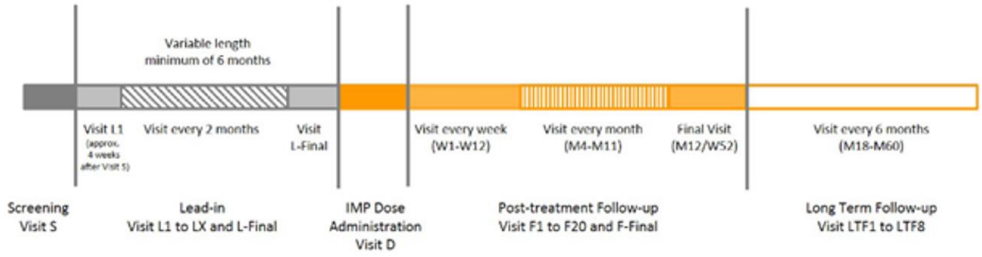
The search strategy in PubMed resulted in 16 references, of which 1 published study met the in- and exclusion criteria.

3.2 Characteristics included studies

HOPE-B is the phase 3 trial, included in the analysis *(Ref.[20]; Pipe et al. 2023; EPAR; CSR, [21])*. Phase 1 & 2 studies, as well as research with AMT-060, etranacogene dezaparvovec's predecessor, will be briefly discussed in the section 'other considerations' and appendix 8.

Study Design

HOPE-B (Health Outcomes with Padua gene; evaluation in haemophilia-B) is a non-randomized, uncontrolled, multicentre, open-label, single-arm phase 3 study. There was a lead-in period of a minimum of 6 months of FIX prophylaxis. Patients served as their own comparator. During the lead-in period, subjects recorded their use of FIX replacement therapy and bleeding episodes in their dedicated e-diary in order to provide a baseline of bleeding event frequency and FIX consumption.
Continuous routine prophylaxis was defined in the eligibility criteria as the intent of treating with an a priori defined frequency of infusions, as decided by the principal investigator and documented in the medical records. There was no treatment optimisation before or during the lead-in period. The FIX treatment exposure compared to the total of FIX prophylaxis therapy that the patients were supposed to receive during the lead-in period was not captured. Therefore, there is no information on how compliant patients were to FIX therapy before receiving etranacogene dezaparvovec.
After the lead-in period, one infusion of etranacogene dezaparvovec 2 x 10^{13} gc/kg was administered to the study subjects.
Initial follow-up was 18 months after treatment for evaluation of efficacy and safety. Later, 24-month post-hoc efficacy and safety data were published. A longer-term follow-up period extends through 5 years after dosing.



Abbreviations: D = dosing; F = post-treatment follow-up; IMP = investigational medicinal product; L = lead-in; LTF = long-term follow-up; M = Month; S = screening; W = week.

The EPAR mentions that the applicant changed the primary and secondary efficacy endpoints during the ongoing study; changes were accepted by EMA. *(Ref. EPAR)*

<u>Population</u>
Main inclusion criteria
- Adult men with haemophilia B classified as severe or moderately severe factor IX deficiency (≤2% of normal circulating FIX) for which the subject was on continuous FIX prophylaxis, defined as the intent of treating with an a priory defined frequency of infusions, as documented in the medical records.
- Patients were included regardless of their pre-existing AAV5 neutralizing antibodies (nAb) titre.

Main exclusion criteria
- Participants with a history of FIX inhibitors
- Uncontrolled human immunodeficiency virus infection
- Advanced liver fibrosis

<u>Patient flow</u>
67 men enrolled in the lead-in period of which 54 proceeded to receive etranacogene dezaparvovec. *(Ref. EPAR)*
13 out of 67 patients discontinued from the lead-in period. As per the registration holder, 5 patients discontinued because of an ineligible fibroscan-score (or equivalent scan), 1 patient discontinued because of concomitant medication, 2

patients because of comorbidities, 2 patients because of the covid-19 pandemic, 1 patient withdrew consent and for 2 patients no reason was provided by the registration holder.

- One participant prematurely discontinued treatment after an adverse event of hypersensitivity that occurred after a partial dose, +/- 10% of the full dose. The participant did not have a response to etranacogene dezaparvovec but continued to participate in the study. *(Ref. Pipe et al. 2023)*
- The 24-month post-treatment follow-up was completed by 53 participants. *(Ref. Coppens et al. 2024)*

Appendix 5 gives an overview of the baseline characteristics of the included population. *(Ref. Pipe et al. 2023)*

3.3 Clinical efficacy

The risk of bias of the studies was assessed based on a questionnaire appropriate to the study design. The following checklist was used in this report: Cochrane risk of bias tool.

The assessment of the risk of bias is set out in Appendix 6. The effects of the intervention and the quality of the evidence are summarised in the *GRADE evidence* profile (Appendix 7). The quality of the evidence was assessed using the GRADE method. In GRADE, the quality of evidence is determined per outcome measure, and, in addition to risk or bias, several factors are important: inconsistency, circumstantial evidence, inaccuracy and publication bias. When one or more of these factors are present, the quality of evidence may be reduced by one or two levels per outcome measure. This results in a grading of the quality of evidence: it can be high, reasonable, low, or very low.

<u>Annualized bleeding rate (ABR)</u>
The ABR for all bleeding episodes decreased from 4,19 (95% confidence interval [CI]: 3,22 to 5,45) during the lead-in period to 1,51 (95% CI: 0,83 to 2,76) during months 7 through 24 after treatment. *(Ref. Coppens et al. 2024)*
The observed adjusted ABR rate ratio was 0,36 (95% CI: 0,21 to 0,63; p<0,001), demonstrating noninferiority and superiority of etranacogene dezaparvovec as compared with FIX prophylaxis during the lead-in period. *(Ref. CSR)* Both the rate ratio point estimate (0,36) and the entire 95% CI are below the clinical relevance boundary of 0,75. There is a very serious risk of bias as a result of the observational nature of HOPE-B, in which there was no blinding or randomisation, and bleeds were self-reported. As a result, the quality of evidence is low.

Grade conclusion:
Etranacogene dezaparvovec may result [low quality of evidence] in a clinically relevant reduction of the ABR compared to FIX prophylaxis.

<u>Percentage of patients who are required to continue or resume FIX prophylaxis</u>
All subjects (100%) received routine FIX prophylaxis during the ≥6-month lead-in period. A total of 52/54 (96%) participants discontinued FIX prophylaxis during the period from day 21 through months 7 to 24 after treatment. *(Ref. CSR)*
The remaining 2/54 (4%) participants, whose FIX activity was less than 5% from day 21 through months 7 to 24 after treatment, did not discontinue FIX prophylaxis. One of these participants received only a partial etranacogene dezaparvovec dose (± 10% of the dose) due to hypersensitivity. The second participant did not respond

to treatment with etranacogene dezaparvovec. This participant had the highest day-of-dosing AAV5 neutralizing antibody titre in the study (pre-dose anti-AAV5 antibody titre of 1:3.212). *(Ref. Pipe et al. 2023)*
The RR, as calculated by the Beneluxa assessment team, is 0,04 (95% CI: 0,01 to 0,14). Both the RR point estimate (0,04) and 95% CI are below the clinically clinical relevance boundary of 0,75.
The quality of evidence is, for the same reasons as mentioned under ABR, low.

Grade conclusion:
Etranacogene dezaparvovec may result [low quality of evidence] in a clinically relevant reduction of the percentage of patients who are required to continue or resume FIX prophylaxis.

Quality of life
In the analysis of quality-of-life measures, no significant differences were observed in the EQ-5D-5L VAS scores between the lead-in period and month 12 after treatment (least-squares mean difference in EQ-5D-5L VAS score, 12 months after treatment vs. lead-in period 0,1 (−3,5 to 3,8).
At month 12 after treatment, the mean total score on the Haemophilia Quality of Life Questionnaire for Adults (Hem-A-QoL), examined as an exploratory endpoint, had decreased by 21,5% as compared with the lead-in period (least-square mean change in score -5,5; 95% CI: -7,4 to -3,6), from a least-square mean score of 25,6 at lead-in to 20,1 at month 12. *(Ref. Pipe et al. 2023)*
Although statistically significant, the improvement was lower than the clinical relevance boundary of a 7-point reduction. However, the lower limit of the 95% CI was -7,4, which means that the result could be either clinically relevant or not. Because of this serious risk of inaccuracy and of the same reasons as mentioned under ABR, the quality of evidence is very low.

Grade conclusion:
It is uncertain if etranacogene dezaparvovec results in a clinically relevant increase in quality of life [very low-quality evidence].

Long-term prevention of haemophilic arthropathy
The occurrence of haemophilic arthropathy is not part of the objectives of the HOPE-B study. *(Ref. CRS)* There are no long-term data on haemophilic arthropathy yet because the follow-up period is too short.

3.3.1 Other considerations

Study Overview
The clinical development program of etranacogene dezaparvovec and its predecessor, AMT-060, includes 4 studies in adult subjects with severe or moderately severe haemophilia B. The main evidence for efficacy and safety derives from the pivotal trial HOPE and is discussed above. Data from the studies with AMT-060 are considered by EMA as supportive. *(Ref. EPAR)* Only the studies with etranacogene dezaparvovec are included in the SmPC.
The difference between AMT-060 and etranacogene dezaparvovec is discussed in appendix 8.

Table 1. Study characteristics of AMT-060 and AMT-061.

Product	**AMT-060**		**Etranacogene dezaparvovec (AMT-061) – Padua variant**	
Study	CT-AMT-060-01		CT-AMT-061-01	HOPE-B
Phase	1/2	1/2	2b	3
Number of patients	N=5	N=5	N=3	N=54
Dose	5 x 10^{12} gc/kg	2 x 10^{13} gc/kg	2 x 10^{13} gc/kg	2 x 10^{13} gc/kg
Follow-up status (unpublished data*)	6 years	6 years	4 years	3 years
Follow-up status (published data or captured in CSR)	5 years	5 years	3 years	2 years

*Most recent data available as abstract only and as data provided by the company (not captured in CSR).
Gc/kg = genome copies per kilogram body weight

Study CT-AMT-060-01 *(Ref.[22]; EPAR)* is an open-label, uncontrolled study. Two dose levels were administered. FIX activity levels remained stable in both cohorts for one year.6 Dutch patients participated to the study.

Study CT-AMT-061-01 *(Ref. Von Drygalski et al. 2019; EPAR)* is an open-label, single-arm study. The average FIX activity at 26 weeks was 47 IU/dL (SD: 33,2 – 57,0). No proper dose finding study for etranacogene dezaparvovec has been done, although dosing was based on the previous Study CT-AMT-060-01 in this bridging study. After one year of follow-up, mean FIX activity levels remained in the near-normal range.

HOPE-B study *(Ref. Pipe et al. 2023 ; EPAR)*

- **Percentage of patients with zero bleeds over a period of time**
  14 participants (26%) had no bleeding episodes during the lead-in. This number increased to 34 participants (63%) after treatment during month 7 to 18 and to 27 (50%) during month 7 to 24.
  There is a serious risk of bias, for the same reasons as mentioned under ABR. In addition, there is a relevant difference in follow-up time between the lead-in period and the follow-up after treatment with etranacogene dezaparvovec. On the other hand, even with a longer follow-up time after treatment (18 months), the percentage of patients with zero bleeds was higher compared to the lead-in period (minimum of 6 months). This highlights the effective therapy on short term.

- **Endogenous FIX activity level (x) months (years) after treatment administration**
  Although highly uncertain, the trend of the laboratory value 'endogenous FIX activity' may be used to estimate the long-term effectiveness of etranacogene dezaparvovec. Its effectiveness is dependent on the ability to retain endogenous FIX levels that correlate to a severity of haemophilia B that does not require prophylaxis (see 1.2.1.).
  Obtaining and retaining an endogenous FIX activity of >5%, corresponding to mild haemophilia B, that does not require prophylactic FIX, would be clinically relevant. This is in line with the criteria for discontinuation of FIX prophylaxis in HOPE-B. Continuous routine FIX prophylaxis was discontinued if the endogenous FIX activity result was >5%. Further management was based on the Investigator's clinical judgement and subject preference. Continuation or re-

initiation of continuous routine FIX prophylaxis may have been considered if the endogenous FIX activity was between 2 and 5% in at least 2 consecutive laboratory measurements, based on the Investigator's clinical judgement and subject preference. If endogenous FIX activity was <2%, continuous routine prophylaxis must have been continued or reinstated. Additional on-demand and/or intermittent prophylactic FIX treatment may have been given after treatment with etranacogene dezaparvovec, if considered necessary. *(Ref. CSR)*

Endogenous FIX activity has been measured at 6, 12, and 18 months after treatment (see figure 1).

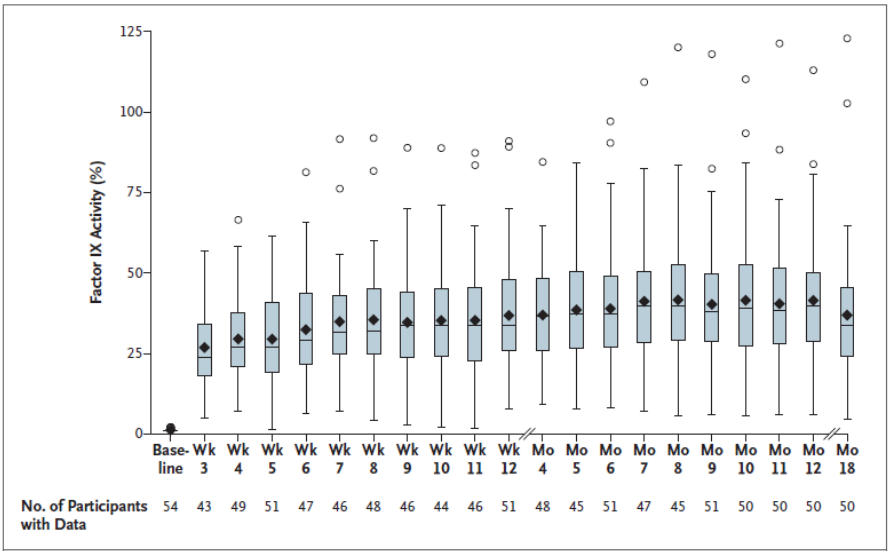


Figure 1. Endogenous Factor IX Activity over 18 Months after Treatment (Full Analysis Population).

Factor IX activity (from the one-stage assay based on activated partial-thromboplastin time) is shown only for blood sampling that did not occur within 5 half-lives of exogenous factor IX use (i.e., "uncontaminated" data). Factor IX activity beginning with the week 3 assessment was used in the analysis. Both the date and the time of the exogenous factor IX use (start) and the blood sampling were considered in determining contamination. Participants with no uncontaminated central laboratory post-treatment values had their postbaseline values set to equal their baseline value. The lower and upper edges of the box indicate the interquartile range, the line at the middle of the box indicates the median, and the I bars indicate the lowest and highest observation within 1.5 times the interquartile range of the bottom and top of the box, respectively. The diamond is the arithmetic mean. Any points outside the whiskers are plotted individually. Baseline factor IX activity was imputed on the basis of each participant's historical hemophilia B severity. If the participant had documented severe factor IX deficiency (plasma factor IX activity of <1%), the baseline factor IX activity was imputed as 1%. If the participant had documented moderately severe factor IX deficiency (plasma factor IX activity of 1 to 2%), the baseline factor IX activity was imputed as 2%. The mean and median are provided at baseline.

Most participants (n=44; 81%) had FIX activity of less than 1% at diagnosis. Increases in endogenous FIX activity were apparent from 3 weeks after treatment.
At 6 months after treatment, FIX activity increased to clinically relevant values 39,0 ± 18,7% (range 8,2 to 97,1), with a least square mean increase from baseline of 36,2 percentage points (95% CI: 31,4 to 41,0; p<0,001). Increases in FIX activity were sustained through month 12 (least-squares mean increase from baseline: 38,8 percentage points (95% CI, 34,0 to 43,6; p<0,001) and slightly decreased until month 18 (least-squares mean increase from baseline: 34,3 percentage points (95% CI: 29,5 to 39,1; p<0,001). At 24 months, as reported in the CSR, FIX levels were slightly decreased compared to at 18 months (least-squares mean increase from baseline: 34,1 percentage points (95% CI: 29,6 to 38,7; p<0,001). *(Ref. CSR).* Mean and median FIX activity were 36,7% and 33,9% respectively. *(Ref. Coppens et al. 2024)*
Notably, one subject had a 4,7% FIX activity at month 24 post-treatment with

etranacogene dezaparvovec. *(Ref. Coppens et al. 2024)* No subject recorded values above 150%. *(Ref. Pipe et al. 2023)*

Endogenous FIX levels were stable and slightly increasing from month 6 to month 12 after administration of etranacogene dezaparvovec. It is expected that maintenance of stable endogenous FIX levels may lead to less bleeds compared to fluctuating levels of FIX, as with conventional FIX prophylaxis. As mentioned above, ABR was based on self-reporting, which may be considered as subjective. However, the endogenous FIX levels are considered a hard endpoint. ABR results and endogenous FIX levels go in the same direction, which is reassuring. On the other hand, no information about compliance to FIX prophylaxis during the lead-in period is available. This could lead to inaccuracy in the control arm and therefore also in the comparison between FIX prophylaxis and etranacogene dezaparvovec.

Based on the available data, short-term effectiveness of etranacogene dezaparvovec is probably at least non-inferior and probably superior compared to FIX prophylaxis.
However, a small decline (4,5%) in endogenous FIX levels can be observed from month 12 to 18 after administration. As treatment success is dependent of endogenous FIX activity levels, stable >5% endogenous FIX levels are required for long-term effectiveness. In Coppens et al. 2024 and the CSR of HOPE-B additional data was reported until a 24 month follow-up. The decline in endogenous FIX levels between month 18 and 24 is markedly flattened compared to the decline that is seen between month 12 and 18. It is unclear if the decline in endogenous FIX levels is sustained, lessened, or enhanced over time. The related uncertainty is relevant for the evaluation of the long-term effect, as this one-time treatment is aimed to have a life-long effect. As stated in the SmPC, etranacogene dezaparvovec can only be administered once. Furthermore, there is no indication that repetition of etranacogene dezaparvovec or administration of another gene therapy (based on the same or another vector) will be possible in case of failure of etranacogene dezaparvovec to show sustainable efficiency. Reason for failure of re-administration (of any subtype) would be high levels of anti-AAV antibodies, as per expert opinion provided by the registration holder.

The preferred follow-up for short-term effectiveness of 3-5 years has not been reached with a follow-up of 24 months.

CT-AMT-060-01 and CT-AMT-061-01 overall showed stable endogenous FIX levels over time. Their longer follow-up time (5 and 2,5 years respectively) may indirectly allow for some insight on the expected long-term results of HOPE-B. The slow decline in endogenous FIX levels shown in CT-AMT-060-01 and CT-AMT-061-01 suggests there are no indications for a fast decline in effectiveness. However, although encouraging, these studies have the same uncertainties due to their comparable single-arm study design. Moreover, the numbers of included patients are very low (n=10 and n=3 respectively), thus leading to an even higher level of uncertainty. Therefore, the use of CT-AMT-060-01's and CT-AMT-061-01's study results for the prediction of HOPE-B's long-term results should be done with caution.

Additionally, long-term endogenous FIX levels were estimated in Shah et al. 2022[23]. FIX activity levels were extrapolated, using Bayesian and Frequentist linear mixed models, over a time horizon of 25,5 years post-infusion of etranacogene dezaparvovec. These models suggest less than 11% of patients' FIX activity will decrease to levels <2%. No data was available for levels <5%, although visual inspection of the available graphs indicate a long-term (>10

years) >5% FIX activity.
Despite the promising estimations, this study has several important limitations. Firstly, individual patients' progression of FIX activity is not available. Estimates are based on a group level. It is unclear if there is variability on a patient level besides a higher or lower starting point as displayed in the Frequentist approach. Furthermore, there is a noticeable variance between models, perhaps caused by the relatively limited clinical data. At the 25,5 year time point, the proportion of patients with FIX activity of <2% was twofold higher in the Bayesian model (10,91%) than the Frequentist model (5,45%). This may possibly underline the uncertainty in precision of the models. In addition, the two patients who did not show a sufficient response to etranacogene dezaparvovec and were required to continue FIX prophylaxis were excluded. This may lead to an overestimation of FIX activity in the included population compared to the actual FIX activity on the group level. Moreover, after month 24 one patient had a FIX activity of 4,7%. It is to be expected that this patient would need to resume FIX prophylaxis within the foreseeable future if FIX activity would continue to decrease. Along with the two patients described above who never interrupted their FIX prophylaxis, 3/54 (5,6%) patients will need to proceed with or resume FIX prophylaxis after only a relatively short period of time post treatment. This can possibly indicate a severe overestimation of the predicted proportion of patients with FIX activity of <2% after 25,5 years of 5,45% to 10,91%. Lastly, as the study was funded and executed by the registration holder (CSL Behring), there may be a risk of bias towards favorable models. The uncertainties, as a result of the limitations of Shah et al. 2022, lead to a low confidence and can therefore not be used to accurately estimate long term FIX activity, in particular on an individual patient level.

- **Haemophilic arthropathy**
  The Beneluxa assessment team acknowledges the fact that the current follow-up is not long enough to capture the number of haemophilic arthropathies.
  The number of joint bleeds may be used as a surrogate measure for haemophilic arthropathy. The rate ratio for the lead-in period as compared with the post-treatment period (months 7-18 after treatment) was 0,22 (95% CI: 0,10 to 0,46; p <0,001). *(Ref. Pipe et al. 2023)* The rate ratio remained similar (0,20 [95% CI: 0,10 to 0,37) compared with the post-treatment period with a longer follow-up (months 7-24 after treatment). *(Ref. CSR)*
  The haemophilia joint health score can also give an indication about the short-term joint health status. HOPE-B showed a statistically significant decrease (improvement) in the score: -2,1 (p=0,0019) two years post-dose versus the lead-in period. *(Ref. CSR)*

- **Subgroups**
  All investigated subgroups showed an improvement regarding ABR and FIX activity level in the post-treatment period compared to the lead-in period.
  - Patients who experienced an ALT elevation post treatment, and especially those patients who received corticosteroids as a consequence, demonstrated appreciably lower FIX activity levels compared to the other subgroups. *(Ref. EPAR)*
  - Up to a titre of 1:678, no clinically meaningful correlation was identified between patients' pre-existing anti-AAV5 antibody titre and their FIX activity at 18 months post-dose. In one patient with a titre of 1:3.212 for pre-existing anti-AAV5 antibodies at screening, no response to etranacogene dezaparvovec treatment was observed, i.e., no FIX expression and activity. *(Ref. Pipe et al. 2023)*

- **Onset of effect**
  The SmPC states: the onset of effect from etranacogene dezaparvovec treatment may occur within several weeks post-dose. Therefore, haemostatic support with exogenous human FIX may be needed during the first weeks after etranacogene dezaparvovec infusion to provide sufficient FIX coverage for the initial days post-treatment. Monitoring of the FIX activity (e.g., weekly for 3 months) is recommended post-dose to follow the patient`s response to etranacogene dezaparvovec.
  From the data in HOPE-B it is not clear which part of the treatment is for
  - Continued prophylaxis post-treatment post etranacogene dezaparvovec administration
  - Treatment of bleeds
  - Resuming of FIX prophylaxis.

Differences between PICO and inclusion criteria

The inclusion criteria *(Ref. CSR)* do not mention a 'severe bleeding phenotype'. The inclusion criteria include the severe form (FIX level <1% of normal) and the moderate severe form (FIX levels between 1 and 2%), the moderate form being defined as FIX level 1-5% of normal. In addition, the inclusion criteria mention that patients had to be on continuous FIX prophylaxis. The company states that some patients on 'on demand treatment' could benefit from etranacogene dezaparvovec. At our knowledge there are no data in this population.

Table 2. Difference between HOPE-B inclusion criteria, indication and target population for reimbursement:

HOPE-B main inclusion and exclusion criteria	**Indication (SmPC)**	**Reimbursement claim**
Adult men	Adult patients	Adult patients
Haemophilia B classified as severe or moderately severe FIX deficiency (≤ 2% of normal circulating FIX) for which the subject was on continuous FIX prophylaxis, defined as the intent of treating with an a priory defined frequency of infusions, as documented in the medical records.	Severe and moderately severe haemophilia B	Severe and moderately severe Haemophilia B, whereby moderately severe patients are defined as patients classified as moderate haemophilia B with a severe bleeding type*
Patients were included regardless of their pre-existing AAV5 neutralizing antibodies (nAb) titre.		
No history of FIX inhibitor use	No history of FIX inhibitors	No history of FIX inhibitors
Excluded: uncontrolled human immunodeficiency virus infection		
Excluded: advanced liver fibrosis		

* Clinical experts in Belgium and the Netherlands treat patients based on bleeding phenotype.

Representativeness of HOPE-B for Dutch and Belgian population
6 Belgian and 12 Dutch patients participated to the HOPE-B study, which represents around 30% of the HOPE-B trial participants. Therefore, one can expect the study population to reflect the Belgian and Dutch population.
However, the lead-in period of ≥6 months in HOPE-B is used as the control-arm within this study. EHL FIX was used in 57,4% of patients while 42,6% used SHL pre-screening. Most patients in the Netherlands (83%) and all of the patients in Belgium (100%) receive EHL. Based on the received FIX treatment in the control-arm, the representativeness of the control-arm for the true patient population is reduced as fewer or no patients use SHL in the Netherlands and Belgium respectively. (Available treatment options in Belgium are listed in appendix 10)
Although specific ABRs for Dutch or Belgian populations are not available, bleeding rates have shown to be lower in EHL treatment compared to SHL treatment[24, 25, 26]. ABRs varied between a mean of 0,8 and 1,4 *(Ref. Chhabra et al. 2020; Malec et al. 2020)* and median of 2 *(Brennan et al. 2020)* for EHL vs a mean between 2,1 and 3 *(Chhabra et al. 2020; Malec et al. 2020)* and a median of 3 *(Ref. Brennan et al. 2020)* for SHL in different retrospective studies. This would suggest an overestimation of the ABR in the control-arm.
Also, ABRs were, in particular for EHL, lower in these studies than the reported mean ABR of 4,19 in the lead-in period of HOPE-B. Meanwhile, the retrospective nature of the mentioned studies allow for a risk of bias as bleeds reporting could be limited compared to a prospective study like HOPE-B.
Moreover, as mentioned by Keipert et al. 2020[27], definitions of bleeding episodes and ABR observational periods differed substantially in clinical trials.
Alongside this issue, the variance in ABRs are also considered as a major challenge in statistical analyses, further implying the difficulty to compare the efficacy of different treatment regimens and products in haemophilia patients. *(Ref. Keipert et al. 2020)* On the other hand, it is likely that in real-life, treatment compliance to FIX prophylaxis will be lower than in the clinical trial and hence, bleeding rates during the lead-in period may be an underestimation.

Other HTA evaluations and pipeline: discussed in appendix 9

Non published extended follow-up data.
The registration holder provided confidential 3 years post-treatment data of HOPE-B. These additional data were not provided in the form of a peer-reviewed publication or a CSR. These results can therefore not be considered in the final assessment.

3.4 Clinical safety

67 patients were included in the lead-in safety population of HOPE-B. A total of 54 subjects received etranacogene dezaparvovec, were followed for efficacy and safety and were included in the post-treatment safety population. *(Ref. EPAR)*

Most common adverse events during the lead in-period with FIX prophylaxis were nasopharyngitis (11,9%), arthralgia (7,5%) and oropharyngeal pain (7,5%).
Most common adverse events after etranacogene dezaparvovec administration were arthralgia (35,2%), headache (29,6%) and nasopharyngitis (27,8%). *(Ref. CSR)*

Table 2. Unfavourable effects of etranacogene dezaparvovec compared to FIX prophylaxis (lead-in period) in adult patients with severe and moderately severe haemophilia B (congenital FIX deficiency), with a severe bleeding phenotype, without a history of FIX inhibitors. (*Ref. HOPE-B study, EPAR*)

	etranacogene dezaparvovec	FIX prophylaxis (lead-in period)
Most frequent (>10%)*	arthralgia, headache, nasopharyngitis, fatigue, alanine aminotransferase increased, back pain, COVID-19, pain in extremity, aspartate aminotransferase increased, blood creatine phosphokinase increased, influenza-like illness, oropharyngeal pain, toothache, hypertension, cough, diarrhoea, nausea	nasopharyngitis
Serious adverse events (>2%)*	Blood loss, anaemia	-

*Follow-up time was longer for etranacogene dezaparvovec (18 months) than for FIX prophylaxis (lead in period of ≥6 months). Based on the follow-up time, odds for events to occur were higher after etranacogene dezaparvovec administration.

Incidence of treatment-related serious adverse events
No SAEs were assessed as treatment-related at the time of the data cut-off, neither during the lead-in period, nor after administration of etranacogene dezaparvovec. During the post-treatment period, 14/54 (25,9%) subjects experienced a total of 17 serious adverse events, regardless of whether they were treatment-related or not, compared to 4/67 (5,97%) subjects in the lead-in period. *(Ref. CSR)*
As no treatment-related serious adverse events occurred in either the lead-in period nor after treatment with etranacogene dezaparvovec, no RR is calculated.
Despite the fact that no treatment-related serious adverse events occurred after treatment with etranacogene dezaparvovec, there is a very serious risk of bias for the same reasons as mentioned under ABR. Additionally, because of the difference in follow-up time, there is another serious risk of bias. Therefore, the quality of evidence is very low.
Data from more patients, as well as long-term data are needed to be able to make an ultimate assessment of treatment-related serious adverse events.

Gradeconclusie:
There is no indication [low quality of evidence] that etranacogene dezaparvovec leads to an increase in the incidence of treatment-related serious adverse events compared to factor IX prophylaxis.

3.4.1 Other considerations

In the HOPE-B study, all 54 participants had adverse events (regardless of whether these were related to treatment) that occurred or worsened during or after treatment: 465 adverse events in total; 364 mild, 87 moderate and 14 severe. Adverse events were similar among participants with or without pre-existing AAV5 neutralizing antibodies. *(Ref. Pipe et al. 2023)*

During the short follow-up of the study, some serious adverse events of interest

took place. One patient died approximately 15 months after treatment from cardiogenic shock that was considered by the investigators to be unrelated to treatment.
Also, a serious adverse event of hepatocellular carcinoma occurred 12 months after treatment in a 68-year-old participant with multiple independent risk factors for hepatocellular carcinoma (including a history of Hepatitis B, Hepatitis C, alcohol use, and fatty liver disease), although this patient did not show evidence of significant fibrosis, cirrhosis or steatosis at screening before etranacogene dezaparvovec. The event was determined to be unrelated to the AAV5 vector, on the basis of independent molecular tumour characterization and vector-integration analysis. *(Ref. Pipe et al. 2023)*

In the HOPE-B study one patient received only ± 10% of the dose of etranacogene dezaparvovec due to hypersensitivity. *(Ref. Pipe et al. 2023)*

No new safety signals have been identified after 5 years of follow-up for AMT-060 and up to 3 years of follow-up for etranacogene dezaparvovec in the AMT-060-01- and AMT-061-01-study. *(Ref. EPAR)*

The evaluation of adverse events of etranacogene dezaparvovec compared to EHL FIX prophylaxis is challenging due to a number of aspects.
Firstly, the small sample size and relatively short follow-up time do not allow for extensive detection of uncommon or rare but serious adverse events or long-term safety. A post-authorisation safety study (PASS) is requested by EMA, with final CSR expected in 2044.
Furthermore, in the absence of a control-arm, the lead-in period does not serve as an accurate control-arm for uncommon or rare events (as serious adverse events) as follow-up time was even shorter and differs from post-treatment follow-up.
Additionally, potential consequences of non-clinical and clinical findings related to integration of AAV and the impact of neutralising anti-AAV capside antibodies on efficacy and safety are unclear.
Lastly, as mentioned earlier in *3.3.1 Other considerations*, a large proportion of patients (42,6%) received SHL instead of EHL FIX prophylaxis during the lead in period. Although it is unlikely that SHL FIX prophylaxis will lead to increased drug related adverse events compared to EHL FIX prophylaxis, it is possible that it could cause more administration related adverse events due to an increased frequency of administration. This may lead to an overestimation in adverse events in the control-arm.

<u>FIX replacement therapy</u>
As lead-in follow-up time in HOPE-B was short (≥6 months), there is a high probability of underestimation of adverse events compared to the post-treatment follow up (18 months). The comparison between FIX prophylaxis (during lead-in period) and etranacogene dezaparvovec-treatment reported adverse event may not be representative. Serious adverse events that can occur during therapy with FIX prophylaxis are hypersensitivity reactions and formation of neutralizing antibodies to FIX.

Table 3. EHL FIX replacement therapy – most frequently occurring AEs (for full list, please consult the SmPCs)

	Alprolix®	**Idelvion®**	**Refixia®**
Common AEs (≥1/10 to 1/100)	Hypersensitivity Injection site erythema Headache FIX inhibition Oral paraesthesia Obstructive uropathy	Hypersensitivity Injection site reactions Rash Headache Dizziness	Hypersensitivity Injection site reactions Rash Anaphylactic reaction Pruritis FIX inhibition Nausea Fatigue

References: SmPCs

3.5 Experience

To date, etranacogene dezaparvovec has been used in 57 patients, through different clinical trials.
Although FIX replacement therapy experience is extensive (> 10 years), EHL FIX prophylaxis products were approved from 2016.

Table 2: Experience with etranacogene dezaparvovec compared to EHL FIX replacement therapy

	etranacogene dezaparvovec	*EHL FIX replacement therapy*
Limited: < 3 years on the market or < 100.000 prescriptions (non-chronic indication)/20.000 patient years (chronic medication)	X	
Sufficient : ≥ 3 years on the market and > 100.000 prescriptions/ 20.000 patient years		X
Extensive: > 10 years on the market		

3.6 Applicability

Extensive information about the applicability can be found in the SmPC. In this paragraph only the most important differences between the treatment options are discussed.

Main contra-indications
Etranacogene dezaparvovec-specific contra-indications are active infections, either acute or uncontrolled chronic, and known advanced hepatic fibrosis or cirrhosis.

Specific patient groups
For 12 months after administration of etranacogene dezaparvovec treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using barrier contraception.
Males treated with etranacogene dezaparvovec must not donate semen to minimise the potential risk of paternal germline transmission.

Interactions
No in vivo interaction studies have been performed. Monitoring of concomitant medication, with special attention with hepatotoxic medicinal products or substances or agents that may reduce or increase plasma concentrations of corticosteroids.

Warnings and precautions
Initiation of treatment with etranacogene dezaparvovec:
- **Pre-existing antibodies to the AAV5 vector capsid**

Prior to the treatment with etranacogene dezaparvovec, patients should be assessed for the titre of pre-existing neutralising anti-AAV5 antibodies. Pre-existing neutralising anti-AAV antibodies above a titre of 1:678 may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of etranacogene dezaparvovec therapy. There is limited data in patients with neutralising anti-AAV5 antibodies above 1:678.
The cut-off titre, proposed to EMA by the registration holder, to confirm treatment eligibility with Hemgenix was <1:700. However, in order to avoid a restriction of the indication with this arbitrary cut-off limit based on data from one patient only, the Committee for Advanced Therapies (CAT) has requested the registration holder to further investigate the effectiveness of etranacogene dezaparvovec in a post-authorisation efficacy study regardless of the preexisting anti-AAV5 antibody titre. *(Ref. EPAR)*

- **Baseline hepatic function**

Prior to the treatment with etranacogene dezaparvovec, patient`s liver transaminases should be evaluated and liver ultrasound and elastography performed.

- **Infusion-related reactions** during or shortly after etranacogene dezaparvovec infusion

In the clinical studies with etranacogene dezaparvovec, infusion-related reactions of mild to moderate severity have been observed in 7/57 (12,3%) subjects. The infusion was temporarily interrupted in 3 patients and resumed at a slower infusion rate upon treatment with antihistamines and/or corticosteroids. In 1 patient, infusion was stopped and not resumed.
Infusion reactions, including hypersensitivity reactions and anaphylaxis, are possible. Patients should be closely monitored for infusion reactions throughout the infusion period and at least for 3 hours after end of infusion.

Monitoring after the treatment with etranacogene dezaparvovec
- **Hepatotoxicity**

Intravenous administration of a liver-directed AAV vector may potentially lead to liver transaminase elevations (transaminitis). The transaminitis is presumed to occur due to immune-mediated injury of transduced hepatocytes and may reduce the therapeutic efficacy of the gene therapy. In the clinical studies, treatment-emergent adverse reactions of ALT increases occurred in 13/57 (22,8%) patients. Nine of the 13 patients with ALT elevations received a tapered course of

corticosteroid. All treatment-emergent adverse events of elevated ALTs were non-serious and resolved within 3 to 127 days.

- **Hepatic function and FIX monitoring**

In the first 3 months after etranacogene dezaparvovec administration, the purpose of hepatic and FIX monitoring is to detect increases in ALT.
After the first 3 months of administration, hepatic and FIX monitoring is intended to routinely assess liver health and bleeding risk, respectively.

- **Risk of malignancy** as a result of AAV vector integration into human genome

Vector integration was observed in nonclinical studies. While recombinant AAV are not expected to integrate their genome in host cells at high frequency, all integration events could potentially contribute to tumoral transformation.
In the clinical studies, no malignancies were identified in relation to treatment with etranacogene dezaparvovec.
Considering the small sample size and the limited follow-up duration, the theoretical risk of malignancy due to vector integration cannot be estimated.
The currently available information suggests that there might be a lifelong risk of insertional mutagenesis and subsequently carcinogenesis.
It is recommended that patients with pre-existing risk factors for hepatocellular carcinoma (such as hepatic fibrosis, hepatitis C or B disease, non-alcoholic fatty liver disease) undergo regular liver ultrasound screenings and are regularly monitored for alpha-fetoprotein (AFP) elevations (e.g., annually) for at least 5 years after etranacogene dezaparvovec administration.

Immunogenicity
In the clinical studies with etranacogene dezaparvovec, no FIX inhibitor development was observed.

AAV vector DNA shedding via body fluids
In the absence of respective assays, infectivity of the shed material has to be assumed. At 18 months after treatment, clearance of vector DNA (i.e., absence of shedding) was confirmed in semen specimens obtained from 33 participants (61%) and in blood specimens obtained from 25 participants (46%).
Samples from 9 subjects were still positive for vector DNA at or after day 182. A total of 47/54 (87%) and 40/54 (74%) patients were identified to have reached absence of vector DNA from blood and semen, respectively, at 24 months post-dose.

Risk Management Plan
The company committed in the context of the conditional marketing authorisation to submit the final study results, including 5 years' follow-up, of studies CT-AMT-061-01 and the HOPE-B study.
During long-term monitoring post marketing, safety and efficacy parameters will be collected up to 15 years and increase the understanding of the durability of the achieved FIX activity.

3.7 Ease of Use

The ease of use of etranacogene dezaparvovec is shown in table 4.

Table 4: Ease of use of etranacogene dezaparvovec compared to EHL FIX replacement therapy

	etranacogene dezaparvovec	*EHL FIX replacement: prophylaxis*

Way of administration	Intravenous infusion under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Personal protective equipment.	Intravenous use. In case of self-administration or administration by caregiver, training is needed.
Frequency of administration	Single dose	Dosing intervals range from once weekly to 14 days and longer.

Discontinuation of prophylaxis with exogenous human FIX
The onset of effect from etranacogene dezaparvovec treatment may occur within several weeks post-dose. Therefore, haemostatic support with exogenous human FIX may be needed during the first weeks after etranacogene dezaparvovec infusion to provide sufficient FIX coverage for the initial days post-treatment. Monitoring of the FIX activity (e.g., weekly for 3 months) is recommended post-dose to follow the patient`s response to etranacogene dezaparvovec.

Etranacogene dezaparvovec should only be administered to patients who have demonstrated absence of FIX inhibitors. In case of a positive test result for human FIX inhibitors, a re-test within approximately 2 weeks should be performed. If both the initial test and re-test results are positive, the patient should not receive etranacogene dezaparvovec.

4 Final Assessment

4.1 Discussion relevant aspects

Etranacogene dezaparvovec is indicated for the treatment of severe and moderately severe haemophilia B (congenital FIX deficiency) in adult patients without a history of FIX inhibitors. EMA has approved etranacogene dezaparvovec under a conditional marketing authorization.

The current standard of care for these patients with a severe bleeding phenotype is prophylactic FIX replacement therapy both in Belgium and the Netherlands. All of the Belgian patients and a large majority of patients in Netherlands use EHL FIX prophylactic therapy.

Etranacogene dezaparvovec is currently studied in HOPE-B, a non-randomized, uncontrolled, multicentre, open-label, single-arm phase 3 study. There was a lead-in period of minimum 6 months, in which patients were treated with FIX prophylaxis. This lead-in period serves as a control-arm. After the lead-in period, patients were administered etranacogene dezaparvovec and followed over time.
Based on the HOPE-B study, the following conclusions can be drawn:

1 Etranacogene dezaparvovec may result in a clinically relevant reduction of the **ABR** compared to FIX prophylaxis. Etranacogene dezaparvovec showed a decrease in ABR from 4,19 (95% CI: 3,22 to 5,45) during the lead-in period to 1,51 (95% CI: 0,83 to 2,76) during months 7 through 18 after treatment, resulting in an ABR rate ratio of 0,36 (95% CI: 0,21 to 0,63; p<0,001). The rate ratio and 95% CI are below the clinical relevance boundary of 0,75. However, because of a very serious risk of bias and the fact that bleeding rates are based on self-reporting and not objectively measured, the quality of evidence is low.
2 Etranacogene dezaparvovec may result in a clinically relevant reduction of the percentage of patients who are required to continue or resume FIX prophylaxis. Of all patients completing the lead-in period, of which 100% continued FIX prophylaxis during the lead-in period, 96% (52/54) discontinued **FIX prophylaxis** post-treatment with etranacogene dezaparvovec and did not resume it during the study period, resulting in a RR of 0,04 (95% CI: 0,01 to 0,14). The two participants, whose FIX activity was less than 5% at month 18, did not discontinue FIX prophylaxis throughout the entire follow-up. Because of a very serious risk of bias, the quality of evidence is low.
3 Etranacogene dezaparvovec has shown a statistically significant improvement of **quality of life** on the disease-specific Haemophilia Quality of Life Questionnaire for Adults (Hem-A-QoL). At month 12 after treatment, the mean total score has decreased by 21,5% as compared with the lead-in period (least-square mean change in score -5,5; 95% CI: -7,4 to -3,6), from a least-square mean score of 25,6 at lead-in to 20, 1 at month 12. The clinical relevance of the effect is uncertain. Quality of the evidence is very low, because of the inaccuracy and uncertainties related to the study design. Additionally, this study endpoint was exploratory. No significant differences were observed in the generic instrument EQ-5D-5L VAS scores between the lead-in period and month 12 after treatment (least-squares mean difference in EQ-5D-5L VAS score, 12 months after treatment vs. lead-in period 0,1 (−3,5 to 3,8).
4 The occurrence of **haemophilic arthropathy** is not part of the objectives of the HOPE-B study. No comparison between follow-up period and lead-in period

is available. Currently, the follow-up period is too short to draw conclusions.

5 The effect of etranacogene dezaparvovec on the incidence of **treatment-related serious adverse events** compared to factor IX prophylaxis is considered acceptable in the short-term. No treatment-related serious adverse events were reported during the entire follow-up period (lead-in and after etranacogene dezaparvovec administration). However, the quality of the evidence is low, due to the uncertainties related to the study design. Moreover, for the long-term follow-up, diligent post-marketing surveillance is of utmost importance to detect potential rare adverse events and to investigate the potential risk of malignancy, due to vector integration.

While etranacogene dezaparvovec shows promising results based on the results of HOPE-B, the study design leads to several uncertainties, which are listed in appendix 11.

Due to the rarity of severe or moderately severe haemophilia B with a severe bleeding phenotype, it is expected that large sample sizes within this indication are challenging to obtain. However, albeit the current standard of care, FIX prophylaxis, negatively impacts the quality of life due to the need of frequent intravenous infusions, FIX prophylaxis is effective. A control arm could therefore be considered as obtainable.
In the absence of a control-arm, the lead-in period functions as an intra-patient control. Compared to FIX prophylaxis in the lead-in period, etranacogene dezaparvovec showed short-term improvements in most of the outcome measures. Despite the fact that the number of bleeds were based on patient-reporting, the major surrogate outcome measure for bleeding, endogenous FIX, showed a significant increase after etranacogene dezaparvovec administration.

On the other hand, the short follow-up of the lead-in period does not allow to capture uncommon or rare events. As a result, evaluating differences in the incidence of treatment-related serious adverse events is challenging or even not feasible.
It should also be noted that in the study almost half of the patients used SHL FIX prophylaxis, even though EHL is mostly used in the Netherlands and exclusively used in Belgium. Hence, there may be an overestimation in the improvements of outcomes of etranacogene dezaparvovec compared to EHL FIX prophylactic therapy that is used in the Belgian and Dutch practice.

Furthermore, the most important uncertainties are the long-term effectiveness and safety, due to the relatively short follow-up time of 18 months. As it is a one-time administration, long-term effectiveness and safety is required. Compared to the required follow-up of at least 3-5 years for short-term effectiveness, and preferably a minimum follow-up of 10 years for long-term effectiveness and safety, the currently available data of 24 months do not allow for complete certainty. Moreover, some decline of endogenous FIX activity could be noticed from month 12 to 24, which may be a chance finding. However, if this decline were to continue, it could lead to failure of treatment or return to FIX prophylactic treatment over time. One patient had an endogenous FIX activity of <5% at month 24. This increases the uncertainty of durability of effectiveness. Based on the mean and median FIX activity levels of the study population as a whole, it is unlikely that failure of treatment will happen within the foreseeable future.

Lastly, it is important to note that patients may not be treated with etranacogene dezaparvovec or another AAV-vector once they have received etranacogene dezaparvovec. Due to the uncertainties regarding the impact of neutralizing anti-

AAV capsid antibodies on efficacy and safety, EMA has considered a full marketing authorization as not acceptable.

In summary, despite the risk of bias in the design of the HOPE-B study and the uncertainties, all short-term outcome measures indicate that etranacogene dezaparvovec may be similar or possibly better compared to FIX prophylaxis. Taking into account the results in general and in particular the endogenous FIX activity level, an imminent ineffectiveness is highly unlikely, in view of the mean and median FIX levels at the end of the 24-months follow-up period that far exceeded 5%.
It is very plausible that the effect will continue beyond 24 months and maybe 3 years, which is the current follow-up period. Based on the currently available data and in consultation with the Dutch Scientific Advisory Council – committee on Medicinal Products, the Beneluxa assessment team considers there is sufficient confidence in a durability of the effectiveness of 4 to 5 years. However, due to the relatively short follow-up time of 2 years post-treatment and a lack of long term data, there is high uncertainty in the effectiveness of etranacogene dezaparvovec beyond this time point. As a result, there is not enough confidence to determine effectiveness beyond 4 to 5 years. Lack of durability of effect could lead to the need of resuming FIX prophylaxis. In addition, there is substantial uncertainty about the long-term safety profile of etranacogene dezaparvovec.

4.2 End Conclusion

The Beneluxa assessment team (the Belgian CRM and Zorginstituut Nederland) concludes that etranacogene dezaparvovec (Hemgenix®) for adult patients with severe and moderately severe haemophilia B (congenital FIX-deficiency) with a severe bleeding phenotype, without a history of FIX inhibitors, meets the current state of science and practice based on the currently available data. However, substantial level of uncertainty remains, the durability of effectiveness and the safety profile of etranacogene dezaparvovec.

Appendix 1: Search Strategy literature

The literature search was done in PubMed in October 2023 with following search terms: ((etranacogene dezaparvovec) OR (hemgenix) OR (AMT-061)) AND ((Haemophilia B) OR (Hemophilia B))

Furthermore, the Summary of Product Characteristics (SmPC) of the registration dossier and the European Public Assessment Report (EPAR) of the European Medicines Agency (EMA) were used in the assessment.

Appendix 2: Overview included studies

First author, year of publication	Type of clinical trial, proof category, follow-up duration	Number of patients	Patient characteristics	Intervention and comparator	Relevant outcome measures	Comments, risk of bias
Pipe, 2023	Non-randomised, uncontrolled, open-label, multicentre, single-arm phase 3 trial. Lead-in period at least 6 months 52 weeks follow-up after stable FIX expression (months 7 through 18 after treatment)* Second follow-up through 5 years	N = 54	-Men -At least 18 years of age -Inherited haemophilia B, classified as: severe (plasma FIX activity of <1%) or moderately severe (plasma FIX activity of 1 to 2%) with a severe bleeding phenotype -Patients received stable continuous FIX prophylaxis	Intervention: Etranacogene dezaparvovec single IV dose $2x10^{13}$ gc/kg Comparator: Lead-in period of at least 6 months	-Annualized Bleeding Rate (ABR) -Percentage of patients with zero bleeds over a period of time -Annual consumption of FIX -Percentage of patients who did not resume FIX prophylaxis -Quality of Life -Serious adverse reactions -Prevention of haemophilic arthropathy -Endogenous FIX activity level x time after treatment administration	Important risk of bias because there is no randomisation. Patients serve as their own control.

* FIX expression was considered stable, and the primary end-point analysis began after all participants who received glucocorticoids discontinued this concomitant medication (i.e., 6 months after receipt of etranacogene dezaparvovec).

Appendix 3: Overview excluded studies

First author, year of publication	Reason for exclusion
von Drygalski, 2023	Phase 2 study
von Drygalski, 2019	Phase 2 study
Von Drygalski, 2019	Erratum
Majowicz, 2019	Phase 1/2 study with AMT-060
Shah, 2023	Modelling analysis
Nathwani, 2022	Review article
Nathwani, 2022	Review article
Heo, 2023	Review article
Thornburg, 2021	Review article
Valentino, 2023	Review article
Thornburg, 2023	Review article
Med Lett. Drugs Ther. 2023; 65(1668):9-10	Review article
De Wolf, 2023	Review article
Spronck, 2019	Non-clinical study
Jordan, 2023	Review article in French

Appendix 4: Overview guidelines

Organisatie, ref	**Datum**	**Titel**
EMA / CBG / FAGG	20/06/2023	Summary of Product Characteristics etranacogene dezaparvovec
EMA	20/06/2023	European Public Assessment Report (EPAR) etranacogene dezaparvovec
NVHB	Website accessed October 2023	Richtlijn Diagnostiek en Behandeling van Hemofilie 2020. Nederlandse Vereniging van Hemofiliebehandelaars (NVHB)
WFH	2020	Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6:1-158.

Appendix 5: Baseline table

Variabele	**Value (n=54)**
Age — yr	
mean	41,5±15,8
range	19–75
Male sex — no. (%)	54 (100)
Race or ethnic group — no. (%)†	
White	40 (74)
Other	6 (11)
Middle Eastern	3 (6)
Spanish or Hispanic	2 (4)
East Indian	1 (2)
Missing data	5 (9)
Asian	2 (4)
Black	1 (2)
Hispanic or Latino ethnic group — no. (%)†	
Not Hispanic or Latino	45 (83)
Missing data	5 (9)
Hispanic or Latino	4 (7)
Geographic location — no. (%)	
European Union or United Kingdom	34 (63)
United States	20 (37)
BMI‡	
Mean	27,2±5,1
Range	21–51
BMI category — no. (%)‡	
<35	52 (96)
35 to <40	1 (2)
≥40	1 (2)
Severity of haemophilia B at time of diagnosis — no. (%)§	

Severe	44 (81)
Moderately severe	10 (19)
Any bleeding episodes in year before screening — no. (%)	44 (81)
History of infection — no. (%)	
HIV-positive 3 (6)	3 (6)
Previous HBV infection	9 (17)
Previous HCV infection	28 (52)
HCV-positive at screening	0
FIX replacement therapy type — no. (%)¶	
Prophylactic	54 (100)
On demand	4 (7)
Most recent prescreening FIX therapy category — no. (%)	
Extended half-life	31 (57)
Standard half-life	23 (43)
Detectable neutralizing antibodies to AAV5 at baseline — no. (%)	21 (39)
Maximum titre	3212,3
No bleeds in lead-in period — no. (%)	14 (26)
Unadjusted mean annualized exogenous FIX consumption during lead-in period — IU/yr	257,339±149,013
Adjusted annualized FIX replacement therapy infusion rate during lead-in period — infusions/yr	72,49

* Plus–minus values are means ±SD. The safety population included all participants who were enrolled and received etranacogene dezaparvovec. AAV denotes adeno-associated virus, HBV hepatitis B virus, HCV hepatitis C virus, and HIV human immunodeficiency virus.

† Race and ethnic group were reported by the investigator. Participants with missing data on race and ethnic group came from two centers in a single Northern European country in which collection and reporting of these data were not permitted by the ethics committee because of the European Union General Data Protection Regulation at the time of enrollment.

‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ Severe haemophilia B was defined as plasma FIX activity of less than 1%, and moderately severe haemophilia B was defined as plasma FIX activity of 1 to 2%.

¶ Some participants received both prophylactic and on-demand FIX replacement therapy during the lead-in period.

Appendix 6: Assessment risk of bias

Answer options: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.	
SELECTION	
1) Representativeness of the exposed cohort Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of estrogen). a) Truly representative of the average _____ (describe) in the community * b) Somewhat representative of the average _____ in the community * c) Selected group of users e.g. nurses, volunteers d) No description of the derivation of the cohort	Somewhat representative of the average haemophilia B patient in the community. Around 30% of the included patients in HOPE-B were Dutch or Belgian. The standard of care in Belgium and the Netherlands is EHL FIX. A minority (17%) of the Dutch patient population still uses SHL the Netherlands. 57,4% of the included study population in HOPE-B used EHL.
2) Selection of the non exposed cohort a) Drawn from the same community as the exposed cohort * b) Drawn from a different source c) No description of the derivation of the non exposed cohort	Drawn from the same community as the exposed cohort. Control-arm is the lead-in period before administration of etranacogene dezaparvovec.
3) Ascertainment of exposure a) Secure record (e.g. surgical records) * b) Structured interview * c) Written self report	Secure record

Answer options: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.	
d) No description	
4) Demonstration that outcome of interest was not present at start of study a) Yes * b) No	n/a
COMPARABILITY	
1) Comparability of Cohorts on the Basis of the Design or Analysis A maximum of 2 stars can be allotted in this category. Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never) a) Study controls for _____ (Select the most important factor) * b) Study controls for any additional factor * (These criteria could be modified to indicate specific control for a second important factor)	n/a. Intra-patient control-arm.
OUTCOME	
1) Assessment of outcome a) Independent blind assessment * b) Record linkage * c) Self report	Self report

Answer options: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.	
e) No description	
2) Was follow up long enough for outcomes to occur? An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. For exposure to breast implants) a) Yes (select an adequate follow up period of interest) * b) No	No. For short-term effectiveness and safety a follow-up of 3 to 5 years is adequate. Short-term, and especially long-term, effectiveness and safety will not be covered with the relative short follow-up of 24 months.
3) Adequacy of follow up of cohorts This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome. a) Complete follow up – all subject accounted for * b) Subjects lost to follow up unlikely to introduce bias, small number lost: > …% (select and adequate %) follow up) or description provided of those lost * c) Follow up rate < …% (select an adequate %) and no description of those lost d) No statement	Complete follow up – all subject accounted for.

Appendix 7: GRADE evidence profile

Comparison etranacogene dezaparvovec versus FIX prophylaxis for severe and moderate haemophilia B (congenital FIX deficiency) with a severe bleeding phenotype in adults without a history of FIX inhibitors. GRADE evidence profile.

Certainty assessment							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistent	Indirect evidence	Imprecision	Other factors	Etranacogene dezaparvovec	FIX (lead-in period)	Relative (95% CI)	Absolute (95% CI)	
Annual bleeding rate (follow up: 24 months with a lead-in period of ≥ 6 months; MCID 0,75-1,25)											
1	Single-arm, non-controlled study	not serious[a,b,c]	not serious	not serious	not serious	not found	54[d]	54[e]	**Rate ratio 0,36** (95% CI: 0,21 to 0,63; p<0,001)	FIX (lead-in period): 4,19 (3,22 to 5,45) Etranacogene dezaparvovec: 1,51 (0,83 to 2,76)	⨁⨁◯◯ Low
Percentage of patients who are required to continue or resume FIX prophylaxis (follow up: 24 months with a lead-in period of ≥ 6 months; MCID 0,75-1,25)											
1	Single-arm, non-controlled study	not serious[a,b]	not serious	not serious	not serious	not found	2/54 (3,7%) (month 7 to 24)	54/54 (100%)	**RR 0,037** (0,01 to 0,14)[f]	**963 less per 1.000** (from 990 less to 860 less)	⨁⨁◯◯ Low
Long-term outcome: prevention of haemophilic arthropathy											
No data is available on the prevention of haemophilic arthropathy											
Quality of Life (median follow up: 24 months with a lead-in period of ≥ 6 months; MCID: 7-point reduction in Total Score for the Hem-A-QoL)											
1	Single-arm, non-controlled study	not serious[a,b]	not serious	not serious	serious	not found	54[d]	54[e]	**Ls mean change in score 5,5 points lower** (7,4 lower to 3,6 lower)	FIX (lead-in period): Ls mean score 25,6 Etranacogene dezaparvovec: Ls mean score 20,1 (month 12)	⨁◯◯◯ Very low
Treatment related serious adverse events (follow up: 24 months with a lead-in period of ≥ 6 months; MCID 0,75-1,25)											

Certainty assessment							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistent	Indirect evidence	Imprecision	Other factors	Etranacogene dezaparvovec	FIX (lead-in period)	Relative (95% CI)	Absolute (95% CI)	
1	Single-arm, non-controlled study	not serious[b,f]	not serious	not serious	not serious	not found	0/54 (0,0%)	0/67 (0,0%)[g]	**As no treatment-related adverse events were reported in either arm, no RR was calculated**		⨁⨁◯◯ Low

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. A depreciation in the quality of evidence has already been effected based on the trial setting, which does not include randomisation and blinding. No additional relevant bias has been found.

b. The data can only be interpreted for short-term effect as the follow-up is relatively short (24 months) for a life-long treatment. Long-term effectiveness and safety is still unclear.

c. This outcome was self-reported. However, this did not result in an additional downgrade of this outcome measure.

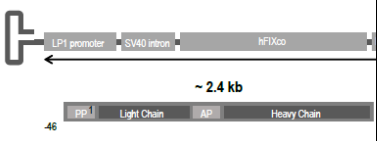
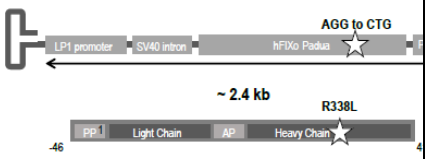
d. After lead-in period of at least 6 months, 54 patients received etranacogene dezaparvovec, 1 patient discontinued after receiving the initial administration.

e. 67 patients were enrolled in the lead-in period. 13 discontinued during lead-in period and did not receive etranacogene dezaparvovec.

f. Due to longer time of follow-up after administration of etranacogene dezaparvovec (18 months) compared to the lead-in period follow-up (≥ 6 months), there is less time for events to occur in the lead-in period.

g. Number provided by CSL Behring. This data in not published in HOPE-B, nor was it published in the EPAR Assessment report.

Appendix 8: differences between AMT-060 and etranacogene dezaparvovec

	AMT-060	**Etranacogene dezaparvovec (AMT-061)**
Chemical name	AAV5-hFIXco or rAAV5-hFIXco	AAV5-hFIXco-Padua
Structure of vector genome and corresponding expressed FIX protein	 The hFIXco expression cassette is flanked by two ITRs (hairpin structures) and consists of the LP1 promoter, SV40 intron, hFIXco coding sequence, and polyA signal, in that order. The vector genome is approximately 2,4kb in size. Below the vector genome a schematic representation of the translated protein is provided.	 The AMT-061 vector genome is identical to the AMT-060 vector genome except for a two-nucleotide substitution (AGG to CTG). This substitution results in an Arginine to Leucine substitution in the translated protein, at position 338 (R338L).

AAV: adeno-associated virus; AP: activation peptide; hFIXco: human FIX, codon-optimised; ITR: inverted terminal repeats; PolyA: polyadenylation signal; PP: pre-pro-peptide; SV40
Sources: adapted from Miesbach W et al. *Blood* 2018; Von Drygalski A et al. *Blood* Adv 2019; Hemgenix® SmPC 2023

Greater FIX activity levels were achieved with etranacogene dezaparvovec. EMA considers AMT-060 and etranacogene dezaparvovec to be similar in terms of transduction efficacy, hFIX transcription and translation efficacy, biodistribution pattern and safety.

Appendix 9 Other HTA evaluations and pipeline

HTA evaluations

Haute Autorité de Santé (HAS), https://www.has-sante.fr, accessed October 2023
Unfavourable advice on early access authorization

National Institute for Health and Care Excellence (NICE)
https://www.nice.org.uk/, accessed October 2023
Expected final publication: November 29th, 2023.
Draft guidance: The committee concluded that it could not recommend etranacogene dezaparvovec for treating moderately severe or severe haemophilia B. The cost-effectiveness estimates are highly uncertain, do not contain all of the committee's preferred assumptions and are above the range that NICE usually considers an acceptable use of NHS resources. Further analyses are needed to yield more robust cost-effectiveness estimates.

Gemeinsamer Bundesausschuss (G-BA) www.g-ba.de, accessed September 22nd, 2023
Decision expected mid October.

Pipeline *(ref.* Beneluxa website, status 2022, and EMA website, October 2023)

- **Recombinant FIX replacement therapy:** dalcinonacog alfa (phase 2); trenonacog alfa (phase 3)
- **FVIIa replacement therapy:** marzeptacog alfa (phase 3)
- **Other treatments**
  Marstacimab: monoclonal antibody against TFPI (tissue factor pathway inhibitor) (phase 3 top-line results announced, Pfizer website, accessed 25th of September 2023)
  Concizumab: anti-TFPI antibody (phase 3 trial results published, NEJM, Matsushita et al. 2023)
  Fitusiran: anti-thrombin RNAi (phase 3 trial results published, NEJM, Matsushita et al. 2023)
  SerpinPC: recombinant serine protease inhibitor (phase 1 trial results published, Blood, Baglin et al. 2022)
- **Gene therapy**
  Fidanacogene etaparvovec (phase 3)
  In a press-release (December 29, 2022) Pfizer disclosed positive top-line results from the phase 3 BENEGENE-2 study, evaluating fidanacogene elaparvovec for the treatment of adult males with moderately severe to severe haemophilia B. The study met its primary endpoint of non-inferiority and superiority in the ABR of total bleeds post fidanacogene elaparvovec infusion *versus prophylaxis regimen with FIX, administered as part of usual care.* (Website Pfizer, accessed October 2023)

Appendix 10: treatments available in Belgium (October 2023)

Ref. BCFI, NIHDI website

Short-acting				
Benefix®	Recombinant	Nonacog alfa	Pfizer	Chapter IV, category A
Octanine®	Human plasma	Clotting FIX	Octapharma	Chapter IV, category A
Rixubis®	Recombinant	Nonacog gamma	Takeda	Chapter IV, category A
Long-acting				
Alprolix®	Recombinant	Eftrenonacog alfa	Swedish Orphan	Chapter IV, category A
Idelvion®	Recombinant	Albutrepenonacog alfa	CSL Behring	Chapter IV, category A
Refixia®	Recombinant	Nonacog beta pegol	Novo Nordisk	Chapter IV, category A

Comment:
Novoseven® (eptacog alfa) is currently under evaluation by the Belgian Commission for Reimbursement of Medicines.
In 2022, eptacog beta – Cevenfacta® has been EMA approved (EMA website accessed 25th of September 2023). Cevenfacta® is not on the Belgian market.

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Zorginstituut Nederland

Budget Impact Analysis of etranacogene dezaparvovec (Hemgenix®) for the treatment of severe and moderately severe Hemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors

Element of the initial assessment of specialty medicines

Final version | 16 April 2024

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Content

1 Introduction

The purpose of this budget impact analysis is to estimate the costs associated with the use of etranacogene dezaparvovec (Hemgenix®). If relevant, the analysis also includes possible cost savings by substitution of the current treatment. For the Dutch perspective, only costs of medicines are taken into account. For the Belgian perspective, a broader view is applied, including also other related health care costs, such as monitoring costs and hospitalization costs.

1.1 Registered indication

Etranacogene dezaparvovec is indicated for the treatment of severe and moderately severe Hemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.[1]

1.1 Definition of eligible patients under the Reimbursement Claim

The applicant's reimbursement claim is for a smaller indication than stated above. Their reimbursement claim is 'for the treatment of severe and moderately severe Hemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors and with an AAV5 neutralizing antibody titer below the threshold as mentioned in the SmPC'. The threshold mentioned in the SmPC is 1:678. In section 4.4 of the SmPC, the EMA stated that 'pre-existing neutralizing anti-AAV antibodies above a titer of 1:678 may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of Hemgenix therapy. In 1 patient with a preexisting neutralising anti-AAV5 antibody titer of 1:3212 in the clinical study, no Factor IX expression was observed and restarting of exogenous Factor IX prophylaxis was needed.'[1] However, data in patients with a titer above 1:678 are limited (since it applies to approximately 6% of the population) and therefore this is not applied as an exclusion criterion in the labelled indication. Dutch physicians stated that they will not exclude patients from treatment with etranacogene dezaparvovec with an AAV5 neutralizing antibody titer above 1:678, based on currently available data. Taking into account a similar healthcare system, the Beneluxa assessment team assumes that the situation will be the same in Belgium.

Clinical experts (both from Belgium and the Netherlands) position etranacogene dezaparvovec in adults who are treated or should be treated prophylactically with (EHL) FIX concentrates. This is in accordance with the approved label.
The severity of hemophilia B generally depends on the degree of the coagulation FIX deficiency. Depending on residual FIX activity level, hemophilia B is categorized as either severe (<1%), moderate (1-5%) or mild (5-40%). Patients with severe or moderate hemophilia B may have a severe bleeding phenotype. These patients have repeating spontaneous bleeding episodes. Patients who are classified as moderate and who present with a severe bleeding phenotype, are classified as patients with moderately severe hemophilia B. Patients with severe hemophilia B always have a severe bleeding phenotype. Patients with a severe bleeding phenotype are treated prophylactically using FIX therapy. However, a few patients choose to not be treated prophylactically (for various reasons) and only use FIX therapy on demand instead.

2 Data and assumptions

2.1 Size of the eligible population

The SmPC lists three exclusion criteria for treatment with etranacogene dezaparvovec:[1]

- -Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC. None of the patients who were screened for eligibility fulfilled this exclusion criterion. Therefore, it is assumed that this occurs in 0% of the patients in this BIA.
- -Active infections, either acute or uncontrolled chronic. If there are signs or symptoms of acute or uncontrolled chronic active infections, administration of etranacogene dezaparvovec must be postponed until the infection has resolved or is controlled. Therefore, a percentage of 0% is applied, since administration of etranacogene dezaparvovec can be postponed until infections are under control.
- -Patients with known advanced hepatic fibrosis, or cirrhosis. This is frequently seen in patients with hemophilia B but it is difficult to estimate how often. Based on a calculation, using outcomes of a Dutch study by Hassan et al., it is assumed that this applies to 10.8% of the patients (see **Table S1** for the calculation).[2] It should be noted that this percentage is very uncertain due to a lot of missing values in the study.

Furthermore, as stated in the labeled indication, patients with a history of FIX inhibitors should not receive etranacogene dezaparvovec.[1] Based on the study by Hassan et al., it is assumed that 3.5% of the targeted population has a history of FIX inhibitors (see **Table S2** for the calculation).[2]

Since physicians stated to not exclude patients from treatment with etranacogene dezaparvovec with an AAV5 neutralizing antibody titer above 1:678, based on currently available data. Patients with an AAV5 antibody titer above 1:678 are therefore not excluded in this BIA (see **paragraph 1.1** for more information).

Table 1 provides an overview of the exclusion criteria applied in this BIA, for both countries.

Table 1: Percentage of patients fulfilling exclusion criteria for treatment with etranacogene dezaparvovec

	Percentage	**Source**
Hypersensitivity	0%	Assumption
Active infections	0%	Assumption
Advanced hepatic fibrosis, or cirrhosis	10.8%	For calculation see **table S1**
History of FIX inhibitors	3.5%	For calculation see **table S2**
Total percentage of patients fulfilling exclusion criteria	**14.4%**	

To calculate the size of the eligible population, two groups of patients are distinguished: a prevalent pool and incident patients. The prevalent pool consists of patients already eligible at the time of reimbursement approval; incident patients become eligible each year.

2.1.1 Size of the eligible population in Belgium

The applicant stated that Belgian physicians estimated a total of 53 adult patients to be treated with FIX prophylaxis under the supervision of the Belgian Hemophilia reference centers UZ Leuven, UCL and Hemowab in 2024. It is assumed that this is approximately 90% of all prophylactically treated patients. This number already accounts for the patients who were treated with etranacogene dezaparvovec in the HOPE-B trial (n=6). The Beneluxa assessment team assumes that the other 10% will not be interested in treatment with etranacogene dezaparvovec in the first three years after availability.

There are also a few patients with a severe bleeding phenotype who do not use FIX prophylaxis, but on-demand therapy instead. It is unclear to how many patients in Belgium this applies.

Therefore, an estimation is made based on Dutch data, assuming that 5.8% of the patients use on-demand therapy.[3]

Previously, Belgian physicians stated a larger estimation of the adult prevalent population: 75 to 85 patients. However, when looking at the total expenses of FIX therapy in Belgium (€14.3 million in 2022) and taking into account the average costs per patient (see **paragraph 2.2.1.2**), the estimation of 75-85 patients was probably an overestimation (because multiplying this number of patients with the costs per year exceeds the total expenses).

According to the percentages in **Table 1**, 8.1 patients are not eligible for treatment with etranacogene dezaparvovec due to exclusion criteria. Based on these numbers, the total eligible prevalent population consists of 48.1 patients in Belgium (**Table 2**).

Based on information from the Belgian physicians, it is assumed that the eligible incident population will consist of 1 patient turning 18 years old every year, and 1 migrant with the labelled indication moving to Belgium every year (mainly from Eastern-Europe and Syria).

Table 2. Size of eligible population in Belgium

	N	**Source**
Adult cases with severe or moderate hemophilia B with a severe bleeding phenotype, treated in a reference center	53	Estimated by Belgian physicians
Adults cases with severe or moderate hemophilia B with a severe bleeding phenotype using on-demand therapy (5.8%)	3.3	HemoNED[3]
Number of prevalent cases meeting any of the exclusion criteria (14.4%)	8.1	Calculated based on **table 1**
Total number of eligible prevalent patients	**48.1**	Calculated
Total number of eligible incident patients	**2.0**	Calculated

During the scoping meeting, both Belgian physicians and Dutch physicians estimated that approximately 50% of the eligible patient population currently being eligible will get etranacogene dezaparvovec. Patients who were most enthusiastic about etranacogene dezaparvovec, already received it by participating in the HOPE-B trial. Most patients are enthusiastic but also hesitant. Another pharmaceutical company is currently also developing a gene therapy for the same indication so some patients may want to wait for the phase III study results to be published.

Based on input from Dutch physicians, it is assumed that most patients will be treated during the first two years. The market penetration is assumed to be 30% during the first year, 20% during the second year and 10% during the third year (**Table 3**).

The Beneluxa assessment team emphasizes that the market penetration is difficult to estimate and is therefore highly uncertain.

Table 3: Number of patients undergoing treatment with etranacogene dezaparvovec per year in Belgium

	Year 1	**Year 2**	**Year 3**
Eligible prevalent patients	48.1	35.1 ((48.1–14.4)+(2.0-0.6)	29.7 ((35.1-7.0)+(2.0-0.4)
Eligible incident patients	2.0	2.0	2.0
Market penetration (prevalent patients)	30%	20%	10%
Prevalent patients taking etranacogene dezaparvovec	14.4	7.0	3.0
Incident patients taking etranacogene dezaparvovec	0.6	0.4	0.2

Total number of patients who get etranacogene dezaparvovec†	15	7	3

† These numbers are rounded to zero decimal places for the next steps in this BIA.

2.1.2 Size of the eligible population in the Netherlands

Based on a report of HemoNED, 182 patients with hemophilia B are registered in the Netherlands.[3] A total of 86 patients have severe hemophilia B, of which 81 patients use prophylactic therapy and 5 patients (5.8%) use on-demand therapy. A total of 36 patients have moderate hemophilia B, of which 13 patients use prophylactic therapy. The HemoNED report does not state the number of patients with moderate hemophilia B with a severe bleeding type that use on-demand therapy. Therefore, the same percentage was assumed as severe hemophilia B patients (5.8%). This results in 0.8 moderate hemophilia B patients that use on-demand therapy ((5.8%*13)/(100%-5.8%)). Based on this, it is assumed that a total of 5.8 patients with severe or moderate hemophilia B with a severe bleeding type, use on demand therapy (5+0.8). This is lower than the assumption of the applicant. The applicant assumed a total of 10 patients with a severe bleeding type (severe or moderate hemophilia B) who do not use prophylactic therapy. However, during the scoping meeting, Dutch physicians stated that this number (n=10) should be lower.

Based on the World Federation of Hemophilia (WFH) report of 2022, 79% of the Dutch patients is aged ≥19 years.[4] According to the percentages in **Table 1**, 11.4 patients are not eligible for treatment with ED due to exclusion criteria. Eighteen patients have already been treated with etranacogene dezaparvovec due to participation in the HOPE-B trial. Based on these numbers, the total eligible prevalent population consists of 49.5 patients in the Netherlands (**Table 4**).

The applicant estimated an average of 1.5 incident patients per year in the Netherlands (patients who turn 18 years old). Based on input from Dutch physicians, the Beneluxa assessment team assumes that there will be 2 eligible incident patients every year (patients turning 18 years old and migrants moving to the Netherlands).

Table 4. Size of eligible population in the Netherlands

	N	**Source**
Prevalent cases with hemophilia B	182	HemoNED[3]
Cases with severe hemophilia B on prophylactic treatment	81	HemoNED[3]
Cases with moderate hemophilia B with a severe bleeding phenotype on prophylactic treatment	13	HemoNED[3]
Cases with severe or moderate hemophilia B with a severe bleeding phenotype not on prophylactic treatment	5.8	Based on HemoNED[3]
Adult cases with hemophilia B (79%)	78.8	Percentage from WFH report[4]
Number of prevalent cases meeting any of the exclusion criteria (14,4%)	11.4	Calculated based on **table 1**
Cases who are already treated with etranacogene dezaparvovec	18	Stated by Dutch physicians
Total number of eligible prevalent patients	**49.5**	
Total number of eligible incident patients	**2.0**	Estimated based on input from Dutch physicians

For the Dutch situation, the same market penetration is assumed as in Belgium. This means that approximately 50% of the remaining eligible patients will undergo treatment with etranacogene dezaparvovec. Based on input from Dutch physicians it is assumed that most patients will be treated during the first two years. The market penetration is assumed to be 30% during the first year, 20% during the second year and 10% during the third year (**Table 5**). The Beneluxa assessment team emphasizes that the market penetration is difficult to estimate and is therefore

highly uncertain. The Dutch patient association (NVHP) stated that they assume that it may take some time before patients will undergo treatment with etranacogene dezaparvovec, due to for example the development of protocols, facilities, capacity in treatment centers and because of screening of the individual patients. Therefore, they assume that the patient flow will be low during the first year and will become higher over the years.

Table 5: Number of patients undergoing treatment with etranacogene dezaparvovec per year in the Netherlands

	Year 1	**Year 2**	**Year 3**
Eligible prevalent patients	49.5	36.0 ((49.5–14.8)+(2.0-0.6))	30.4 ((36.0–7.2)+(2.0-0.4))
Eligible incident patients	2.0	2.0	2.0
Market penetration (prevalent patients)	30%	20%	10%
Prevalent patients taking etranacogene dezaparvovec	14.8	7.2	3.0
Incident patients taking etranacogene dezaparvovec	0.6	0.4	0.2
Total number of patients who get etranacogene dezaparvovec†	15	8	3

† These numbers are rounded to zero decimal places for the next steps in this BIA.

2.2 Costs per patient per year

In this paragraph costs per patient per year related to treatment of hemophilia B in a situation with etranacogene dezaparvovec and in a situation without etranacogene dezaparvovec are calculated. In line with the Belgian approach for BIA's, this entails costs related to treatment, hospitalizations, treatment administration, screening, adverse events and disease monitoring. For the Dutch approach only costs related to medication are calculated. In the Belgian approach VAT is included, while in the Dutch approach costs are calculated without VAT.

2.2.1 Costs per patient per year in Belgium

2.2.1.1 Treatment costs: etranacogene dezaparvovec

The applicant stated a price of €2,968,000 (incl. 6% VAT) per patient for etranacogene dezaparvovec in Belgium. This price is mainly based on a proposed outcome-based agreement by the applicant. The outcome based agreement involves annual payments for a period of 10 years. For Belgium this payment would equal €296,800 (incl. 6% VAT) per patient per year, in case the patients stays prophylactic-free during each year. In this BIA, only the one-time cost of €2,968,000 is applied, which is approximately the cost of ambulatory treatment. More reflection on this price in provided in **paragraph 2.2.1.6**.

2.2.1.2 Treatment costs: prophylactic therapy

The amount of IU FIX needed for prophylactic use differs per patient, based on their need and bodyweight. Based on an analysis by HemoNED (conducted for the Beneluxa assessment team, results not published) the average amount of extended half-life (EHL) FIX used per week is 3,281 IU. This equals 171,081 IU per year. Based on claims data (hospital pharmacy data) it is assumed that 45% of the patients use eftrenonacog alfa (Alprolix®) and 55% of the patients use albutrepenonacog alfa (Idelvion®). Prices per IU are shown in **table S3**. Based on this, one year of prophylactic FIX therapy costs €271,973 in Belgium ((45%*€1.20*171,081)+(55%*€1.91*171,081)).

It is known that patients with hemophilia do not always fully adhere to their prophylaxis scheme. Non-adherence includes any missed infusions, dose changes and changes in timing of infusions).[5, 6] However, it is unknown what percentage of the intended doses is on average

administered. Therefore the Beneluxa assessment team does not take into account non-adherence.

It should be noted that hospitals negotiate on the prices of EHL-FIX therapies in Belgium. These confidential negotiated prices are not used in this BIA, because the difference between the list price and the negotiated price stays in the hospital, and the perspective of the BIA is RIZIV-INAMI.

When patients are treated with etranacogene dezaparvovec they need another three weeks of FIX prophylactic therapy after administration of etranacogene dezaparvovec. This equals €15.637 (€271,793/(365/7)*3), assuming 100% adherence during this period.

2.2.1.3 Treatment costs: on demand therapy

Some patients decide to not use prophylactic therapy, but only use on demand FIX therapy instead. These patients probably use less amounts of FIX than patients on prophylactic use but they likely have more bleedings and related hospital visits. Since this applies only to a very low number of patients, the costs for prophylactic therapy are applied to all patients in this BIA.

2.2.1.4 Treatment costs related to bleedings

Patients with severe or moderately severe hemophilia B often have spontaneous bleedings, particularly in joints and muscles. A bleed is treated with (additional) FIX therapy. The applicant assumed the application of one additional dose of FIX therapy, which is also applied in this BIA. However, for severe bleedings more doses may be needed. Prices per IU Alprolix® and Idelvion® are shown in **Table S3**. Based on the average BMI of male of 25.9 and length of 181 cm, the average weight of Belgian males is assumed at 85 kg.[7] Using Alprolix® to treat a bleed would cost €5,104 (50IU/kg*85kg*€1.20). Using Idelvion® would cost €5,670 (35IU/kg*85kg*€1.91) per bleed. Assuming a 45%/55% distribution for these products, the total costs of FIX therapy for the treatment of a bleed are €5,415.

2.2.1.5 Other related health care costs

For the Belgian situation, also additional health care costs are included in the BIA. Four cost categories can be distinguished when calculating the additional costs for hemophilia B patients: (1) hospital costs per bleeding, (2) costs for drug administration and screening, (3) costs for the management of adverse events, and (4) costs for hemophilia-related monitoring.

<u>Costs of bleeding events</u>

Besides the use of FIX therapy in case of a bleed, also additional health care costs are incurred. The applicant used a study by Ten Ham et al. to estimate the additional health care costs per bleed.[8] Ten Ham et al. showed additional health care costs of €904.55 and €3,735.80 per bleed in hemophilia A patients of 19-44 years old and 44+ years old, respectively. Assuming an equal distribution of these age groups, and converting these costs to the Belgian price level of 2023 (using purchasing price parities from OECD, and the CPI from statbel), the weighted average of additional health care costs is estimated at €2,643.62 per bleed.

To calculate the annual costs per patient related to bleeds, an estimation of the number of bleeds per patient per year is needed. The HOPE-B trail started with a lead-in period of 6 months in which participants received continuous prophylactic therapy. After these 6 months, patients received a single dose of etranacogene dezaparvovec.[9] The annual bleeding rate (ABR) of FIX-treated bleedings was 3.65 during the lead-in period and 0.84 during the 12 month follow-up period after administration of etranacogene dezaparvovec (months 7-18), as shown in published data.[9] The applicant decided to exclude one patient from the data who had an AAV5 antibody titer of >1:3000 and thereby not responded to etranacogene dezaparvovec. In doing so, they calculated an ABR of 0.5. Since clinical experts stated that they will currently not exclude patients from treatment with etranacogene dezaparvovec if they have a titer above 1:678, the Beneluxa assessment team decided to apply an ABR based on all study participants. More recent data has shown an ABR of 0.99 during months 7-24 post treatment, which is applied in this BIA.[10]
The Beneluxa assessment team would like to emphasize that it is uncertain whether the ABR remains the same over time.

During the lead-in period, 57% of the participants used extended half-life (EHL) FIX therapy and 43% used standard half-life (SHL) FIX therapy.[9] In Belgian and Dutch clinical practice, most patients use EHL FIX therapy. Although specific ABRs for Dutch or Belgian populations are not available, bleeding rates have shown to be lower with EHL therapy compared to SHL therapy.[11-13] Therefore, the applicant performed an indirect-treatment comparison (ITC) to calculate ABRs for EHL FIX therapy, using Phase 3 trial data of Alprolix® and Idelvion® (and for the Dutch situation also nonacog bèta pegol (Refixia®)). The ITC showed an ABR of FIX-treated bleeding of 3.07 and 3.38 in Belgium and the Netherlands respectively. These ABRs are applied in this BIA but the Beneluxa assessment team assumes that these ABRs may be overestimated.

Taking into account the costs per bleed and the ABRs, the total costs related to bleedings per patient per year were estimated at €24,741 for FIX prophylactic therapy, and €7,978 for etranacogene dezaparvovec (see **Table 6**).

Table 6: Calculation of bleeding costs per patient per year in Belgium

	FIX prophylactic treatment	**Etranacogene dezaparvovec**
FIX therapy costs per bleeding event	€5,415 (45%*50 IU/kg*85 kg*€1.20) + (55%*35 IU/kg*85kg*€1.91)	
Additional healthcare costs per bleeding event	€2,610 ((50%*904.55)+(50%*3,735.80))*(0.74/0.77)*(129.5/109.0)	
ABR of treated bleeds	3.07	0.99
Total FIX therapy costs per patient per year	€16,625	€5,361
Total bleeding costs per patient per year	€24,741	€7,978

Cost of drug administration and screening

No administration costs of FIX prophylactic therapies are applied in this BIA because these are self-administered by the patients.

Based on the SmPC of etranacogene dezaparvovec,[1] patients need to undergo several eligibility screening tests before administration of etranacogene dezaparvovec. Since the costs of these tests are negligible compared to the price of etranacogene dezaparvovec and the costs of prophylactic FIX therapy, these costs are not taken into account in this BIA.
Costs of testing the AAV5 antibody titers will be paid by the registration holder (in Belgium).

Costs of adverse events

During the HOPE-B study, several adverse events occurred in patients treated with etranacogene dezaparvovec.[9] It is assumed that these adverse events do not lead to substantial health care costs and were therefore not quantified in this BIA.

Costs of hemophilia-related monitoring

Patients with hemophilia B in Belgium are often treated in a so called reference center, which is a specialized center for hemophilia B. It is assumed that most patients with the labelled indication are treated in one of the reference centers, which costs €2,009.94 per patient per year (based on RIZIV nomenclatuur). Since this is the same for patients who are treated with FIX therapy and patients who a treated with etranacogene dezaparvovec, these costs are not applied in this BIA.

Based on the SmPC of etranacogene dezaparvovec, patients who undergo treatment with etranacogene dezaparvovec need to be monitored extensively during the first year.[1] During the years thereafter, only one or two monitoring visits to the reference center per year are needed. It is assumed that the monitoring costs are negligible compared to the price of etranacogene dezaparvovec, and are therefore not quantified in this BIA.

2.2.1.6 *Extrapolation and average costs per patient in Belgium*

In the previous paragraphs, costs per patient per year were calculated. However, use of etranacogene dezaparvovec not only substitutes costs during one year but on a longer time horizon. In this paragraph we therefore show a comparison of the costs in a situation with etranacogene dezaparvovec and a situation without etranacogene dezaparvovec, applying different time horizons. This also shows whether the costs in a situation with etranacogene dezaparvovec exceed the costs in a situation without etranacogene dezaparvovec. In principle, when no superiority is concluded in the pharmacotherapeutic assessment, the costs in the new situation may not exceed the costs in the current situation. Based on this, the cumulative costs in a situation without etranacogene dezaparvovec and in a situation with etranacogene dezaparvovec are calculated and subtracted. In doing so, the maximum price of etranacogene dezaparvovec is calculated following the 'equal costs principle'. In these calculations, not only the costs are taken into account but also the percentage of patients remaining prophylaxis-free over time.

The applicant performed an extrapolation of the number of patients remaining prophylaxis-free for a time horizon of 80 years. The methods of this extrapolation can be found in a published study.[14] They asumed that 97% of the patiënts is still prophylaxis-free for 10 years. However, they excluded 2 patients from the analysis who did not become prophylaxis-free. Therefore, the Beneluxa assessment team adjusted the extrapolation by adding these two patients. These adjusted extrapolated outcomes are shown in **table 7**. This extrapolation is still highly uncertain (see paragraph 3.3.1 of the pharmacotherapeutic assessment report).

Table 7: Extrapolation of FIX activity levels

	% patients FIX activity <5%	**% patients FIX activity ≥5%**
Year 1	3.7%	96.3%
Year 2	3.7%	96.3%
Year 3	3.8%	96.2%
Year 4	3.9%	96.1%
Year 5	4.1%	95.9%
Year 6	4.2%	95.8%
Year 7	4.9%	95.1%
Year 8	5.1%	94.9%
Year 9	6.4%	93.6%
Year 10	6.7%	93.3%

All costs mentioned in the previous paragraphs are multiplied with the extrapolated percentages. The outcomes were then added up to calculate the average costs per patient per year. **Table 8** shows the average cumulative costs in a situation with and a situation without etranacogene dezaparvovec, applying various time horizons. When subtracting the average cumulative costs per patient in a situation with etranacogene dezaparvovec from the costs in a situation without etranacogene dezaparvovec, the maximum price of etranacogene dezaparvovec is calculated, following the 'equal costs principle' (see **table 8**). Based on the currently available data, the Beneluxa assessment team considers there is sufficient confidence in a durability of the effectiveness of 4 to 5 years. Beyond this period, there is too much uncertainty in the effectiveness. When a time horizon of 4 and 5 years is applied, the maximum price of etranacogene dezaparvovec would be €1,1 million and €1.4 million respectively.

Table 8: Cumulative costs and the maximum price of etranacogene dezaparvovec at different time horizons, following the 'equal costs principle'

	Cumulative costs in a situation without etranacogene dezaparvovec	**Cumulative costs after treatment with etranacogene dezaparvovec***	**Maximum price of etranacogene dezaparvovec**
1 year	€ 296,534	€ 33,724	€ 262,811
2 years	€ 593,069	€ 52,390	€ 540,679

3 years	€ 889,603	€ 71,333	€ 818,270
4 years	€ 1,186,138	€ 90,554	€ 1,095,584
5 years	€ 1,482,672	€ 110,331	€ 1,372,341
6 years	€ 1,779,207	€ 130,386	€ 1,648,820
7 years	€ 2,075,741	€ 152,387	€ 1,923,355
8 years	€ 2,372,276	€ 175,220	€ 2,197,056
9 years	€ 2,668,810	€ 201,666	€ 2,467,144
10 years	€ 2,965,345	€ 228,946	€ 2,736,399

* This contains costs related to treatment failure (re-initiation of FIX-prophylaxis) for some patients and costs of bleedings. Costs of etranacogene dezaparvovec itself are not included in this category.

It should be noted that the longer the time horizon, the higher the uncertainty. As mentioned above, the number of patients needing to reinitiate FIX prophylaxis is uncertain, as well as the ABR over time. Coppens et al. reported that, after month 24, one patient had a FIX activity of <5% (4,7%). It is to be expected that this patient would need to resume FIX prophylaxis within the forseeable future, if FIX activity would continue to decrease. This indicates an overestimation of the predicted percentage of patients with FIX activity levels ≥5% (**table 7**).[10] Furthermore, the costs of the situation without etranacogene dezaparvovec are also uncertain since new treatments may be developed in the upcoming years.
Lastly, patients may die due to any cause unrelated to treatment. The older the patient, the higher the probability of death. Other uncertainties are reported in the pharmacotheraputic assessment report.

2.2.2 Costs per patient per year in the Netherlands

2.2.2.1 Treatment costs: etranacogene dezaparvovec

As described in **paragraph 2.1.1.1** of this BIA, the applicant proposed a payment scheme for etranacogene dezaparvovec. For the Netherlands, the annual price equals €280,000 (excl. VAT) per patient, in case the patient stays prophylactic-free during each year. For a patient staying prophylactic-free for ten years, the total price of etranacogene dezaparvovec amounts €2,800,000 (excl. VAT). The total price is applied in this BIA as a one-off payment. More reflection on this price in provided in **paragraph 2.2.2.5**.

2.2.2.2 Treatment costs: prophylactic therapy

For the Dutch situation, the calculations are also based on the average amount of 171.081 IU EHL FIX per patient per year based on the HemoNED analysis (see **paragraph 2.2.1.2**). Based on data of the annual report of HemoNED, 93% of the patients with hemophilia B used EHL FIX therapy in 2022.[3] In this BIA, it is assumed that all patients will be switched to EHL FIX therapy in year 1 of this BIA. Based on the GIP data it is assumed that 93% of the patients use Alprolix® and 7% of the patients use Refixia®.[15] Prices per IU are shown in **table S4**. For the Dutch situation, two scenarios are calculated, using different prices. In the first scenario list prices are applied.[16] Using list prices, the annual cost of prophylactic therapy equals **€350,526** ((93%*€2.03*171,081)+(7%*€2.26*171,081)).

Since health insurance companies and hospitals negotiate on these prices, a second scenario is conducted in which price reductions are applied. Data of the GIPdatabank shows that the annual expenses per patient of Alprolix® decreased from €585,832 in 2018 to €251,443 in 2022 (a decrease of 57%). This can be caused by price negotiations but also by dose reductions and extended dose intervals. Based on confidential declaration data, the Beneluxa assessment team concludes that the reduction in expenses is mainly caused by price negotiations. Therefore, the list prices of 2018 (which are equal to current list prices) are adjusted by applying a 57% reduction. According to the price reductions, the annual cost of prophylactic therapy equal **€150,448** ((93%*€0.87*171,081)+(7%*€0.97*171,081)).

As explained in **paragraph 2.2.1.2**, patients with hemophilia do not always fully adhere to their prophylaxis scheme.[5, 6] However, it is unknown what percentage of the intended doses is on average administered. Therefore, no correction for adherence is applied.

Prices of Alprolix® and Refixia® are based on the Z-index of March 2024 (see **table S4**).

When patients are treated with etranacogene dezaparvovec they need another three weeks of FIX prophylactic therapy after administration of etranacogene dezaparvovec. This equals €20,167 (€350,526/(365/7)*3) in scenario 1, and €8,656 (€150,488/(365/7)*3) in scenario 2.

2.2.2.3 Treatment costs: on demand therapy

As explained in **paragraph 2.2.1.3**, since only a few patients use on demand therapy instead of prophylactic therapy, these costs are not substantiated in this BIA. The costs of prophylactic therapy are applied for all patients.

2.2.2.4 Treatment costs related to bleeds

As explained in **paragraph 2.2.1.4**, one additional dose of FIX therapy is needed to treat a bleed. In scenario 1, list prices are used, which results in €8,571 per bleed. According to scenario 2, in which a price reduction is applied, the costs per bleed are €3,679.

To calculate the annual costs per patient related to bleedings, an estimation of the number of bleedings per patient per year is needed. See **paragraph 2.2.1.5** for more information about the estimation of the ABRs. Based on the ITC, the ABR for treated bleedings in the Netherlands is estimated at 3.38. The costs per patient per year related to bleedings are shown in **Table 9**.

Table 9: Calculation of bleeding costs per patient per year in the Netherlands

	Scenario1		**Scenario 2**	
	FIX treatment	**Etranacogene dezaparvovec**	**FIX treatment**	**Etranacogene dezaparvovec**
FIX therapy costs per bleeding event†	€8,571		€3,679	
ABR of treated bleeds	3.38	0.99	3.38	0.99
Bleeding costs per patient per year	€28,969	€8,485	€12,433	€3,642

† Calculated: (93%*50 IU/kg*85 kg*€) + (7%*40 IU/kg*85kg*€)

Scenario 1 is based on list prices; scenario 2 is based on price reductions due to negotiations.

2.2.2.5 Average costs per patient in the Netherlands

In the previous paragraphs, costs per patient per year are calculated. However, use of etranacogene dezaparvovec not only substitutes costs during one year but on a longer time horizon. In this paragraph we therefore show a comparison of the costs in a situation with etranacogene dezaparvovec and a situation without etranacogene dezaparvovec, applying different time horizons. This also shows whether the costs in a situation with etranacogene dezaparvovec exceed the costs in a situation without etranacogene dezaparvovec. In principle, when no superiority is concluded in the pharmacotherapeutic assessment, the costs in the new situation may not exceed the costs in the current situation. Based on this, the cumulative costs in a situation without etranacogene dezaparvovec and in a situation with etranacogene dezaparvovec are calculated and subtracted. In doing so, the maximum price of etranacogene dezaparvovec is calculated following the 'equal costs principle'. In these calculations, not only the costs are taken into account but also the percentage of patients remaining prophylaxis-free over time.

All costs mentioned in the previous paragraphs are multiplied with the extrapolated percentages of patients with a FIX activity level >5% (see **paragraph 2.2.1.6**). The outcomes were then added up to calculate the average costs per patient per year. **Table 10** shows the average cumulative costs in a situation with and a situation without etranacogene dezaparvovec, applying various time horizons. Based on the currently available data, the Beneluxa assessment team considers there is sufficient confidence in a durability of the effectiveness of 4 to 5 years. Beyond this period, there is too much uncertainty in the effectiveness. When subtracting the average cumulative costs per patient, the maximum price of etranacogene dezaparvovec is calculated, following the 'equal costs principle' (see **table 10**). When a time horizon of 4 years is

applied, the maximum price of etranacogene dezaparvovec is €1.4 million according scenario 1, and €604,574 according to scenario 2. When a time horizon of 5 years is applied, the maximum price is €1.8 million according to scenario 1 and €757,302 according to scenario 2.

It should be noted that the longer the time horizon, the higher the uncertainty. As mentioned before, the number of patients needing to reinitiate FIX prophylaxis is uncertain, as well as the ABR over time. Coppens et al. reported that, after month 24, one patient had a FIX activity level <5%. It is to be expected that this patient would need to resume FIX prophylaxis within the forseeable future, if FIX activity would continue to decrease. This indicates an overestimation of the predicted percentage of patients with FIX activity levels ≥5% (**table 7**).[10]
Furthermore, the costs of the situation without etranacogene dezaparvovec are also uncertain since new treatments may be developed in the upcoming years, and prices of FIX may decrease even further.
Lastly, patients may die due to any cause unrelated to treatment. The older the patient, the higher the probability of death. Other uncertainties are reported in the pharmacotherapeutic assessment report.

Table 10: Cumulative costs and the maximum price of etranacogene dezaparvovec at different time horizons, following the 'equal costs principle'

	Cumulative costs in a situation without etranacogene dezaparvovec	**Cumulative costs after treatment with etranacogene dezaparvovec***	**Maximum price of etranacogene dezaparvovec**
Scenario 1: list prices			
1 year	€ 379,495	€ 41,646	€ 337,848
2 years	€ 758,989	€ 63,872	€ 695,117
3 years	€ 1,138,484	€ 86,455	€ 1,052,028
4 years	€ 1,517,978	€ 109,396	€ 1,408,582
5 years	€ 1,897,473	€ 133,051	€ 1,764,422
6 years	€ 2,276,967	€ 157,063	€ 2,119,904
7 years	€ 2,656,462	€ 183,577	€ 2,472,885
8 years	€ 3,035,956	€ 211,162	€ 2,824,795
9 years	€ 3,415,451	€ 243,391	€ 3,172,060
10 years	€ 3,794,945	€ 276,692	€ 3,518,253
Scenario 2: price reductions			
1 year	€ 162,882	€ 17,875	€ 145,007
2 years	€ 325,764	€ 27,414	€ 298,349
3 years	€ 488,645	€ 37,107	€ 451,538
4 years	€ 651,527	€ 46,954	€ 604,574
5 years	€ 814,409	€ 57,106	€ 757,302
6 years	€ 977,291	€ 67,413	€ 909,878
7 years	€ 1,140,172	€ 78,792	€ 1,061,380
8 years	€ 1,303,054	€ 90,632	€ 1,212,422
9 years	€ 1,465,936	€ 104,465	€ 1,361,471
10 years	€ 1,628,818	€ 118,758	€ 1,510,059

* This contains costs related to treatment failure (re-initiation of FIX-prophylaxis) for some patients and costs of bleedings. Costs of etranacogene dezaparvovec itself are not included in this category. Scenario 1 is based on list prices; scenario 2 is based on price reductions due to negotiations.

These calculations only include costs of medication (etranacogene dezaparvovec and FIX therapy). Treatment with etranacogene dezaparvovec is expected to result in less hospitalizations and physiotherapy, which is not included in the calculations.

3 Budget Impact

3.1 Belgium

Tables 11-13 provides an overview of the total budget impact when etranacogene dezaparvovec becomes available for treatment of severe and moderately severe hemophilia B in Belgium with a total price of €2,968,000 per patient. The budget impact will be highest in year 1: health care expenditure will increase with €40.2 million during that year.

Table 11: budget impact in Belgium – expenses of etranacogene dezaparvovec (level 1)

	Year 1	**Year 2**	**Year 3**
Budget impact L1 (treatment expenses etranacogene dezaparvovec)	€ 44,520,000	€ 20,776,000	€ 8,904,000

Table 12: budget impact in Belgium – impact on medicines budget (level 2)

	Year 1	**Year 2**	**Year 3**
Treatment expenses related to etranacogene dezaparvovec			
Etranacogene dezaparvovec	€ 44,520,000	€ 20,776,000	€ 8,904,000
FIX therapy to treat bleeds	€80,418	€117,946	€134,029
Total	€44,600,418	€20,893,946	€9,038,029
Treatment expenses related to current therapy			
FIX prophylactic therapy	€4,076,902	€5,979,457	€6,794,837
FIX therapy to treat bleeds	€249,376	€365,752	€415,627
Total	€4,326,278	€6,345,208	€7,210,464
Budget impact L2	€40,274,139	€14,548,738	€1,827,566

Table 13: budget impact in Belgium – impact on health care budget (level 3)

	Year 1	**Year 2**	**Year 3**
Expenses related to etranacogene dezaparvovec			
Treatment expenses	€ 44,520,000	€ 20,776,000	€ 8,904,000
Expenses due to bleeds	€119,675	€175,524	€199,459
Total	€44,639,675	€20,951,524	€9,103,459
Expenses related to current therapy			
Treatment expenses	€4,076,902	€5,979,457	€6,794,837
Expenses due to bleeds	€371,115	€544,302	€618,525
Total	€4,448,017	€6,523,758	€7,413,362
Budget impact L3	€40,191,658	€14,427,766	€1,690,097

3.2 The Netherlands

Table 14 and 15 provide an overview of the total budget impact when etranacogene dezaparvovec becomes available for treatment of severe and moderately severe Hemophilia B in the Netherlands with a total price of €2,800,000 per patient. Based on scenario 1, the budget impact will be €36.4 million in year 1, which will decrease to €13.9 million in year 2, and €-1.2 million in year 3. Based on scenario 2, the budget impact will be €39.6 million in year 1, which will decrease to €18.7 million in year 2, and €4.3 million in year 3.

Table 14: budget impact in the Netherlands: scenario 1

	Year 1	**Year 2**	**Year 3**
Expenses related to etranacogene dezaparvovec			
Treatment expenses	€42,000,000	€22,400,000	€8,400,000
Expenses due to bleeds	€127,273	€195,152	€220,607
Total	€42,127,273	€22,595,152	€8,620,607
Expenses related to current therapy			
Treatment expenses	€5,257,890	€8,062,097	€9,113,675
Expenses due to bleeds	€434,528	€666,277	€753,182
Total	€5,692,418	€8,728,374	€9,866,858
Budget impact	€36,434,855	€13,866,778	€-1,246,251

Scenario 1 is based on list prices.

Table 15: budget impact in the Netherlands: scenario 2

	Year 1	**Year 2**	**Year 3**
Expenses related to etranacogene dezaparvovec			
Treatment expenses	€42,000,000	€22,400,000	€8,400,000
Expenses due to bleeds	€54,626	€83,760	€94,686
Total	€42,054,626	€22,483,760	€8,494,686
Expenses related to current therapy			
Treatment expenses	€2,256,724	€3,460,310	€3,911,655
Expenses due to bleeds	€186,502	€285,970	€323,270
Total	€2,443,226	€3,746,280	€4,234,926
Budget impact	€39,611,400	€18,737,480	€4,259,760

Scenario 2 is based on price reductions due to negotiations.

4 Conclusion

This BIA showed that a total of 25 and 26 patients in Belgium and the Netherlands respectively will be treated with etranacogene dezaparvovec in 3 years. When etranacogene dezaparvovec becomes available for treatment of patients with severe or moderately severe hemophilia B, health care expenditure will rise with €40.2 million during the first year in Belgium. In the Netherlands, this will be €36.4 to €39.6 million during the first year.

The price etranacogene dezaparvovec is €3.0 million (incl. 6% VAT) per patient in Belgium an d €2.8 million (excl. VAT) per patient in the Netherlands. Etranacogene dezaparvovec will substitute the use of FIX prophylactic therapy. In principle, when no superiority is concluded in the pharmacotherapeutic assessment, the costs in the new situation may not exceed the costs in the current situation ('equal costs principle'). Based on the currently available data, the Beneluxa assessment team considers there is sufficient confidence in a durability of the effectiveness of 4 to 5 years. Beyond this period, there is too much uncertainty in the effectiveness. When a time horizon of 4 years is applied, the maximum price of etranacogene dezaparvovec would be €1.1 million in Belgium. When a time horizon of 5 years is applied, the maximum price would be €1.4 million. For the Dutch situation two different scenarios were calculated, using different prices for FIX therapy (scenario 1: list prices, scenario 2: negotiated prices). When a time horizon of 4 years is applied, the maximum price of etranacogene dezaparvovec would be €1.4 million according scenario 1, and €604,574 according to scenario 2 in the Netherlands. When a time horizon of 5 years is applied, the maximum price is €1.8 million according to scenario 1 and €757,302 according to scenario 2.

Regarding the calculations of the budget impact, there is uncertainty in the number of patients, the number of bleeds per year and the market penetration of etranacogene dezaparvovec. In case the market penetration differs in reality from what is assumed in this BIA, the total expenditure may be much higher or lower than estimated in this BIA. This is caused by the high price of etranacogene dezaparvovec.

In the long-term calculations of the average cumulative costs per patient using different time horizons, there is uncertainty in the extrapolation of FIX activity levels, the ABR over time and whether the prices of FIX therapy may further decrease and whether other treatment options will become available.

5 Referenties

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6 Supplementary appendix

Table S1: Calculation of the percentage of patients with advanced hepatic fibrosis or cirrhosis

Age group	Calculation	Source
<50 years	(82/613)*(3/35)=1.1%.	Table 6 by Hassan et al. [2]
≥50 years	(96/115)*(12/49)=20.4%.	Table 6 by Hassan et al. [2]
All adult ages	(50%*1.1%)+(50%*20.4%)=10.8%	Equal age distribution based on WFH report.[4]

Table S2: calculation of the percentage of patients with a history of FIX inhibitors

	Percentage	N	Source
Patients with a history of FIX inhibitors among patients with severe hemophilia B	4.1% (2/49)		Supplementary appendix Hassan et al.[2]
Adult patients with severe hemophilia B (of all patients with hemophilia B)	34%	69.3 (33%*210)	WFH report[4]
Adult patients with severe or moderate hemophilia B with a severe bleeding phenotype	N/A	80	Estimated by Belgian physicians
% adult patients with severe hemophilia B (of patients with severe or moderate hemophilia B with a severe bleeding phenotype)	86.6% (69,3/80)		Calculation
% adult patients with severe or moderate hemophilia B with a severe bleeding phenotype and a history of FIX inhibitors (of patients with severe or moderate hemophilia B with a severe bleeding phenotype)	3.5% (4.1*86.6)		Calculation

Note: FIX inhibitors occur almost exclusively among patients with severe hemophilia B.[17]

Table S3: Prices of Alprolix® and Idelvion® in Belgium

Alprolix®	Public pharmacy price per vial(€)	Hospital pharmacy price per vial(€)	Weighted price per vial*	Weighted price (€) per IU
250 IU	€ 311.24	€ 298.61	€ 305.56	€ 1.22
500 IU	€ 612.33	€ 590.11	€ 602.33	€ 1.20
1000 IU	€ 1,214.52	€ 1,173.11	€ 1,195.89	€ 1.20
2000 IU	€ 2,418.88	€ 2,339.11	€ 2,382.98	€ 1.19
3000 IU	€ 3,623.24	€ 3,505.11	€ 3,570.08	€ 1.19
				€ 1.20
Idelvion®				
250 IU	€ 490.11	€ 471.78	€ 481.86	€ 1.93
500 IU	€ 970.06	€ 936.45	€ 954.94	€ 1.91
1000 IU	€ 1,930.00	€ 1,865.81	€ 1,901.11	€ 1.90
2000 IU	€ 3,849.85	€ 3,724.51	€ 3,793.45	€ 1.90
3500 IU	€ 6,729.62	€ 6,512.55	€ 6,631.94	€ 1.89
				€ 1.91

*55% public pharmacy, 45% hospital pharmacy, based on claims data

Table S4: Prices of Alprolix® and Refixia® in the Netherlands

Alprolix®	**List price per vial (€)**	**List price (€) per IU***	**Assumed declared price (€) per IU**
250 IU	€ 508.16	€ 2.03	€ 0.87
500 IU	€ 1,016.32	€ 2.03	€ 0.87
1000 IU	€ 2,032.65	€ 2.03	€ 0.87
2000 IU	€ 4,065.31	€ 2.03	€ 0.87
3000 IU	€ 6,097.96	€ 2.03	€ 0.87
		€ 2.03	€ 0.87
Refixia®			
500 IU	€ 1,130.00	€ 2.26	€ 0.97
1000 IU	€ 2,260.00	€ 2.26	€ 0.97
2000 IU	€ 4,520.00	€ 2.26	€ 0.97
		€ 2.26	€ 0.97

* based on the Z-index of March 2024