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SKEDULERINGSTATUS S4

1 NAAM VAN DIE MEDISYNE
VALOMA 1 poeier vir oplossing vir inspuiting
VALOMA 2,5 poeier vir oplossing vir inspuiting
VALOMA 3,5 poeier vir oplossing vir inspuiting

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
VALOMA 1: Elke flessie bevat 1,0 mg bortesomib (as 'n mannitol boroniese ester).
Alleenlik vir Intraveneuse (IV) gebruik.
VALOMA 2,5: Elke flessie bevat 2,5 mg bortesomib (as 'n mannitol boroniese ester).
Intraveneuse (IV) of subkutaneuse (SK) gebruik.
VALOMA 3,5: Elke flessie bevat 3,5 mg bortesomib (as 'n mannitol boroniese ester).
Intraveneuse (IV) of subkutaneuse (SK) gebruik.
Na hersamestelling, bevat 1 ml van die oplossing vir intraveneuse inspuiting 1 mg bortesomib.
Na hersamestelling, bevat 1 ml van die oplossing vir subkutaneuse inspuiting 2,5 mg bortesomib.
VALOMA 1: Bevat suiker (mannitol) 10 mg per flessie
VALOMA 2,5: Bevat suiker (mannitol) 25 mg per flessie
VALOMA 3,5: Bevat suiker (mannitol) 35 mg per flessie
Vir 'n volledige lys van bestanddele, sien afdeling 6.1

3 FARMASEUTIESE VORM
Poeier vir oplossing vir inspuiting. Wit tot naaswit koek of poeier.
Die hersaamgestelde oplossing is helder en kleurloos, met 'n finale pH van 4 tot 7.

4 KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
VALOMA is aangedui as:
- Primêre behandeling van meervoudige miëloom in kombinasie met mefalaan en prednisoon.
- Monoterapie vir die behandeling van pasiënte met meervoudige miëloom wat ten minste een vorige behandeling ontvang het en wie progressiewe siekte het.
- Behandeling van terugval- of refraktoriese mantelsellimfoom vir pasiënte wat ten minste een voorafgaande behandelingslyn ontvang het, waarvan een 'n antrasiklien (of mitosantroon) en/of rituksimab moes insluit as deel van hul chemoterapie-regime.

4.2 Posologie en metode van toediening
Posologie
VALOMA 1 poeier vir oplossing vir inspuiting is beskikbaar vir:
- Intraveneuse toediening slegs in 'n konsentrasie van 1 mg/ml (as 'n 3-5 sekonde bolusinspuiting).

VALOMA 2,5 en VALOMA 3,5 poeier vir oplossing vir inspuiting is beskikbaar vir:
- Intraveneuse toediening in 'n konsentrasie van 1 mg/ml (as 'n 3-5 sekonde bolusinspuiting) of
- Subkutaneuse toediening in 'n konsentrasie van 2,5 mg/ml.

Aangesien elke toedieningsroete 'n ander hersaamgestelde konsentrasie het, moet die berekening van die volume wat toegedien moet word met versigtigheid gedoen word (sien afdeling 6.6).

VALOMA moet slegs intraveneus of subkutaan toegedien word. Intratekale toediening het tot die dood gelei.

Sien **(Hersamestellings instruksies hieronder)**

Aanbevole dosis vir monoterapie
Die aanbevole aanvangsdosis van VALOMA is 1,3 mg/m² liggaamsoppervlakte twee keer per week vir twee weke (dag 1, 4, 8 en 11), gevolg deur 'n rustydperk van 10 dae (dag 12 tot 21) in 'n 21-dag behandelingsiklus. Hierdie 3 weke-periode word as 'n behandelingsiklus beskou. Daar moet minstens 72 uur verloop tussen opeenvolgende dosisse van VALOMA. Daar word aanbeveel dat pasiënte met 'n bevestigde volledige reaksie, 2 addisionele siklusse van VALOMA verder ontvang as 'n bevestiging. Daar word ook aanbeveel dat reagerende pasiënte wat nie 'n volledige remissie bereik nie, in totaal 8 siklusse van VALOMA-behandeling ontvang. Daar is beperkte data rakende herbehandeling met VALOMA.

Aanbevole dosisaanpassings tydens behandeling en heraanvang van behandeling vir monoterapie
VALOMA behandeling moet weerhou word aan die begin van enige Graad 3-nie-hematologiese of enige Graad 4-hematologiese toksisiteit, uitgesluit neuropatie soos hieronder bespreek (sien afdeling 4.4). Sodra die simptome van die toksisiteit opgeklaar het, kan die behandeling met VALOMA weer begin word teen 'n 25 % verlaagde dosis (1,3 mg/m² verminder tot 1,0 mg/m²; 1, 0 mg/m² verminder tot 0,7 mg/m²). Indien die toksisiteit nie opgeklaar is nie, of indien dit by die laagste dosis weer voorkom, moet dit oorweeg word om VALOMA te staak.

Neuropatiese pyn en/of perifere neuropatie
Pasiënte wat VALOMA-verwante neuropatiese pyn en/of perifere neuropatie ervaar, moet hanteer word soos in die onderstaande tabel aangetoon. Pasiënte met bestaande ernstige neuropatie kan slegs met VALOMA behandel word na deeglike risiko/voordele-assessering.

Aanbevole dosisaanpassings vir VALOMA-verwante neuropatiese pyn en/of perifere sensoriese neuropatie.

Erns van perifere neuropatie	Aanpassing van dosis en regime
Graad 1 (parastesie, swakheid en/of verlies van diep tendonreflekse) sonder pyn of verlies van funksie	Geen aksie
Graad 1 met pyn of Graad 2 (beïnvloed die funksie, maar nie die daaglikse aktiwiteite nie)	Verlaag tot 1,0 mg/m²
Graad 2 met pyn of Graad 3 (beïnvloed daaglikse aktiwiteite)	Weerhou die VALOMA behandeling, totdat die simptome van toksisiteit opgeklaar het. Indien die toksisiteit opklaar, begin weer met die VALOMA behandeling en verminder die dosis tot 0,7 mg/m² en verander die behandelingskedule na een keer per week.
Graad 4 (sensoriese neuropatie wat ongeskiktheid kan veroorsaak of motoriese neuropatie wat lewensgevaarlik is of tot verlamming lei)	Staak VALOMA

Dosisbestuursriglyne vir kombinasie-terapie
VALOMA vir inspuiting word toegedien in kombinasie met orale melfalaan en orale prednisoon vir nege behandelingsiklusse van 6 weke, soos aangedui in die onderstaande tabel. In Siklusse 1 – 4, word VALOMA twee keer per week toegedien (dag 1, 4, 8, 11, 22, 25, 29 en 32). In Siklusse 5 tot 9, word VALOMA een keer per week toegedien (dag 1, 8, 22 en 29).

Aanbevole doserings regime vir VALOMA wanneer gebruik word in kombinasie met melfalaan en prednisoon vir pasiënte met vorige onbehandelde meervoudige miëloom.

Twee keer per week VALOMA (Siklusse 1 - 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
VI (1,3 mg/m²)	Dag 1	-	-	Dag 4	Dag 8	Dag 11	Rus periode	Dag 22	Dag 25	Dag 29	Dag 32	Rus periode
m (9 mg/m²) p (60 mg/m²)	Dag 1	Dag 2	Dag 3	Dag 4	-	-	Rus periode	-	-	-	-	Rus periode

Eenkeer per week VALOMA (Siklusse 5 - 9)									
Week	**1**				**2**	**3**	**4**	**5**	**6**
VI (1,3 mg/m²)	Dag 1	-	-	-	Dag 8	Rus periode	Dag 22	Dag 29	Rus periode
m (9 mg/m²) p (60 mg/m²)	Dag 1	Dag 2	Dag 3	Dag 4	-	Rus periode	-	-	Rus periode

VI = VALOMA; m = melfalaan, p = prednisoon

Dosisaanpassings en herinstelling van behandeling wanneer VALOMA toegedien word in kombinasie met melfalaan en prednisoon
Voor die aanvang van 'n nuwe siklus van behandeling:
- Aantal bloedplaatjies moet ≥ 70 x 10^9/L wees en die ANT moet ≥ 1,0 X 10^9/L wees.
- Nie-hematologiese toksisiteite behoort tot Graad 1 of basislyn opgeklaar het.

Dosis aanpassings tydens daaropvolgende siklusse

Toksisiteit	Dosisaanpassing of -vertraging
Hematologiese toksisiteit gedurende 'n siklus	
Indien langdurige Graad 4-neutropenie of trombositopenie, of trombositopenie met bloeding waargeneem is in die vorige siklus	Oorweeg 'n 25 % verlaging in die melfalaan dosis in die volgende siklus.
Indien die bloedplaatjie-telling ≤ 30 x 10^9/L of ANT ≤ 0,75 x 10^9/L op 'n VALOMA-doseringsdag (anders as dag 1)	VALOMA dosis moet weerhou word
Indien verskeie VALOMA dosisse in 'n siklus weerhou word (≥ 3 dosisse tydens twee keer per week toediening of ≥ 2 dosisse tydens weeklikse toediening)	VALOMA dosis moet verminder word met 1 dosisvlak (van 1,3 mg/m² tot 1 mg/m², of van 1 mg/m² tot 0,7 mg/m²)
Graad ≥ 3 *nie-hematologiese toksisiteite*	VALOMA behandeling moet weerhou word totdat die simptome van die toksisiteit tot Graad 1 of basislyn opgeklaar het. Daarna kan daar weer met VALOMA begin word met een dosisvlak verlaging (van 1,3 mg/m² tot 1 mg/m², of van 1 mg/m² tot 0,7 mg/m²) Vir VALOMA verwante neuropatiese pyn en/of perifere neuropatie, behou, en/of verander VALOMA soos uiteengesit in die tabel hierbo: "Aanbevole dosisaanpassings vir VALOMA verwante neuropatiese pyn en/of perifere sensoriese neuropatie"

Vir addisionele inligting rakende melfalaan en prednisoon, verwys na hul onderskeidelike Professionele Inligtingstukke.

Spesiale populasies
Bejaarde pasiënte
Daar is geen bewyse wat daarop dui dat dosisaanpassings in bejaardes nodig is nie (sien afdeling 4.8).
Pasiënte met nierinkorting.
Die farmakokinetika van VALOMA word nie beïnvloed deur die graad van nierinkorting nie. Dosisaanpassings van VALOMA is dus nie nodig vir pasiënte met renale ontoereikendheid nie. Aangesien dialise VALOMA konsentrasies kan verlaag, moet VALOMA toegedien word na die dialise-prosedure (sien afdeling 5.2).
Pasiënte met lewerinkorting.
Pasiënte met ligte inkorting van lewerfunksie het geen aanpassing van die aanvangsdosis nodig nie en moet volgens die aanbevole dosis van VALOMA behandel word. Pasiënte met matige of ernstige lewerinkorting moet begin word met VALOMA teen 'n verlaagde dosis van 0,7 mg/m² per inspuiting gedurende die eerste siklus, en 'n daaropvolgende dosisverhoging tot 1,0 mg/m² of verdere dosisverlaging tot 0,5 mg/m² kan oorweeg word gebaseer op die pasiënt se verdraagsaamheid (sien Tabel hieronder).

Aanbevole aanpassing van die aanvangsdosis vir VALOMA in pasiënte met lewerinkorting

Graad van lewerinkorting *	Bilirubienvlak	SGOT (AST) vlakke	Aanpassing van aanvangsdosis
Lig	≤ 1,0 x BLN	> BLN	Geen
	> 1,0 x -1,5 x BLN	Enige	Geen
Matig	> 1,5 x -3 x BLN	Enige	Verminder VALOMA tot 0,7 mg/m² in die eerste siklus. Oorweegdosis eskalasie tot 1,0 mg/m² of verdere dosisvermindering tot 0,5 mg/m² in die daaropvolgende siklus gebaseer op pasiënt verdraagsaamheid.
Ernstig	> 3 x BLN	Enige	

Afkortings: SGOT = serum glutamiese oksaloasetiese transaminase; AST = aspartaat aminotransferase; BLN = boonste limiet van die normalereeks.
*Gebaseer op NCI-orgaandisfunksie-werksgroepklassifikasie vir die kategorisering van lewerinkorting (lig, matig, ernstig).

Pediatriese populasie
VALOMA is nie in kinders en adolessente bestudeer nie. Dit moet dus nie gebruik word in die pediatriese ouderdomsgroep nie, totdat verdere data beskikbaar is.
Metode van toediening
Voorsorgmaatreëls vir toediening
Daar was noodlottige gevalle met die nie opsetlike intratekale toediening van VALOMA.
Vir IV of SK gebruik alleenlik.
MOET NIE VALOMA INTRATEKAAL TOEDIEN NIE.
VALOMA 1 is vir IV gebruik alleenlik.
Sodra dit opgelos is, onttrek die geskikte hoeveelheid van die hersaamgestelde oplossing volgens die berekende dosis gebaseer op die liggaamsoppervlakte van die pasiënt. Maak seker van die dosis en konsentrasie in die spuit voor gebruik (bevestig dat die spuit as intraveneuse toediening gemerk is). Die hersaamgestelde oplossing word toegedien as 'n 3 tot 5 sekonde intraveneuse bolusinspuiting deur 'n perifere of sentrale intraveneuse kateter gevolg deur 'n uitspoeling met 0,9 % natriumchloriedoplossing vir inspuiting. Daar moet ten minste 72 uur verloop tussen opeenvolgende dosisse van VALOMA.
VALOMA 2,5 EN VALOMA 3,5
Intraveneuse inspuiting
Sodra dit opgelos is, onttrek die geskikte hoeveelheid van die hersaamgestelde oplossing volgens die berekende dosis gebaseer op die liggaamsoppervlakte van die pasiënt. Maak seker van die dosis en konsentrasie in die spuit voor gebruik (bevestig dat die spuit as intraveneuse toediening gemerk is). Die hersaamgestelde oplossing word toegedien as 'n 3 tot 5 sekonde intraveneuse bolusinspuiting deur 'n perifere of sentrale intraveneuse kateter gevolg deur 'n uitspoeling met 0,9 % natriumchloriedoplossing vir inspuiting. Daar moet ten minste 72 uur verloop tussen opeenvolgende dosisse van VALOMA.
Subkuteuse inspuiting
Die hersaamgestelde oplossing word in die dye (regs of links) of in die buik (regs of links) ingespuit. Die oplossing moet subkutaneus ingespuit word, teen 'n hoek van 45 tot 90°. Inspuitingsplekke moet geroteer word vir opeenvolgende inspuitings. Indien lokale reaksies by die toedieningsplek plaasvind na die subkutaneuse VALOMA inspuiting, kan 'n minder gekonsentreerde VALOMA oplossing (1 mg/ml in plaas van 2,5 mg/ml) subkutaneus toegedien word of daar kan na 'n IV-inspuiting verander word. Wanneer subkutaneus toegedien, moet die toedieningsplek afgewissel word vir elke inspuiting (dy of buik). Nuwe inspuitings moet minstens 2,5 cm vanaf 'n vorige toedieningsplek gegee word en nooit in 'n area waar die plek sag, gekneus, rooi of hard is nie.
Instruksies vir hersamestelling
VALOMA 1 is vir IV gebruik alleenlik. VALOMA 2,5 en VALOMA 3,5 is vir IV of SK gebruik. Vir instruksies oor die hersamestelling van VALOMA voor toediening, sien afdeling 6.6.

4.3 Kontraindikasies
- Hipersensitiwiteit vir bortesomib, boor of enige van die onaktiewe bestanddele van VALOMA.
- Akute diffuse infiltrerende pulmonale en perikardiale siekte.
- Wanneer VALOMA in kombinasie met ander medisyne gegee word, verwys na hul Professionele Inligting vir bykomende kontraindikasies.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Behandeling moet begin, en toegedien word onder die toesig van 'n mediese praktisyn wat ervaring het in die gebruik van chemoterapeutiese medisyne.
Intratekale toediening
Daar was noodlottige gevalle met die nie opsetlike intratekale toediening van VALOMA.
MOET NIE VALOMA INTRATEKAAL TOEDIEN NIE.
Herpes zoster virus reaktivering
Antivirale profilakse word aanbeveel in pasiënte wat met VALOMA behandel word (sien afdeling 4.8).
Pasiënte met mantelsellimfoom
Die veiligheidsprofiel van VALOMA in pasiënte met mantelsellimfoom is soortgelyk aan die wat waargeneem is in pasiënte met meervoudige miëloom. Merkbare verskille tussen die twee pasiëntpopulasies is dat trombositopenie, neutropenie, anemie, naarheid, braking en koors meer gereeld aangemeld word in die pasiënte met meervoudige miëloom as in diegene met mantelsellimfoom; terwyl perifere neuropatie, uitslag en pruritus hoër is onder pasiënte met mantelsellimfoom in vergelyking met pasiënte met meervoudige miëloom. Oor die algemeen is die veiligheidsprofiel van pasiënte wat met VALOMA behandel is in monoterapie, soortgelyk aan die wat waargeneem is in pasiënte wat behandel is met VALOMA in kombinasie met melfalaan en prednisoon.
Laboratoriumtoetse
Volledige bloedtellings (VBT), insluitende bloedplaatjie tellings, moet gereeld, gedurende die behandeling met VALOMA gemonitor word.
Gastroïntestinale toksisiteit
Gastroïntestinale toksisiteit, insluitende diarree, konstipasie, naarheid en braking is baie algemeen met VALOMA behandeling (sien afdeling 4.8). Reaksies kom gewoonlik vroeg in die behandeling voor (Siklus 1 en 2) en kan vir verskeie siklusse voortduur. Pasiënte wat behandeling opkomende gastroïntestinale toksisiteit ervaar, kan baat vind by die toediening van anti-emetika en anti-diarree behandeling. Vloeistof en elektrolietvervanging moet toegedien word om dehidrasie te voorkom of te behandel. Gevalle van ileus is aangemeld, daarom moet pasiënte wat hardlywigheid ervaar, noukeurig gemonitor word.
Hematologiese toksisiteit
Hematologiese toksisiteit (trombositopenie, neutropenie en anemie) word baie algemeen geassosieer met VALOMA behandeling. Febriele neutropenie is egter nie 'n algemene ongunstige effek nie. Die mees algemene hematologiese toksisiteit is verbygaande trombositopenie, wat gewoonlik tussen behandelingsiklusse opklaar. Bloedplaatjies is die laagste op dag 11 van elke siklus van VALOMA behandeling en herstel gewoonlik tot basislyn teen die volgende siklus. Die sikliese patroon van bloedplaatjies het afgeneem, en herstel bly konstant oor die 8 siklusse van twee keer per week doserings, en daar is geen bewyse van kumulatiewe trombositopenie nie. Die gemiddelde laagtepunt van die aantal bloedplaatjies gemeet, is ongeveer 40 % van basislyn. Ernstige bloeding, insluitende sentrale senuweestelsel (SSS) en gastroïntestinale bloeding, wat geassosieer is met trombositopenie, is aangemeld. In pasiënte met gevorderde miëloom hou die erns van trombositopenie verband met die aantal bloedplaatjies voor behandeling. Bloedplaatjietellings moet voor elke dosis VALOMA gemonitor word. Behandeling moet tydelik gestaak word wanneer die bloedplaatjietelling < 25 000/µL is, of in die geval van kombinasie met melfalaan en prednisoon, wanneer die plaatjietelling ≤ 30 000/µL is, en behoort teen 'n verlaagde dosis heringestel te word na resolusie (sien afdeling 4.2). Potensiële voordele van die behandeling moet versigtig teen die risiko's opgeweeg word. Bloedplaatjietransfusies, rooibloedsel (RBS)-transfusies en toediening van groeifaktore kan gebruik word in die hantering van hematologiese toksisiteite. Profilaktiese bloedplaatjietransfusies moet oorweeg word in pasiënte met trombositopenie met 'n hoë risiko vir bloeding. Aangesien pasiënte met neutropenie 'n verhoogde risiko vir infeksies het, behoort hulle vir tekens en simptome van infeksie gemonitor te word en onmiddellik behandel te word. Granulosiet kolonie stimulerende faktore kan toegedien word vir hematologiese toksisiteit volgens plaaslike standaardpraktyk. Proflaktiese gebruik van granulosiet kolonie stimulerende faktore moet oorweeg word in geval van herhaalde vertragings in siklustoediening.
Perifere neuropatie
VALOMA behandeling veroorsaak 'n perifere neuropatie wat hoofsaaklik sensories is. Gevalle van ernstige motoriese neuropatie met of sonder sensoriese perifere neuropatie is egter al aangemeld. Pasiënte met vooraf bestaande simptome (gevoelloosheid, pyn of 'n brandgevoel in die voete of hande) en/of tekens van perifere neuropatie sal waarskynlik erger wordende perifere neuropatie (insluitend ≥ Graad 3) ervaar tydens behandeling met VALOMA. Die voorkoms van perifere neuropatie neem vroeg tydens die behandeling toe en daar is waargeneem dat 'n hoogtepunt tydens siklus 5 bereik word. Daar word aanbeveel dat pasiënte versigtig gemonitor word vir simptome van neuropatie, soos 'n brandsensasie, hiperestesie, hipoëstesie, parestesie, ongemak of neuropatiese pyn of swakheid. Pasiënte wat nuwe of erger wordende perifere neuropatie ervaar, moet neurologiese evaluering ondergaan en dit mag nodig wees om die dosis, skedule of toedieningsroete na subkutaneus te verander (sien afdeling 4.2). Neuropatie moet met ondersteunende sorg en ander terapieë beheer word. Perifere neuropatie kan moontlik nie omkeerbaar wees nie. Vroeë en gereelde monitering met neurologiese evaluering, vir simptome van neuropatie wat tydens behandeling ontwikkel, moet oorweeg word in pasiënte wat VALOMA ontvang in kombinasie met medisyne wat daarvoor bekend is dat dit met neuropatie geassosieer word (bv. talidomied), en gepaste dosisverlaging of staking van behandeling moet oorweeg word. Bykomend tot perifere neuropatie, kan daar 'n bydrae van outonome neuropatie tot sommige ongunstige reaksies wees, soos posturale hipotensie en erge hardlywigheid met ileus. Inligting oor outonome neuropatie en die bydrae daarvan tot hierdie ongewenste effekte is beperk.
Aanvalle
Aanvalle is aangemeld in pasiënte sonder 'n vorige geskiedenis van aanvalle of epilepsie. Spesiale sorg word vereis wanneer pasiënte met enige risikofaktore vir aanvalle, behandel word.
Hipotensie
VALOMA behandeling word oor die algemeen geassosieer met ortostatiese/posturale hipotensie. Meeste van die pasiënte het behandeling benodig vir hul ortostatiese hipotensie. Pasiënte met ortostatiese hipotensie het sinkopale gebeure ervaar. Die meganisme van hierdie gebeurtenis is onbekend, alhoewel outonome neuropatie verantwoordelik kon wees vir 'n komponent hiervan. Outonome neuropatie kan verband hou met VALOMA of VALOMA kan 'n onderliggende toestand soos diabetiese- of amiloïede neuropatieë vererger. Versigtigheid word aangeraai wanneer pasiënte met 'n geskiedenis van sinkopee behandel word, wat medisyne ontvang wat bekend is daarvoor om geassosieer te word met hipotensie; of wat gedehidreer is as gevolg van herbeskikbaarheid van vloeistof of elektroliete. Die beheer van ortostatiese/posturale hipotensie is simptomaties en kan die aanpassing van antihipertensiewe medisyne, rehidrasie of toediening van minerale kortikosteroïede en/of simpatomimetika insluit. Pasiënte moet aangesê word om mediese advies in te win indien hulle simptome van duiseligheid, lighoofdigheid of floutes ervaar.
Kardiale versteurings
Akute ontwikkeling of verergering van kongestiewe hartversaking, en/of nuwe aanvang van verminderde linkerventrikulêre uitwerpingstrekkrag is met bortesomib, soos in VALOMA behandeling, gerapporteer. Pasiënte met risikofaktore vir, of bestaande hartsiekte, moet noukeurig gemonitor word. Vloeistofretensie kan 'n predisponerende faktor vir tekens en simptome van hartversaking wees. Daar was gevalle van QT-intervalverlenging in kliniese proewe; oorsaaklikheid is nie vasgestel nie. Pasiënte wat angiotensien omskakelings ensiem-inhibeerders, beta-blokkers, antihipertensiewe middels, kalsiumkanaalblokkers, angiotensien reseptorblokkeerders en diuretika gebruik, kan 'n hoër voorkoms van hartversaking tydens VALOMA behandeling hê.
Pulmonêre versteurings
Daar was verslae van akute diffuse infiltrerende pulmonale siekte van onbekende etiologie soos longontsteking, interstisiële longontsteking, longinfiltrasie en Akute Respiratoriese Noodsindroom (ARNS) in pasiënte wat VALOMA ontvang het. Sommige van hierdie gevalle was noodlottig gewees. Radiografie van die borskas voor behandeling word aanbeveel om as basislyn te dien vir potensiële longveranderinge na behandeling. In die geval van nuwe of verergerende pulmonale simptome, moet 'n diagnostiese evaluering onmiddellik uitgevoer word en pasiënte moet toepaslik behandel word.
Renale inkorting
Renale komplikasies kom dikwels voor in pasiënte met meervouldige miëloom. Sulke pasiënte moet noukeurig gemonitor word.
Hepatiese inkorting
VALOMA word deur lewerensieme gemetaboliseer. Blootstelling aan VALOMA word verhoog in pasiënte met matige of ernstige lewerinkorting. Hierdie pasiënte moet met VALOMA behandel word teen verlaagde aanvangsdosisse en moet noukeurig gemonitor word vir toksisiteite (sien afdelings 4.2 en 5.2).
Hepatiese reaksies
In pasiënte wat VALOMA en gepaardgaande medisyne ontvang het, en met ernstige onderliggende mediese toestande, is gevalle van akute lewerversaking aangemeld. Ander hepatiese voorvalle wat aangemeld is, het asimptomatiese toename in lewerensieme, hiperbilirubinemie en hepatitis ingesluit. Sodanige veranderinge kan omkeerbaar wees na staking van VALOMA (sien afdeling 4.8). Daar is beperkte heruitdagings inligting in hierdie pasiënte beskikbaar.
Tumorlise sindroom
Aangesien VALOMA 'n sitotoksiese middel is en maligne plasmaselle en mantelsellimfoom (MSL) selle kan doodmaak, kan die komplikasies van tumorlise sindroom voorkom. Die pasiënte met die risiko vir tumorlise sindroom is diegene met 'n hoë tumorlading voor die behandeling. Simptome van tumorlise sindroom is swakheid, braking, krampe, aanvalle, edeem en vloeistofoorlading, kongestiewe hartversaking, disritmieë en sinkopee. Hierdie pasiënte moet noukeurig gemonitor word en toepaslike voorsorgmaatreëls moet getref word.
Amiloïdose
Die impak van die proteasoom inhibisie deur VALOMA op versteurings wat verband hou met proteïen akkumulasie soos amiloïdose, is onbekend. Versigtigheid word aangeraai in hierdie pasiënte.
Potensiële immuunkompleks-bemiddelde reaksies
Potensiële immuunkompleks-bemiddelde reaksies, soos serumsiekte-tipe reaksie, poliartritis met uitslag en proliferatiewe glomerulonefritis, is minder algemeen aangemeld. VALOMA moet gestaak word indien ernstige reaksies voorkom.
Posterior Omkeerbare Enkefalopatie Sindroom ("PRES") of Omkeerbare Posterior Leukoënkefalopatie Sindroom ("RPLS")
Daar is verslae van PRES (RPLS) in pasiënte wat VALOMA ontvang het. PRES (RPLS) is 'n seldsame, omkeerbare, neurologiese afwyking wat kan presenteer met aanvalle, hipertensie, hoofpyn, lusteloosheid, verwardheid, blindheid en ander visuele en neurologiese steurings. Breinbeeldvorming, verkieslik MRB (Magnetiese Resonans Beelding), word gebruik om die diagnose te bevestig. VALOMA moet gestaak word in pasiënte wat PRES (RPLS) ontwikkel. Die veiligheid vir die herinstelling van VALOMA behandeling in pasiënte wat voorheen PRES (RPLS) ervaar het, is nie bekend nie.

Progressiewe multifokale leukoënkefalopatie (PML)
Baie seldsame gevalle met onbekende oorsaaklikheid van John Cunningham (JC) virusinfeksie, wat PML en dood tot gevolg gehad het, is gerapporteer in pasiënte wat behandel is met VALOMA. Pasiënte wat met PML gediagnoseer is, het vorige of gelyktydig immuunonderdrukkende terapie gehad. Die meeste gevalle van PML is binne 12 maande na hul eerste dosis VALOMA gediagnoseer. Pasiënte moet met gereelde tussenposes gemonitor word vir enige nuwe of verergerende neurologiese simptome of tekens wat op PML kan dui, as deel van die differensiële diagnose van SSS-probleme. Indien 'n diagnose van PML vermoed word, moet pasiënte na 'n PML-spesialis verwys word en toepaslike diagnostiese maatreëls vir PML moet geïnisieer word. Staak VALOMA as PML gediagnoseer word.
Gepaardgaande medisyne gebruik
Pasiënte moet noukeurig gemonitor word wanneer VALOMA in kombinasie met kragtige SIP3A4-inhibeerders toegedien word. Versigtigheid moet uitgeoefen word wanneer VALOMA met SIP3A4- of SIP2C19-substrate gekombineer word (sien afdeling 4.5). Normale lewerfunksie moet bevestig word, en versigtigheid moet uitgeoefen word in pasiënte wat orale hipoglukemiese middels ontvang (sien afdeling 4.5).
Ander bestanddele
VALOMA bevat mannitol en kan 'n lakserende effek hê.

4.5 Interaksie met ander medisyne en ander vorms van interaksie
VALOMA is 'n swak inhibeerder van die sitochroom P450 (SIP) isosieme 1A2, 2C9, 2C19, 2D6 en 3A4. Gebaseer op die beperkte bydrae (7 %) van SIP2D6 tot die metabolisme van VALOMA, word daar nie verwag dat SIP2D6, die swak metaboliseerder fenotipe, die algehele disposisie van VALOMA sal beïnvloed nie. Gelyktydige gebruik van ketokonasool, 'n kragtige SIP3A4-inhibeerder, het 'n gemiddelde AOK-toename van bortesomib van 35 % getoon. Pasiënte moet om die rede dus noukeurig gemonitor word wanneer VALOMA toegedien word in kombinasie met kragtige SIP3A4- inhibeerders (bv. ketokonasool, ritonavier). Gelyktydige gebruik van omeprasool, 'n kragtige inhibeerder van SIP2C19, het geen beduidende effek op die farmakokinetika van bortesomib getoon nie. Gelyktydige gebruik van rifampisien, 'n kragtige SIP3A4-induseerder, het 'n gemiddelde AOK-vermindering van bortesomib van 45 % getoon. Die gelyktydige gebruik van VALOMA met sterk SIP3A4-induseerders (bv. rifampisien, karbamasepien, fenitoïen, fenobarbitoon en Johanneskruid) word dus nie aanbeveel nie, aangesien die effektiwiteit kan verminder. Deksametasoon, 'n swakker SIP3A4-induseerder, het geen beduidende effek op die farmakokinetika van bortesomib getoon nie. Gelyktydige gebruik van melfalaan-prednisoon op VALOMA het 'n toename van 17 % in gemiddelde bortesomib-AOK getoon. Dit word nie as klinies relevant beskou nie. Hipoglukemie en hiperglukemie is aangemeld in diabetiese pasiënte wat orale hipoglukemiese middels ontvang het. Pasiënte op orale antidiabetiese medisyne wat VALOMA behandeling ontvang, mag noukeurige monitering van hul bloedglukosevlakke en aanpassing van die dosis van hul antidiabetiese medisyne, vereis. Normale lewerfunksie moet bevestig word, en versigtigheid moet uitgeoefen word in pasiënte wat orale hipoglukemiese middels ontvang. Gelyktydige blootstelling aan narkotika kan die voorkoms van hardlywigheid, naarheid en braking verhoog.

Fertiliteit, swangerskap en laktasie
Kontrasepsie in mans en vrouens
Mans en vrouens wat nog kan kinders hê, moet effektiewe kontraseptiewe maatreëls gebruik tydens die behandeling en vir 3 maande na behandeling met VALOMA.
Swangerskap
Veiligheid tydens swangerskap is nog nie vasgestel nie. Indien VALOMA tydens swangerskap gebruik word, of indien die pasiënt swanger raak terwyl sy VALOMA ontvang, moet die pasiënt oor die moontlike gevare vir die fetus ingelig word.
Borsvoeding
Veiligheid tydens borsvoeding is nog nie vasgestel nie.
Dit is nie bekend of VALOMA in menslike melk uitgeskei word nie. Vanweë die moontlikheid van ernstige ongewenste effekte in babas wat geborsvoed word deur moeders op VALOMA, moet vrouens nie hul babas borsvoed terwyl hulle VALOMA ontvang nie.
Effekte op vermoë om te bestuur en gebruik van masjiene
VALOMA kan 'n matige invloed hê op die vermoë om te bestuur en om masjiene te gebruik. VALOMA kan geassosieer word met moegheid, duiseligheid, sinkopee, ortostatiese/posturale hipotensie of dowwe visie. Pasiënte moet dus versigtig wees wanneer hulle bestuur of masjiene gebruik, en moet aangeraai word om nie te bestuur of masjiene te gebruik indien hulle hierdie simptome ervaar nie.
Ongewenste effekte
a. Opsomming van die veiligheidsprofiel
Ernstige ongunstige reaksies wat nie algemeen tydens die behandeling met VALOMA gerapporteer is nie, sluit in hartversaking, tumorlisesindroom, pulmonale hipertensie, posterior omkeerbare enkefalopatiesindroom, akute diffuse infiltrerende pulmonale afwykings en selde outonome neuropatie.
Die mees algemeenste gerapporteerde ongunstige reaksies tydens behandeling met VALOMA is naarheid, diarree, hardlywigheid, braking, moegheid, koors, trombositopenie, anemie, neutropenie, perifere neuropatie (insluitend sensoriese), hoofpyn, parestesie, verminderde eetlus, dispnee, uitslag, herpes zoster en mialgie.
b. Opsomming van nadelige reaksies in tabelvorm

MedDRA Sisteem Orgaan Klas	Frekwensie	Newe-effekte
Infeksies en infestasies	Algemeen	Herpes zoster (insluitend verspreide en oftalmies), pneumonie, swaminfeksies, sepsis (insluitend septiese skok), bakteriële infeksies, boonste/onderste respiratoriese infeksies, soos brongitis, sinusitis, nasofaringitis, Herpes simplex infeksies
	Minder algemeen	Bakteremie (insluitend stafilokokkaal), influensa infeksies, toestelverwante infeksies, herpes meningoënkefalitis, pleurale infeksies, hemofilusinfeksies, sitomegalovirusinfeksie, aansteeklike mononukleose, waterpokkies, urienweginfeksies, gastroënteritis, candida infeksies, post herpetiese neuralgie, orale candidiasis, blefaritis , hordeolum, sellulitis, Hepatitis B-infeksie, brongopneumonie, virusinfeksies, velinfeksies, oorinfeksies, Stafilokokkale infeksies, tandinfeksies, meningitis (insl. bakteriese), Epstein-Barr-virusinfeksie, genitale herpes, tonsillitis, mastoditis, post-virale moegheidsindroom .
	Frekwensie onbekend	Progressiewe multifokale leukoënkefalopatie
Bloed- en limfstelselversteurings	Algemeen	Trombositopenie, febriele neutropenie, neutropenie, leukopenie, anemie, limfopenie
	Minder algemeen	Pansitopenie, hemolitiese anemie,trombositopeniese purpura, limfadenopatie, koagulopatie, leukositose
	Frekwensie onbekend	Gedissemineerde intravaskulêre koagulasie
Immuunsisteem versteurings	Algemeen	Hipersensitiwiteit
	Minder algemeen	Tipe III immuunkompleks-bemiddelde reaksies, potensiële immuunkompleks- bemiddelde reaksies, soos serumsiekte-tipe reaksie, poliartritis met uitslag en proliferatiewe glomerulonefritis (sien afdeling 4.4), angioëdeem, anafilaktiese skok, amiloïdose
Metabolisme en voedingsversteurings	Algemeen	Verminderde eetlus, hipokalemie, hiperglukemie, hiponatremie, dehidrasie, hiperkalsemie, ensiem abnormaliteite, diabetes mellitus, vogretensie
	Minder algemeen	Tumorlise sindroom (sien afdeling 4.4), hipomagnesemie, hipofosfatemie, hiperkalsemie, hipernatremie, hiperurisemie, vitamien B12-tekort, verhoogde eetlus, kageksie, vogretensie, versuim om te floreer, asidose, elektrolietwanbalans, vloeistofoorlading, hipochloremie, hipovolemie, hiperfosfatemie, vitamine B-kompleks tekort, jig, alkohol-intoleransie
Endokriene versteurings	Minder algemeen	Ontoepaslike antidiuretiese hormoon (ADH) sekresie, Cushing se sindroom, hipertiroïdisme, hipotiroïdisme
Psigiatriese versteurings	Algemeen	Angstigheid, slaapversteurings en -afwykings, depressie, insomnie
	Minder algemeen	Delirium, hallusinasie, rusteloosheid, gemoedskommelinge, geestesveranderinge, verwarring, prikkelbaarheid, abnormale drome, agitasie, psigotiese versteurings, selfmoordgedagtes, aan

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE
VALOMA 1 powder for solution for injection
VALOMA 2,5 powder for solution for injection
VALOMA 3,5 powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
VALOMA 1: Each vial contains 1,0 mg of bortezomib (as a mannitol boronic ester). Intravenous (IV) use only.
VALOMA 2,5: Each vial contains 2,5 mg bortezomib (as a mannitol boronic ester). Intravenous (IV) or subcutaneous (SC) use.
VALOMA 3,5: Each vial contains 3,5 mg bortezomib (as a mannitol boronic ester).
Intravenous (IV) or subcutaneous (SC) use.
After reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib.
After reconstitution, 1 ml of solution for subcutaneous injection contains 2,5 mg bortezomib.
VALOMA 1: Contains sugar (mannitol) 10 mg per vial
VALOMA 2,5: Contains sugar (mannitol) 25 mg per vial
VALOMA 3,5: Contains sugar (mannitol) 35 mg per vial
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Powder for solution for injection. White to off-white cake or powder.
The reconstituted solution is clear and colourless, with a final pH of 4 to 7.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
VALOMA is indicated as:
- Primary treatment of multiple myeloma in combination with melphalan and prednisone.
- Monotherapy for the treatment of patients with multiple myeloma who have received at least one prior therapy and who have progressive disease.
- Treatment of relapsed or refractory mantle cell lymphoma for patients who have received at least 1 prior line of therapy, one of which should have included an anthracycline (or mitoxantrone) and/or rituximab as part of their chemotherapy regimen.

4.2 Posology and method of administration
Posology
VALOMA 1 powder for solution for injection is available for:
- Intravenous administration only at a concentration of 1 mg/ml (as a 3-5 second bolus injection).

VALOMA 2,5 and VALOMA 3,5 powder for solution for injection is available for:
- Intravenous administration at a concentration of 1 mg/ml (as a 3-5 second bolus injection) or
- Subcutaneous administration at a concentration 2,5 mg/ml.

Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered (see section 6.6).

VALOMA should only be given by the intravenous or subcutaneous route. Intrathecal administration has resulted in death.

See (**Reconstitution instructions below**).

Monotherapy recommended dosage
The recommended starting dose of VALOMA is 1,3 mg/m² body surface area twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12 to 21) in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VALOMA. It is recommended that patients with a confirmed complete response receive 2 additional cycles of VALOMA beyond a confirmation. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of VALOMA therapy. There is limited data concerning re-treatment with VALOMA.

Recommended dose adjustments during treatment and re-initiation of treatment for monotherapy
VALOMA treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy as discussed below (see section 4.4). Once the symptoms of the toxicity have resolved, VALOMA treatment may be re-initiated at a 25 % reduced dose (1,3 mg/m² reduced to 1,0 mg/m²; 1 ,0 mg/m² reduced to 0,7 mg/m²). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of VALOMA must be considered.

Neuropathic pain and/or peripheral neuropathy
Patients who experience VALOMA related neuropathic pain and/or peripheral neuropathy are to be managed as presented in the table below. Patients with pre-existing severe neuropathy may be treated with VALOMA only after careful risk/benefit assessment.

Recommended dose modifications for VALOMA related neuropathic pain and/or peripheral sensory neuropathy.

Severity of peripheral neuropathy	Modification of dose and regimen
Grade 1 (paresthesia, weakness and/or loss of deep tendon reflexes) with no pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not activities of daily living)	Reduce to 1,0 mg/m²
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VALOMA treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate VALOMA treatment and reduce dose to 0,7 mg/m² and change treatment schedule to once per week.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue VALOMA

Dose management guidelines for combination therapy
VALOMA for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in the table below. In Cycles 1-4, VALOMA is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 to 9, VALOMA is administered once weekly (days 1, 8, 22 and 29).

Recommended dosage regimen for VALOMA when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma

Twice weekly VALOMA (Cycles 1 - 4)												
Week	**1**				**2**		**3**	**4**		**5**		
VI (1,3 mg/m²)	Day 1	-	-	Day 4	Day 8	Day 11	Rest period	Day 22	Day 25	Day 29	Day 32	Rest period
m (9 mg/m²) p (60 mg/m²)	Day 1	Day 2	Day 3	Day 4	-	-	Rest period	-	-	-	-	Rest period

Once weekly VALOMA (Cycles 5 - 9)									
Week	**1**				**2**	**3**	**4**	**5**	**6**
VI (1,3 mg/m²)	Day 1	-	-	-	Day 8	Rest period	Day 22	Day 29	Rest period
m (9 mg/m²) p (60 mg/m²)	Day 1	Day 2	Day 3	Day 4	-	Rest period	-	-	Rest period

VI = VALOMA; m = melphalan, p = prednisone

Dose modification and re-initiation of therapy when VALOMA is administered in combination with melphalan and prednisone
Prior to initiating a new cycle of therapy:
- Platelet count should be ≥ 70 x 10⁹/L and the ANC should be ≥ 1,0 X 10⁹/L.
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

Dose modifications during subsequent cycles

Toxicity	Dose modification or delay
Haematological toxicity during a cycle:	
If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle.
If platelet count ≤ 30 x 10⁹/L or ANC ≤ 0,75 x 10⁹/L on a VALOMA dosing day (other than day 1)	VALOMA dose should be withheld
If several VALOMA doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	VALOMA dose should be reduced by 1 dose level (from 1,3 mg/m² to 1 mg/m², or from 1 mg/m² to 0,7 mg/m²)
Grade ≥ 3 *non-haematological toxicities*	VALOMA therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, VALOMA may be reinitiated with one dose level reduction (from 1,3 mg/m² to 1 mg/m², or from 1 mg/m² to 0,7 mg/m²). For VALOMA-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VALOMA as outlined in the table above: "Recommended dose modifications for VALOMA related neuropathic pain and/or peripheral sensory neuropathy"

For additional information concerning melphalan and prednisone, refer to their respective Professional Information inserts.

Special populations
Elderly patients
There is no evidence to suggest that dose adjustments are necessary in the elderly (see section 4.8).
Patients with renal impairment
The pharmacokinetics of VALOMA are not influenced by the degree of renal impairment. Therefore, dosing adjustments of VALOMA are not necessary for patients with renal insufficiency. Since dialysis may reduce VALOMA concentrations, VALOMA should be administered after the dialysis procedure (see section 5.2).
Patients with hepatic impairment
Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VALOMA dose. Patients with moderate or severe hepatic impairment should be started on VALOMA at a reduced dose of 0,7 mg/m² per injection during the first cycle, and a subsequent dose escalation to 1,0 mg/m² or further dose reduction to 0,5 mg/m² may be considered based on patient tolerance (see Table below).

Recommended starting dose modification for VALOMA in patients with hepatic impairment

Grade of hepatic impairment *	Bilirubin level	SGOT (AST) levels	Modification of starting dose
Mild	≤ 1,0 x ULN	> ULN	None
	> 1,0 x -1,5 x ULN	Any	None
Moderate	> 1,5 x -3 x ULN	Any	Reduce VALOMA to 0,7 mg/m² in the first cycle. Consider dose escalation to 1,0 mg/m² or further dose reduction to 0,5 mg/m² in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase; AST= aspartate aminotransferase, ULN = upper limit of the normal range.
*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Paediatric population
VALOMA has not been studied in children and adolescents. Therefore, it should not be used in the paediatric age group until further data becomes available.
Method of administration
Administration precautions
There have been fatal cases of inadvertent intrathecal administration of VALOMA. For IV or SC use only. **DO NOT ADMINISTER VALOMA INTRATHECALLY.**
VALOMA 1 is for IV use only.
Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s body surface area. Confirm the dose and concentration in the syringe prior to use (check that the syringe is marked as intravenous administration).
The reconstituted solution is administered as a 3 to 5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0,9 % sodium chloride solution for injection. At least 72 hours should elapse between consecutive doses of VALOMA.
VALOMA 2,5 and VALOMA 3,5
Intravenous injection
Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s body surface area. Confirm the dose and concentration in the syringe prior to use (check that the syringe is marked as intravenous administration). The reconstituted solution is administered as a 3 to 5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0,9 % sodium chloride solution for injection. At least 72 hours should elapse between consecutive doses of VALOMA.
Subcutaneous injection
The reconstituted solution is injected into the thighs (right or left) or abdomen (right or left). The solution should be injected subcutaneously, at a 45 to 90° angle. Injection sites should be rotated for successive injections. If local injection site reactions occur following VALOMA injection subcutaneously, a less concentrated VALOMA solution (1 mg/ml instead of 2,5 mg/ml) may be administered subcutaneously or changed to IV injection. When administered subcutaneously, alternate sites for each injection (thigh or abdomen). New injections should be given at least 2,5 cm from an old site and never into areas where the site is tender, bruised, red, or hard.
Reconstitution instructions
VALOMA 1 is for IV use only.
VALOMA 2,5 and VALOMA 3,5 is for IV or SC use.
For instructions on reconstitution of VALOMA before administration, see section 6.6.

4.3 Contraindications
- Hypersensitivity to bortezomib, boron or any of the excipients of VALOMA.
- Acute diffuse infiltrative pulmonary and pericardial disease.
- When VALOMA is given in combination with other medicines, refer to their Professional Information for additional contraindications.

4.4 Special warnings and precautions for use
Treatment must be initiated and administered under the supervision of a medical practitioner experienced in the use of chemotherapeutic medicines.

Intrathecal administration
There have been fatal cases of inadvertent intrathecal administration of VALOMA. **DO NOT ADMINISTER VALOMA INTRATHECALLY**.
Herpes zoster virus reactivation
Antiviral prophylaxis is recommended in patients being treated with VALOMA (see section 4.8).
Patients with mantle cell lymphoma
The safety profile of VALOMA in patients with mantle cell lymphoma is similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations are that thrombocytopenia, neutropenia, anaemia, nausea, vomiting and pyrexia are reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas peripheral neuropathy, rash and pruritus are higher among patients with mantle cell lymphoma compared to patients with multiple myeloma. Overall, the safety profile of patients treated with VALOMA in monotherapy is similar to that observed in patients treated with VALOMA in combination with melphalan and prednisone.
Laboratory tests
Complete blood counts (CBC) including platelet counts should be frequently monitored throughout treatment with VALOMA.
Gastrointestinal toxicity
Gastrointestinal toxicity, including diarrhoea, constipation, nausea and vomiting are very common with VALOMA treatment (see section 4.8). Reactions usually occur early in treatment (Cycles 1 and 2) and may persist for several cycles. Patients experiencing treatment emergent gastrointestinal toxicity may benefit from administration of anti-emetics and anti-diarrhoea treatment. Fluid and electrolyte replacement should be administered to prevent or treat dehydration. Cases of ileus have been reported therefore patients who experience constipation should be closely monitored.
Haematological toxicity
VALOMA treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). However, febrile neutropenia is an uncommon undesirable effect. The most common haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment cycles. Platelets are the lowest at day 11 of each cycle of VALOMA treatment and typically recovers to baseline by the next cycle. The cyclical pattern of platelet decreased, and recovery remains consistent over the 8 cycles of twice weekly dosing and there is no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured is approximately 40 % of baseline. Severe bleeding, including central nervous system (CNS) and gastrointestinal bleeding, associated with thrombocytopenia, has been reported. In patients with advanced myeloma, the severity of thrombocytopenia is related to pre-treatment platelet count. Platelet counts should be monitored prior to each dose of VALOMA. Therapy should be withheld when the platelet count is < 25 000/µL, or in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30 000/µL and re-initiated at a reduced dose after resolution (see section 4.2*)*. Potential benefit of the treatment should be carefully weighed against the risks. Platelet transfusions, red blood cell (RSC) transfusions and administration of growth factors may be utilised in the management of haematologic toxicities. Prophylactic platelet transfusions should be considered in thrombocytopaenic patients at high risk of bleeding. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration.
Peripheral neuropathy
VALOMA treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy are likely to experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with VALOMA. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5. It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperaesthesia, hypoaesthesia, paraesthesia, discomfort or neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose, schedule or route of administration to subcutaneous (see section 4.2). Neuropathy must be managed with supportive care and other therapies. Peripheral neuropathy may not be reversible. Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving VALOMA in combination with medicines known to be associated with neuropathy (e.g. thalidomide) and appropriate dose reduction or treatment discontinuation should be considered. In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.
Seizures
Seizures have been reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.
Hypotension
VALOMA treatment is commonly associated with orthostatic/ postural hypotension. Most patients required treatment for their orthostatic hypotension. Patients with orthostatic hypotension experienced syncopal events. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to VALOMA or VALOMA may aggravate an underlying condition such as diabetic or amyloid neuropathies. Caution is advised when treating patients with a history of syncope receiving medicines known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension is symptomatic and may include adjustment of antihypertensive medicines, rehydration or administration of mineral corticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.
Cardiac disorders
Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection traction has been reported during bortezomib, as in VALOMA treatment. Patients with risk factors for, or existing heart disease should be closely monitored. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. There have been cases of QT-interval prolongation in clinical trials; causality has not been established. Patients using angiotensin converting enzyme inhibitors, beta-blockers, antihypertensives, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during VALOMA treatment.
Pulmonary disorders
There have been reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving VALOMA. Some of these events have been fatal. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed, and patients treated appropriately.
Renal impairment
Renal complications are frequent in patients with multiple myeloma. Such patients should be monitored closely.
Hepatic impairment
VALOMA is metabolised by liver enzymes. VALOMA exposure is increased in patients with moderate or severe hepatic impairment. These patients should be treated with VALOMA at reduced starting doses and closely monitored for toxicities (see sections 4.2 and 5.2).
Hepatic reactions
Cases of acute hepatic failure have been reported in patients receiving VALOMA and concomitant medicines and with serious underlying medical conditions. Other reported hepatic events include asymptomatic increases in liver enzymes, hyperbilirubinaemia and hepatitis. Such changes may be reversible upon discontinuation of VALOMA (see section 4.8). There is limited re-challenge information in these patients.
Tumour lysis syndrome
Because VALOMA is a cytotoxic medicine and can kill malignant plasma cells and mantle cell lymphoma (MCL) cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Symptoms of tumour lysis syndrome are weakness, vomiting, cramps, seizure, oedema and fluid overload, congestive heart failure, dysrhythmias and syncope. These patients should be monitored closely, and appropriate precautions taken.
Amyloidosis
The impact of proteasome inhibition by VALOMA on disorders associated with protein accumulation such as amyloidosis is unknown. Caution is advised in these patients.
Potentially immunocomplex-mediated reactions
Potentially immunocomplex-mediated reactions, such as serumsickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. VALOMA should be discontinued if severe reactions occur.
Posterior Reversible Encephalopathy Syndrome (PRES) or Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
There have been reports of PRES (RPLS) in patients receiving VALOMA. PRES (RPLS) is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES (RPLS), VALOMA should be discontinued. The safety of reinitiating VALOMA therapy in patients previously experiencing PRES (RPLS) is not known.
Progressive multifocal leukoencephalopathy (PML)
Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with VALOMA. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of VALOMA. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue VALOMA if PML is diagnosed.
Concomitant medicine use
Patients should be closely monitored when given VALOMA in combination with potent CYP3A4-inhibitors. Caution should be exercised when VALOMA is combined with CYP3A4- or CYP2C19 substrates (see section 4.5). Normal liver function should be confirmed, and caution should be exercised in patients receiving oral hypoglycaemics (see section 4.5).
Excipients
VALOMA contains mannitol and may have a laxative effect

4.5 Interaction with other medicines and other forms of interaction
VALOMA is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7 %) of CYP2D6 to the metabolism of VALOMA the CYP2D6, poor metaboliser phenotype is not expected to affect the overall disposition of VALOMA. Concomitant use of ketoconazole, a potent CYP3A4 inhibitor, showed a bortezomib AUC mean increase of 35 %. Therefore, patients should be monitored closely when given VALOMA in combination with potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). Concomitant use of omeprazole, a potent inhibitor of CYP2C19 showed no significant effect on the pharmacokinetics of bortezomib. Concomitant use of rifampicin, a potent CYP3A4 inducer, showed a mean bortezomib AUC reduction of 45 %. The concomitant use of VALOMA with strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbitone and St. John's Wort) is therefore not recommended, as efficacy may be reduced. Dexamethasone, a weaker CYP3A4 inducer showed no significant effect on bortezomib pharmacokinetics. Concomitant use of melphalan-prednisone on VALOMA showed a 17 % increase in mean bortezomib AUC. This is not considered clinically relevant. Hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic medicines receiving VALOMA treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medicines. Normal liver function should be confirmed, and caution should be exercised in patients receiving oral hypoglycaemics. Concomitant exposure to narcotics may increase the incidence of constipation, nausea and vomiting.

4.6 Fertility, pregnancy and lactation
Contraception in males and females
Males and females of childbearing capacity should use effective contraceptive measures during treatment and for 3 months following VALOMA therapy.
Pregnancy
Safety in pregnancy has not been established. If VALOMA is used during pregnancy, or if the patient becomes pregnant while receiving VALOMA, the patient needs to be informed of potential for hazards to the foetus.
Breastfeeding
Safety during lactation has not been established. It is not known whether VALOMA is excreted in human milk. Because of the potential for serious undesirable effects in breastfed infants from mothers on VALOMA, women should not breastfeed their infants while receiving VALOMA.

4.7 Effects on ability to drive and use machines
VALOMA may have a moderate influence on the ability to drive and use machines. VALOMA may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension or blurred vision. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms.

4.8 Undesirable effects
a. Summary of the safety profile
Serious adverse reactions uncommonly reported during treatment with VALOMA include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy. The most commonly reported adverse reactions during treatment with VALOMA are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.
b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Side effects
Infections and infestations	Frequent	Herpes zoster (incl. disseminated and ophthalmic), pneumonia, fungal infections, sepsis (incl. septic shock), bacterial infections, upper/lower respiratory infections, such as bronchitis, sinusitis, nasopharyngitis, Herpes simplex infections
	Less frequent	Bacteraemia (incl. staphylococcal), influenza infections, device related infections, herpes meningoencephalitis, pleural infections, haemophilus infections, cytomegalovirus infection, infectious mononucleosis, varicella, urinary tract infections, gastroenteritis, candida infections, post herpetic neuralgia, oral candidiasis, blepharitis, hordeolum, cellulitis, Hepatitis B infection, bronchopneumonia, viral infections, skin infections, ear infections, Staphylococcal infections, tooth infections, meningitis (incl. bacterial), Epstein-Barr virus infection, genital herpes, tonsillitis, mastoiditis, post viral fatigue syndrome.
	Frequency unknown	Progressive multifocal leukoencephalopathy
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, febrile neutropenia, neutropenia, leukopenia, anaemia, lymphopenia
	Less frequent	Pancytopenia, haemolytic anaemia, thrombocytopenic purpura, lymphadenopathy, coagulopathy, leucocytosis
	Frequency unknown	Disseminated intravascular coagulation
Immune system disorders	Frequent	Hypersensitivity
	Less frequent	Type III immune complex mediated reaction, potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis (see section 4.4), angioedema, anaphylactic shock, amyloidosis
Metabolism and nutrition disorders	Frequent	Decreased appetite, hypokalaemia, hyperglycaemia, hyponatremia, dehydration, hypercalcemia, enzyme abnormality, diabetes mellitus, fluid retention
	Less frequent	Tumour lysis syndrome (see section 4.4), hypomagnesaemia, hypophosphatemia, hypercalcaemia, hypernatremia, hyperuricaemia, vitamin B12 deficiency, appetite increased, cachexia, fluid retention, failure to thrive, acidosis, electrolyte imbalance, fluid overload, hypochloraemia, hypovolemia, hyperphosphatemia, vitamin B complex deficiency, gout, alcohol intolerance
Endocrine disorders	Less frequent	Inappropriate antidiuretic hormone (ADH) secretion, Cushing's syndrome, hyperthyroidism, hypothyroidism
Psychiatric disorders	Frequent	Anxiety, sleep disorders and disturbances, depression, insomnia
	Less frequent	Delirium, hallucinations, restlessness, mood swings, mental status changes, confusion, irritability, abnormal dreams, agitation, psychotic disorders, suicidal ideation, adjustment disorder, libido decreased
Nervous system disorders	Frequent	Peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, headache, dizziness (excluding vertigo), dysgeusia, dysesthesia, loss of consciousness, incl. syncope hypoesthesia, polyneuropathy, paresthesia, neuralgia, lethargy
	Less frequent	Intracranial haemorrhage, subarachnoid haemorrhage, disturbance in attention, migraine, sciatica, speech disorder, restless leg syndrome, tremor, convulsions (seizure disorders), encephalopathy, autonomic neuropathy, Posterior Reversible Encephalopathy Syndrome (PRES), paraplegia, paresis, increased activity, ageusia, somnolence, cognitive disorder, jerky movements, postural dizziness, mononeuropathy, peripheral sensorimotor neuropathy, dyskinesia, cerebellar coordination and balance disturbances, memory loss (excl. dementia), neurotoxicity, post herpetic neuralgia, abnormal reflexes, parosmia, brain oedema, transient ischaemic attack, coma, autonomic nervous system imbalance, cranial palsy, paralysis, presyncope, brain stem syndrome, cerebrovascular disorder, nerve root lesion, psychomotor hyperactivity, spinal cord compression, cognitive disorder, motor dysfunction, nervous system disorder, radiculitis, drooling, hypotonia
Eye disorders	Frequent	Blurred or abnormal vision, conjunctivitis, eye swelling
	Less frequent	Eye haemorrhage, eye discharge, photophobia, eye irritation, lacrimation increased, eye pain, keratitis sicca, conjunctival hyperaemia, corneal lesion, eye lid infection, chalazion, blepharitis, eye inflammation, diplopia, dry eye, exophthalmos, retinitis, scotoma, acquired dacryoadenitis, photopsia, optic neuropathy, different degrees of visual impairment
	Frequency unknown	Ophthalmic herpes, optic neuropathy, blindness
Ear and labyrinth disorders	Frequent	Vertigo
	Less frequent	Dysacusis, incl. tinnitus, hearing impaired (up to and incl. deafness), hypoacusis, ear discomfort, ear haemorrhage, vestibular neuritis, ear disorder
Cardiac disorders	Frequent	Dysrhythmia, cardiac failure (incl. left and right ventricular), cardiac fibrillation (incl. atrial), ventricular dysfunction, myocardial ischaemia
	Less frequent	Unstable angina pectoris, tachycardia, palpitations, cardiac tamponade, cardiogenic shock, cardiac arrest, myocardial infarction, development or exacerbation of congestive heart failure (see section 4.4*)*, ventricular hypokinesia, pulmonary oedema and acute pulmonary oedema, sinus arrest, complete atrioventricular block, sinus tachycardia, supraventricular tachycardia, atrial fibrillation, new onset of decreased left ventricular ejection fraction (see section 4.4), cardio-pulmonary arrest, pericarditis (incl. pericardial effusion), cardiomyopathy, bradycardia
Vascular disorders	Frequent	Hypotension, hypertension orthostatic hypotension, postural hypotension (see section 4.4)
	Less frequent	Cerebral haemorrhage, vasculitis, cerebrovascular accident, phlebitis, haematoma (incl. perirenal), wound haemorrhage, flushing, hot flushes, vein discolouration, pulmonary hypertension, petechiae, ecchymosis, purpura, distended vein, deep vein thrombosis, thrombophlebitis (incl. superficial), circulatory collapse (incl. hypovolemic shock), poor peripheral circulation, hyperaemia (incl. ocular), peripheral embolism, lymph oedema, pallor, erythromelalgia, vasodilatation, venous insufficiency
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, epistaxis, cough, exertional dyspnoea, upper/lower respiratory tract infection, hiccups
	Less frequent	Hypoxia, pleural effusion, rhinorrhoea, wheezing, hyperventilation, orthopnoea, throat tightness, pulmonary hypertension, acute diffuse infiltrative pulmonary disease such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) (see section 4.4), productive cough, respiratory arrest, pulmonary congestion, asthma respiratory alkalosis, tachypnoea, nasal congestion, hoarseness, rhinitis, chest wall pain, sinus pain, pulmonary embolism, pulmonary oedema (incl. acute), pulmonary alveolar haemorrhage, bronchospasm, chronic obstructive pulmonary disease, hypoxemia, respiratory tract congestion, pleurisy, hiccups, dysphonia, respiratory failure, apnoea, pneumothorax, atelectasis, haemoptysis, respiratory alkalosis, tachypnoea, pulmonary fibrosis, bronchial disorder, hypocapnia, dry throat, increased upper airway secretion, throat irritation, upper-airway cough syndrome
Gastrointestinal disorders	Frequent	Vomiting, diarrhoea, nausea, constipation, abdominal pain (incl. gastrointestinal and splenic pain), stomatitis, dyspepsia, flatulence, abdominal distension, gastrointestinal haemorrhage (incl. mucosal), loose stools, upper abdominal pain, hiccups, pharyngolaryngeal pain, dry mouth, oropharyngeal pain, oral disorder
	Less frequent	Acute and chronic pancreatitis, colitis (incl. *clostridium difficile*), haematemesis, enteritis, dysphagia, abdominal discomfort, gastrointestinal motility disorder, gastritis, gastro-esophageal reflux disease, gingival bleeding, irritable bowel syndrome, coated tongue, faecal impaction, mouth ulceration, gastrointestinal obstruction (incl. small intestinal obstruction, ileus), paralytic ileus, antibiotic associated colitis, haemorrhagic diarrhoea, gastrointestinal haemorrhage, rectal haemorrhage, eructation, retching, change in bowel habit, spleen pain, esophagitis, gingival pain, hiatus hernia, oral mucosal petechiae, salivary hypersecretion, tongue discolouration, lip swelling, oral ulceration, gastrointestinal inflammation, salivary gland disorder peritonitis, tongue oedema, ascites, esophagitis, cheilitis, anal sphincter atony, faecaloma, gastrointestinal ulceration and perforation, gingival hypertrophy, megacolon, rectal discharge, oropharyngeal blistering, lip pain, periodontitis, anal fissure, change of bowel habit, proctalgia, abnormal faeces
Hepatobiliary disorders	Frequent	Hepatic enzyme abnormality, hepatotoxicity (incl. liver disorder)
	Less frequent	Hepatitis, hepatic haemorrhage, hypoproteinaemia, hyperbilirubinaemia, cholestasis, hepatic failure, hepatomegaly, Budd-Chiari syndrome, cytomegalovirus hepatitis, cholelithiasis
Skin and subcutaneous disorders	Frequent	Rash, urticaria, pruritic rash, pruritus, erythaema, dry skin, dermatitis, increased sweating, eczema, periorbital oedema, hair disorder
	Less frequent	Photosensitivity reaction, psoriasis, nail disorder, skin discolouration, atopic dermatitis, night sweats, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), acute febrile neutrophilic dermatosis (Sweet's syndrome), vasculitic rash (incl. leukocytoclastic vasculitis), erythematous rash, contusion, generalised pruritus, macular rash, papular rash, generalised rash, eyelid oedema, face oedema, alopecia, abnormal hair texture, heat rash, pressure sore, ichthyosis, skin nodule, erythema multiforme, urticaria, toxic skin eruption, petechiae, ecchymosis, skin lesion, purpura, skin mass, decubitus ulcer, acne, blister, Jessner's lymphocytic infiltration, Palmar plantar erythrodysesthesia syndrome, subcutaneous haemorrhage, Livedo reticularis, skin induration, papule, seborrhoea, cold sweat, erythroses, skin ulcer
Musculoskeletal and connective tissue disorders	Frequent	Muscle spasms, muscle weakness, musculoskeletal pain, pain in extremity, myalgia, muscle cramps, arthralgia, bone pain, back pain, peripheral swelling.
	Less frequent	Muscle twitching, sensation of heaviness, joint swelling, joint stiffness, pain in jaw, buttock pain, swelling, muscle stiffness, arthritis, myopathies, rhabdomyolysis, temporomandibular joint syndrome, fistula, joint effusion, bone disorder, musculoskeletal and connective tissue infections and inflammations, synovial cyst
Renal and urinary disorders	Frequent	Renal impairment, dysuria, urinary tract infection
	Less frequent	Acute renal failure, chronic renal failure, oliguria, haematuria, proteinuria, urinary retention, difficulty in micturition, renal colic, loin pain, urinary incontinence, micturition urgency, urinary frequency, proteinuria, azotaemia, pollakiuria, bladder irritation
Reproductive system and breast disorders	Less frequent	Testicular pain, erectile dysfunction, vaginal haemorrhage, genital pain, erectile dysfunction, testicular disorder, prostatitis, breast disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration
General disorders and administration site conditions	Frequent	Fatigue, pyrexia, asthenia, peripheral oedema, pain, weakness, lethargy, rigors, influenza like illness, oedema, malaise
	Less frequent	Chest pain, injection site phlebitis, extravasation inflammation tenderness, feeling cold, chest pressure sensation, chest discomfort, fall, mucosal haemorrhage, mucosal inflammation, neuralgia, groin pain, chest tightness, injection site erythema, general physical health deterioration, gait disturbance, catheter related complication, change in thirst, injection site pain, sudden death, multi-organ failure, injection site haemorrhage, impaired healing, catheter site pain, sensation of foreign body
Congenital, familial and genetic disorders	Less frequent	Aplasia, gastrointestinal malformation, ichthyosis
Investigations	Frequent	Decreased weight, increased blood lactate dehydrogenase
	Less frequent	Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, increased blood alkaline phosphatase, increased blood creatinine, increased blood urea, increased gamma-glutamyl transferase, increased blood amylase, abnormal liver function tests, decreased red blood cell count, decreased white blood cell count, decreased blood bicarbonate, irregular heart rate, increased C-reactive protein, dec