Anidulafungin for the Treatment of Candidaemia / Invasive Candidiasis in Selected Critically ill Patients

M. Ruhnke et al.
Clin Microbiol Infect 2012; 18: 680–687

Ecalta® (anidulafungin IV)

Indication:
Treatment of invasive candidiasis in adult patients

Study Design and Methodology

- Phase 3b, prospective, multicentre, exploratory, open-label study to evaluate the efficacy and safety of anidulafungin for the treatment of C/IC in specific ICU patient populations

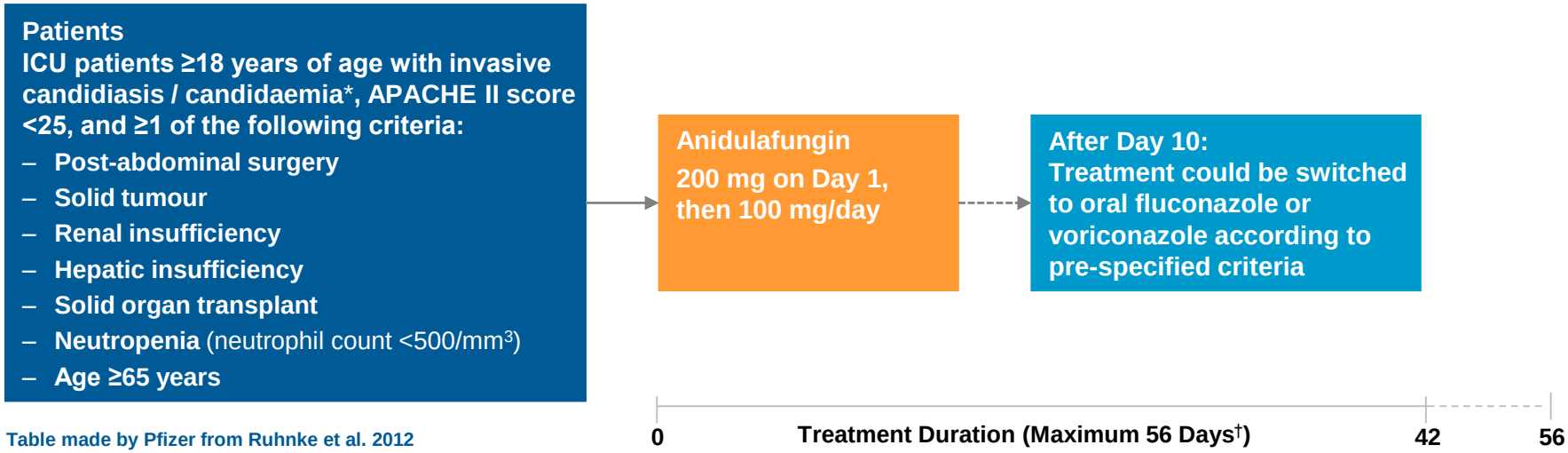


Table made by Pfizer from Ruhnke et al. 2012

- Primary endpoint: Global success (clinical and microbiologic) at the end of all therapy (EOT) in the MITT population#
- Secondary endpoints included: Global response at the end of IV therapy (EOIVT) and at 2 weeks and 6 weeks post-EOT; 90-day survival in the MITT population; incidence of adverse events in the safety population‡

C/IC = candidaemia / invasive candidiasis

* Patients with suspected Candida osteomyelitis, endocarditis, meningitis and/or endophthalmitis were excluded.
† Overall therapy (with anidulafungin or step-down azole) was continued for ≥14 days after the last positive blood / tissue culture and resolution / significant improvement.
# Patients with confirmed C/IC at study entry who received ≥1 anidulafungin dose
‡ Patients who received ≥ 1 dose of anidulafungin

Baseline Characteristics of the MITT Population (n=170)

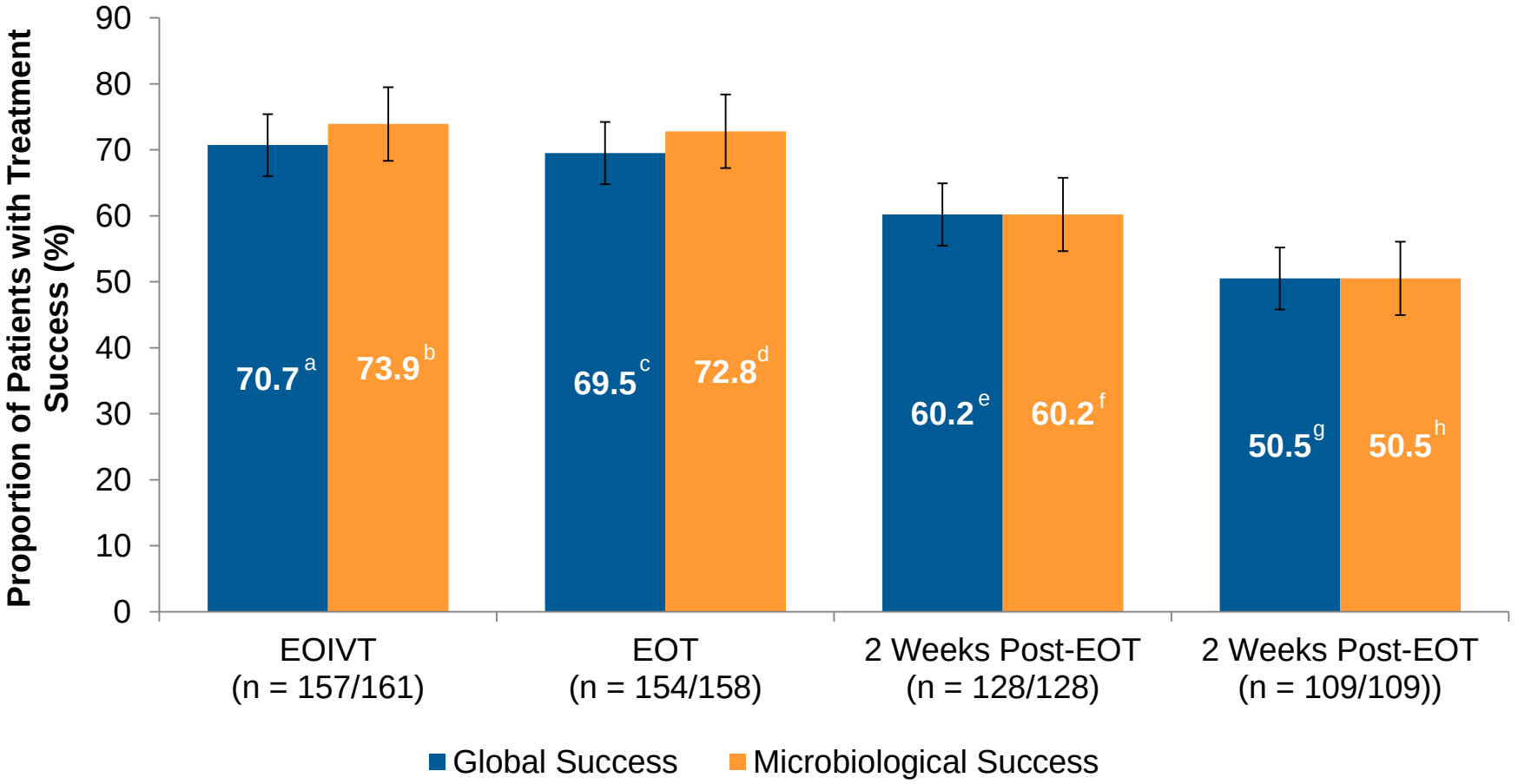
Characteristic	MITT Population *(n = 170)*
Demographic characteristics	
Male, *n* (%)	101 (59.4%)
Mean age (range)	62.2 years (25–89)
Race, *n* (%)	
White	160 (94.1%)
Other (includes unspecified)	10 (5.9%)
Mean BMI (range)[a]	25.7 kg/m^2 (15.4–83.0)
Risk factors for candidaemia / invasive candidiasis, *n* (%)	
Broad-spectrum antibiotics	153 (90.0%)
Central venous catheter	148 (87.1%)
Prior surgery	113 (66.5%)
Total parenteral nutrition	99 (58.2%)
Dialysis / renal failure	59 (34.7%)
Systemic steroids or other immunosuppressives / immunosuppressive therapy	57 (33.5%)
Mucosal colonization by Candida species	52 (30.6%)
Chemotherapy	21 (12.4%)
Neutropaenia (neutrophil count <500/mm^3)	13 (7.6%)
HIV infection	2 (1.2%)
Clinical characteristics	
Post-abdominal surgery	90 (52.9%)
Elderly (≥65 years)	80 (47.1%)
Renal insufficiency / failure / dialysis[b]	67 (39.4%)
Solid tumour	45 (26.5%)
Hepatic insufficiency[b]	27 (15.9%)
Neutropaenic	13 (7.6%)
Solid organ transplant recipient	10 (5.9%)
Infection site, *n* (%)	
Blood only	114 (67.1%)
Other normally sterile site only	49 (28.8%)
Blood and other normally sterile site	7 (4.1%)
Mean Candida score (95% CI)[c]	3.4 (3.2–3.6)
Mean colonization index (95% CI)[d]	53.1 (45.7–60.6)
Mean SOFA score (95% CI)[e]	7.2 (6.6–7.9)
Septic shock[f]	41 (24.1%)
APACHE II score	
≤20	128 (75.3%)
>20	42 (24.7%)
Mean (range)	16.2 (4–26[g])
Intravascular catheter status	
All catheters removed / replaced[h]	40 (23.5%)
Not all catheters removed / replaced[i]	49 (28.8%)
No catheter inserted before first positive culture	81 (47.6%)
Baseline pathogen	
C. albicans	95 (55.9%)
C. glabrata	25 (14.7%)
C. parapsilosis	17 (10.0%)
C. tropicalis	13 (7.6%)
C. kefyr	3 (1.8%)
C. dubliniensis	2 (1.2%)
C. pelliculosa	2 (1.2%)
Other *Candida* spp.[j]	3 (1.8%)
Multiple *Candida* spp.	10 (5.9%)

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; SOFA, Sequential Organ Failure Assessment.

Ruhnke et al. 2012

a Assessed in n = 165 patients; **b** The presence / absence of these characteristics was determined by the local investigator there were no prespecified protocol definitions; **c** Assessed in n = 167 patients; **d** Assessed in n = 90 patients, expressed as a percentage; **e** Assessed in n = 166 patients. **f** Defined as having 'severe sepsis' (per the Candida score assessment) and a value of 3 or 4 on the cardiovascular system component of the SOFA score; **g** A single patient with a score ≥ 25 (i.e. 26) was included in the MITT population; **h** Patients with ≥ 1 intravascular catheter inserted before the day of first positive culture, all of which were removed or replaced by day 3 of anidulafungin therapy; **i** Patients with ≥1 intravascular catheters inserted before the day of first positive culture, ≥ 1 of which had not been removed or replaced by day 3 of anidulafungin therapy; **j** One each of *C. krusei*, *C. lusitaniae* and *C. norvegensis*.

Global and Microbiological Success Rates



Ruhnke et al. 2012

Global and microbiological success rates (with 95% confidence intervals) in modified intent-to-treat patients at the end of intravenous therapy (EOIVT), end of therapy (EOT), 2 weeks post EOT and 6 weeks post EOT.

Missing and unknown global or microbiological responses were excluded in these analyses. a95% confidence interval (CI), 62.9–77.7; b 95% CI, 66.4–80.5; c 95% CI, 61.6-76.6; d 95% CI, 65.1–79.6; e 95% CI, 51.1–68.7; f 95% CI, 51.1–68.7; g 95% CI, 40.7–60.2; h 95% CI, 40.7–60.2.

Global and Microbiological Success in Modified Intent-to-treat Patients at the End of Therapy According to Specific ICU Patient Population and Baseline Characteristics

	Global Success, *n* (%) [95% CI]	Microbiologicl Success, *n* (%) [95% CI]
ICU patient population		
Post-abdominal surgery	54/79 (68.4%) [56.9–78.4%]	55/80 (68.8%) [57.4–78.7%]
Elderly (≥65 years)	49/72 (68.1%) [56.0–78.6%]	54/75 (72.0%) [60.4–81.8%]
Renal insufficiency	44/58 (75.9%) [62.8–86.1%]	48/61 (78.7%) [66.3–88.1%]
Solid tumour	31/41 (75.6%) [59.7–87.6%]	32/42 (76.2%) [60.5–87.9%]
Hepatic insufficiency	18/25 (72.0%) [50.6–87.9%]	21/25 (84.0%) [63.9–95.5%]
Neutropaenic	6/12 (50.0%) [21.1–78.9%]	7/12 (58.3%) [27.7–84.8%]
Solid organ transplant recipient	3/8 (37.5%) [8.5–75.5%]	4/8 (50.0%) [15.7–84.3%]
Baseline pathogen[a]		
C. albicans[b]	64/86 (74.4%) [63.9–83.2%]	69/89 (77.5%) [67.4–85.7%]
C. glabrata	15/22 (68.2%) [45.1–86.1%]	15/22 (68.2%) [45.1–86.1%]
C. parapsilosis	10/15 (66.7%) [38.4–88.2%]	11/15 (73.3%) [44.9–92.2%]
C. Tropicalis	4/11 (36.4%) [10.9–69.2%]	6/12 (50.0%) [21.1–78.9%]
Any non-*albicans*[b]	37/58 (63.8%) [50.1–76.0%]	40/59 (67.8%) [54.4–79.4%]
Baseline infection site		
Blood[c,d]	73/108 (67.6%) [57.9–76.3%]	81/112 (72.3%) [63.1–80.4%]
Other normally sterile site only[d]	34/46 (73.9%) [58.9–85.7%]	34/46 (73.9%) [58.9–85.7%]

Ruhnke et al. 2012

Missing and unknown global or microbiological responses were excluded from these analyses.

a Excluding patients with multiple pathogens at baseline
b The differences between success rates in patients with *C. albicans* and *non-albicans* infections were not statistically significant (p 0.17 for global response, p 0.19 for microbiological response)
c Includes patients with baseline infection site, either blood only or blood and other normally sterile site
d The differences between success rates in patients with candidaemia and without candidaemia were not statistically significant (p 0.44 for global response, p 0.84 for microbiological response)
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Global Success Rates

Global Success Rates† Over the Course of the Study According to baseline APACHE II Score, Treatment Strategy and Septic Shock Status in the Modified ITT Population

		EOIVT	EOT	2 Weeks Post EOT	6 Weeks Post EOT
APACHE II ≤20‡	n(%) 95% CI	84/119 (70.6%) 61.5-78.6%	80/116 (69.0%) 59.7-77.2%	60/9 (61.2%) 50.8-70.9%	44/84 (52.4%) 41.2-63.4%
APACHE II >20‡	n(%) 95% CI	27/38 (71.1%) 54.1-84.6%	27/38 (71.1%) 54.1-84.6%	17/30 (56.7%) 37.4-74.5%	11/25 (44.0%) 24.4-65.1%
Switched to oral azoles§	n(%) 95% CI	51/58 (87.9%) 76.7-95.0%	47/55 (85.5%) 73.3-93.5%	38/48 (79.2%) 65.0-89.5%	29/41 (70.7%) 54.5-83.9%
IV anidulafungin only§	n(%) 95% CI	60/99 (60.6%) 50.3-70.3%	60/99 (60.6%) 50.3-70.3%	39/80 (48.8%) 37.4-60.2%	26/68 (38.2%) 26.7-50.8%
Septic shock‡	n(%) 95% CI	27/36 (75.0%) 57.8-97.9%	25/34 (73.5%) 55.6-87.1%	14/25 (56.0%) 34.9-75.6%	10/22 (45.5%) 24.4-67.8%
No septic shock‡	n(%) 95% CI	84/121 (69.4%) 60.4-77.5%	82/120 (68.3%) 59.2-76.5%	63/103 (61.2%) 51.1-70.6%	45/87 (51.7%) 40.8-62.6%

Ruhnke et al. 2012

† Missing and unknown global or microbiological responses were excluded from these analyses.
‡ Differences between global success rates were not statistically significant (p>0.05) at any time-point.
§ Differences between global success rates were statistically significant (p<0.05) at all time-points.

Safety Profile†

Treatment-related Adverse Events		33/216 Patients (15.3%)
Most Frequent Treatment-related Adverse Events:	Erythema	1.9%
	Hypotension	1.4%
	Increased blood alkaline phosphatase	1.4%
	Increased aspartate aminotransferase	1.4%
	Diarrhoea	1.4%
	Atrial fibrillation	1.4%

Serious Treatment-related Adverse Events (Convulsions, n=2; Infusion-related Adverse Events, n=1; Bronchospasm, n=1)	4 patients (1.9%)
Discontinued Due to Treatment-related Adverse Events	5 patients (2.3%)

Table made by Pfizer from Ruhnke et al. 2012

† Safety population (n=216): 151 received Ecalta® only; 49 and 16 also received step-down therapy with fluconazole or voriconazole, respectively.

Conclusion

- Results demonstrate that **anidulafungin is an effective and well-tolerated** treatment for confirmed C/IC (including deep-tissue infection) in critically ill patients[1]

- Efficacy appears consistent across certain high-risk patient groups, regardless of a multitude of clinical factors and the causative pathogen[1]

- Provides support to current guidelines recommending echinocandins as first-line therapy for the treatment of C/IC in moderately to severely ill patients[1,2]

1. M. Ruhnke et al.,Clin Microbiol Infect 2012; 18: 680–687. 2. RADS Baggrundsnotat vedr. systemisk antimykotisk behandling af kritisk syge, herunder patienter indlagt på intensive afdelinger inkl. børn, Marts 2016

Forkortet produktinformation for Ecalta® (anidulafungin)

100 mg pulver til koncentrat til infusionsvæske, opløsning

Indikationer: Behandling af invasiv candidiasis hos voksne. **Dosering***: Behandling bør initieres af læge med erfaring i behandling af invasive svampeinfektioner. Før behandling initieres, bør der tages prøver med henblik på svampedyrkning. Behandlingen kan initieres før dyrkningsresultat foreligger, og behandlingen kan herefter justeres, når resultaterne foreligger. En enkelt initialdosis på 200 mg bør administreres på dag 1. Herefter gives 100 mg dagligt. Behandlingens varighed afhænger af patientens kliniske respons. Svampebehandling bør sædvanligvis fortsættes i mindst 14 dage efter sidste positive dyrkning. Behandlingsvarighed: Data for anvendelse af doser på 100mg i mere end 35 dage er utilstrækkelige. Nedsat nyre- og leverfunktion: Dosisjustering er ikke nødvendig hos patienter med let, moderat eller svært nedsat leverfunktion. Dosisjustering er ikke nødvendig hos patienter med alle grader af nedsat nyrefunktion, herunder patienter i dialyse. ECALTA kan gives uden hensyntagen til tidspunkt for dialyse. Andre særlige populationer: Dosisjusteringpga. køn, vægt, race, hiv-status og alder er ikke nødvendig hos voksne. Pædiatrisk population: Sikkerhed og virkning hos børn under 18 år er ikke klarlagt. Administration: Kun til intravenøs anvendelse. ECALTA skal rekonstitueres med vand til injektionsvæsker til en koncentration på 3,33 mg/ml, og derefter fortyndes til en koncentration på 0,77 mg/ml.. Infusionshastigheden må ikke overstige 1,1 mg/minut (sv. t. 1,4 ml/minut efter rekonstituering og fortynding). Infusionsrelaterede reaktioner er sjældne, når infusionshastigheden ikke overstiger 1,1 mg/minut. Må ikke administreres som en bolusinjektion. **Kontraindikationer**: Overfølsomhed over for indholdsstofferne. Overfølsomhed over for andre lægemidler af echinocandin-klassen. **Særlige advarsler og forsigtighedsregler vedr. brugen***: Ecalta er ikke undersøgt hos patienter med Candida endocarditis, osteomyelitis eller meningitis. Effekten af Ecalta er kun vurderet hos et begrænset antal neutropene patienter. Leverpåvirkning kan forekomme. Patienter med stigning i leverenzymer under behandling med andulafungin skal monitoreres for tegn på forværring af leverfunktion og risk/benefit-forholdet ved fortsat behandling vurderes. Anafylaktiske reaktioner herunder shock er rapporteret. Hvis disse reaktioner opstår skal anidulafungin seponeres og passende behandling iværksættes. Infusionsrelaterede reaktioner: Der er rapporteret infusionsrelaterede reaktioner efter brug af anidulafungin, herunder udslæt, urticaria, flushing, pruritus, dyspnø, bronkospasmer og hypotension. Forsigtighed tilrådes, når anidulafungin anvendes sammen med anæstetika. Fructoseindhold: Bør ikke anvendes til patienter med hereditær fructoseintolerans. **Interaktioner***: Anidulafungin er ikke et klinisk betydende substrat, en induktor eller hæmmer af cytochrom P450-isoenzymerne (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A). In vitro-forsøg udelukker ikke fuldt ud mulige in vivo-interaktioner. Der er udført interaktionsundersøgelser med andulafungin og andre lægemidler, som det sandsynligvis vil blive anvendt sammen med. Dosisjustering er ikke nødvendig for hverken anidulafungin eller ciclosporin, voriconazol eller tacrolimus, når disse anvendes samtidig. Dosisjustering er ikke nødvendig for anidulafungin, når det anvendes samtidigt med amphotericin B eller rifampicin. Interaktionsstudier er kun udført hos voksne. **Graviditet og amning***: Bør ikke anvendes. **Bivirkninger***: Sikkerhedsprofilen er baseret på 840 patienter med candidæmi/invasiv candidiasis som fik den anbefalede dosis på 100 mg dgl. Der er rapporteret infusionsrelaterede bivirkninger i studier herunder ansigtsrødme/hedeture, pruritus, udslæt og urticaria. Meget almindelige bivirkninger: Hypokaliæmi og diarré, kvalme. Almindelige bivirkninger: Hyperglykæmi, kramper, hovedpine, hypotension, hypertension, bronkospasme, dyspnø, opkastning, forhøjet ALAT/ASAT/alkalisk fosfata-se/bilirubin, kolestase, udslæt, pruritus, forhøjet serumkreatinin. Ikke almindelige bivirkninger: Koagulopati, ansigtsrødme, hedeture, øvre abdominalsmerter, forhøjet gammaglutamyltransferase, urticaria, smerter på infusionsstedet. Hyppighed ikke kendt: Anafylaktisk shock, anafylaktisk reaktion. **Overdosering***: Generelt understøttende behandling. Ecalta er ikke dialyserbart. **Indehaver af markedsføringstilladelsen**: Pfizer Ltd. Ramsgate Road, Sandwich, Kent, CT13 9NJ, Storbritannien.

Vnr	**Lægemiddelform og styrke**	**Pakningsstørrelse**
05 96 44	**100 mg pulver koncentrat til infusionsvæske, opløsning**	1 stk.

Dagsaktuel pris findes på www.medicinpriser.dk

Udlevering: Begrænset. **Tilskud**: Nej.

De med * mærkede afsnit er omskrevet og/eller forkortet i forhold til det af EMA godkendte produktresumé dateret 20. juni 2016. Produktresuméet kan vederlagsfrit rekvireres hos Pfizer ApS, Lautrupvang 8, 2750 Ballerup, tlf. 44 20 11 00.

ecalta 033 ASmPC V37.0 20juni2016