NAME OF THE MEDICINAL PRODUCT
NATRECOR™ for injection

International Non-Proprietary Name:
Nesiritide, recombinant human B-type natriuretic peptide [rhBNP]

QUALITATIVE AND QUANTITATIVE COMPOSITION
Nesiritide as the citrate salt of rhBNP 1.58 mg, providing 1.5 mg nesiritide
For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Lyophilized, for injection
NATRECOR is a single-use vial containing a white to off-white sterile lyophilized powder for reconstitution.

CLINICAL PARTICULARS
Therapeutic Indications
NATRECOR is indicated for the treatment of patients with acutely decompensated heart failure who have dyspnea at rest or with minimal activity. In this population, the use of NATRECOR reduced pulmonary capillary wedge pressure and improved dyspnea.

Posology and Method of Administration
NATRECOR is for intravenous use only. There is limited experience with administering NATRECOR for longer than 48 hours. Blood pressure should be monitored closely during NATRECOR administration.
The recommended dose of NATRECOR is an IV bolus of 2 mcg/kg followed by a continuous infusion of 0.01 mcg/kg/min. NATRECOR should not be initiated at a dose that is above the recommended dose. (See Instructions for Use and Handling)
If hypotension occurs during the administration of NATRECOR, the dose should be reduced or discontinued and other measures to support blood pressure should be started (changes in body position, IV fluids). In clinical trials, when symptomatic hypotension occurred, NATRECOR was discontinued and subsequent could be restarted at a dose that was reduced by 30% (with no bolus administration) once the patient was stabilized. Because hypotension caused by NATRECOR may be prolonged (a mean of 2.2 hours in a large double-blind controlled trial), a period of observation may be necessary before restarting the drug.

Dose Adjustments
The dose-limiting side effect of NATRECOR is hypotension. Do not initiate NATRECOR at a dose that is higher than the recommended bolus dose of 2 mcg/kg followed by an infusion of 0.01 mcg/kg/min. In clinical trials there was limited experience with increasing the dose of NATRECOR above the recommended dose (23 patients, all of whom had central hemodynamic monitoring). In these patients, the infusion dose of NATRECOR was increased by 0.005 mcg/kg/min (preceded by a bolus of 1 mcg/kg), no more frequently than every 3 hours up to a maximum dose of 0.03 mcg/kg/min. NATRECOR should not be titrated at more frequent intervals.

Pediatric Patients
The safety and effectiveness of NATRECOR in pediatric patients (<18 years) has not been established.

Geriatric Patients
No dose adjustment is required in the elderly (>65 years).

Patients with Renal Impairment
No dose adjustment is required for patients with renal insufficiency. (See Pharmacological Properties, Pharmacokinetic Properties, Special Populations, Renal Impairment)

Patients with Hepatic Impairment
No dose adjustment is required for patients with hepatic impairment.

Contraindications
NATRECOR is contraindicated in patients who are hypersensitive to any of its components.
NATRECOR should not be used as primary therapy for patients with cardiogenic shock or in patients with a systolic blood pressure <90 mm Hg at initiation of therapy.

Special Warnings and Special Precautions for Use

Administration of NATRECOR should be avoided in patients suspected of having, or known to have, low cardiac filling pressures.

NATRECOR is not recommended in patients for whom vasodilating agents are not appropriate, such as patients with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, or other conditions in which cardiac output is dependent upon venous return, or for patients suspected to have low cardiac filling pressures. (See Contraindications)

Cardiovascular

NATRECOR may cause hypotension.

In one large double-blind controlled trial, in patients given the recommended dose with or without dose adjustment, the incidence of symptomatic hypotension in the first 24 hours was similar for NATRECOR (4%) and for IV nitroglycerin (5%). When hypotension occurred, the duration of symptomatic hypotension was longer with NATRECOR (mean of 2.2 hours) than with nitroglycerin (mean of 0.7 hours).

In other controlled clinical trials, when NATRECOR was initiated at doses higher than recommended (i.e., 0.015 and 0.03 mcg/kg/min preceded by a small bolus), there were more hypertensive episodes and these were of greater intensity and duration. They were also more often symptomatic and/or more likely to require medical intervention. (See Undesirable Effects) The rate of symptomatic hypotension may be increased in patients with a blood pressure <100 mm Hg at baseline, and NATRECOR should be used cautiously in these patients.

The potential for hypotension may be increased by combining NATRECOR with other drugs that may cause hypotension, e.g., ACE inhibitors.

NATRECOR should be administered only in settings where blood pressure can be monitored closely, and the dose of NATRECOR should be reduced or the drug discontinued in patients who develop hypotension. (See Posology and Method of Administration)

Renal

NATRECOR may affect renal function in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with NATRECOR may be associated with increases in serum creatinine.

When NATRECOR was initiated at doses higher than recommended, there was an increased rate of elevated serum creatinine over baseline, although the rate of acute renal failure and need for dialysis was not increased. In the 30-day follow-up period in a large double-blind controlled trial, 2% (5/216 patients) in the IV nitroglycerin group and 3% (9/273 patients) in the NATRECOR group required first-time dialysis.

Interactions with Other Medicinal Products and Other Forms of Interaction

Trials specifically examining potential drug interactions with NATRECOR were not conducted. Drug interactions were not detected in clinical trials except for an increase in symptomatic hypotension in patients receiving oral ACE inhibitors.

During clinical studies, NATRECOR was administered concomitantly with other medications, including: diuretics, digoxin, oral ACE inhibitors, anticoagulants, oral nitrates, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, class III antiarrhythmics, betablockers, dobutamine, calcium channel blockers, angiotensin II receptor antagonists, and dopamine. Although pharmacokinetic interactions were not specifically assessed, there did not appear to be evidence suggesting any clinically significant PK interaction.

Pregnancy and Lactation

Use During Pregnancy

It is not known whether NATRECOR can cause fetal harm when administered to pregnant women. A developmental reproductive toxicology study was
conducted in pregnant rabbits using doses up to 1440 mcg/kg/day given by constant infusion for 13 days. At this level of exposure (based on AUC, approximately 500x human exposure at the recommended dose) no adverse effects on live births or fetal development were observed. NATRECOR should be used during pregnancy only if the potential benefit justifies any possible risk to the fetus.

Use During Lactation
It is not known whether this drug is excreted in human milk. Therefore, caution should be exercised when NATRECOR is administered to a nursing woman.

Effects on Ability to Drive and Use Machines
Not applicable.

Undesirable Effects
Clinical Trials
Adverse drug reactions that occurred with at least a 3% frequency during the first 24 hours of NATRECOR infusion are shown in Table 1.

Adverse drug reactions that are not listed in the above table that occurred in at least 1% of patients who received any of the doses specified above included: increased creatinine, sweating, pruritus, and rash.

Clinical Laboratory
Elevation of serum creatinine >0.5 mg/dl (44.2 μmol/l) above baseline at any time was 28% in NATRECOR-treated patients vs. 21% of patients treated with IV nitroglycerin (not statistically different).

Effect on Mortality
NATRECOR has not been studied in a trial designed or powered to assess mortality as a primary or key secondary endpoint. A large double-blind controlled trial included 273 patients receiving NATRECOR and 216 patients receiving IV nitroglycerin. The mortality rates at thirty days from any cause did not significantly differ between NATRECOR and control and were 8.1% in the NATRECOR arm and 5.1% in the nitroglycerin arm (hazard ratio of 1.56 [95% CI: 0.75–3.24]). The mortality rates at six months in patients receiving NATRECOR or nitroglycerin were 25.1% and 20.8% respectively (hazard ratio of 1.22 [95% CI: 0.83–1.79]).

Table 1: Adverse Drug Reactions Reported at ≥ 3% Frequency During the First 24 Hours After the Start of Infusion in Controlled Clinical Trials of NATRECOR

<table>
<thead>
<tr>
<th>Undesirable Effect</th>
<th>Large Double-Blind Controlled Trial</th>
<th>Other Long Infusion Trials***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV Nitroglycerin (n = 216)</td>
<td>NATRECOR at Recommended Dose* (n = 273)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20%</td>
<td>8%</td>
</tr>
<tr>
<td>Nervous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* Includes dose adjustment in 23 patients as described in Dose Adjustments.
** Includes dobutamine, milrinone, nitroglycerin, placebo, dopamine, nitroprusside, or amrinone.
*** Trials in which NATRECOR was administered as a continuous infusion for ≥24 hours.
In a pooled analysis of adequate and well-controlled clinical trials, no statistically significant difference in all-cause mortality was observed at 30 days (7 trials) when mortality with NATRECOR was compared to control treatment (30 day hazard ratio of 1.34 [95% CI: 0.85–2.11]). Of the 1059 patients treated with NATRECOR in these 7 trials, 58 died at 30 days of any cause (Kaplan-Meier estimate, 5.5%), whereas 28 of the 658 control patients died (Kaplan-Meier estimate, 4.3%).

There was no statistically significant difference in all-cause mortality from 5 trials where 180-day mortality data were collected (180-day hazard ratio of 1.08 [95% CI: 0.85–1.37]). At the 180-day follow-up (5 trials), 178/844 patients treated with NATRECOR (Kaplan-Meier estimate, 21.5%) and 114/560 control patients (Kaplan-Meier estimate, 20.7%) died of any cause.

There were few deaths in these studies, so the confidence limits around the hazard ratios were wide. The studies were small and some potentially important baseline imbalances existed among the treatment groups, the effects of which could not be ascertained.

**Post-Marketing**

In addition to the previously mentioned clinical trials safety data, spontaneous adverse drug reactions (ADRs) from the worldwide post-marketing experience with NATRECOR are listed below. The spontaneous adverse drug reactions are ranked by frequency, using the following convention:

- Very common (>1/10)
- Common (>1/100, <1/10)
- Uncommon (>1/1,000, <1/100)
- Rare (>1/10,000, <1/1,000)
- Very Rare (<1/10,000), including isolated reports

The frequency provided is a reflection of reporting rates for spontaneous adverse drug reactions and does not represent true incidence or frequency as seen with clinical trials or epidemiologic studies. ADRs reported in the post-marketing period by System Organ Class include: Immune System Disorders: very rare – hypersensitivity reactions

**Overdose**

Overdose with NATRECOR therapy has been reported and is primarily the result of either a miscalculated dose or a mechanical error such as an infusion pump programming error. The most frequently reported adverse event with NATRECOR overdose is hypotension, which may be asymptomatic and most often resolves with drug stoppage, although, in some cases, hypotension may persist for several hours after discontinuation. Treatment of NATRECOR overdose should include drug discontinuation and the administration of supportive measures.

**PHARMACOLOGICAL PROPERTIES**

Nesiritide is recombinant human B-type natriuretic peptide (rhBNP). It has the same 32-amino acid sequence as the endogenous peptide produced by the ventricular myocardium.

**Pharmacodynamic Properties**

**Pharmacotherapeutic Group (ATC code)**

CO1DX19

**Mechanism of Action**

Human BNP (hBNP) is secreted by the ventricular myocardium in response to stretch and exists in several isoforms in the human body. Elevated levels of BNP have been associated with advanced heart failure and are considered to be a compensatory mechanism in this disease.

Circulating hBNP may have lower bioactivity than nesiritide. Human BNP exerts its effects on the vasculature, the heart, and the kidneys. Human BNP binds to the particulate guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to increased intracellular concentrations of guanosine 3’-5’-cyclic monophosphate (cGMP) and smooth muscle relaxation.

Cyclic GMP serves as a secondary messenger to dilate veins and arteries. Nesiritide has been shown to relax isolated human arterial and venous tissue preparations that were preconstricted with either endothelin-1 or the alpha-adrenergic agonist, phenylephrine. Human BNP also suppresses the renin-aldosterone-angiotension system and has natriuretic and diuretic effects.
**Pharmacodynamic Effects**

Nesiritide produces dose-dependent reductions in pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure in patients with heart failure. With the recommended dosing regimen, 60% of the 3-hour effect on PCWP reduction is achieved within 15 minutes after the bolus, reaching 95% of the 3-hour effect within 1 hour. Approximately 70% of the 3-hour effect on systolic blood pressure (SBP) reduction is reached within 15 minutes. The pharmacodynamic half-life of the onset and offset of the hemodynamic effect of NATRECOR is longer than what the pharmacokinetic half-life of 18 minutes would predict. For example, in patients who developed symptomatic hypotension, half of the recovery of SBP toward the baseline value after discontinuation or reduction of the dose of NATRECOR was observed in about 60 minutes.

When higher doses of NATRECOR were infused, the duration of hypotension was sometimes several hours.

Following discontinuation of NATRECOR, PCWP returns to within 10% of baseline within 2 hours, with no rebound increase to levels above baseline state. There is no evidence of tachyphylaxis to the hemodynamic effects of NATRECOR.

**Clinical Efficacy**

In a large double-blind controlled trial of 489 patients (246 patients requiring a right heart catheter), who required hospitalization for management of acutely decompensated heart failure, the effects of NATRECOR were compared to placebo and IV nitroglycerin when added to background therapy (IV and oral diuretics, non-IV cardiac medications, dobutamine, and dopamine). Patients with acute coronary syndrome, preserved systolic function, arrhythmia, and renal insufficiency were not excluded. Primary endpoints were change from baseline in PCWP and change from baseline in dyspnea, at three hours. The occurrence and persistence of hypotension, given nesiritide’s relatively long effects (compared to nitroglycerin) were examined.

In a double-blind dose-response study, 127 patients requiring hospitalization for symptomatic heart failure were randomized and treated with either placebo or one of two doses of NATRECOR (0.015 mcg/kg/min preceded by an IV bolus of 0.3 mcg/kg, and 0.03 mcg/kg/min preceded by an IV bolus of 0.6 mcg/kg). The primary endpoint of the trial was the change in PCWP from baseline to 6 hours; effects on symptoms also were examined.

**Effects on Symptoms**

In a large double-blind controlled trial, patients receiving the recommended dose of NATRECOR reported greater improvement in dyspnea at 3 hours than patients receiving placebo (\( p = 0.034 \)).

In a double-blind dose-response study, patients receiving both doses of NATRECOR (0.015 mcg/kg/min preceded by an IV bolus of 0.3 mcg/kg, and 0.03 mcg/kg/min preceded by an IV bolus of 0.6 mcg/kg) reported greater improvement in dyspnea at 6 hours than patients receiving placebo (\( p < 0.001 \)).

**Effects on Hemodynamics**

In a large double-blind controlled trial, PCWP, right atrial pressure (RAP), cardiac index (CI), and other hemodynamic variables were monitored in 246 cath-

NATRECOR was administered as a 2 mcg/kg bolus over 60 seconds, followed by a continuous fixed dose infusion of 0.01 mcg/kg/min. After a 3-hour placebo-controlled period, patients receiving placebo crossed over to double-blinded therapy with either NATRECOR or nitroglycerin. The nitroglycerin dose was titrated at the physician’s discretion. A subset of patients in the trial with central hemodynamic monitoring who were treated with NATRECOR (62 of 124 patients) were allowed dose increases of NATRECOR after the first 3 hours of treatment if the PCWP was >20 mm Hg and the SBP was >100 mm Hg. Dose increases (1 mcg/kg bolus followed by an increase of the infusion dose by 0.005 mcg/kg/min) were allowed every 3 hours, up to a maximum dose of 0.03 mcg/kg/min. Overall, 23 patients had their dose of NATRECOR increased.

Following discontinuation of NATRECOR, PCWP returns to within 10% of baseline within 2 hours, with no rebound increase to levels above baseline state. There is no evidence of tachyphylaxis to the hemodynamic effects of NATRECOR.

In a large double-blind controlled trial of 489 patients (246 patients requiring a right heart catheter), who required hospitalization for management of acutely decompensated heart failure, the effects of NATRECOR were compared to placebo and IV nitroglycerin when added to background therapy (IV and oral diuretics, non-IV cardiac medications, dobutamine, and dopamine). Patients with acute coronary syndrome, preserved systolic function, arrhythmia, and renal insufficiency were not excluded. Primary endpoints were change from baseline in PCWP and change from baseline in dyspnea, at three hours. The occurrence and persistence of hypotension, given nesiritide’s relatively long effects (compared to nitroglycerin) were examined.
eterized patients. There was a reduction in mean PCWP within 15 minutes of starting NATRECOR infusion, with most of the effect seen at 3 hours being achieved within the first 60 minutes of the infusion. Table 2 and Figure 1 summarize the changes in PCWP and other measures during the first 3 hours.

This study does not constitute an adequate effectiveness comparison with nitroglycerin. In this trial, the nitroglycerin group provides a reference using a familiar therapy and regimen. Following discontinuation of NATRECOR, PCWP returns to within 10% of baseline within 2 hours, and no rebound increase to above pretreatment levels was observed. There was no evidence of tachyphylaxis to the hemodynamic effects of NATRECOR.

**Effect on Urine Output**

In a large double-blind controlled trial, in which the use of diuretics was not restricted, the mean change in volume status (output minus input) during the first 24 hours in the nitroglycerin and NATRECOR groups was similar: 1279 ± 1455 ml and 1257 ± 1657 ml, respectively.

**Pharmacokinetic Properties**

**Distribution**

In patients with heart failure, NATRECOR administered intravenously by infusion or bolus exhibits biphasic disposition from the plasma with a mean steady-state volume of distribution of 0.19 l/kg.

**Elimination**

The mean terminal elimination half-life of nesiritide is approximately 18 minutes. The mean clearance is approximately 9.2 ml/min/kg. Nesiritide is eliminated in a manner similar to endogenous BNP clearance from the circulation via three independent mechanisms: binding to cell surface clearance receptors with subsequent cellular internalization and lysosomal proteolysis, proteolytic cleavage of the peptide by endopeptidases, such as neutral endopeptidase present on the vascular luminal surface and renal filtration. Pharmacokinetic analyses showed that clearance of nesiritide is proportional to body weight, supporting the administration of weight-adjusted dosing of NATRECOR, i.e., administration on a mcg/kg/min basis.

**Special Populations**

Renal Impairment: Although nesiritide is eliminated, in part, through renal clearance, clinical data suggest that dose adjustment is not required in patients with renal insufficiency. The effects of nesiritide on PCWP, CI, and SBP were not significantly different between patients with chronic renal insufficiency [baseline serum creatinine ranging from 2mg/dL (176.8 μmol/l) to 4.3mg/dL (380.1 μmol/l)] and patients with normal renal function.

Other: Clearance was not influenced significantly by age, gender, race/ethnicity, baseline endogenous
hBNP concentration, severity of heart failure (as indicated by baseline PCWP, baseline Cl, or NYHA classification), or concomitant administration of an ACE inhibitor.

Preclinical Safety Data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, developmental reproductive toxicology, and genotoxicity. Carcinogenicity studies were not conducted with nesiritide.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**
Mannitol
Citric acid monohydrate
Sodium citrate dihydrate

**Incompatibilities**
The preservative sodium metabisulfite is incompatible with NATRECOR. Injectable drugs that contain sodium metabisulfite should not be administered in the same infusion line as NATRECOR. NATRECOR is physically and/or chemically incompatible with heparin, insulin, ethacrynic acid, bumetanide, enalapril, hydralazine, and furosemide injections. These drugs should not be co-administered with NATRECOR through the same IV catheter. NATRECOR binds to heparin and therefore could bind to the heparin lining of a heparin-coated catheter, decreasing the amount of nesiritide delivered to the patient for some period of time. Therefore, NATRECOR must not be administered through a heparin-coated catheter or a multiple lumen catheter with heparin on any lumina. Concomitant administration of a heparin infusion through a separate catheter is acceptable. Concomitant administration of heparin and NATRECOR into the same vein is not acceptable. Catheters must be flushed between administration of NATRECOR and incompatible drugs. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Shelf Life**
Observe expiry date on the outer pack.
Shelf life after reconstitution and dilution is 24 hours.

**Special Precautions for Storage**
Do not store above 25°C
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
NATRECOR contains no antimicrobial preservative. Use reconstituted and diluted solution within 24 hours.

**Nature and Contents of Container**
Clear type I glass vial with grey bromobutyl rubber stopper and aluminum flip-off seal.

**Instructions for Use and Handling**

**Preparation of the Bolus Injection and IV Infusion**
The NATRECOR bolus must be drawn from the prepared infusion bag.

1. Reconstitute one vial of NATRECOR by adding 5 ml of diluent removed from a pre-filled 250 ml plastic IV bag containing one of the following preservative-free solutions: 5% dextrose injection (D5W), 0.9% sodium chloride injection, 5% dextrose and 0.45% sodium chloride injection, or 5% dextrose and 0.2% sodium chloride injection.

2. Do not shake the vial. Rock the vial gently so that all surfaces, including the stopper, are in contact with the diluent to ensure complete reconstitution. Use only a clear, essentially colorless solution.

3. **Withdraw the entire contents of the reconstituted vial** and add these contents to the 250 ml plastic IV bag. The IV bag should be inverted several times to ensure complete mixing of the solution. This will yield a final solution with a concentration of NATRECOR of approximately 6 mcg/ml.

4. Visually inspect the solution for particulate matter and discoloration prior to administration whenever container permits. Use the reconstituted solution within 24 hours.

5. Prime the IV tubing with 5 ml of the prepared solution for infusion before connecting to the patient’s vascular access port and before administering the bolus or starting the infusion.
Administration of the Bolus Injection and IV Infusion

The administration of the recommended dose of NATRECOR is a two-step process as follows:

Bolus Injection

Withdraw the bolus volume (see Table 3 - Weight-Adjusted Bolus Volume) from the prepared infusion bg, and administer it over approximately 60 seconds through an access port in the tubing.

Bolus Volume (ml) = Patient Weight (kg)/3

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Volume of Bolus (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>20.0</td>
</tr>
<tr>
<td>70</td>
<td>23.3</td>
</tr>
<tr>
<td>80</td>
<td>26.7</td>
</tr>
<tr>
<td>90</td>
<td>30.0</td>
</tr>
<tr>
<td>100</td>
<td>33.3</td>
</tr>
<tr>
<td>110</td>
<td>36.7</td>
</tr>
</tbody>
</table>

Continuous Infusion

Immediately following the administration of the bolus injection, infuse NATRECOR at a flow rate of 0.1 ml/kg/hr. This will deliver a NATRECOR dose of 0.01 mcg/kg/min.

To calculate the infusion flow rate to deliver a 0.01 mcg/kg/min dose, use the following formula or see Table 4 - Weight-Adjusted Infusion Flow Rate:

Infusion Flow Rate (ml/hr) = Patient Weight (kg) x 0.1

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Infusion Flow Rate (ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>80</td>
<td>8</td>
</tr>
<tr>
<td>90</td>
<td>9</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
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<tr>
<td>110</td>
<td>11</td>
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</tbody>
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DATE OF REVISION OF THE TEXT

December 2008