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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) Title: TREATMENT OF ASCITES

(57) Abstract: A method for treating ascites patients by administering the peptide drug terlipressin by continuous infusion. The patients include those whose ascites condition has not progressed to hepatorenal syndrome (HRS). Administration may be accomplished with a continuous infusion pump.

TREATMENT OF ASCITES

Related Applications

[0001] This application claims the benefit of US provisional patent application 62/321,558, filed April 12, 2016, US provisional patent application 62/267,510, filed December 15, 2015, and US provisional patent application 62/186,638, filed June 30, 2015, each of which is incorporated by reference herein their entirety

Field

[0002] The disclosure is directed to a method for treating ascites patients by administering the peptide drug terlipressin.

Background

[0003] Ascites is a frequent and life-threatening complication of advanced liver cirrhosis with an expected 40% mortality rate within two years of diagnosis. To date the US FDA has not approved any therapies specifically to treat ascites, although a few drugs (*e.g.*, diuretics) are being used off-label with limited and temporary efficacy. Studies have shown that intravenous (IV) injections of terlipressin every 4 to 6 hours in hospitalized patients with type 1 hepatorenal syndrome (HRS) can save their lives. HRS is the beginning of renal failure and frequently occurs in patients with ascites that has become refractory to treatment with diuretics. Additionally, investigational studies have shown that IV injections of terlipressin every 4 to 6 hours in combination with diuretics may resolve refractory ascites in hospitalized patients and decrease the need for large volume paracentesis (ascites fluid withdrawal by needle). However these intermittent high-dose IV injections (typically 1 or 2 mg in a single dose) carry a high risk of

side-effects. More recent studies with hospitalized HRS patients indicate that a continuous infusion of terlipressin can achieve similar efficacy to intermittent injections with a much better safety profile. However to date there have been no published studies of using a continuous low-dose infusion terlipressin to manage ascites in non-hospitalized patients with cirrhosis.

[0004] Accordingly, the inventors have identified a need in the art for a method to treat ascites patients on an outpatient basis and potentially avoid or delay the need for hospitalization due to HRS or other life-threatening complications.

SUMMARY

[0005] In one aspect, the disclosure is directed to a method for treating a patient diagnosed with ascites due to liver cirrhosis. The method including administering terlipressin or salt thereof as a continuous infusion. The condition of the patient may not have progressed to HRS.

[0006] In another aspect, the disclosure is directed to a method for reducing the volume of ascitic fluid during a paracentesis procedure in an ascites patient. The method includes administering terlipressin or salt thereof as a continuous infusion.

[0007] In yet another aspect, the disclosure is directed to a method for reducing the number of monthly paracentesis procedures in an ascites patient. The method includes administering terlipressin or salt thereof as a continuous infusion.

[0008] Still further, the disclosure is directed to a method for improving renal function in an ascites patient. The method includes administering terlipressin or salt thereof as a continuous infusion. In various aspects, the improvement in renal function includes one or more of the following: a reduction in serum creatinine concentration, an increase in plasma sodium

concentration, an increase in urinary sodium excretion, and a decrease in urea concentration in serum.

[0009] The disclosure is also directed to a method for correcting hyponatremia in an ascites patient. The method includes administering to the patient terlipressin or salt thereof as a continuous infusion.

[0010] In a further aspect, the disclosure is directed to a method for improving the health status of the ascites patient with liver cirrhosis due to hepatitis C. The method includes method comprising administering a hepatitis C antiviral medication in combination with administering terlipressin or salt thereof as a continuous infusion.

[0011] In another aspect, the disclosure is directed to a method of improving the Model for End-Stage Liver Disease (MELD) score of an ascites patient. The method includes administering terlipressin or salt thereof with a continuous infusion.

[0012] In each of the aspects of the invention, the condition of the patient may not have progressed to HRS. Also, the terlipressin dose may range from about 1.0 mg to about 12.0 mg per day, and the terlipressin dose may be escalated over the course of the therapy. In addition, the terlipressin may be administered for a time period of about 1 day to about 12 months. Further, the continuous terlipressin may be administered with an ambulatory infusion pump.

DESCRIPTION

[0013] Terlipressin is a synthetic vasopressin that is approved in many countries outside of the United States to treat the life-threatening complications of cirrhosis, including hepatorenal syndrome (HRS) and esophageal bleeding (EVB). Its use is limited to the hospital setting due to

its short half-life (26 minutes) (Nilsson, et al., 1990), necessitating its administration as an intravenous bolus usually every 4 to 6 hours. Additionally, terlipressin can cause side effects in up to 40% of patients. Severe side effects – including myocardial infarction, arrhythmia and intestinal infarction – can require discontinuation of treatment in up to 10% of the patients (Angeli, 2011). Indeed, due to the rapid vasoconstrictor properties, IV bolus dosed terlipressin must be used with caution in patients with severe asthma, severe hypertension, advanced atherosclerosis, cardiac dysrhythmias, and coronary insufficiency.

[0014] In one aspect, the disclosure is directed to the administering terlipressin or a salt thereof for the treatment of patients suffering from ascites due to, for example, advanced liver cirrhosis. These patients are typically non-hospitalized (or ambulatory) and may include patients whose condition has not progressed to type 2 HRS (ambulatory HRS patients) or type 1 HRS (requiring hospitalization). Treatment includes a continuous infusion of terlipressin by means of a pump device, typically a portable ambulatory pump, for a period of several hours, lasting up to days, weeks, or months. The treatment is effective at reducing or resolving ascites disease on, for most patients, an outpatient basis.

[0015] Patients with cirrhosis exhibiting type 1 hepatorenal syndrome (HRS-1) have been safely treated with terlipressin administered continuously. Dosage ranged from 2.0-12.0 mg per 24 hours (Angeli, et al., 2009: 2 -12 mg/24h; Gerbes, 2009: starting dose 3mg/day; Robertson, et al., 2014: 3mg/day; Ding, 2013: 4 mg/day; Cavallin 2015: 3 – 12 mg/day). However, none of these studies have either evaluated or reported an effect of terlipressin infusion on ascites burden or the effect of continuous infusion terlipressin on patients whose condition have not progressed to HRS.

[0016] Ambulatory pumps are commonly used to infuse parenteral drugs directly into the bloodstream via catheters to increase efficacy and/or decrease toxicity. This has been found to be safer than some approved terlipressin drug therapy that require the administration of terlipressin to hospitalized hepatorenal syndrome (HRS) patients and esophageal bleed (EVB) patients using slow bolus IV injections. Accordingly, in one aspect of the disclosure, terlipressin is administered continuously by a pump at a dosage rate of about 0.5 mg to about 20 mg every 24 hours, more particularly for example, about 1 mg to about 12 mg every 24 hours, more particularly for example, about 5 to about 15 mg every 24 hours, or for instance, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg every 24 hours. Administration can continue for, typically, at least about one day and may continue for about 12 months or longer as necessary to bridge a patient until a transplant is available. For example, the administration can continue for about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, one week, two weeks, three weeks, one month, two months, three months, six months, 9 months or twelve months. In some instances, the dose of terlipressin escalates over the course of the therapy. For example, patients may begin therapy at 2 mg/day, and be increased to 3 mg/day or up to 12 mg/day over the course of treatment.

[0017] Accordingly, in various aspects, the disclosure is directed to a method for treating a patient diagnosed with ascites due to liver cirrhosis. The method can improve renal function in an ascites patient and reduce the volume of ascitic fluid during paracentesis procedure in the patient. Still further, the method can be used for reducing the risk of spontaneous bacterial peritonitis, improving the Model for End-Stage Liver Disease (MELD) score of an ascites patient and/or correcting hyponatremia in an ascites patient. In another aspect, the method disclosed herein can be used in combination with hepatitis C antiviral medications to improve the health

status of the ascites patient with liver cirrhosis due to hepatitis C. In each case terlipressin or salt thereof is administered with a continuous infusion pump. In each of these aspects, the patient's ascites condition may not have progressed to hepatorenal syndrome.

[0018] In addition, the determination of the presence, progression, or improvement of disease can be determined by measuring one or more of the following: serum creatinine concentration, plasma sodium concentration, urinary sodium excretion, and urea concentration in serum. For example, an improvement in renal function that indicates an improvement in disease condition includes one or more of the following: a reduction in serum creatinine concentration, an increase in plasma sodium concentration, an increase in urinary sodium excretion, a decrease in urea concentration in serum of disease.

[0019] The use of ambulatory pump delivery of continuous infusion of terlipressin would avoid the need for patient hospitalization and make such therapy available to the vast majority of ascites patients who have not yet been hospitalized for severe complications that often follow advanced ascites, such as post-paracentesis circulatory dysfunction, HRS, EVB, hepatic encephalopathy, spontaneous bacterial peritonitis and other life-threatening conditions.

Examples

[0020] The following are provided for exemplification purposes only and are not intended to limit the scope of the disclosure described in broad terms above.

Example 1: Treatment of Ascites with Continuous Infusion Pump Terlipressin Therapy

[0021] 15 subjects that are to be confirmed to have ascites, but not type 1 or type 2 HRS, due to liver cirrhosis will be administered continuous low dose (escalating from 2.0 to 3.0 mg per 24

hours) terlipressin via ambulatory infusion pump. These patients are expected to experience a decrease the severity of ascites and the accumulation of ascites fluid over the course of treatment ranging from 1 day to 28 days. This method is also expected to reduce the number of paracentesis procedures required to remove ascitic fluid over a 28-day period, compared to the 28-day period prior to treatment inception, and some patients should avoid paracentesis altogether. Additionally the average amount of fluid withdrawn after beginning continuous infusion pump terlipressin therapy should be significantly less than prior to the start of treatment. Furthermore the improvement in patient health status can be achieved safely with no serious side effects. Accordingly, continuous infusion pump (CIP) terlipressin represents a potentially life-saving solution for these seriously ill patients who are still ambulatory (have not yet been administered to the hospital for treatment) and have not developed type 1 or type 2 HRS.

Example 2: Treatment of Ascites with Continuous Infusion Pump Terlipressin Therapy

[0022] Six HRS patients treated with continuous infusion terlipressin were evaluated for improvement in acsites. All six patients had diuretic intractable or refractory ascites (5 of 6 with hyponatremia). The patients were evaluated for the following parameters before, during and after treatment: number of paracentesis procedures per month, volume of ascites removed, weight, serum sodium, urinary sodium excretion, serum creatinine, serum urea, and whether diuretics were included in the treatment regimen. None of the six patients had a complete set of data for all parameters. The effect of continuous infusion terlipressin on each parameter is presented in Tables 1-7.

[0023] Reduction in frequency of paracentesis and fluid volume during therapy

[0024] The average number of monthly paracentesis procedures decreased from three prior to initiation of continuous infusion therapy to two during therapy, and the average monthly ascites fluid volume removed was reduced by 55%.

Table 1

			Paracenteses/Month			Volume Fluid Removed/Month (L)		
Patient # M/F	**Max. Dose (mg/day)**	**Duration (days)**	**Before**	**During**	**% Change**	**Before**	**During**	**% Change**
1 M	12	63	1	0	-100%	--	--	--
2 F	12	195	8	6	-25%	80	42	-48%
3 M	3	10	4	2	-50%	40	14	-65%
4 M	10	11	2	3	50%	14	9	-36%
5 F	3	22	3	2	-33%	21	6	-71%
6 F	2	12	1	0	-100%	2	0	-100%
Average (excludes patient #1):			3	2	-32%	31	14	-55%

"--" indicates missing data

[0025] Reduction in body weight during therapy

[0026] Average body weight per patient, a proxy for ascitic fluid accumulation in the abdominal cavity, decreased by 11% or 9kg (~ 19.8 lbs).

Table 2

			Body Weight (kg)			
Patient # M/F	**Max. Terli. Dose (mg/day)**	**Duration (days)**	**Before**	**During**	**% Change**	**After**
1 M	12	63	83	74	-11%	74
2 F	12	195	64	71	11%	--
3 M	3	10	128	99	-23%	128
4 M	10	11	60	--	--	--

5 F	3	22	71	64	-10%	77
6 F	2	12	64	55	-14%	68
Average (excludes Patient #4):			82	73	-11%	87

"--" indicates missing data

[0027] Requirement for diuretics for effect on ascites

[0028] During treatment, improvement of ascites was seen without diuretics in four of six patients.

Table 3

	Treatment			% Change		
Patient # M/F	**Max. Terli. Dose (mg/day)**	**Diuretics Before**	**Diuretics During**	**Paracentesis per Month**	**Volume Fluid Removed**	**Body Weight**
1 M	12	A	A	-100%	--	-11%
2 F	12	A	None	-25%	-48%	11%
3 M	3	F + A	None	-50%	-65%	-23%
4 M	10	F + A	None	50%	-36%	--
5 F	3	A	None	-33%	-71%	-10%
6 F	2	F + A	F + A	-100%	-100%	-14%
			Average:	-32%	-55%	-11%

F = furosemide; A = anti-aldosteronic drug. '"--" indicates missing data.

[0029] Increase in urinary sodium excretion during therapy

[0030] The observed improvement in ascites and renal function was further supported by a substantial increase in excretion of sodium into the urine. The average urinary sodium increased from 7 to 127 mEq/24h in three of sis patients with data recorded before and after starting continuous infusion terlipressin therapy.

Table 4

			Urinary Na over 24 hours (mEq/24 hr)		
Patient # M/F	**Max. Terli. Dose (mg/day)**	**Duration (days)**	**Before**	**During**	**% Change**
1 M	12	63	5	46	820%
2 F	12	195	--	301	--
3 M	3	10	--	--	--
4 M	10	11	1	20	1900%
5 F	3	22	--	33/140	--
6 F	2	12	16	315	1869%
Average (excludes patients #2, #3, #5):			7	127	1632%

"--" indicates missing data

[0031] Improvement in plasma sodium

[0032] Treatment with continuous infusion terlipressin corrected severe hyponatremia in two patients: Plasma Na increased by 15% in patient #4 and by 19% in patient #6. Importantly, after the cessation of therapy, plasma sodium remained normal in patient #6 (data "after therapy" available for one of the two patients).

Table 5

			Plasma Sodium (mEq/L)			
Patient # M/F	**Max. Terli. Dose (mg/day)**	**Duration (days)**	**Before**	**During**	**% Change**	**After**
1 M	12	63	140	137	-2%	--
2 F	12	195	125	128	2%	--
3 M	3	10	133	136	2%	140
4 M	10	11	123	141	15%	--
5 F	3	22	131	128	-2%	--
6 F	2	12	118	140	19%	131
		Average:	128	135	5%	136

"--" indicates missing data

[0033] Reduction in blood urea during treatment

[0034] The concentration of urea in patients' blood serum decreased in all patients by an overall average of 45%. This increase in urea clearance is indicative of improved renal function.

Table 6

			Serum Urea (mmol/L)			
Patient # M/F	**Max. Terli. Dose (mg/day)**	**Duration (days)**	**Before**	**During**	**% Change**	**After**
1 M	12	63	31.1	8.8	-72%	--
2 F	12	195	36.6	23.2	-37%	--
3 M	3	10	17.0	9.1	-46%	10.8
4 M	10	11	51.8	37.3	-28%	--
5 F	3	22	6.4	5.3	-17%	10.5
6 F	2	12	20.4	6.6	-68%	10.0
		Average:	27.2	15.1	-45%	10.4

"--" indicates missing data

[0035] Reduction in serum creatinine

[0036] Levels of the metabolic waste product serum creatinine are indicative of renal health. An average decrease of 47% was seen in serum creatinine levels for the treated group of patients. This was consistent with the decrease in serum urea and indicates improved renal function, contributing to a decrease in ascites severity.

Table 7

Serum Creatinine (mmol/L)

Patient # M/F	Max. Terli. Dose (mg/day)	Duration (days)	Before	During	% Change	After
1 M	12	63	248	189	-24%	--
2 F	12	195	383	208	-46%	--
3 M	3	10	233	116	-50%	122
4 M	10	11	319	104	-67%	--
5 F	3	22	68	55	-19%	55
6 F	2	12	195	90	-54%	137
		Average:	241	127	-47%	105

"--" indicates missing data

[0037] All references cited in this disclosure are incorporated herein by reference.

[0038] Nilsson, G. et al., 1990. Nilsson G, Lindblom P, OhlPharmacokinetics of Terlipressin After Single i.v. Doses to Healthy Volunteers. Drugs Under Experimental and Clinical Research, Volume 16, pp. 307-314.

[0039] Angeli, P., 2011. Terlipressin for Hepatorenal Syndrome: Novel Strategies and Future Perspectives. Frontiers of Gastrointestinal Research, Volume 28, pp. 189-197.

[0040] Angeli, P. et al., 2009. Terlipressin Given as Continous Intravenous Infusion Versus Terlipressin Given as Intravenous Boluses in the Treatment of Type 1 Hepatorenal Syndrome (HRS) in Patients with Cirrhosis. Journal of Hepatology, 50(Supplement 1), p. S73.

[0041] Gerbes AL, Huber E, Gülberg V. 2009 Terlipressin for hepatorenal syndrome: continuous infusion as an alternative to i.v. bolus administration. 2009 Gastroenterology. 137(3):1179; author reply 1179-81

[0042] Ding, C. et al., 2013. Hemodynamic effects of continuous versus bolus infusion of terlipressin for portal hypertension: A randomized comparison. Journal of Gastroenterology and Hepatology, 28(7), pp. 1242-1246.

[0043] Robertson, M. et al., 2014. Continuous outpatient terlipressin infusion for hepatorenal syndrome as a bridge to successful liver transplantation. Hepatology Mar 2014. Hepatology, Volume March, pp. 1-2.

[0044] Cavallin M, et. al., 2015 Terlipressin Plus Albumin Versus Midodrine and Octreotide Plus Albumin in the Treatment of Hepatorenal Syndrome: A Randomized Trial. Hepatology, 2015 (in press)

[0045] Fimiani, B. et al., 2011. The Use of Terlipressin in Cirrhotic Patients with Refractory Ascites and Normal Renal Function: A Multicentric Study. European Journal of Internal Medicine, Volume 22, pp. 587-590.

[0046] Krag, A. et al., 2007. Telipressin Improves Renal Function in Patients with Cirrhosis and Ascites Without Hepatorenal Syndrome. Hepatology, 46(6), pp. 1863-1871.

[0047] Although various specific embodiments of the present disclosure have been described herein, it is to be understood that the disclosure is not limited to those precise embodiments and that various changes or modifications can be affected therein by one skilled in the art without departing from the scope and spirit of the disclosure.

WHAT IS CLAIMED IS:

1. A method for treating a patient diagnosed with ascites due to liver cirrhosis, the method comprising administering terlipressin or salt thereof as a continuous infusion.

2. A method for reducing the volume of ascitic fluid during a paracentesis procedure in an ascites patient, the method comprising administering terlipressin or salt thereof as a continuous infusion.

3. A method for reducing the number of monthly paracentesis procedures in an ascites patient, the method comprising administering terlipressin or salt thereof as a continuous infusion

4. A method for improving renal function in an ascites patient, the method comprising administering terlipressin or salt thereof as a continuous infusion.

5. A method for correcting hyponatremia in an ascites patient, the method comprising administering to the patient terlipressin or salt thereof as a continuous infusion.

6. A method for improving the health status of the ascites patient with liver cirrhosis due to hepatitis C, the method comprising administering a hepatitis C antiviral medications in combination with administering terlipressin or salt thereof as a continuous infusion.

7. A method of improving the Model for End-Stage Liver Disease (MELD) score of an ascites patient, the method comprising administering terlipressin or salt thereof with a continuous infusion.

8. A method according to any one of claims 1-7, wherein a terlipressin dose ranges from about 1.0 to about 12.0 mg per day.

9. The method of any one of claims 1-8 wherein the terlipressin is administered for about one day to about 12 months.

10. The method of any one of claims 1-8 wherein the continuous terlipressin is administered with an ambulatory infusion pump.

11. The method of any one of claims 1-10 wherein a condition of the patient has not progressed to hepatorenal syndrome (HRS).

12. The method of any one of claims 1-11, wherein the administration is provided on an out-patient basis.

13. The method of claim 9, wherein the terlipressin dose escalates over the about one day to about 12 months.

14. The method of claim 4, wherein the improvement comprises a reduction in serum creatinine concentration.

15. The method of claim 4, wherein the improvement comprises an increase in plasma sodium concentration.

16. The method of claim 4, wherein the improvement comprises an increase in urinary sodium excretion.

17. The method of claim 4, wherein the improvement comprises a decrease in urea concentration in serum.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/40284

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/11; C07K 7/16 (2016.01)
CPC - C07K 14/575, 7/16
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 38/11; C07K 7/16 (2016.01)
CPC: C07K 14/575, 7/16

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); EBSCO; PubMed; Google/Google Scholar; liver, cirrhosis, terlipressin, continuous, infusion, paracentesis, ascites, renal, hyponatremia, hepatitis, MELD, end-stage, creatinine, sodium, urea, plasma, urinary, excretion, concentration

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0102362 A1 (LEBREC, D et al.) 27 May 2004; paragraphs [0001], [0008], [0013]-[0015], [0018]-[0020]	1, 6, 8/1, 8/6
Y	US 2011/0300109 A1 (TEPIC, S et al.) 08 December 2011; paragraphs 0086], [0089], [0093], [0107]	1-7, 8/1-7, 14-17
Y	US 2015/0126432 A1 (FERRING B.V.) 07 May 2015; paragraphs [0006]-[0008], [0046], [0050], [0182]-[0186]	2-5, 7, 8/2-5, 8/7, 14-17
Y	US 2015/0056194 A1 (GEORGIA REGENTS RESEARCH INSTITUTE, INC.) 26 February 2015; abstract; paragraphs [0012]-[0013], [0092]-[0093]	6, 8/6
Y	US 2014/0147875 A1 (THE REGENTS OF THE UNIVERSITY OF COLORADO, A BODY CORPORATE) 29 May 2014; figure 11; paragraphs [0057], [0182], [0350]	7, 8/7
Y	WO 2013/106072 A1 (SORBENT THERAPEUTICS, INC.) 18 July 2013; paragraphs [0003], [0015]	14, 17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 August 2016 (29.08.2016)	15 SEP 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/40284

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 9-13
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

摘要：

通过经连续输注施用多肽药物特利加压素治疗腹水患者的方法。所述患者包括那些腹水状况尚未发展成肝肾综合征(HRS)的患者。施用可用连续输注泵实现。