FLOW DIVERSION –
A minimally invasive treatment option for certain brain aneurysms using the Pipeline™ Flex Embolization device.
WHAT IS A BRAIN ANEURYSM?

A cerebral or brain aneurysm is a bulge or ballooning in an artery in the brain caused by weakness in the blood vessel wall.

Untreated brain aneurysms may have risk of rupture, resulting in what’s called hemorrhagic or cerebral stroke. The annual rate of rupture is approximately 8-10 per 100,000 people, or about 30,000 people in the United States.1,2

It is slightly more common in women than men, especially those who are in their late 40s to mid-50s. However, an aneurysm may occur at any age.3

BRAIN ANEURYSMS ARE MORE COMMON THAN YOU MAY THINK. AN ESTIMATED 1 IN 50 PEOPLE HAS A BRAIN ANEURYSM.1,3
ABOUT THE CONDITION

TYPES OF BRAIN ANEURYSMS

The types of brain aneurysms can be classified by both size and shape.¹

### ANEURYSM SIZE CLASSIFICATIONS:

<table>
<thead>
<tr>
<th>Size</th>
<th>Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>&lt; 7 mm</td>
</tr>
<tr>
<td>Medium</td>
<td>7 - &lt; 13 mm</td>
</tr>
<tr>
<td>Large</td>
<td>13-25 mm</td>
</tr>
<tr>
<td>Giant</td>
<td>&gt; 25 mm</td>
</tr>
</tbody>
</table>

### SHAPE CLASSIFICATIONS:

#### Saccular Aneurysm
Also known as “berry” aneurysms due to their round, sac-like shape, saccular aneurysms are the most common type, accounting for 80-90% of cases.¹-³

#### Fusiform Aneurysm
This aneurysm resembles an engorged blood vessel and can extend several centimeters in length. Fusiform aneurysms rarely rupture.¹-³

#### Wide-Necked Aneurysm
A saccular aneurysm with a neck 4 millimeters wide, or twice as wide as the aneurysm is tall, is known as a wide-necked aneurysm.¹,⁵-⁶
MOST COMMON SIGNS AND SYMPTOMS OF RUPTURED ANEURYSMS

In cases of small and unchanging brain aneurysms, there can be no symptoms. However, as an aneurysm grows larger, it can put pressure on surrounding tissues and nerves, causing neurologic symptoms sometimes called mass effect.¹

SYMPTOMS OF UNRUPTURED ANEURYSM INCLUDE,¹ BUT NOT LIMITED TO:

- Sudden and severe headache, often described as “the worst headache of my life”
- Dilated pupils
- Blurred or double vision
- Pain above or behind the eye
- Weakness/numbness on one side of the face
- Difficulty speaking
- Nausea, vomiting

If not treated, a brain aneurysm can continue to expand and eventually rupture.
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CAUSES OF BRAIN ANEURYSM: ARE YOU AT RISK?

A brain aneurysm can result from a congenital defect, some inherited diseases, or other degenerative conditions, such as hypertension (high blood pressure) or atherosclerosis (fat build-up inside the arteries, often leading to heart attack or stroke). Other risk factors include cigarette smoking, cocaine use, blood vessel wall infection, and head trauma. There is no known way to prevent brain aneurysms.
Aneurysm flow diversion is a minimally invasive treatment in which a device known as a neurovascular stent placed in the parent blood vessel of a brain aneurysm may divert blood flow away from the aneurysm. Over time, blood flow into the aneurysm may slow down, eventually ceasing to enter the aneurysm altogether. As the body’s natural healing process works with the flow diversion device, the blood vessel may heal, and the aneurysm may shrink.4,9–11

The Pipeline™ Flex embolization device is designed to divert blood flow away from brain aneurysms in certain segments of the internal carotid artery (ICA). The device features a braided cylindrical mesh tube that is implanted across the base or neck of the aneurysm. The device decreases blood flow to the aneurysm, reconstructing the diseased section of the parent vessel. This may result in the aneurysm shrinking in size or resolving over time. Pipeline is the first flow diversion device approved by the FDA.9,10,12

Other treatment methods for cerebral or brain aneurysm include no treatment, surgical clipping, endovascular embolization or observation (non-intervention).8,13

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**Flow Diversion Technique**

After treatment with Pipeline Flex, blood flow into the aneurysm slows. Over time, blood may no longer flow into the aneurysm.

**After Flow Diversion**

As the body’s natural healing process works with the Pipeline Flex stent implant, the aneurysm may shrink.

**Benefits and Risks**

The Pipeline Flex Embolization Device has been shown to be effective at treating small, medium, large or giant wide-necked aneurysms, located in specific segments of the internal carotid artery (ICA).†5,11 Potential complications include (but are not limited to):9

- Death
- Transient and permanent neurological deficits including stroke and transient ischemic attack (TIA), intra- and extracranial bleeding
- Vascular injuries including vasospasms and perforation
- Device deformation, fracture, and migration
- Complications of using contrast media and anticoagulant, antiplatelet medications
- Infections

Refer to IFU for complete potential complications.

**Complete Occlusion** for small + medium aneurysms, over 76% of patients treated with Pipeline Flex experienced complete aneurysm occlusion with no recurrence by one-year follow-up.11

**95% Occlusion** for large + giant aneurysms and 0% recurrence of aneurysms after complete occlusion by 5-year follow-up, for subjects with available imaging.5

**Invasive Surgical Clipping**

- Surgical procedure requiring an opening of the skull or a craniotomy
- Placement of a clip on the neck of the aneurysm to prevent blood flow into the aneurysm

**Endovascular Coil Embolization**

- Minimally invasive approach through a small incision in the leg
- Placement of embolic coils into aneurysm to prevent blood flow into aneurysm

**Before Flow Diversion**

Blood flows freely into the aneurysm.

**Flow Diversion Technique**

After treatment with Pipeline Flex, blood flow into the aneurysm slows. Over time, blood may no longer flow into the aneurysm.

**After Flow Diversion**

As the body’s natural healing process works with the Pipeline Flex stent implant, the aneurysm may shrink.

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WHAT IS THE PIPELINE™ FLEX FLOW DIVERSION PROCEDURE LIKE?

While your doctor is your primary resource for diagnosis and care, this page will offer you a better understanding of your condition and your treatment options.

Here’s what you can expect BEFORE, DURING AND AFTER the aneurysm flow diversion treatment.

PRE-PROCEDURE

First, the doctor will perform a series of exams and diagnostic procedures to fully assess the size, shape, and location of the brain aneurysm. Exams and procedures generally include diagnostic imaging, medical history review, physical examination, and blood tests‡. The doctor will also prescribe some medications before the procedure. These will include but are not limited to:

- Taking dual antiplatelet and/or anticoagulation therapy such as aspirin and clopidogrel
- Possible additional medications depending on your general health and other medications you may be taking

DURING PROCEDURE

The procedure may be done under local or general anesthesia. It is important to remain still for long periods of time, so general anesthesia is usually preferred. However, your doctor will determine the best and safest method for the procedure.
The Pipeline Flex device procedure consists of accessing the aneurysm via an artery in your groin using access devices such as guidewires, microcatheters to deliver the Pipeline Flex device.‡

During the procedure, the Pipeline Flex device is implanted across the aneurysm neck, which can divert blood flow and may allow the diseased vessel to heal. Before treatment, blood flows freely into the aneurysm. Immediately after treatment with Pipeline Flex, blood flow into the aneurysm slows.

Over time, blood may no longer flow into the aneurysm. As the body’s natural healing process works with the Pipeline Flex stent implant, the aneurysm may shrink.⁹,¹⁰,¹⁴

After placing the implant, the physician will remove the access devices and close the access site. Your physician will use multi-dimensional neurologic imaging to ensure the device is properly placed.

**POST-PROCEDURE**

After the brain aneurysm treatment is complete, it’s time to rest in a recovery room. It’s not uncommon to experience some pain and tenderness in the groin area where the micro catheter was inserted into your artery for treatment access. For a full list of symptoms that may occur post procedure, please consult your doctor or the safety and warnings page. Your doctor will prescribe medications after the procedure and provide specific instructions for recovery.

It is very important to carefully follow the directions and medications prescribed by your doctor. Please take and keep the MRI card your doctor provides – it explains how the Pipeline Flex device will behave under different medical scans. You should keep this card available at all times.

Pipeline™ Flex Embolization Device
ESSENTIAL PRESCRIBING INFORMATION (EPI) STATEMENT:

Indications for Use: The Pipeline™ Flex embolization device is indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments. The Pipeline™ Flex embolization device is also indicated for use in the internal carotid artery up to the terminus for the endovascular treatment of adults (22 years of age or older) with small and medium wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysm (IAs) arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm. CAUTION: Federal (USA) law restricts this device to sale, distribution and use by or on the order of a physician. Indications, contraindications, warnings and instructions for use can be found in the product labeling supplied with each device. Warnings:

1) Resheathing of the Pipeline™ Flex embolization device more than 2 full cycles may cause damage to the distal or proximal ends of the braid. 2) Persons with known allergy to platinum or cobalt/chromium alloy (including the major elements platinum, cobalt, chromium, nickel, molybdenum or tungsten) may suffer an allergic reaction to the Pipeline™ Flex embolization device implant. 3) Person with known allergy to tin, silver, stainless steel or silicone elastomer may suffer an allergic reaction to the Pipeline™ Flex embolization device delivery system. 4) Do not reprocess or resterilize. Reprocessing and resterilization increase the risk of patient infection and compromised device performance. 5) Post-procedural movement (migration and/or foreshortening) of the Pipeline Flex Embolization Device implant may occur following implantation and can result in serious adverse events and/or death. 6) Factors which may contribute to post procedural device movement include (but are not limited to) the following: Failure to adequately size the implant (i.e., under sizing), Failure to obtain adequate wall apposition during the implant deployment, Implant stretching, Vasospasm, Severe vessel tapering, Tortuous anatomy 7) Delayed rupture may occur with large and giant aneurysms. 8) Placement of multiple Pipeline™ Flex embolization devices may increase the risk of ischemic complications. 9) Use in anatomy with severe tortuosity, stenosis or parent vessel narrowing may result in difficulty or inability to deploy the Pipeline Flex Embolization Device and can lead to damage to the Pipeline™ Flex Embolization Device and microcatheter. Refer to page 4 in the instructions for use for additional information. 10) Do not attempt to reposition the device after full deployment.

11) The benefits may not outweigh the risks of treatment for small and medium asymptomatic extradural intracranial aneurysms, including those located in the cavernous internal carotid artery. The risk of rupture for small and medium asymptomatic extradural intracranial aneurysms is very low if not negligible. 12) A decrease in the proportion of patients who achieve complete aneurysm occlusion without significant parent artery stenosis has been observed with the use of the device in the communicating segment (C7) of the internal carotid artery (47.4% (9/19 subjects in the PREMIER study at 1 year)), including those IAs fed by the posterior circulation or have retrograde filling. Ensure appropriate patient selection and weigh the benefits and risks of alternative treatments prior to use of this device for the treatment of intracranial aneurysms located in this region of the ICA. The following anatomical characteristics, associated with retrograde filling, should be carefully considered during procedural planning of C7 intracranial aneurysms: Observed PComm of fetal origin (A PCA of fetal origin is defined as a small, hypoplastic, or absent P1 segment of the PCA with the PComm artery supplying a majority of blood flow to the ICA); PComm overlapping with the aneurysm neck; and/or PComm branch arising from the dome of the aneurysm. 13) Pushing delivery wire without retracting the micro catheter at the same time will cause the open end braid to move distally in the vessel. This may cause damage to the braid or vessel. 14) Use in tortuous anatomy may result in difficulty or inability to deploy the Pipeline Flex Embolization Device and can lead to damage to the Pipeline Flex Embolization Device and microcatheter. To mitigate potential problems as a result of increased delivery forces, reduce the load in the system by: Unloading the microcatheter to the inner curves of vessel by pulling back on the system (i.e., the microcatheter and delivery wire together). Continue unloading the system until advancement of the device (inside the microcatheter is observed, while minimizing the distal tip movement prevent loss of position. Begin to re-advance the delivery wire.
while the device passes through tortuous area and the delivery force is decreased. Precautions: 1) The Pipeline™ Flex embolization device should be used only by physicians trained in percutaneous, intravascular techniques and procedures at medical facilities with the appropriate fluoroscopy equipment. 2) Physicians should undergo appropriate training prior to using the Pipeline™ Flex embolization device in patients. 3) The Pipeline™ Flex embolization device is provided sterile for single use only. Store in a cool, dry place. Carefully inspect the sterile package and device components prior to use to verify that they have not been damaged during shipping. Do not use kinked or damaged components. Do not use product if the sterile package is damaged. 4) Use the Pipeline™ Flex embolization device system prior to the “Use By” date printed on the package. 5) The appropriate anti-platelet and anti-coagulation therapy should be administered in accordance with standard medical practice. 6) A thrombosing aneurysm may aggravate pre-existing, or cause new, symptoms of mass effect and may require medical therapy. 7) Use of implants with labeled diameter larger than the parent vessel diameter may result in decreased effectiveness and additional safety risk due to incomplete foreshortening resulting in an implant longer than anticipated. 8) The Pipeline™ Flex embolization device may create local field inhomogeneity and susceptibility artifacts inhomogeneity and susceptibility artifacts during magnetic resonance angiography (MRA), which may degrade the diagnostic quality to assess effective intracranial aneurysm treatment. 9) Take all necessary precautions to limit X-radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible. 10) Carefully weigh the benefits of treatment vs. the risks associated with treatment using the device for each individual patient based on their medical health status and risks factors for intracranial aneurysm rupture during their expected life time such as age, medical comorbidities, history of smoking, intracranial aneurysm size, location, and morphology, family history, history of prior asymptomatic subarachnoid hemorrhage (aSAH), documented growth of intracranial aneurysm on serial imaging, presence of multiple intracranial aneurysms, and presence of concurrent pathology. The benefits of device use may not outweigh the risks associated with the device in certain patients; therefore, judicious patient selection is recommended. 11) The safety and effectiveness of the device has not been established for treatment of fusiform IAs. 12) There may be a decrease in effectiveness and increase in safety events when the device is used in patients ≥ 60 years old. 13) The safety and effectiveness of the device has not been evaluated or demonstrated for ruptured aneurysms. Potential Complications: Potential complications of the device and the endovascular procedure include, but are not limited to the following: Adverse reaction to anti-platelet/anticoagulation agents, anesthesia, reactions due to radiation exposure (such as alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia) or contrast media, including organ failure; Vascular Complications like vasospasm, stenosis, dissection, perforation, rupture, fistula formation, pseudo aneurysm, occlusion, thromboembolic complications including ischemia (to unintended territory); Device complications like fracture, breakage, misplacement, migration/delayed foreshortening or reaction to device materials; Systemic Complications like: Infection, Pain, fever, allergic reactions, organ failure, nerve damage; Bleeding/hemorrhagic complication including retroperitoneal hemorrhage; Neurological Deficits or dysfunctions including Stroke, Infarction, Loss of vision, Seizures, TIA, Headache, Cranial Nerve Palsies, Confusion, Coma; Decreased therapeutic response including need for target aneurysm retreatment; Risks associated with visual symptoms include Amaurosisfugax/transient blindness, Blindness, Diplopia, Reduced visual acuity/field, Retinal artery occlusion, Retinal ischemia, Retinal infarction, Vision impairment including scintillations, blurred vision, eye floaters; Intra-Cranial Hemorrhage (including from Aneurysm Rupture) Brain Edema, Hydrocephalus, Mass Effect; Death Contraindications: 1) Patients with active bacterial infection. 2) Patients in whom dual anti-platelet and/or anticoagulation therapy (aspirin and clopidogrel) is contraindicated. 3) Patients who have not received dual antiplatelet agents prior to the procedure. 4) Patients in whom a pre-existing stent is in place in the parent artery at the target aneurysm location. 5) Patients in whom the parent vessel size does not fall within the indicated range.
REFERENCES:

* The PUFS study only included the Pipeline Embolization device. The Pipeline Flex Embolization Device contains the same implant as the Pipeline Embolization Device. The PREMIER study included both the Pipeline and Pipeline Flex Embolization device.

† As outlined in PUFs and PREMIER trial results. ‡ Please discuss all risks and warnings with your doctor.

9. Pipeline™ Flex Embolization Device IFU
11. PREMIER Clinical Study Report Medtronic FD3563 Rev B. 12-SEP-2018