Instituto de Salud Pública
Ministerio de Salud
Gobierno de Chile

Nº Ref.:RF895548/17

CONCEDE A PFIZER CHILE S.A., EL REGISTRO SANITARIO Nº F-23721/18 RESPECTO DEL PRODUCTO FARMACÉUTICO SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL (ACETATO DE MEDROXIPROGESTERONA).<

RESOLUCIÓN EXENTA RW N° 3364/18
Santiago, 14 de febrero de 2018

VISTO ESTOS ANTECEDENTES: La presentación de Pfizer Chile S.A., por la que solicita registro sanitario de acuerdo a lo señalado en el artículo 52º del D.S. Nº 3 de 2010, del Ministerio de Salud, para el producto farmacéutico **SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL (ACETATO DE MEDROXIPROGESTERONA)**, para los efectos de su importación y distribución en el país, el que será fabricado como producto terminado por Pfizer Manufacturing Belgium NV, Bélgica, procedente de Pfizer Service Company BVBA, y en uso de licencia de Pfizer Inc., U.S.A.; el Certificado de Libre venta correspondiente; el acuerdo de la Sexta Sesión de Evaluación de Productos Farmacéuticos Simplificados, de fecha 8 de febrero de 2018; el Informe Técnico respectivo N° 27; el Informe Técnico de Jurídica N° 583; el Informe Técnico Analítico N° 8;

CONSIDERANDO: PRIMERO: Que se han adecuado los rótulos para el cumplimiento de los Arts. 90° y 91° del D.S. N°3 de 2010 del Ministerio de Salud, incorporando fecha (mes-año) de fabricación; **SEGUNDO**: Que se ha eliminado como parte del re-acondicionamiento local la transformación de envases de presentación de Venta a Público a Muestra Médica, debido a que deben solicitarse por separado como "Reacondicionamiento Local por Única Vez", pagando el arancel respectivo, donde se debe declarar la cantidad, lote y fecha de vencimiento de los lotes a transformar y al momento de emitir la resolución de re-acondicionado, la fecha de caducidad de los lotes transformados deberá tener a lo menos 6 meses por sobre la fecha de la resolución para poder distribuirlos; **TERCERO**: Que se hace necesario ajustar el contenido de envase de la presentación de venta al público de acuerdo a la naturaleza del producto y el esquema posológico autorizado; **CUARTO**: Que en la solicitud se han hecho ajustes a las empresas que participan del proceso de fabricación del producto, de acuerdo a lo aclarado por el solicitante mediante correo electrónico el día 13 de Febrero de 2018; y

TENIENDO PRESENTE: Las disposiciones del artículo 96º del Código Sanitario; del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, aprobado por el Decreto Supremo N° 3 de 2010, del Ministerio de Salud y los artículos 59º letra b) y 61º letra b), del D.F.L. Nº 1 de 2005, y las facultades delegadas por la Resolución Exenta Nº 292 de 12 de febrero de 2014, del Instituto de Salud Pública de Chile, dicto la siguiente:

R E S O L U C I Ó N

1.- **INSCRÍBASE** en el Registro Nacional de Productos Farmacéuticos, bajo el Nº F-23721/18, el producto farmacéutico SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL (ACETATO DE MEDROXIPROGESTERONA) a nombre de Pfizer Chile S.A., para los efectos de su importación y distribución en el país, el que será fabricado como producto terminado por Pfizer Manufacturing Belgium NV, ubicado en Rijksweg 12, Puurs, 2870, Bélgica, procedente de Pfizer Service Company BVBA, ubicado en Hoge Wei 10, Zaventem, 1930, Bélgica, y en uso de licencia de Pfizer Inc., ubicado en 235 East 42nd Street, New York, New York 10017, U.S.A., en las condiciones que se indican:

a) Este producto será importado como producto terminado con reacondicionamiento local por Pfizer Chile S.A., ubicado en Av. Cerro El Plomo N° 5680, Santiago, Chile. Este producto será almacenado y distribuido por la droguería propiedad de Novofarma Service S.A., ubicada en Av. Víctor Uribe 2280, Quilicura, Santiago, Chile. El reacondicionamiento local será efectuado por el laboratorio farmacéutico acondicionador de propiedad de Novofarma Service S.A., ubicado en Av. Víctor Uribe 2300, Quilicura, Santiago, Chile. El reacondicionamiento local consistirá en estuchar y/o reestuchar, transformar envases de presentación Venta Público en envases de presentación Venta Público de otro contenido de unidades, agregar con etiqueta autoadhesiva y/o ink-jet los textos autorizados en el registro sanitario para los rótulos, además de incorporar o reemplazar el folleto de información al paciente y agregar sello de seguridad.

b) El principio activo ACETATO DE MEDROXIPROGESTERONA será fabricado por Pharmacia and Upjhon Company LLC, ubicado en 7000 Portage Road, Kalamazoo, Michigan (MI) 49001, U.S.A.

c) Periodo de Eficacia: 36 meses, almacenado a no más de 30°C.

RESOLUCIÓN EXENTA RW Nº 3364/18
Santiago, 14 de febrero de 2018

"SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL (ACETATO DE MEDROXIPROGESTERONA)"
Registro ISP Nº F-23721/18

d) Presentaciones:

Venta Público:	Estuche de cartulina impreso, debidamente sellado y rotulado, que contiene bolsa de PET/Aluminio/PE impresa, con 1 envase unidosis de sistema de inyección prellenado de dosis única, compuesto por un depósito de PEBD sellado etiquetado con la suspensión y conectado con una aguja de acero inoxidable para uso subcutáneo y capucha, más folleto de información al paciente en su interior.
Muestra Médica:	Estuche de cartulina impreso, debidamente sellado y rotulado, que contiene bolsa de PET/Aluminio/PE impresa, con 1 envase unidosis de sistema de inyección prellenado de dosis única, compuesto por un depósito de PEBD sellado etiquetado con la suspensión y conectado con una aguja de acero inoxidable para uso subcutáneo y capucha, más folleto de información al paciente en su interior.
Envase Clínico:	Estuche de cartulina impreso, debidamente sellado y rotulado, que contiene bolsas de PET/Aluminio/PE impresa, con 1 a 100 envases unidosis de sistema de inyección prellenado de dosis única, compuesto por un depósito de PEBD sellado etiquetado con la suspensión y conectado con una aguja de acero inoxidable para uso subcutáneo y capucha, más folleto de información al paciente en su interior.

Los envases clínicos están destinados al uso exclusivo de los Establecimientos Asistenciales y deberán llevar en forma destacada la leyenda "ENVASE CLÍNICO SÓLO PARA ESTABLECIMIENTOS MÉDICO-ASISTENCIALES".

e) Condición de venta: Receta Médica en Establecimientos Tipo A.

f) Grupo Terapéutico: Progestágenos.

Código ATC : G03AC06.

2.- La fórmula aprobada corresponde a la detallada en el anexo adjunto, el cual forma parte de la presente resolución.

3.- Los rótulos de los envases, folleto de información al profesional y folleto de información al paciente aprobados, deben corresponder exactamente en su texto y distribución a lo aceptado en los anexos timbrados de la presente Resolución, copia de los cuales se adjunta a ella para su cumplimiento, sin perjuicio de respetar lo dispuesto en el Art. 74º del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, D.S. N° 3 de 2010, del Ministerio de Salud y cumplir con la Resolución Exenta N° 9991/05 del Instituto de Salud Pública de Chile.

4.- La indicación aprobada para este producto es: "Prevención del embarazo, tratamiento de la endometriosis con dolor asociado".

Nº Ref.:RF895548/17
NVS

RESOLUCIÓN EXENTA RW Nº 3364/18
Santiago, 14 de febrero de 2018

"SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL (ACETATO DE MEDROXIPROGESTERONA)"
Registro ISP Nº F-23721/18

5.- Las especificaciones de calidad del producto terminado, deberán conformar al anexo timbrado adjunto y cualquier modificación deberá solicitarse oportunamente a este Instituto.

6.- La metodología analítica aprobada corresponde a la presentada junto a la solicitud.

7.- Pfizer Chile S.A. se responsabilizará de la calidad del producto que importa y distribuye, debiendo efectuar las operaciones analíticas correspondientes antes de su distribución en el Laboratorio de Control de Calidad de su propiedad, ubicado en Obispo Arturo Espinoza Campos Nº 2526-A, Macul, Santiago, Chile y/o en el Laboratorio Externo De Control De Calidad Condecal Ltda., ubicado en Alberto Riesco N° 0245, Huechuraba, Santiago, Chile, según convenio notarial de prestación de servicios, quien será responsable de la toma de muestras de producto a analizar, sin perjuicio de la responsabilidad que le compete a Pfizer Chile S.A. como propietario del registro sanitario.

8.- La prestación de servicios autorizada deberá figurar en los rótulos, individualizando con su nombre y dirección al distribuidor.

9.- El titular del registro sanitario, cuando corresponda, deberá solicitar al Instituto de Salud Pública de Chile el uso y disposición de las partidas internadas, en conformidad a las disposiciones de la Ley Nº 18164 y del Decreto Supremo Nº 3 de 2010 del Ministerio de Salud.

10.- Pfizer Chile S.A., deberá comunicar a este Instituto la distribución de la primera partida o serie que se importe de acuerdo a las disposiciones de la presente Resolución, adjuntando una muestra en su envase definitivo.

11.- El solicitante deberá cumplir fielmente con lo dispuesto en el Art.71° del D.S. N°3 de 2010, relativo a las obligaciones de los titulares de registros sanitarios, teniendo presente que la autoridad regulatoria podrá requerir de los titulares, cualquier documento legal debidamente actualizado, que acredite el cumplimiento de las buenas prácticas de manufactura del fabricante y la fórmula del producto, en cualquier instante de la vida administrativa del Registro.

12.- Déjese establecido, que la información evaluada en la solicitud para la aprobación del presente registro sanitario, corresponde a la entregada por el solicitante, el cual se hace responsable de la veracidad de los documentos conforme a lo dispuesto en el articulo 210° del Código Penal y que la información proporcionada deberá estar a disposición de la Autoridad Sanitaria para su verificación cuando ésta lo requiera.

ANÓTESE Y COMUNÍQUESE

INSTITUTO DE SALUD PÚBLICA CHILE
Agencia Nacional de Medicamentos
Incorpora Firma Electrónica Avanzada

Q.F. ISABEL SÁNCHEZ CEREZZO
JEFA
DEPARTAMENTO AGENCIA NACIONAL DE MEDICAMENTOS
INSTITUTO DE SALUD PÚBLICA DE CHILE

La presente resolución podrá ser validada en www.ispdocel.ispch.cl con el siguiente identificador: Código de Verificación: **569A1F7B33C6699404258233006C9001**

Nº Ref.:RF895548/17
NVS

RESOLUCIÓN EXENTA RW Nº 3364/18
Santiago, 14 de febrero de 2018

"SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL (ACETATO DE MEDROXIPROGESTERONA)"
Registro ISP Nº F-23721/18

Cada dispositivo de suspensión inyectable contiene:

Nº Ref.:RF895548/17
NVS

RESOLUCIÓN EXENTA RW Nº 3364/18
Santiago, 14 de febrero de 2018

"SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL (ACETATO DE MEDROXIPROGESTERONA)"
Registro ISP Nº F-23721/18

Clave de fabricación del producto es: LXXXXX

Interpretación de la clave : En base sistema SAP, los números possen 6 caracteres y tienen la siguiente estructura: El primer carácter es una letra, por ejemplo "Lxxxxx"; Los cinco caracteres siguientes son números; por ejemplo "L12345"; Una vez que se llega a la numeración L99999, se utiliza la siguiente letra del alfabeto, con excepción de las letras "I" y "O", y se reanuda el conteo a partir de 00001.

URL Rótulo Gráfico :
http://www.ispdocel.ispch.cl/domdoc/GADN-AUAHUH.nsf/All+Documents/9A3F75F0AB23F21904258264006E6828/$File/RF895548_569A1F7B33C6699404258233006C9001_Rotulos_firmado.pdf
URL Folleto Paciente :
http://www.ispdocel.ispch.cl/domdoc/GADN-AUAHUH.nsf/All+Documents/94AC54771E83C10004258264006E6854/$File/RF895548_569A1F7B33C6699404258233006C9001_FolletoPaciente_firmado.pdf
URL Folleto Profesional :
http://www.ispdocel.ispch.cl/domdoc/GADN-AUAHUH.nsf/All+Documents/4488D76DCFAC1E9C04258264006E6895/$File/RF895548_569A1F7B33C6699404258233006C9001_FolletoProfesional_firmado.pdf
URL Especificación de Producto Terminado :
http://www.ispdocel.ispch.cl/domdoc/GADN-AUAHUH.nsf/All+Documents/DDA5B42D22CECDDB04258264006E67C4/$File/RF895548_569A1F7B33C6699404258233006C9001_EPT_firmado.pdf

La presente resolución podrá ser validada en www.ispdocel.ispch.cl con el siguiente identificador:
Código de Verificación: **569A1F7B33C6699404258233006C9001**

Instituto de Salud Pública
Ministerio de Salud
Gobierno de Chile

Nº Ref.:RR993267/18
VEY/NVS/spp

RESOLUCIÓN EXENTA RW N° 11285/18
Santiago, 5 de junio de 2018

VISTO ESTOS ANTECEDENTES: la Resolución Exenta RW Nº 3364 de fecha 14 de febrero de 2018, por la que se autorizó el Registro Sanitario para el producto farmacéutico SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL (ACETATO DE MEDROXIPROGESTERONA), Registro Sanitario Nº F-23721/18, concedido a Pfizer Chile S.A.;

CONSIDERANDO: Que la rectificación solicitada, ha sido motivada por error en la emisión de la resolución de registro; Y

TENIENDO PRESENTE: las disposiciones del artículo 96º del Código Sanitario; el Reglamento del Sistema Nacional de Control de Productos Farmacéutico, aprobado por el Decreto Supremo Nº 3 de 2010 del Ministerio de Salud; en uso de las facultades que me confieren los artículos 59º letra b) y 61º letra b), del Decreto con Fuerza de Ley Nº 1, de 2005 y las facultades delegadas por la Resolución Exenta N° 292 de 12 de febrero de 2014 del Instituto de Salud Pública de Chile, dicto la siguiente:

R E S O L U C I Ó N

1.- **RECTIFÍCASE** la Resolución Exenta RW Nº 3364 de fecha 14 de febrero de 2018 , referencia Nº RF895548, en el siguiente sentido:

En el Inscríbase, párrafo 1 letra b):

Donde dice: b) El principio activo ACETATO DE MEDROXIPROGESTERONA será fabricado por Pharmacia and Upjhon Company LLC, ubicado en 7000 Portage Road, Kalamazoo, Michigan (MI) 49001, U.S.A.

Debe decir: b) El principio activo ACETATO DE MEDROXIPROGESTERONA será fabricado por Pharmacia and **Upjohn** Company LLC, ubicado en 7000 Portage Road, Kalamazoo, Michigan (MI) 49001, U.S.A.

2.-**DÉJESE ESTABLECIDO** que los rótulos de los envases, el folleto de información al profesional y el folleto de información al paciente, deben corresponder exactamente en su texto y distribución a lo aceptado en los anexos timbrados de la presente Resolución, copia de los cuales se adjuntan a ella para su cumplimiento, teniendo presente que este producto será individualizado primero con la denominación SAYANA PRESS, seguido a continuación en línea inferior e inmediata del nombre genérico ACETATO DE MEDROXIPROGESTERONA, en caracteres claramente legibles, sin perjuicio de respetar lo dispuesto en los Arts. 74º y 82º del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, D.S. N° 3 de 2010, del Ministerio de Salud.

ANÓTESE Y COMUNÍQUESE

JEFA (S) SUBDEPTO. REGISTRO Y AUTORIZACIONES SANITARIAS
AGENCIA NACIONAL DE MEDICAMENTOS
INSTITUTO DE SALUD PÚBLICA DE CHILE

Q.F. GUISELA ZURICH RESZCZYNSKI
JEFA (S) SUBDEPARTAMENTO REGISTRO Y AUTORIZACIONES SANITARIAS
DEPARTAMENTO AGENCIA NACIONAL DE MEDICAMENTOS
INSTITUTO DE SALUD PÚBLICA DE CHILE

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INTERESADO
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INSTITUTO DE SALUD PÚBLICA DE CHILE
MINISTRO DE FE

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Av. Marathon 1.000, Ñuñoa. Santiago
Casilla 48, Correo 21 – Código Postal 7780050
Mesa Central: (56) 22575 51 01
Informaciones: (56) 22575 52 01
www.ispch.cl

ROTULADO GRÁFICO

SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL

PROYECTO ROTULADO GRÁFICO

SAYANA PRESS
Acetato de Medroxiprogesterona
Suspensión Inyectable 104 mg/0,65 mL

1. Presentación Venta Público
1.1 Envase secundario:

SAYANA PRESS ~~104 mg/0, 65 mL~~
Acetato de Medroxiprogesterona
Suspensión Inyectable **104 mg/0,65 mL**
~~MEDROXIPROGESTERONA ACETATO~~

X ~~Jeringas Prellenadas~~ **sistemas de inyección prellenados** en envase de dosis única
Administración Subcutánea

Composición:
Cada ~~jeringa prellenada~~ **sistema de inyección prellenado** contiene:
~~Medroxiprogesterona~~ Acetato **de Medroxiprogesterona** 104 mg

Excipientes c.s.: ~~Polietilenglicol~~ **Macrogol** 3350, cloruro de sodio, povidona K17 PF, polisorbato 80, metilparabeno, metionina, fosfato de sodio monobásico monohidratado, fosfato ~~de sodio dibásico dodecahidrato~~ **disódico dodecahidratado**, propilparabeno, hidróxido de sodio, ácido clorhídrico, agua para inyectables, c.s.

USO BAJO SUPERVISIÓN MÉDICA.
R = Receta Simple
VENTA EN ESTABLECIMIENTOS TIPO A

MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS
No refrigerar ni congelar.
Almacenar a temperatura no mayor a ~~25~~ **30**°C.

Fabricado por Pfizer Manufacturing Belgium NV, **Rijksweg 12,** Puurs, **2870,** Bélgica.
Titular e Importador Pfizer Chile S.A., Av. Cerro El Plomo 5680, Torre 6, Piso 16, Las Condes, Santiago, Chile.
Distribuido por Novofarma Service S.A., Av. Víctor Uribe 2280, Quilicura, Santiago, Chile.
Bajo licencia de Pfizer Inc. USA.
Reg. I.S.P. N°
Mayor información en www.ispch.cl

INSTITUTO DE SALUD PÚBLICA DE CHILE
AGENCIA NACIONAL DE MEDICAMENTOS
SUBDEPTO. REGISTRO Y AUTORIZACIONES SANITARIAS
OFICINA PRODUCTOS FARMACÉUTICOS SIMILARES
07 JUN. 2018
N° Rel.: RB 99326/18
N° Registro: F-23721/18
Firma Profesional:

Lote:
Exp:
Elab **(mes-año)**:

1.2 Envase Primario: Pouch y etiqueta

Pouch

SAYANA PRESS ~~104 mg/0, 65 mL~~
Acetato de Medroxiprogesterona
Suspensión Inyectable **104 mg/0,65 mL**
~~MEDROXIPROGESTERONA ACETATO~~

X ~~Jeringas Prellenadas~~ **sistemas de inyección prellenados** en envase de dosis única
Administración Subcutánea

Composición:
Cada ~~jeringa prellenada~~ **sistema de inyección prellenado** contiene:
~~Medroxiprogesterona~~ Acetato **de Medroxiprogesterona** 104 mg

Excipientes c.s.: ~~Polietilenglicol~~ **Macrogol** 3350, cloruro de sodio, povidona K17 PF, polisorbato 80, metilparabeno, metionina, fosfato de sodio monobásico monohidratado, fosfato ~~de sodio dibásico dodecahidrato~~ **disódico dodecahidratado**, propilparabeno, hidróxido de sodio, ácido clorhídrico, agua para inyectables, c.s.

USO BAJO SUPERVISIÓN MÉDICA.
R = Receta Simple
Reg. I.S.P. N°

MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS
No refrigerar ni congelar.
Almacenar a temperatura no mayor a ~~25~~ **30**°C.

Lote:
Exp:
Elab

INSTITUTO DE SALUD PÚBLICA DE CHILE
AGENCIA NACIONAL DE MEDICAMENTOS
SUBDEPTO. REGISTRO Y AUTORIZACIONES SANITARIAS
OFICINA PRODUCTOS FARMACÉUTICOS SIMILARES
07 JUN. 2019
N° Ref.: RE 993267/19
N° Registro: F-23721/18
Firma Profesional:

Etiqueta

SAYANA PRESS ~~104 mg/0, 65 mL~~
Acetato de Medroxiprogesterona
Suspensión inyectable 104 mg/0, 65 mL
~~S.C.~~ **Vía subcutánea**
Exp:
Reg. I.S.P. N°
Lote

2. Presentación Muestra Médica
2.1 Envase secundario:

SAYANA PRESS ~~104 mg/0, 65 mL~~
Acetato de Medroxiprogesterona
Suspensión Inyectable **104 mg/0,65 mL**
~~MEDROXIPROGESTERONA ACETATO~~

X ~~Jeringas Prellenadas~~ **sistemas de inyección prellenados** en envase de dosis única
Administración Subcutánea

MUESTRA MÉDICA PROHIBIDA SU VENTA

Composición:
Cada ~~jeringa prellenada~~ **sistema de inyección prellenado** contiene:
~~Medroxiprogesterona~~ Acetato **de Medroxiprogesterona** 104 mg

Excipientes c.s.: ~~Polietilenglicol~~ **Macrogol** 3350, cloruro de sodio, povidona K17 PF, polisorbato 80, metilparabeno, metionina, fosfato de sodio monobásico monohidratado, fosfato ~~de sodio dibásico dodecahidrato~~ **disódico dodecahidratado**, propilparabeno, hidróxido de sodio, ácido clorhídrico, agua para inyectables, c.s.

USO BAJO SUPERVISIÓN MÉDICA.
R = Receta Simple
VENTA EN ESTABLECIMIENTOS TIPO A

MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS
No refrigerar ni congelar.
Almacenar a temperatura no mayor a ~~25~~ **30**°C.

Fabricado por Pfizer Manufacturing Belgium NV, **Rijksweg 12,** Puurs, **2870,** Bélgica.
Titular e Importador Pfizer Chile S.A., Av. Cerro El Plomo 5680, Torre 6, Piso 16, Las Condes, Santiago, Chile.
Distribuido por Novofarma Service S.A., Av. Víctor Uribe 2280, Quilicura, Santiago, Chile.
Bajo licencia de Pfizer Inc. USA.
Reg. I.S.P. N°
Mayor información en www.ispch.cl

Lote:
Exp:
Elab **(mes-año)**:

INSTITUTO DE SALUD PÚBLICA DE CHILE
AGENCIA NACIONAL DE MEDICAMENTOS
SUBDEPTO. REGISTRO Y AUTORIZACIONES SANITARIAS
OFICINA PRODUCTOS FARMACÉUTICOS
07 JUN. 2018
N° Ref.: AR-8932 67/18
N° Registro: F-23721/18
Firma Profesional:

1.2 Envase Primario: Pouch y etiqueta

Pouch

SAYANA PRESS ~~104 mg/0, 65 mL~~
Acetato de Medroxiprogesterona
Suspensión Inyectable **104 mg/0,65 mL**
~~MEDROXIPROGESTERONA ACETATO~~

X ~~Jeringas Prellenadas~~ **sistemas de inyección prellenados** en envase de dosis única
Administración Subcutánea

MUESTRA MÉDICA PROHIBIDA SU VENTA

Composición:
Cada ~~jeringa prellenada~~ **sistema de inyección prellenado** contiene:
~~Medroxiprogesterona~~ Acetato **de Medroxiprogesterona** 104 mg

Excipientes c.s.: ~~Polietilenglicol~~ **Macrogol** 3350, cloruro de sodio, povidona K17 PF, polisorbato 80, metilparabeno, metionina, fosfato de sodio monobásico monohidratado, fosfato ~~de sodio dibásico dodecahidrato~~ **disódico dodecahidratado**, propilparabeno, hidróxido de sodio, ácido clorhídrico, agua para inyectables, c.s.

USO BAJO SUPERVISIÓN MÉDICA.
R = Receta Simple
Reg. I.S.P. N°

MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS
No refrigerar ni congelar.
Almacenar a temperatura no mayor a ~~25~~ **30**°C.

Lote:
Exp:
Elab

INSTITUTO DE SALUD PÚBLICA DE CHILE
AGENCIA NACIONAL DE MEDICAMENTOS
SUBDEPTO. REGISTRO Y AUTORIZACIONES SANITARIAS
OFICINA PRODUCTOS FARMACÉUTICOS SIMILARES
07 JUN. 2018
N° Ref.: RTE 993267/18
N° Registro: F-23721/18
Firma Profesional:

Etiqueta

SAYANA PRESS ~~104 mg/0, 65 mL~~
Acetato de Medroxiprogesterona
Suspensión inyectable 104 mg/0, 65 mL
~~S.C.~~ **Vía subcutánea**
Exp:
Reg. I.S.P. N°
Lote
MUESTRA MÉDICA PROHIBIDA SU VENTA

3. Presentación Envase clínico
3.1 Envase secundario:

SAYANA PRESS ~~104 mg/0, 65 mL~~
Acetato de Medroxiprogesterona
Suspensión Inyectable **104 mg/0,65 mL**
~~MEDROXIPROGESTERONA ACETATO~~

X ~~Jeringas Prellenadas~~ **sistemas de inyección prellenados** en envase de dosis única
Administración Subcutánea

ENVASE CLÍNICO SOLO PARA ESTABLECIMIENTOS MÉDICO-ASISTENCIALES

Composición:
Cada ~~jeringa prellenada~~ **sistema de inyección prellenado** contiene:
~~Medroxiprogesterona~~ Acetato **de Medroxiprogesterona** 104 mg

Excipientes c.s.: ~~Polietilenglicol~~ **Macrogol** 3350, cloruro de sodio, povidona K17 PF, polisorbato 80, metilparabeno, metionina, fosfato de sodio monobásico monohidratado, fosfato ~~de sodio dibásico dodecahidrato~~ **disódico dodecahidratado**, propilparabeno, hidróxido de sodio, ácido clorhídrico, agua para inyectables, c.s.

USO BAJO SUPERVISIÓN MÉDICA.
R = Receta Simple
VENTA EN ESTABLECIMIENTOS TIPO A

MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS
No refrigerar ni congelar.
Almacenar a temperatura no mayor a ~~25~~ **30**°C.

Fabricado por Pfizer Manufacturing Belgium NV, **Rijksweg 12,** Puurs, **2870,** Bélgica.
Titular e Importador Pfizer Chile S.A., Av. Cerro El Plomo 5680, Torre 6, Piso 16, Las Condes, Santiago, Chile.
Distribuido por Novofarma Service S.A., Av. Víctor Uribe 2280, Quilicura, Santiago, Chile.
Bajo licencia de Pfizer Inc. USA.
Reg. I.S.P. N°
Mayor información en www.ispch.cl

INSTITUTO DE SALUD PÚBLICA DE CHILE
AGENCIA NACIONAL DE MEDICAMENTOS
SUBDEPTO. REGISTRO Y AUTORIZACIONES SANITARIAS
OFICINA PRODUCTOS FARMACÉUTICOS SIMILARES
07 JUN. 2018
N° Ref.: RB 99326/18
N° Registro: F-23721/18
Firma Profesional:

Lote:
Exp:
Elab **(mes-año)**:

ROTULADO GRÁFICO

SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 mL

1.2 Envase Primario: Pouch y etiqueta

Pouch

SAYANA PRESS ~~104 mg/0, 65 mL~~
Acetato de Medroxiprogesterona
Suspensión Inyectable **104 mg/0,65 mL**
~~MEDROXIPROGESTERONA ACETATO~~

X ~~Jeringas Prellenadas~~ **sistemas de inyección prellenados** en envase de dosis única
Administración Subcutánea

ENVASE CLÍNICO SOLO PARA ESTABLECIMIENTOS MÉDICO-ASISTENCIALES

Composición:
Cada ~~jeringa prellenada~~ **sistema de inyección prellenado** contiene:
~~Medroxiprogesterona~~ Acetato **de Medroxiprogesterona** 104 mg

Excipientes c.s.: ~~Polietilenglicol~~ **Macrogol** 3350, cloruro de sodio, povidona K17 PF, polisorbato 80, metilparabeno, metionina, fosfato de sodio monobásico monohidratado, fosfato ~~de sodio dibásico dodecahidrato~~ **disódico dodecahidratado**, propilparabeno, hidróxido de sodio, ácido clorhídrico, agua para inyectables, c.s.

USO BAJO SUPERVISIÓN MÉDICA.
R = Receta Simple
Reg. I.S.P. N°

MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS
No refrigerar ni congelar.
Almacenar a temperatura no mayor a ~~25~~ **30**°C.

Lote:
Exp:
Elab

INSTITUTO DE SALUD PÚBLICA DE CHILE
AGENCIA NACIONAL DE MEDICAMENTOS
SUBDEPTO. REGISTRO Y AUTORIZACIONES SANITARIAS
OFICINA PRODUCTOS FARMACEUTICOS SIMILARES
07 JUN. 2013
N° Ref.: RE 9932 61/18
N° Registro: F-23721/18
Firma Profesional:

Etiqueta

SAYANA PRESS ~~104 mg/0, 65 mL~~
Acetato de Medroxiprogesterona
Suspensión inyectable 104 mg/0, 65 mL
~~S.C.~~ **Vía subcutánea**
Exp:
Reg. I.S.P. N°
Lote

Instituto de Salud Pública
Ministerio de Salud
Gobierno de Chile

Nº Ref.:MT1372116/20
JMC

RESOLUCIÓN EXENTA RW N° 12319/20
Santiago, 16 de mayo de 2020

VISTO ESTOS ANTECEDENTES: la solicitud de D. Dinka Joyce Basic Eissler, Responsable Técnico y D. Ricardo Muza Galarce, Representante Legal de Pfizer Chile S.A., ingresada bajo la referencia Nº MT1372116, de fecha de 12 de mayo de 2020, mediante la cual solicita la actualización del rotulado gráfico del Registro Sanitario N° F-23721/18 del producto farmacéutico SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 ml (ACETATO DE MEDROXIPROGESTERONA); el pago de los derechos arancelarios correspondientes, mediante el comprobante de recaudación Nº 2020051200582061, emitido por Tesorería General de la República; y

CONSIDERANDO:

PRIMERO: que, mediante la presentación de fecha 12 de mayo de 2020, de D. Dinka Joyce Basic Eissler, Responsable Técnico y D. Ricardo Muza Galarce, Representante Legal de Pfizer Chile S.A., se solicitó actualización del rotulado gráfico del registro sanitario N° F-23721/18 del producto farmacéutico SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 ml (ACETATO DE MEDROXIPROGESTERONA).

SEGUNDO: que, consta el pago de los derechos arancelarios correspondientes, mediante el comprobante de recaudación Nº 2020051200582061, emitido por Tesorería General de la República con fecha 12 de mayo de 2020; y

TENIENDO PRESENTE: las disposiciones del artículo 96º del Código Sanitario; del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, aprobado por el Decreto Supremo Nº 3 de 2010 del Ministerio de Salud; en uso de las facultades que me confieren los artículos 59º letra b) y 61º letra b), del Decreto con Fuerza de Ley Nº 1, de 2005 y las facultades delegadas por la Resolución Exenta N° 56 de 11 de enero de 2019 del Instituto de Salud Pública de Chile, dicto la siguiente:

R E S O L U C I Ó N

1.- AUTORÍZASE para el producto farmacéutico **SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 ml (ACETATO DE MEDROXIPROGESTERONA)**, registro sanitario Nº F-23721/18, concedido a Pfizer Chile S.A. la incorporación en el rotulado gráfico de la información descrita a continuación: "En la Etiqueta en Jeringa Precargada debe señalar: Sayana Press Suspensión Inyectable 104 mg/0,65 mL; Vía Subcutánea; Exp:; Reg ISP; Lote"; la eliminación en el rotulado gráfico de la información descrita a continuación: " Etiqueta Jeringa Precargada de: "Presentación Venta Público "Acetato de Medroxiprogesterona "; "Presentación Muestra Médica: "MUESTRA MÉDICA PROHIBIDA SU VENTA" y "Acetato de Medroxiprogesterona " y ; Presentación Envase Clínico: "ENVASE CLÍNICO SOLO PARA ESTABLECIMIENTOS MÉDICO-ASISTENCIALES" y "Acetato de Medroxiprogesterona ".
.

La presente resolución podrá ser validada en www.ispdocel.ispch.cl con el siguiente identificador:
Código de Verificación: **0688429B982E2E380325856700477131**

2.- Las modificaciones autorizadas deben ser aplicadas en todas las presentaciones autorizadas que corresponda, sin perjuicio de cumplir lo dispuesto en los artículos 74°, 75° y 82° del reglamento del Sistema Nacional de Control de Productos Farmacéuticos.

3.- DÉJASE ESTABLECIDO que la información evaluada en la solicitud para la aprobación de esta modificación al registro sanitario, corresponde a la entregada por el solicitante, el cual se hace responsable de la veracidad de los documentos que adjunta, conforme a lo dispuesto en el Art.210° del Código Penal y que la información proporcionada deberá estar a disposición de la Autoridad Sanitaria, para su verificación, cuando ésta lo requiera.

4.- DÉJASE ESTABLECIDO que el titular del registro tendrá un plazo de 6 meses a contar de la fecha de la presente resolución para actualizar la información en los anexos del registro que así lo requieran, sin necesidad de solicitar expresamente esta modificación al Instituto.

ANÓTESE Y COMUNÍQUESE

INSTITUTO DE SALUD PÚBLICA
Agencia Nacional de Medicamentos
Incorpora Firma Electrónica Avanzada
CHILE

Q.F. PATRICIA CARMONA SEPÚLVEDA
JEFA SUBDEPARTAMENTO DE AUTORIZACIONES Y REGISTRO SANITARIO
DEPARTAMENTO AGENCIA NACIONAL DE MEDICAMENTOS
INSTITUTO DE SALUD PÚBLICA DE CHILE

La presente resolución podrá ser validada en www.ispdocel.ispch.cl con el siguiente identificador: Código de Verificación: **0688429B982E2E380325856700477131**

N° Ref: ML1451689/20

Resolución Exenta RW N° 22747/20
Santiago, 10 de septiembre de 2020

VISTO ESTOS ANTECEDENTES: la solicitud de Pfizer Chile S.A., ingresada bajo la referencia Nº ML1451689 de fecha 9 de septiembre de 2020, por la que solicita la ampliación de procedencia para el producto farmacéutico SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 ml (ACETATO DE MEDROXIPROGESTERONA) registro sanitario Nº F-23721/18.

CONSIDERANDO: Que la prestación solicitada es avalada por el convenio entre las partes y los respectivos Certificado vigentes, debidamente legalizados; y

TENIENDO PRESENTE: las disposiciones del artículo 96º del Código Sanitario; del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, aprobado por el Decreto Supremo Nº 3 de 2010, del Ministerio de Salud; en uso de las facultades que me confieren los artículos 59º letra b) y 61º letra b), del Decreto con Fuerza de Ley Nº 1, de 2005 y las facultades delegadas por la Resolución Exenta N° 56 de 11 de enero de 2019, del Instituto de Salud Pública de Chile, dicto la siguiente:

R E S O L U C I Ó N

1.- **AUTORÍZASE** la ampliación de procedencia para el producto farmacéutico SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 ml (ACETATO DE MEDROXIPROGESTERONA) registro sanitario Nº F-23721/18, desde Henri Essers & Zonen International Transport Nv domiciliado en Transportlaan 4, Genk, 3600, Bélgica, 4, Genk, Bélgica concedido a Pfizer Chile S.A., manteniendo la procedencia anteriormente autorizada.

2.- Los rótulos del producto indicado deben corresponder exactamente en su texto y distribución a lo autorizado en el registro sanitario y sólo podrán modificarse en lo referente a la materia que trata la presente resolución.

3.- Pfizer Chile S.A., se responsabilizará de la calidad del producto que importa, debiendo efectuar las operaciones analíticas correspondientes antes de su venta o distribución en el laboratorio de control de calidad autorizado en el registro sanitario.

4.- DÉJASE ESTABLECIDO que la información para la emisión de esta modificación al registro sanitario, corresponde a la entregada por el solicitante, el cual se hace responsable de la veracidad de los documentos que adjunta, conforme a lo dispuesto en el Artículo 210° del Código Penal y que la información proporcionada corresponde a los antecedentes requeridos para la presente modificación de acuerdo a la normativa vigente y los requisitos técnicos establecidos por este Instituto, los que deberán estar a disposición de la Autoridad Sanitaria, para su verificación, cuando ésta lo requiera.

5.- DÉJASE ESTABLECIDO que la modificación podrá ser implementada de forma inmediata a la recepción de esta resolución. Si esta Agencia detecta en forma posterior a la emisión del presente documento que los antecedentes aportados no son suficientes o que la modificación puede afectar la seguridad, eficacia y/o calidad del producto, el titular deberá hacer retiro inmediato de los lotes involucrados.

Q.F. Patricia Carmona Sepúlveda
JEFA SUBDEPARTAMENTO DE AUTORIZACIONES Y REGISTRO SANITARIO
DEPARTAMENTO AGENCIA NACIONAL DE MEDICAMENTOS
Instituto de Salud Pública de Chile

La presente resolución podrá ser validada en www.ispdocel.ispch.cl con el siguiente identificador:7073BF88CE8E3257842585DF004CF9E8

N° Ref: ML1509194/20

Resolución Exenta RW N° 30928/20
Santiago, 15 de diciembre de 2020

VISTO ESTOS ANTECEDENTES: la solicitud de Pfizer Chile S.A., ingresada bajo la referencia Nº ML1509194 de fecha 14 de diciembre de 2020, por la que solicita la ampliación de procedencia para el producto farmacéutico SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 ml (ACETATO DE MEDROXIPROGESTERONA) registro sanitario Nº F-23721/18.

CONSIDERANDO: Que la prestación solicitada es avalada por el convenio entre las partes y los respectivos Certificado vigentes, debidamente legalizados; y

TENIENDO PRESENTE: las disposiciones del artículo 96º del Código Sanitario; del Reglamento del Sistema Nacional de Control de Productos Farmacéuticos, aprobado por el Decreto Supremo Nº 3 de 2010, del Ministerio de Salud; en uso de las facultades que me confieren los artículos 59º letra b) y 61º letra b), del Decreto con Fuerza de Ley Nº 1, de 2005 y las facultades delegadas por la Resolución Exenta N° 2460 de 13 de octubre de 2020, del Instituto de Salud Pública de Chile, dicto la siguiente:

R E S O L U C I Ó N

1.- **AUTORÍZASE** la ampliación de procedencia para el producto farmacéutico SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 ml (ACETATO DE MEDROXIPROGESTERONA) registro sanitario Nº F-23721/18, desde J. Cain & Co., S.A domiciliado en Ave. Randolph, Mit Logistic Park Edificio Zona Libre De Colón, Sn, Ciudad De Panama, Panamá concedido a Pfizer Chile S.A., manteniendo la procedencia anteriormente autorizada.

2.- Los rótulos del producto indicado deben corresponder exactamente en su texto y distribución a lo autorizado en el registro sanitario y sólo podrán modificarse en lo referente a la materia que trata la presente resolución.

3.- Pfizer Chile S.A., se responsabilizará de la calidad del producto que importa, debiendo efectuar las operaciones analíticas correspondientes antes de su venta o distribución en el laboratorio de control de calidad autorizado en el registro sanitario.

4.- DÉJASE ESTABLECIDO que la información para la emisión de esta modificación al registro sanitario, corresponde a la entregada por el solicitante, el cual se hace responsable de la veracidad de los documentos que adjunta, conforme a lo dispuesto en el Artículo 210° del Código Penal y que la información proporcionada corresponde a los antecedentes requeridos para la presente modificación de acuerdo a la normativa vigente y los requisitos técnicos establecidos por este Instituto, los que deberán estar a disposición de la Autoridad Sanitaria, para su verificación, cuando ésta lo requiera.

5.- DÉJASE ESTABLECIDO que la modificación podrá ser implementada de forma inmediata a la recepción de esta resolución. Si esta Agencia detecta en forma posterior a la emisión del presente documento que los antecedentes aportados no son suficientes o que la modificación puede afectar la seguridad, eficacia y/o calidad del producto, el titular deberá hacer retiro inmediato de los lotes involucrados.

Q.F. ALEXIS ACEITUNO ÁLVAREZ PhD
JEFE SUBDEPARTAMENTO DE REGISTRO SANITARIO DE PRODUCTOS FARMACÉUTICOS BIOEQUIVALENTES
DEPARTAMENTO AGENCIA NACIONAL DE MEDICAMENTOS
Instituto de Salud Pública de Chile

La presente resolución podrá ser validada en www.ispdocel.ispch.cl con el siguiente identificador:2FF9340B0D58C97F0325863F004791DB

Cerro El Plomo 5680 Torre 6 Piso 16 Edificio
Las Artes– Las Condes - Santiago
Fono: 241 2000
Casilla 191-D
Santiago, Chile
Pfizer Chile S.A.

A QUIEN CORRESPONDA

Estimados Señores.:

Por medio del presente informo a usted que, Pfizer Chile S.A. es el titular del registro sanitario:

Denominación de Producto Farmacéutico	Principio Activo	Registro Sanitario (ISP)
Sayana Press suspensión inyectable 104mg/ 0,65mL	Medroxiprogesterona Acetato	F-23721/18

Sayana Press suspensión inyectable 104 mg/ 0,65mL, corresponde un producto original e innovador al ser el primero en registrarse en Chile con el principio activo Medroxiprogesterona Acetato, en la dosis y forma farmacéutica señalada.

La información señalada puede ser revisada en la página de la autoridad sanitaria: http://registrosanitario.ispch.gob.cl/

Sin otro particular, saluda atentamente a usted.

Q.F. Fernanda Lobos Anabalón.
Asesor Comercial & Clientes
Pfizer Chile S.A.

Santiago, 2021.

Sistema de Consulta de PRODUCTOS REGISTRADOS

(Medicamentos, cosméticos, plaguicidas, desinfectantes y sanitizantes)

Importante

- Si usted quiere buscar Productos Bioequivalentes haga click en el campo "Tipo de búsqueda" opción "Equivalencia Terapéutica" luego seleccione en "Equivalencia Terapéutica o Biosimilar", la opción "Equivalente Terapéutico" y presione el botón "Buscar" para desplegar la información.
- Diariamente esta base de datos es actualizada conforme se procesan electrónicamente los nuevos registros sanitarios y/o sus modificaciones.

Tipo de Búsqueda:

☐ Nombre Producto ☑ Principio Activo ☐ Empresa(Titular) ☐ Número de Registro ☐ Equivalencia Terapéutica ☐ Condición de Venta ☐ Control Legal

Principio Activo medroxiprogesterona

Estado Vigente

Estados:

- **Vigente**:Producto sin prohibiciones de la autoridad sanitaria.
- **No Vigente**:Producto con prohibiciones de la autoridad sanitaria.
- **Vigente con suspensión voluntaria de la distribución (Artículo N°71, numeral 4, DS 3/2010)**:Producto sin prohibiciones de la autoridad sanitaria.

Buscar

Registros Encontrados : 13

Exportar tabla de registros encontrados, en formato Excel (.xls)

Registro	Nombre	Fecha Registro	Empresa	Principio Activo	Control Legal
F-12974/18	CLIMATROL HT CONTINUO 0,450/1,5 COMPRIMIDOS RECUBIERTOS	2003-07-15	LABORATORIOS LAFI LTDA.	ESTROGENO//MEDROXIPROGESTERONA	
F-12740/17	DEPO - PRODASONE SUSPENSIÓN INYECTABLE 150 mg/1 mL (MEDROXIPROGESTERONA)	2002-12-30	PFIZER CHILE S.A.	MEDROXIPROGESTERONA	
F-24430/18	LYNDAVEL FEMM suspensión inyectable	2018-12-19	DKT CHILE S.p.A..	ESTRADIOL//MEDROXIPROGESTERONA	
F-24429/18	MEDROXIPROGESTERONA ACETATO SUSPENSIÓN INYECTABLE 150 mg/ 1mL	2018-12-19	DKT CHILE S.p.A..	MEDROXIPROGESTERONA	
F-18596/16	MEDROXIPROGESTERONA ACETATO SUSPENSIÓN INYECTABLE 150 mg/1 mL	2011-04-19	ETHON PHARMACEUTICALS S.p.A.	MEDROXIPROGESTERONA	
F-20936/19	MEDROXIPROGESTERONA ACETATO SUSPENSIÓN INYECTABLE 150 mg/1 mL	2014-02-20	MINTLAB Co. S.A.	MEDROXIPROGESTERONA	
F-22976/16	MEDROXIPROGESTERONA ACETATO SUSPENSIÓN INYECTABLE 150 mg/1 mL	2016-08-22	BIOSYNTEC S.A.	MEDROXIPROGESTERONA	
F-11537/16	NOVAFEM SUSPENSIÓN INYECTABLE	1996-05-23	LABORATORIOS SILESIA S.A.	ESTRADIOL//MEDROXIPROGESTERONA	
F-11124/16	PRIMAQUIN MP COMPRIMIDOS RECUBIERTOS	1995-10-24	LABORATORIOS LAFI LTDA.	ESTRADIOL//MEDROXIPROGESTERONA	
F-11125/21	PRIMAQUIN MP CONTINUO COMPRIMIDOS RECUBIERTOS	1997-03-06	LABORATORIOS LAFI LTDA.	ESTRADIOL//MEDROXIPROGESTERONA	
F-7187/20	PRODASONE COMPRIMIDOS 10 mg	1989-07-20	PFIZER CHILE S.A.	MEDROXIPROGESTERONA	
F-12789/18	PRODASONE COMPRIMIDOS 5 mg	2003-02-13	PFIZER CHILE S.A.	MEDROXIPROGESTERONA	

F-23721/18	SAYANA PRESS SUSPENSIÓN INYECTABLE 104 mg/0,65 ml (ACETATO DE MEDROXIPROGESTERONA)	2018-02-14	PFIZER CHILE S.A.	Medroxiprogesterona

Instituto de Salud Pública de Chile

Av. Marathon 1000
Ñuñoa, Santiago
Casilla 48 Correo 21
Código Postal 7780050

Mesa Central
(56-2) 5755 101
Informaciones
(56-2) 5755 201

Contacto con OIRS
Oficina de Informaciones, Reclamos y Sugerencias

REGISTRO DE MARCAS COMERCIALES

Solicitud: ***1007715***

Registro: ***976005***
Renueva a: ***638778***

En conformidad a la Ley 19.039, sobre Propiedad Industrial, concédese a:

PFIZER PRODUCTS INC.

Pais: *ESTADOS UNIDOS DE AMERICA*

Por el plazo legal de diez años, contando desde el **08** de **Agosto 2012**, la propiedad y uso exclusivo de la marca, registro se encuentra vigente:

SAYANA

Distingue : Productos

Clases(s) : ***5***
Clase ***5*** : PREPARACIONES Y SUSTANCIAS FARMACEUTICAS Y VETERINARIAS.

Nota :

Descrip. :

M.R.

MAXIMILIANO SANTA CRUZ S.
Director Nacional

INSTITUTO NACIONAL DE PROPIEDAD INDUSTRIAL CHILE
SUBDIRECCION DE MARCAS
INAPI

XIMENA MANDUJANO BRONSTEIN
Conservadora de Marcas Comerciales (s)

Este documento ha sido firmado electrdnicamente de acuerdo con la ley 19.799. Para verificar la integridad y autenticidad de este documento puede consultar en www.inapi.cl/consulta, donde estará disponible por 60 días contados desde la fecha de emisidn. El documento impreso es copia del documento original.

CVE: 00000041490

Public Summary

Summary for ARTG Entry: 167889 SAYANA medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection syringe

ARTG entry for	Medicine Registered
Sponsor	Pfizer Australia Pty Ltd
Postal Address	38-42 Wharf Road, WEST RYDE, NSW, 2114 Australia
ARTG Start Date	14/07/2011
Product category	Medicine
Status	Active
Approval area	Drug Safety Evaluation Branch

Conditions

Conditions applicable to all therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989" effective 1 July 1995.

Conditions applicable to the relevant category and class of therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989" effective 1 July 1995.

Products

1. SAYANA medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection syringe

Product Type Single Medicine Product **Effective date** 19/01/2018

Permitted Indications

No Permitted Indications included on Record

Indication Requirements

No Indication Requirements included on Record

Standard Indications

No Standard Indications included on Record

Specific Indications

Endometriosis: For use in the treatment of visually proven (laparoscopy) endometriosis where the required end-point of treatment is pregnancy, or for the control of symptoms when surgery is contra- indicated or has been unsuccessful. Contraception (ovulation suppression): For long-term prevention of pregnancy in women when administered at 3-month intervals. Since loss of bone mineral density (BMD) may occur in pre-menopausal women who use SAYANA long-term (greater than 2 years), women should be assessed, before starting treatment for contraception or endometriosis, regarding the risk of osteoporosis. Women under the age of 18 years may be at risk of failing to achieve their predicted peak bone mineral density (See PRECAUTIONS).

Warnings

See Product Information and Consumer Medicine Information for this product

Additional Product information

Container information

Type	Material	Life Time	Temperature	Closure	Conditions
Syringe	Glass	3 Years	Store below 25 degrees Celsius	Not recorded	Do not Freeze

Pack Size/Poison information

Pack Size

1 x pre-filled syringe

Poison Schedule

(S4) Prescription Only Medicine

Components

1. SAYANA medroxyprogesterone acetate 104 mg/0.65 mL suspension for injection syringe

Dosage Form	Suspension
Route of Administration	Subcutaneous
Visual Identification	white to off-white homogeneous suspension in a pre-filled syringe

Active Ingredients

Medroxyprogesterone acetate	**104 mg**

Public Summary

This is not an ARTG Certificate document.
The onus is on the reader to verify the current accuracy of the information on the document subsequent to the date shown.
Visit www.tga.gov.au for contact information

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Public Summary

This is not an ARTG Certificate document.
The onus is on the reader to verify the current accuracy of the information on the document subsequent to the date shown.
Visit www.tga.gov.au for contact information

Public Assessment Report

Mutual Recognition Procedure

SAYANA PRESS 104 mg/0.65 ml suspension for injection

PL 00057/1093; UK/H/0960/002/DC

Medroxyprogesterone acetate

Pfizer Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for SAYANA PRESS 104mg/0.65ml suspension for injection (PL 00057/1093; UK/H/0960/002/DC). It explains how SAYANA PRESS 104mg/0.65ml suspension for injection was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product. For ease of reading, throughout this PAR, the product SAYANA PRESS 104mg/0.65ml suspension for injection will be called SAYANA PRESS.

For practical information about using SAYANA PRESS, patients should read the Package Leaflet or contact their doctor or pharmacist.

What is SAYANA PRESS and what is it used for?
SAYANA PRESS is a line-extension of the existing product licence for SAYANA 104mg/0.65ml suspension for injection in prefilled syringe (PFS) (PL 00057/0589), using the "Uniject" delivery system.

SAYANA PRESS is a contraceptive injection containing the active substance medroxyprogesterone acetate. It can be used:

- For long-term contraception where you and the person who provides your contraception (e.g. your doctor, nurse or healthcare provider) have decided that this method is the most suitable for you. However, if you wish to use SAYANA PRESS for more than 2 years, your health professional/doctor/nurse may wish to re-evaluate the risks and benefits of using SAYANA PRESS to make sure that it is still the best option for you.
- By teenagers, but only after other methods of contraception have been discussed with the person who provides your contraception and are considered unsuitable or unacceptable.

How does SAYANA PRESS work?
The active ingredient in SAYANA PRESS, medroxyprogesterone acetate (MPA), is similar to (but not the same as) the natural hormone progesterone that is produced in the ovaries during the second half of your menstrual cycle. SAYANA PRESS acts by preventing an egg from fully developing and being released from the ovaries during your menstrual cycle. If an egg is not released it cannot become fertilised by sperm and result in pregnancy.

How is SAYANA PRESS used?
Administration of SAYANA PRESS is initiated by a healthcare professional (HCP). If considered appropriate by the HCP, you may be able to self-inject your injections following suitable instruction and training on injection technique and schedule of administration.

SAYANA PRESS is injected under the skin into the front upper thigh or abdomen. The first injection should be performed under the supervision of your doctor, nurse, or healthcare provider. If your doctor considers it appropriate you may choose to give yourself the injections. You will be shown how to give yourself the injection under supervision before you do this on your own at home. The detailed instructions on the injection procedure are provided at the end of this leaflet and should be followed very carefully. You should continue to receive SAYANA PRESS for as long as instructed by your doctor or until you want to have a baby or switch to a different method of contraception.

Please read Section 3 of the Package Leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

How has SAYANA PRESS been studied?
A clinical study has been performed in volunteers with this product, which uses the "Uniject" single-dose delivery system, which delivers the same dose as the current approved product, which uses the "PFS" delivery system.

What are the possible side effects of SAYANA PRESS?
The possible side effects observed with this product are the same as those observed with other marketed SAYANA products. Very common side effects (affecting more than one in 10) are weight decrease and weight increase. Common side effects (affecting up to one in 10 people) include abdominal pain (cramps), nausea, acne, amenorrhea (very light or no period), heavy, frequent or unexpected bleeding, irregular periods; period pain; breast pain/tenderness, depression, weakness or tiredness, headache, injection site reactions, irritability, anxiety, decreased sexual feeling, vaginal irritation or itching, mood changes, dizziness, back pain, pain in limbs, abnormal cervical smear.

For further information, please see Section 4 the Package Leaflet.

Why is SAYANA PRESS approved?
It was concluded that, in accordance with EU requirements, SAYANA PRESS 104mg/0.65ml suspension for injection is an effective contraceptive, with a suitable side-effect profile that was similar to other marketed contraceptives. The benefit-risk profile for this product was considered to be favourable and a product licence was granted.

What measures are being taken to ensure the safe and effective use of SAYANA PRESS?
A risk management plan (RMP) has been developed to ensure that SAYANA PRESS 104mg/0.65ml suspension for injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for SAYANA PRESS 104mg/0.65ml suspension for injection includes the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about SAYANA PRESS
Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, the Netherlands, Norway, Poland and the UK agreed to grant marketing authorisations for this product on 22 May 2011. The UK granted a marketing authorisation for SAYANA PRESS 104mg/0.65ml suspension for injection on 21 June 2011.

The full PAR for SAYANA PRESS 104mg/0.65ml suspension for injection follows this summary.

For more information about treatment with SAYANA PRESS 104mg/0.65ml suspension for injection, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in August 2015.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, the Netherlands, Norway, Poland and the UK agreed to grant marketing authorisations for this product on 22 May 2011 (UK/H/0960/002/DC). The UK granted a marketing authorisation for SAYANA PRESS 104mg/0.65ml suspension for injection on 21 June 2011 (PL 00057/1093).

This product is a prescription-only medicine intended for long-term female contraception. In this line extension application, the only change in the product is the introduction of a new injection device; the product has an injection system that is based on Uniject® technology. The formulation, method of manufacture and route of administration of the proposed product are identical to those already approved for SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589), which is provided in pre-filled syringes (PFS).

This product contains the active substance medroxyprogesterone acetate (MPA). MPA is a synthetic analogue of 17α-hydroxyprogesterone, with antiestrogenic, antiandrogenic and antigonadotropic effects. MPA belongs to the progestagen pharmacological class of drugs (ATC code: G03AC). It acts by inhibiting the secretion of gonadotropins (luteinizing hormone and follicle-stimulating hormone) from the anterior pituitary. This inhibition, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. These actions collectively produce its contraceptive effect. MPA has well established use in contraception by intramuscular injection and sub-cutaneous injection.

This application was made under Article 8(3) of Directive 2001/83/EC, as amended, a line-extension to the current granted licence for Sayana 104mg/0.65ml suspension for injection (PL 00057/1093; UK/H/0960/001/DC), using a prefilled, single-use syringe system.

The RMS for these procedures was the UK and the CMSs were Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, the Netherlands, Norway and Poland.

No new non-clinical studies were conducted, which is acceptable given that the application is for a product containing an existing formulation of a well-known active substance.

Since this product will be used in place of other products that are currently on the market and (with the exception of the delivery system) is identical to the current approved Sayana 104mg/0.65ml suspension for injection (PL 00057/1093; UK/H/0960/001/DC), no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

A randomized, open-label, parallel group study of the pharmacokinetics of medroxyprogesterone acetate in 68 healthy volunteers following subcutaneous administration using the Uniject™ delivery system or depo-subQ provera 104 pre-filled syringe (PFS). The study was conducted in-line with current Good Clinical Practice.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, as certification that acceptable standards of GMP are in place at those non-Community sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

II QUALITY ASPECTS

II.1 Introduction

This is an Article 8(3) line extension application, the only change in the product is the introduction of a new injection device; the proposed product has an injection system that is based on Uniject® technology. The formulation, method of manufacture and route of administration of the proposed product are identical to those already approved for SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589), which is provided in pre-filled syringes (PFS).

SAYANA PRESS suspension for injection is supplied in a single-dose container in the form of a pre-filled injector containing 0.65 ml suspension. The injector comprises a linear low-density polyethylene laminate reservoir with a siliconized AISI type-304 stainless steel 23 gauge ultra-thin wall needle attached via a low density polyethylene port and valve. The pack size is one single-dose container.

One pack of Sayana Press, consists of 104 mg medroxyprogesterone acetate (MPA) in 0.65 mL suspension for injection. In addition to these active substances, Sayana Press also contains the excipients Macrogol 3350, methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), sodium chloride, Polysorbate 80, monobasic sodium phosphate monohydrate, disodium phosphate dodecahydrate, methionine, povidone, hydrochloric acid and/or Sodium Hydroxide (for pH adjustment), and water for injection.

II.2 DRUG SUBSTANCE

INN: Medroxyprogesterone acetate
Chemical name: 6-Methyl-3,20-dioxopregn-4-en-17-yl acetate
Molecular formula: $C_{24}H_{34}O_4$
Molecular weight: 386.5
CAS number: 71-58-9
General Properties: White or almost white, crystalline powder. Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, sparingly soluble in ethanol (96 per cent)

The drug substance is a well-established compound with a European Pharmacopoeia monograph. The data provided confirm that the drug substance used in this product complies with this monograph. The drug substance is the same as that already approved for SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589). This is acceptable.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the development programme was to produce the identical product to SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589; UK/H/0960/001/MR). albeit using the Uniject® injection system instead of the PFS system. The formulation, method of manufacture and route of administration of the proposed product are identical to those already approved for SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589), which is provided in pre-filled syringes (PFS).

The applicant has provided a suitable product development section.

All excipients comply with their respective European Pharmacopoeia monographs.

No excipients of animal or human origin are used in the final products. None of the excipients are sourced from genetically modified organisms.

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale and has shown satisfactory results. Appropriate in-process controls are in place at suitable points during manufacture.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 5 years with the storage conditions "Do not refrigerate or freeze" are acceptable. An additional precaution of "use immediately; discard any unused portion" also exists for the product after opening.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance are well-established. As all active substance are widely used and well-known, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is, thus, appropriate.

Since this product will be used in place of other products that are currently on the market and contains a well-known active substance that is highly stable with a very low toxic potential, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

IV CLINICAL ASPECTS

IV.1 Introduction

One pharmacokinetic study has been submitted. It was conducted in-line with current Good Clinical Practice.

IV. 2 Pharmacokinetics

A randomized, open-label, parallel group study of the pharmacokinetics (PK) of MPA in 68 healthy volunteers was conducted to compare the PK of MPA following SC administration using the Uniject™ delivery system or PFS (depo-subQ provera 104).

The study participants were pre-menopausal women aged 18-45 years with confirmed ovulatory cycles who were at low risk of pregnancy.

Primary objective: To compare the PK of MPA following a single SC administration of MPA (DMPA; 0.65 mL [104 mg]) using the Uniject system or PFS.

Secondary objectives:

- To compare the weight of DMPA suspension delivered following a single SC administration of DMPA using the Uniject delivery system or PFS;
- To compare the PD response of the ovaries following a single SC administration of DMPA using the Uniject delivery system or PFS; and
- To evaluate the safety and tolerability of SC administration of DMPA using the Uniject delivery system.

Results

PK results: Eight subjects were excluded from the primary PK analysis for reasons pre-specified in the protocol: 1 subject for an insufficient number of serum samples; 3 subjects for a non-zero serum MPA level at baseline; and 4 subjects for dosing administration errors. Sixty subjects were included in the primary PK analyses.

Table 10. Geometric Mean (CV%) Serum Medroxyprogesterone Acetate Pharmacokinetic Parameter Values

Pharmacokinetic Parameters (Units)	Planned Analysis population (dosing administration errors excluded)		PK Evaluable Subjects (dosing administration errors included)	
	Uniject	Pre-filled Syringe	Uniject	Pre-filled Syringe
N, n	32, 12	28, 9	32, 12	32, 11
AUC_{2136} (ng.hr/mL)	959.0 (37)	919.3 (37)	959.0 (37)	479.6 (45)
AUC_{3576} (ng.hr/mL)	1393 (31)	1368 (36)	1393 (31)	691.6 (45)
AUC_{inf} (ng.hr/mL)	2111 (25)	1385 (47)	2111 (25)	313.6 (58)
AUC_{last} (ng.hr/mL)	1408 (31)	1376 (36)	1408 (31)	680.2 (45)
C_{max} (ng/mL)	0.9539 (47)	0.7897 (50)	0.9539 (47)	0.5564 (56)
T_{max} [a] (hr)	70.9 (17.1 – 2400)	163 (23.9 – 1500)	70.9 (17.1 – 2400)	160 (23.9 – 1500)
$t_{1/2}$ [a] (hr)	1342 (345 – 2750)	1668 (370 – 2470)	1342 (345 – 2750)	1584[b] (370 – 2470)

Source: Tables 13.5.2 and 13.5.3

[a] median (range)

[b] n = 10

CV = Coefficient of variation; PK = pharmacokinetic; N = Number of subjects; n = Number of subjects contributing to the mean for $t_{1/2}$ and AUC_{inf}; AUC_{2136} = AUC Day 0 to Day 90; AUC_{3576} = AUC Day 0 to Day 150. Other parameters are defined in Table 3.

Table 8. Comparative Pharmacokinetic Parameters in the Planned Analysis Population

	Ratio (Uniject/PFS)	90% CI
AUC_{0-150}	1.02	0.78 - 1.34
AUC_{0-90}	1.04	0.80 - 1.36
C_{max}	1.21	0.96 - 1.52

Source: Table 13.5.5
PFS = pre-filled syringe; CI = confidence interval.
Parameters are defined in Table 3

Pharmacodynamic results: Ovarian function: based on serum levels of progesterone, estradiol, LH and FSH, 4 PFS subjects had cyclic ovarian activity prior to day 92; 3 of these subjects had been excluded from PK analysis due to dosing administration errors, while the fourth subject had very low serum MPA levels but no record of a dosing administration error. One Uniject subject had a single progesterone elevation on days 8 to 11; serum MPA levels for this subject were lower than average throughout the treatment period, but always ≥0.2 ng/mL and, therefore, effective for contraception. No subject showed ovarian activity during days 93 to 150.

Expelled weight results: Five subjects in the PFS arm were excluded from this analysis because their recorded weight differences ('before' – 'after') were not physically possible since the recorded value exceeded the amount of drug suspension in the syringe by several hundred mg. No subjects randomized to the Uniject arm were excluded from this analysis.

Table S5. Expelled Weight of Medroxyprogesterone Acetate Suspension by Treatment Arm

	Uniject	Pre-Filled Syringe
N	34	29
Mean (mg)	650.1	685.9
SEM (mg)	6.3	24.7
95% CI for the Mean	(637.2, 663.0)	(635.4, 736.5)

N = number of subjects; SEM = standard error for the mean; CI = confidence intervals

Day 92 Serum MPA Levels (biomarker for contraceptive efficacy): All subjects who were dosed with Uniject had serum levels of MPA above 0.1ng/mL at Day 92**.**

IV.3 Pharmacodynamics

No new studies have been conducted and none are required.

IV.4 Clinical efficacy

No new studies have been conducted and none are required.

IV.5 Clinical Safety

With the exception of data collected during the pharmacokinetic study, no new safety data were collected and none were required. No new or unexpected safety concerns were raised during the pharmacokinetic study.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an RMP in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to SAYANA 104mg/0.65ml suspension for injection.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

A user consultation with target patient groups on the PIL has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The product is identical in quantitative and qualitative composition to SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589), albeit with an injection system that is based on Uniject® technology. The marketing authorisation holder has provided suitable pharmacokinetic data to show that the levels of serum medroxyprogesterone acetate is comparable between this product and Sayana using the pre-filled syringe system (PL 00057/0589).

No new or unexpected safety issues occurred during the pharmacokinetic study.

The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory with the data collected and consistent with other similar products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The currently approved labels are listed below:


5 013457 028119
Pfizer Limited
Ramsgate Road
Sandwich
Kent, CT13 9NJ,
United Kingdom
PL 00057/1093
Ref: SN 2_0
Pfizer
SAYANA® PRESS 104 mg/0.65 ml
suspension for injection
medroxyprogesterone acetate
0.65 ml suspension for injection
104 mg medroxyprogesterone acetate
Subcutaneous use
1 x Single-dose container
SAYANA® PRESS
104 mg/0.65 ml
suspension for injection
medroxyprogesterone acetate
SAYANA® PRESS 104 mg/0.65 ml
suspension for injection
medroxyprogesterone acetate
LOT/EXP:
Suspension for injection contains: 104 mg medroxyprogesterone acetate.
Also contains: macrogol, E218, E216, sodium chloride, polysorbate 80, monobasic sodium phosphate monohydrate, disodium phosphate dodecahydrate, methionine, povidone, water for injection, hydrochloric acid and/or sodium hydroxide for pH adjustment.
To be used immediately after opening the foil pouch.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not refrigerate or freeze.
Any unused product should be disposed of safely after use, in accordance with local guidance for the disposal of sharps.
POM
GP4493
SP4485

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	**Procedure number**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Approval/ non approval**	**Assessment report attached Y/N (version)**
II	UK/H/0960/ 002/II/029G	SmPC, PIL, RMP			Approval	Yes

Annex I

Reference:	PL 00057/1093-0022 (UK/H/0960/002/II/029G)
Product:	Sayana Press 104mg/0.65ml suspension for injection
Marketing Authorisation Holder:	Pfizer Limited.
Active Ingredients:	Medroxyprogesterone acetate
Reason:	To update the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) to include the option for self-injection.

Background
Sayana Press (DMPA-SC in Uniject) was initially approved for use as an injectable contraceptive when administered by a healthcare professional and requires 3-monthly clinic visits by patients. The marketing authorisation holder (MAH) proposes the self-injection of Sayana Press, as an option to women who according to the MAH can independently perform the procedure reliably and safely.

Supporting Evidence
The assessment of the clinical data submitted in support of this variation is presented below. In addition to the clinical data submitted, an updated SmPC, PIL and Risk Management Plan were submitted in support of this variation.

Assessor's Comment
The proposed changes to the SmPC and PIL are satisfactory. The marketing authorisation holder has also updated the Risk Management Plan suitably in-line with the proposed option to self-inject.

Conclusion
The grant of this variation is recommended.

Decision - Granted
Date - 15 July 2015

The final variation assessment report for the change to the SmPC/PIL is presented below.

Type II variation
Final updated variation Assessment Report

Sayana Press suspension for injection 104mg/0.65ml
Medroxyprogesterone acetate

UK/H/0960/002/II/29G

Marketing Authorisation Holder: Pfizer Limited

I. RECOMMENDATION

Based on the review of the data on the safety and efficacy, the RMS considers that the variation for Sayana Press suspension for injection 104mg/0.65ml (Medroxyprogesterone acetate) for contraception, for the proposed changes to section 4.2 of the Summary of Product Characteristics with consequential changes to the Patient Information and instructions for use to introduce the option of self-injection by patients is approvable.

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

This Grouped Type II C.I.4 variation concerns changes to section 4.2 of the Summary of Product Characteristics with consequential changes to the Patient Information and Instructions for Use for Sayana Press (medroxyprogesterone acetate 104mg/0.65ml) to introduce the option of self-injection by patients.

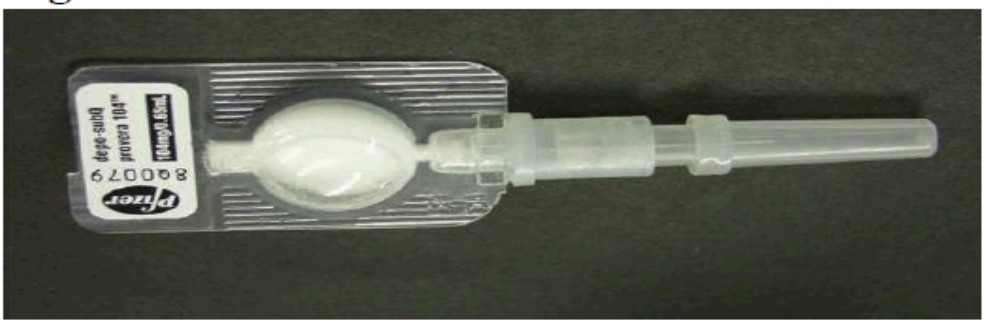
As a consequence of this new proposed mode of administration, the current medroxyprogesterone acetate subcutaneous Risk Management Plan is updated and reformatted in-line with Pharmacovigilance Module V Guidance and to introduce relevant revisions to the Part II: Module SVI section. The RMP is assessed separately to this variation.

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

Sayana Press (DMPA-SC in Uniject) is currently approved for use as an injectable contraceptive when administered by an HCP and requires 3-monthly clinic visits by patients. The MAH proposes the self-injection of Sayana Press, as an option to women who according to the MAH can independently perform the procedure reliably and safely. The container closure system for Sayana Press utilises a prefilled plastic reservoir with needle attached, designed for single use and immediate disposal,

Figure 1. SAYANA PRESS



III.3.1 Clinical pharmacology

N/A

III.3.2 Clinical efficacy

To support the application, the MAH provides data from

- Two (2) MAH-sponsored, 1-year, single-arm, Phase 3 safety and efficacy trials of DMPA-SC in prefilled syringes (Study 267 and Study 269). (These studies were used to demonstrate the efficacy and safety of DMPA-SC in the original application for Sayana).

- One (1) Investigator-initiated, non-randomised, independent study that compared the self-injection of DMPA-SC in prefilled syringes versus administration of DMPA-IM (depot medroxyprogesterone acetate, intramuscular) by a healthcare professional in the clinic (Study GA67815);

- One (1) usability study assessing the ability of representative users to correctly operate the Uniject injection delivery system according to the instructions provided (Study A6791035)

- Relevant clinical studies published in the medical literature.

Main studies
Study 269

A 1-year, Phase III, open-label, non-comparative, multicentre study, conducted to assess the safety and efficacy and subject satisfaction with medroxyprogesterone acetate104mg/0.65ml (DMPA-SC) (prefilled syringe) given every 3 months (13 weeks ± week) via the subcutaneous route.

Study objectives
Primary: The primary objective was to assess the efficacy of DMPA-SC contraceptive injection administered every 3 months.

Secondary: The secondary objective was to assess the safety of DMPA-SC contraceptive injection administered every 3 months. Additionally, subject satisfaction with the treatment results and treatment processes of DMPA-SC self-injected at home were evaluated, and the efficacy and safety of DMPA-SC contraception injection self-injected at home were assessed.

Method
This was a phase 3, open-label, non-comparator, multinational, multicentre study designed to assess the efficacy and safety of and subject satisfaction with DMPA-SC given every 3 months for 1 year. The drug was initially to be administered during office visits that were scheduled at 3-month intervals. However, an amendment to the protocol allowed subjects at selected sites to self-inject the drug at home during the last half of the 1-year study. A total of 1065 women were treated in the trial.

Study participants
Women between the ages of 18 and 49 years; being sexually active; desiring long-term contraception who met all of the following criteria were eligible for the study:

- Being between the ages of 18 and 49 years
- Being sexually active and desiring long-term contraception (including women who currently used oral, intrauterine, or barrier methods and wished to switch to DMPA-SC contraception)
- Having been off of oral contraceptives for the 2 months prior to enrolment when applicable and having used a barrier (excluding intrauterine device) method of contraception or having been sexually inactive during this pre-screening period
- Having a negative urine pregnancy test
- Willing to rely upon DMPA-SC for contraception for at least 1 year (4 doses total, with 1 dose at 0, 13, 26, and 39 weeks)
- Menstruating regularly during the 3 months (cycle length of 25 to 35 days) prior to enrolment
- Willing to sign informed consent and able to comply with the study-specific procedures.

Treatments Administered

Women were treated with a 104-mg dose of DMPA-SC at visit 1 and subsequently every 91 ± 7 days for 1 year. Pre-filled syringes with needles supplied separately were utilised in this study as opposed to prefilled plastic reservoir with needle attached also known as Uniject.

Primary Endpoint

The primary efficacy endpoint was the treatment failure cumulative pregnancy rate at 1 year, which was defined as a positive pregnancy test prior to the next scheduled injection.

Secondary Endpoint(s)

The secondary endpoints included a hormone profile and the incidences of amenorrhea, irregular bleeding, and adverse events. Sitting blood pressure, weight, and routine laboratory safety assays were also evaluated. Secondary endpoints at selected sites included endometrial biopsies and endometrial thickness measurements.

Outcomes Research Endpoints:

Patient Satisfaction Questionnaire

The patient satisfaction (PSQ) instrument was administered at visits 1 (the injection visit), 4 (6 months), and 6 (1 year). It was a self - administered instrument containing 5 to 7 items (depending upon the 10. No formal validation of the instrument was undertaken prior to the trial. Evaluation of the treatment processes included the subjects' evaluations of the instruction they received, confidence in the injection technique, unexpected pain associated with injection, convenience of the treatment method, and the difficulty following the injection schedule.

End-of-Treatment Questionnaire

The End-of-Treatment Questionnaire (EOTQ) was administered at visit 6 (1 year). The questionnaire consisted of 27 items and collected information about the subject satisfaction with the self-injection treatment process. A section was also included in the questionnaire to gather information on why subjects who did not elect to self-inject made such a decision. No formal validation of the instrument was undertaken prior to the trial.

It is noted that home self-injection was not originally the subject of this study but was added on as an amendment to the protocol and this allowed subjects at selected sites to self-inject. In addition the option to self-inject was an outcome research endpoint and not a primary or secondary endpoint.

It is also noted that the tools used to measure subjects' satisfaction were not appropriately validated, however, this is not a major concern.

Statistical Methods:

Primary and secondary endpoint analyses used the intent-to-treat (ITT) populations. The ITT efficacy population included all subjects who received at least 1 dose of study medication and had at least 1 visit after the first dose. The ITT safety population included all subjects who received at least 1 dose of study medication.

Sample size was set to accumulate at least 5000 cycles of experience with DMPA-SC (1 cycle = 1 month) and to include for 1 year at least 200 subjects who were 35 years old or younger. Assuming a subject dropout rate of 12% after each clinic visit if 850 subjects were enrolled, after 1 year in the study, the overall dropout rate was calculated to be approximately 40%, with over 7400 cycles accumulated in DMPA-SC-treated subjects.

For data analyses, a skip pattern within the EOTQ was triggered by whether the subject reported that they had or had not self-injected at home during the course of the study. If discrepancies existed between self-reported and study site-reported home self-injection status, those subjects were dropped from the analyses (n = 3). If no site-reported home self-injection data were available, those subjects were kept in the analysis using their self-reported status. Therefore, for these analyses, the denominator of self-injecting subjects was higher than that reported by the study sites. Applying the decision rules left a total of 533 respondents to the EOTQ

Results

Disposition of Subjects:

The ITT population consisted of 1065 subjects who received at least 1 dose of study medication (6 subjects did not return after their first dose, so the efficacy analyses were based on 1059 subjects; adverse event data were based on 1060 subjects). Of these, 80.4% (856/1065) completed the study. Two hundred and nine subjects discontinued the study treatment prior to 1 year. The most common reasons for subject discontinuation were withdrawal of consent, adverse events, and lost to follow-up.

Table 2. Study 269 - Exposure to DMPA-SC (ITT Population)

Subjects Receiving Injections		DMPA-SC N = 1065		
		n	Total	%*
Within protocol-specified range	3-month	936	995	94.1
	6-month	836	905	92.4
	9-month	834	865	96.4
Total self-injections by visit	Enrolment	62	1065	5.8
	3-month	357	994	35.9
	6-month	468	907	51.6
	9-month	571	868	65.8
Clinic self-injections by visit	Enrolment	62	1065	5.8
	3-month	357	994	35.9
	6-month	466	907	51.4
	9-month	366	868	42.2
Home self-injections by visit	6-month	2	228[t]	0.9
	9-month	205	372[t]	55.1

cm = centimetre; DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects who participated in the study; n = number of subjects with measured characteristic.
* % = (n/total reported within visit) x 100.
t. Number of subjects offered a choice of home self-injection.
Source: Study 269 CSR Table 4.

Baseline Characteristics

The mean subject age was 32.2 years; most of the subjects were 35 years of age or younger (69.4%, 739/1065) and almost all of them were white (97.9%; 1043/1065). The mean BMI was 23.2kg/m^2. Most subjects (81.2%, 865/1065) received 4 injections of DMPA-SC.

Table 1. Study 269 - Summary of Demographic Characteristics (ITT Population)

Characteristic	DMPA-SC (N = 1065)
Age (years)	
Mean ±SD	32.2 ± 7.2

Range	18.0 - 49.6
≤35, n (%)	739 (69.4)
>35, n (%)	326 (30.6)
Race, n (%)	
White	1043 (97.9)
Black	1 (0.1)
Asian/Pacific Islander	20 (1.9)
Mixed/Multiracial	1 (0.1)
Weight (kg)	
Mean ± SD	62.6 ± 11.3
Range	35.0 - 113.2
Height (cm)	
Mean ± SD	164.1 ± 6.4
Range	137.2 - 184.0
Body Mass Index (kg/m^2)	
Mean ± SD	23.2 ± 3.9
Range	15.4 - 40.6
≤25, n (%)	779 (73.1)
>25 to 30, n (%)	219 (20.6)
>30, n (%)	67 (6.3)
cm = centimetre; DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; kg = kilogram; m = metre; N = total number of subjects who participated in the study; n = number of subjects with measured characteristic; SD = standard deviation. Source: Study 269 CSR Table 2.	

Treatment Compliance

More than 92% of the injections were administered within the protocol-specified range. Of the 205 women who self-injected at home, 10 had at least one injection that was out of the compliance range (91 ± 7 days); these injections were outside of the range by 1 or 2 days only.

Efficacy Results

The primary efficacy endpoint of treatment failure cumulative pregnancy rate at 1 year was 0%. =The Pearl Index, the number of pregnancies per 100 woman-years was 0. Therefore, from the information provided it would appear that no pregnancies occurred at all in the study as a whole.

Table 3. Study 269 – Woman-Cycles of Exposure (ITT Population)

Type of Injection	Number of Injections	Woman-Cycles of Exposure	Woman-Cycles of Exposure with Specific Exclusions*		
			Months without consistent barrier use	Months with no consistent or occasional barrier use	Months with intercourse and with no barrier use
Office Injection by Professional	2366	7098	6790	6482	6278
Office Self-Injection	1251	3753	3701	3615	3531
Home Self-Injection	207	621	601	577	566
Total	3824	11472	11093 †	10699†	10407 †

ITT = intent-to-treat.
* In the bleeding pattern diary, subjects were asked each month if they had used a barrier contraceptive (e.g., condom, diaphragm), and if so, how often (every time or sometimes); they were also to note whether they had engaged in sexual intercourse.
†Adding cycle numbers sorted by types of injections will not sum to these totals. If a subject's injection type changed during a given month, exclusion was applied to both types of injections.
Source: Study 269 CSR Table 5.

Self-injection

At least 1 self-injection was performed by 61.6% (656/1065) of the subjects, including self-injections performed at the clinic. Self-injection at home was performed by 19.2% (205/1065) of the subjects. None of the self-injecting subjects experienced a contraceptive failure.

Table 4. Study 269 - Self-Injection Summary by Visit in the ITT Population

Treatment: DMPA-SC (N=1065)		
	Visit	
	Month 6	Month 9
	n	n
Did the Patient Self-Inject?		
Yes	2	205
No	226	167
Total Reported	228	372
Difficulty with injection?		
Yes	No data	7
Total Reported	No data	7
Return to office for assistance with self-injection?		
Yes	No data	3
Total Reported	No data	3

DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects participated in study; n = number of subjects with measured characteristic.
Source: Study 269 CSR Table T3.6.

Assessment of the Self-Injection Experience
The EOTQ was completed by 536 subjects. According to the applicant whether the subject had self-injected at home was not always recorded by the clinical sites therefore data for a few subjects is missing. 523 subjects completed the study and 10 who did not (there is a disparity as some subjects (3) were kept in the analysis using their self-reported status even if site reported data was not available for them).

Among those who received training prior to making a decision about whether to self-inject at home, 80.3% (355/442) reported that the training was valuable in helping to make that decision. Subjects who self-injected at home rated their instruction significantly higher with regard to how well it prepared them for home injection and how well the training materials answered questions than did those who did not self-inject at home.

Subjects who self-injected at home also reported significantly greater confidence in their ability to inject themselves correctly and rated how well the office staff answered their questions about the medication's efficacy, safety, and the injection method significantly higher.

Of the subjects who self-injected at home, 78.2% (158/202) reported that they referred to the take-home injection instructions and 71.9% (146/203) indicated that they had not contacted the doctor's office for additional injection instructions.

No significant difference was found between those who chose home self-injection and those who did not with regard to how well the office staff answered their questions about the medication's efficacy, safety, and the injection method.

Table 5. Study 269 – Subject Evaluation of Training, Training Materials and Support for Self-Injection

	N	%	Did Home Inject, mean (SD) N	Did Not Do Home Inject, mean (SD) N	p-value
When self-injection training was given					
After decision to home inject	41	7.9			
Before decision to home inject	452	86.9			
Received no instruction	27	5.2			
Did instruction help to make home injection decision (among those getting training before decision)					
Yes	355	80.3			
No	87	19.7			
Rating of how well instruction prepared you for home injection (among those getting training)*			9.46 (.98) 202	7.60 (2.15) 286	<.001
Rating of confidence in being able to home inject correctly (among those getting training)*			9.51 (.75) 204	6.86 (2.54) 287	<.001
Rating of how well training materials answered questions (among those getting training)*			9.52 (.88) 175	8.04 (2.19) 288	<.001
Did you review take-home instructions before injecting (among those reporting home injection)?					
Yes	158	78.2			
No	44	21.8			
Did you contact the doctor's office before injecting (among those reporting home injection)?					
Yes	57	28.1			
No	146	71.9			
Rating of how well office staff answered questions (all respondents)*			9.91 (.28) 103	9.28 (1.09) 291	<.001

N = total number of subjects participated in study; SD = standard deviation.
* Rating on a scale of 1 (worst) to 10 (best) with appropriate definition for each question.
Source: Study 269 CSR Table T12.3.

Table 6. Study 269 - EOTQ: Evaluation of Self-Injection Procedures and Experiences

EOTQ QUESTION	N	%	mean (SD)
Did you use the injection reminder stickers?			
Yes	138	31.3	
No	63	68.7	
Rating of the efficacy of the reminder stickers (among those using the stickers)*	63		9.51 (1.12)
Rating of the ease of following the injection schedule correctly*	201		9.59 (0.78)
Rating of the ease of doing home Injection*	204		9.26 (1.03)
Rating of the convenience of home injection*	204		9.42 (1.02)
Rating of the injection pain during home injection*	204		9.07 (1.25)
If you continued using the injectable contraceptive, where would you prefer to obtain the syringes?			
Doctor's office	97	48	
Local pharmacy	90	44.6	
Through the mail	15	7.4	
What factors lead to the decision to home inject? (Subjects may indicate >1 factor)			
More convenient	155	47.8	
Feel more independent	84	25.9	
I am a health professional	45	13.9	
I self-inject other medications	34	10.5	
Other	6	1.9	

EOTQ = End-of-Treatment Questionnaire; N = number of subjects participated in study; SD = Standard deviation.
* Ratings used a scale of 1 (worst) to 10 (best), with definitions appropriate for each of the questions; for example, pain was rated as 1="unbearable pain" to 10="no pain".
Source: Study 269 CSR Table T12.4.

The 204 respondents identified 324 factors which led them to make a decision to self-inject (there was an option to select more than one factor). Convenience was cited most frequently as a factor leading to self-injection, accounting for 47.8% (155/324) of the responses. A feeling of greater independence accounted for another 25.9% (84/324) of the responses.

Similarly, those who did not self-inject were asked to identify what factors led them to their decision (Table 7). The 316 respondents identified a total of 482 factors. Among those who did not self-inject, the most frequently cited reason (25.3%, 122/482) was concern that an error during the injection procedure may result in pregnancy. Concern that they would make an error during the injection that would cause pain accounted for 22.8% (110/482) of the responses. Having difficulty inflicting injection pain on themselves and being afraid of the sight of needles accounted for 18.0% (87/482) and 12.2% (59/482) of the responses, respectively. Never being given the opportunity to self-inject was cited by 8.5% (41/482) of the subjects. Only 3.7% (18/482) of the respondents reported that the training had not adequately prepared them for self-injection.

Table 7. Study 269 - EOTQ: Factors Leading to Decision Not to Self-Inject

What Factors Led to the Decision Not to Home Self-Inject?	N	%*
Concerned error might result in pregnancy	122	25.3
Concerned error might cause pain	110	22.8
Difficult to inflict pain on oneself	87	18.0
Afraid of sight of needle	59	12.2
Other	45	9.3
Never given opportunity to home inject	41	8.5
Training didn't prepare me to home inject	18	3.7

EOTQ = end-of-treatment questionnaire; N = number of subjects participated in study.
* Proportion of N=482 responses (provided by N=316 respondents).
Source: Study 269 CSR Table T12.5.

Of the subjects who had self-injected, 78.8% (160/203) indicated a preference to continue self-injection if they chose to use DMPA-SC for future contraceptive needs, whereas 21.4% (67/313) of those who had not self-injected at home stated that they would prefer to self-inject, as shown in Table 8, which also shows the injection preferences when expressed across all of the EOTQ respondents. Self-injections were preferred by 44.0% (227/516) of all respondents, with 35.5% (183/516) preferring that staff at their doctor's office inject them and 20.5% (106/516) preferring to inject themselves at the doctor's office.

Table 8. Study 269 - EOTQ - Preferences for Future Injections (ITT Population)

Injection if Treatment Is Continued	Did Self-Injection		Did not do Self-Inject		Total	
	N	%	n	%	n	%
Home self-injections	160	78.8	67	21.4	227.0	44.0
Injected by staff at doctor's office	22	10.8	161	51.4	183.0	35.5
Self-injection at doctor's office	21	10.3	85	27.2	106.0	20.5
Total	203	99.9*	313	100.0	516.0	100.0

EOTQ = end-of-treatment questionnaire; ITT = intent-to-treat.
*Total does not equal 100% due to rounding.
Source: Study 269 CSR Table T12.6.

Conclusions

Just over half of the subjects who participated in the trial completed the EOTQ. The results suggest that subjects who received training prior to self-injecting were happy with the training received and able to self-inject using the instructions provided. Overall, however, no firm conclusion can be made regarding the findings of the EOTQ as it was not appropriately validated.

Study 267

A Phase III, open-label, multinational, multicentre 1-year study was conducted to assess the efficacy, safety, and subject satisfaction of DMPA-SC given every 3 months. An amendment to the protocol allowed subjects to self-inject at home during the last half of the 1-year study.

Study participants

Women who met all of the following criteria were eligible for the study: being between the ages of 18 and 49 years; being sexually active; desiring long-term contraception (including women who currently used oral, intrauterine, or barrier methods and wished to switch to DMPA contraception); having been off of oral contraceptives for the 2 months prior to enrolment when applicable and having used a barrier (excluding intrauterine device) method of contraception or having been sexually inactive during this pre-screening period; having a negative urine pregnancy test; willing to rely upon DMPA-SC for contraception for at least 1 year (4 doses total, with 1 dose at 0, 13, 26, and 39 weeks); menstruating regularly during the 3 months (with an average cycle length of 25 to 35 days) prior to enrolment; willing to sign informed consent; and willing and able to comply with the study-specific procedures.

Treatments Administered

Women were treated with a 104-mg dose of DMPA-SC at visit 1 and subsequently every 91 ± 7 days for 1 year.

Endpoints/statistical methods

The endpoints and statistical method used are broadly in line with that of study 269

Results
Baseline Characteristics:

Table 10. Study 267 - Summary of Demographic Characteristics (ITT Population)

Characteristic	DMPA-SC N = 722
Age (years)	
Mean ± SD	28.2 ± 7.0
Range	18.0-49.9
≤35, n (%)	610 (84.5)
>35, n (%)	112 (15.5)
Race, n (%)	
White	485 (67.2)
Black	61 (8.4)
Asian/Pacific Islander	22 (3.0)
Mixed/Multiracial	154 (21.3)
Weight (kg)*	
Mean ± SD	66.5 ± 16.7
Range	38.8-164.9
Height (cm)*	
Mean ± SD	161.7 ± 7.2
Range	129.0-180.3
Body Mass Index (kg/m2)†	
Mean ± SD	25.3 ± 5.7
Range	14.7-57.7
≤25, n (%)	403 (55.8)
>25 to 30, n (%)	189 (26.2)
>30, n (%)	126 (17.5)

cm = centimetre; DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; kg = kilogram; m = metre; N = total number of subjects who participated in the study; n = number of subjects with measured characteristic; SD = standard deviation.
* N=720; † N=718.
Source: Study 267 CSR Table 2.

Extent of Exposure

Over two-thirds (68.8%, 497/722) of the subjects received 4 injections of DMPA-SC. At least 1 self-injection was performed by 53.2% (384/722) of the subjects, with 10.1% (73/722) receiving 1 home self-injection.

Table 11. Study 267 - Exposure to DMPA-SC (ITT Population)

Subjects Receiving Injections		DMPA-SC N=722		
		n	Total	%*
Within protocol-specified range	3-month	607	636	95.4
	6-month	522	550	94.9
	9-month	483	497	97.2
Total self-injections by visit	Enrolment	12	721§	1.7
	3-month	90	636	14.2
	6-month	203	551	36.8
	9-month	330	497	66.4
Clinic supervised self-injections by visit	Enrolment	12	721§	1.7
	3-month	90	636	14.2
	6-month	203	551	36.8
	9-month	257	497	51.7
Home self-injections by visit	9-month	73†	338††	21.6

DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects participated in study.
* % = (n/total reported within visit) x 100. § Data missing for 1 subject.
† Number is 72 in Table T5.4 because 1 subject's attempt at home self-injection was unsuccessful.
††Based on the number of subjects offered home self-injection.
Source: Study 267 CSR Table 4.

Table 12. Study 267 - Woman-Cycles of Exposure (ITT Efficacy Population)

Type of Injection	Number of Injections	Woman-Cycles of Exposure	Woman-Cycles of Exposure with Specific Exclusions*		
			Months with no consistent barrier use	Months with no consistent or occasional barrier use	Months with intercourse and with no barrier use
Office Injection by Professional	1768	5304	5082	4793	4023
Supervised Self- Injection	563	1689	1658	1586	1348
Independent Self-Injection	72	216	214	204	173
Total	2403	7209	6960†	6605†	5616†

ITT = intent-to-treat.
* In the bleeding pattern diary, subjects were asked each month if they had used a barrier contraceptive (e.g., condom, diaphragm), and if so, how often (every time or sometimes); they were also to note whether they had engaged in sexual intercourse.
†Adding cycle numbers sorted by types of injections will not sum to these totals. If a subject's injection type changed during a given month, exclusion was applied to both types of injections.
Source: Study 267 CSR Table 5.

Table 13. Study 267 - Self-Injection Summary by Visit in the ITT Population

Treatment: DMPA-SC (N= 722)		
	Visit	
	Month 6	Month 9
	n	n
Did Patient Self-Inject?		
Yes	0	73
No	174	265
Total Reported	174	338
Difficulty with injection?		
Yes	No data	8
Total Reported	No data	8
Return to office for Injection?		
Yes	No data	1
Total Reported	No data	1

DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects who participated in the study; n = number of subjects with measured characteristic.
Source: Study 267 CSR Table T3.6.

The primary efficacy endpoint of treatment failure cumulative pregnancy rate at 1 year was 0%. None of the 720 subjects with data became pregnant during the study. The Pearl Index, the number of pregnancies per 100 woman-years, was also 0.

Self-injection

The EOTQ was completed by 396 subjects. Application of the rules that applied to study 269 (mentioned above) left a total of 394 respondents to the EOTQ. These included 374 subjects who completed the study and 20 who did not.

The subjects indicated a high level of satisfaction with the injection training they received from study site personnel. Among those who received training prior to making a decision about whether to self-inject, 72.9% (145/199) reported that the training was valuable in helping them to make that decision. Subjects who self-injected rated their instruction significantly higher with regard to how well it prepared them for self-injection and how well the training materials answered questions than did those who did not self-inject. Subjects who self-injected also reported significantly greater confidence in their ability to inject themselves correctly.

Of the subjects who self-injected, 88.6% (70/79) reported that they referred to the take-home injection instructions and 93.6% (73/78) indicated that they had not contacted the doctor's office for additional injection instructions.

Table 15. Study 267 - EOTQ: Evaluation of Home Self-Injection Procedures and Experiences

EOTQ Question	N	%	Mean (SD)
Did you use the injection reminder stickers?			
Yes	25	31.6	
No	54	68.4	
Rating of the efficacy of the reminder stickers (among those using the stickers)*	25		9.64 (1.11)
Rating of the ease of following the injection schedule correctly*	79		9.63 (0.7)
Rating of the ease of doing home Injection*	79		9.43 (0.81)
Rating of the convenience of home injection*	79		9.73 (0.64)
Rating of the injection pain during home injection*	79		8.47 (1.84)
If you continued using the injectable contraceptive, where would you prefer to obtain the syringes?			
Doctor's office	28	36.8	
Local pharmacy	24	31.6	
Through the mail	24	31.6	
What factors lead to the decision to home inject? (Subjects may indicate >1 factor)			
More convenient	69	53.9	
Feel more independent	40	31.3	
I am a health professional	11	8.6	
I self-inject other medications	3	2.3	
Other	5	3.9	

EOTQ = End of Treatment Questionnaire; N = number of subjects participated in study; SD = standard deviation;
* Ratings used a 1 (worst) to 10 (best) scale with appropriate definition for each question
Source: Study 267 CSR Table T10.4.

The calendar reminder stickers that were provided to the subjects were used by 31.6% (25/79) of those who self-injected. Among the subjects who used them, the reminder stickers were considered to be highly effective. Subjects also highly rated the ease of adhering to the injection schedule, the ease of performing the self-injection, and the convenience of the contraception method. The pain associated with self-injection was considered minor (mean of 8.47, wherein 1 was unbearable pain and 10 was no pain). The respondents indicated that if they continued to use DMPA-SC for contraception, 36.8% (28/76) would prefer to get their syringes from the doctor's office, 31.6% (24/76) from the local pharmacy, and 31.6% (24/76) through the mail.

The respondents who had self-injected were asked what led them to that decision; they could have selected more than 1 factor. A total of 128 factors were identified by the 78 respondents. Convenience was cited most frequently as a factor leading to self-injection, accounting for 53.9% (69/128) of the responses. A feeling of greater independence accounted for another 31.3% (40/128) of the responses. Similarly, those who did not self-inject were asked to identify what factors led them to their decision (Table 16). A total of 330 factors were identified by the 225 respondents. Among those who did not self-inject, the most frequently cited reason (24.5%, 81/330) was that they had never been given the opportunity to do so. Other concerns included the possibility that the injection would cause pain; that an injection error might result in pregnancy; and general uneasiness with needles.

Only 4 responses suggested that the training had not adequately prepared the subject for home self-injection.

Table 16. Study 267 - EOTQ: Factors Leading to Decision Not to Self-Inject

What Factors Led to the Decision Not to Home Self-Inject?	N	%*
Never given opportunity to home inject	81	24.5
Concerned error might cause pain	52	15.8
Difficult to inflict pain on	49	14.8
Afraid of sight of needle	39	11.8
Concerned error might result in pregnancy	34	10.3
Training didn't prepare me to home inject	4	1.2
Other	71	21.5

* Proportion out of N=330 total responses reported by N=225 respondents;
EOTQ = end of treatment questionnaire.
Source: Study 267 CSR Table T10.5.

Of the subjects who had self-injected, 94.9% (74/78) indicated a preference to continue self-injection if they chose to use DMPA-SC for future contraceptive needs, whereas 47.9% (139/290) of those who

had not self-injected would prefer to self-inject. Table 17 provides the preferences for future injections expressed across all of the EOTQ respondents. Self-injections were preferred by 57.9% (213/368) of all respondents, whereas preferences for the other alternatives were nearly equal, with 21.5% (79/368) preferring to inject themselves at the doctor's office and 20.7% (76/368) preferring that the staff at their doctor's office inject them.

Table 17. Study 267 - EOTQ: Preferences for Future Injections (ITT Population)

Injection if Treatment Is Continued	Did Self-Injection		Did not do Self-Injection		Total	
	N	%	n	%	n	%
Home self-injections	74	94.9	139	47.9	213	57.9
Self-injection at doctor's office	3	3.8	76	26.2	79	21.5
Injected by staff at doctor's office	1	1.3	75	25.9	76	20.7
Total	78	100	290	100	368	100.1*

EOTQ = End of Treatment Questionnaire; ITT = Intent to treat population; N = number of subjects who participated in the study; n = number of subjects with the measured characteristic.
*Total does not equal 100% due to rounding
Source: Study 267 CSR Table T10.6.

Conclusion

The results suggest that subjects who received training prior to self-injecting were happy with the training received and able to self-inject using the instructions provided. However, only about 31% of the subjects used the calendar reminder stickers

Study GA67815

A prospective, open-label, parallel-group, non-randomised study designed to evaluate the feasibility and acceptability of self-administration of DMPA-SC in terms of efficacy, safety and patient perceptions. This study was independently conducted and not sponsored by the MAH although they supplied the pre-filled syringes with separate needles to the investigators.

Objectives:

The study was designed to determine feasibility of self-administration of hormonal injectable contraception by answering the following questions.

1. Whether self-administration of depot medroxyprogesterone acetate administered subcutaneously (DMPA-SC) will result in improved continuation rates compared with depot medroxyprogesterone acetate administered intra-muscularly (DMPA-IM) after 12 months?

2. Whether self-administration will lead to greater satisfaction with this contraceptive?

3. If women who self-administer DMPA-SC will do so at the correct time interval?

4. Which proportion of women, who expressed a theoretical wish to self-administer DMPA-SC, will do so in practice? (It should be noted that this objective is not addressed in this report).

5. Whether self-administration of DMPA-SC will result in the need for increased non-scheduled contact with Family Planning providers?

Study population and selection criteria

Women aged 18 to 40 years; using DMPA-IM for at least the previous 9 months and wishing to continue using DMPA for more than one year were eligible to participate in the study. Subjects were required to fulfil the following criteria:

- No contraindications to DMPA (World Health Organization [WHO] Medical Eligibility Criteria – category 3 or 4);
- Not wishing to conceive within the next 2 years;
- Not planning to move out of the area for at least 12 months;
- Willing to be contacted at work or at home;
- Without significant pre-existing medical conditions;
- Willing and able to give informed consent.

Study Treatment:

Subjects in the DMPA-SC group received the product SC once every 3 months. For the DMPA-SC group, the injection delivery system used in this study consisted of a pre-filled syringe with a separately packaged, sterile, SC needle (26 gauge) that was required to be attached to the syringe body prior to use (Sayana®). The injection delivery system used in this study consisted of a pre-filled syringe with a separately packaged, sterile, SC needle while Sayana Press consists of a prefilled plastic reservoir with a needle already attached.

Primary efficacy endpoint:

- The continuation rate of the method at 12 months compared to a control group of existing users of DMPA-IM (N=64) who continued to attend clinic to receive HCP-administered DMPA-IM (discontinuation rate).
- The proportion of self-injections that were given at the correct scheduled time
- Injection problems
- Patient's satisfaction with the method

Results

Subject Disposition and Demography:

A total of 178 current users of DMPA-IM were approached to participate in the study; 128 agreed to participate; 64 subjects were randomised to self-administer DMPA-SC and 64 were randomised to receive DMPA-IM administered by a clinician.

Table S1. Subject Disposition

Number of Subjects (%)	DMPA-SC	DMPA-IM
Assigned to study treatment	64	64
Treated	64	64
Completed	50 (78.1)	48 (75.0)
Discontinued	14 (21.9)	16 (25.0)
Analyzed for:		
Safety analysis set	64 (100.0)	64 (100.0)
Efficacy analysis set	58 (90.6)	64 (100.0)
Analyzed for adverse events	64 (100.0)	64 (100.0)

Abbreviations: DMPA-IM = Depot medroxyprogesterone acetate administered intra-muscularly; DMPA-SC = Depot medroxyprogesterone acetate administered subcutaneously.

Table 19. Study GA67815 Demographics at Baseline in the Safety Analysis Set (N=128)

	DMPA-SC Self-Injection Group	DMPA-IM Clinic Group	p-value
No. of women (n)	64	64	
Age (SD), years	28.8 (5.0)	28.3 (5.7)	0.71
Age category: n (%)			
<18 years	0 (0.0)	0 (0.0)	nd
18 - 25 years	17 (26.6)	21 (32.8)	nd
>25 - 40 years	47 (73.4)	43 (67.2)	nd
>40 years	0 (0.0)	0 (0.0)	nd
BMI category (kg/m^2): n (%)			
<18.5	2 (3.1)	2 (3.1)	nd
18.5 - <25	27 (42.2)	28 (43.8)	nd
25 - <30	14 (21.9)	21 (32.8)	nd
30 - <40	14 (21.9)	10 (15.6)	nd
≥40	1 (1.6)	0 (0.0)	nd
missing	6 (9.4)	3 (4.7)	nd
Deprivation Category Index Scores*	3.8 (1.6)	4.0 (1.5)	0.43
Reproductive History			
Births, per subject	0.22 (0.65)	0.19 (0.53)	0.82
Miscarriages, per subject	0.05 (0.21)	0	0.08
Abortions, per subject	0.34 (0.67)	0.23 (0.46)	0.49
Ectopic, per subject	0	0	nd
Total use of DMPA (months)	51 (33)	55 (38)	0.76
Recent continuous use of DMPA (months)	41 (31)	42 (35)	0.99

BMI = body mass index; DMPA = depot medroxyprogesterone acetate; DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; kg = kilogram; N = total number of subjects participated in study; n = number of subjects with measured characteristic; nd = not done; SD = standard deviation.
* Deprivation Score based on postal code and census data, with score = 1 (affluent) and score = 5 (very poor).
Source: Study GA67815 CSR Tables T14.1.2.1 and T14.1.2.2.

Discontinuation Rate:

In the DMPA-SC group, the study medication expired before the last 6 subjects recruited could complete the study. No replacement study medication was available, so these 6 subjects had to be withdrawn from the study prematurely. These 6 subjects were excluded from efficacy analysis.

5 subjects were withdrawn from the study due to adverse events (AEs - 3 had moderate AEs, and 2 had mild AEs), 2 subjects were lost to follow-up and 1 subject was withdrawn from study due to a protocol violation.

In the DMPA-IM group, 4 subjects discontinued due to AEs (2 moderate, 2 mild); 10 subjects were lost to follow-up; 1 subject discontinued as she wished to start a family and 1 subject withdrew consent

Table 4. Discontinuations From the Study

Reason for Discontinuation	DMPA-SC (N = 64)[a]	DMPA-IM (N = 64)
Adverse event[b]	5 (7.8)	4 (6.3)
Lost to follow-up	2 (3.1)	10 (15.6)
Other	7 (10.9)[a]	1 (1.6)
Withdrew consent[c]	0	1 (1.6)
Total number of subjects discontinued	14 (21.9)	16 (25.0)

Sources: Table 14.1.1.2, Table 16.2.1 and Table 16.2.7.2
Abbreviations: DMPA-IM = Depot medroxyprogesterone acetate administered intra-muscularly;
DMPA-SC = Depot medroxyprogesterone acetate administered subcutaneously; N = Total number of subjects.
a. Six of these subjects were withdrawn due to expiry of study medication. One subject was withdrawn due to protocol violation.
b. A subject is represented here as 'discontinued due to an adverse event' if either Table 16.2.1 and/or Table 16.2.7.2 indicate that the subject discontinued for that reason.
c. Subject who had an AE that resulted in discontinuation has been excluded here.

Table 6. Analysis of 12 Month Discontinuation Rate

Treatment Group	N	n	Discontinuation Rate	Asymptotic Standard Error	Asymptotic 95% Confidence Interval		
					Lower	Upper	p-value†
DMPA-SC	58*	8	13.8	4.5	4.9	22.7	
DMPA-IM	64	16	25.0	5.4	14.4	35.6	
Difference			-11.2	7.1	-25.0	2.6	0.1123

Source: Table 14.2.2.2
* Six subjects received medication that expired prior to the end of the study. As these subjects could not complete the trial with all 4 planned injections, these subjects were excluded from the analysis.
† p-value is for comparison of differences based on normal approximation to the binomial.
Abbreviations: DMPA-IM = Depot medroxyprogesterone acetate administered intra-muscularly;
DMPA-SC = Depot medroxyprogesterone acetate administered subcutaneously; N = Total number of subjects;
n = Total number of subjects discontinued by 12 months.

The total number of subjects included in the study is small. However, there does not appear to be any major difference in the reason for discontinuation between the DMPA-SC and DMPA-IM group. It would also appear that a few more subjects were lost to follow-up in the DMPA-IM group which could imply that women were willing and able to continue DMPA-SC

Injection Problems.

A total of 235 DMPA-SC self-injections by 64 DMPA-SC subjects were attempted in this study. Of these, 64 were self-injections performed at the Baseline visit, in the clinic, under supervision, following the training session. A total of 171 self-injections were attempted at home, at the post-baseline time points (3 months, 6 months, and 9 months. Most of the 235 DMPA-SC self-injections were completed without a reported problem, but there were 33 separate reports of problems occurring in 20 of the 64 DMPA-SC subjects. The incidence of injection problems was low (6% of subjects) at the baseline Visit, when the self-injection was done under supervision of the healthcare professional. It was higher at the first self-injection at Month 3 (21% of subjects), but declined for the subsequent self-injections (9% at 6 months; 8% at 9 months). The most commonly reported injection problem in this study was an injection system issue, reported by 14 of the 20 subjects (70%) who reported injection problems. One issue encountered by these subjects was difficulty with the attachment of the needle to the body of the prefilled syringe.

The other self-injection problem was difficulty expelling the suspension through the 26-gauge needle that was supplied with the prefilled syringe.

There were 3 instances where a subject attempting self-injection encountered a problem that led them to return to the clinic in order to have the injection performed by the healthcare professional: (i) Subject SC050 returned to clinic for assistance with self-injection, but at the clinic was given an injection of DMPA-IM in error and the subject was discontinued from the study at Month 3 due to this dosing error (protocol deviation). (ii) Subjects SC045 and SC054 also experienced difficulty at

home and returned to clinic for assistance, where they successfully self-injected DMPA-SC under supervision.

Table 7. Number of DMPA-SC Self-injections Performed and Incidence of Reported Problems with Self-injection of DMPA-SC

DMPA-SC Subjects	No. of Self-Injections performed, n		No. of subjects reporting a 'problem' with the self-injection, n (%)
	Primary Efficacy Population (N = 58)	Safety Analysis Population (N = 64)*	Safety Analysis Population (N = 64)*
Baseline (at clinic)	58	64	4 (6%)
3 months (at home)	56	62	13 (21%)
6 months (at home)	53	58	5 (9%)
9 months (at home)	51	51	4 (8%)
Total 'at home' self-injections	160	171	20† (31%)

Sources: Tables 14.2.3.1, 14.2.3.2, 14.2.2.1, 16.2.5.1, 16.2.6.1
* Includes subjects who were discontinued due to study drug unavailable (expired); n = 6.
† Twenty (20) DMPA-SC subjects provided 33 separate reports of injection problems: 8/64 subjects (13%) reported injection site reaction; 6/64 subjects (9%) reported injection site skin changes; 14/64 subjects (22%) reported injection system problems; 5 of the 33 reports were recurrences of the same problem by the same subject (but occurring at a different time).

A number of self-injection issues occurred during the study including difficulty with the attachment of the needle to the body of the prefilled syringe and difficulty expelling the suspension through the 26-gauge needle. These issues should not occur with Sayana Press as the needle is already attached.

Timeliness of Self-Injections

138 of 171 (81%) self-injections occurred on the scheduled date, with zero deviation. Overall, the timing of self-injections ranged from 35 days early to 14 days late. Only 2 self-injections were given more than 1 week late, but none of the subjects in either treatment group became pregnant during the study. Most subjects self-injected on schedule.

Table 8. Timeliness of Self-Injection Attempts by Subjects

	Total 'At Home Self-Injections' (N)	On Time (scheduled day; no deviation), n (%)	1 to 7 days Early, n (%)	>7 days Early, n (%)*	1 to 7 days Late, n (%)	>7 days Late, n (%)**
DMPA-SC at home self-injections	171†	138 (81%)	14 (8%)	4 (2%)	13 (8%)	2 (1%)

Sources: Table 16.2.5.1
† Two of the self-administration attempts were unsuccessful at home and the drug was actually self-administered under supervision in the clinic, but this table is intended to address the timeliness of a subject's attempt to perform her self-injection.
* The earliest self-injection was performed 35 days prior to the due date; the other early injections in this column were -21, -9, and -8, for a total of n = 4.
** The latest injection was 14 days after the due date; the only other late injection in this column was: +8, for a total of n = 2.

Satisfaction with Method

At the end of the study, 61 of 64 DMPA-SC subjects completed the end-of-study questionnaire. All 61 subjects in the DMPA-SC group who completed a questionnaire were positive about the training that they had received in self-injection, with 54 (88.5%) subjects agreeing that 'self-injection was easy', 5 (8.2%) were not sure and 2 (3.3%) subjects disagreed. Over 90% of subjects also agreed that they had been confident with the technique of self-injection and that they had received the correct dose of medication and that safe disposal of needles was not a problem. 28 subjects (45.9%) considered that the SC injection was less painful than the IM injection, with the same proportion of respondents being 'unsure' if SC injection was less painful (see table below).

Table 9. Agreement With Ease of Use With Method at End of Study

Statement (Responders, N)	Agreed n (%)	Not Sure n (%)	Disagreed n (%)
'Self-injection was easy' (N = 61)	54 (88.5)	5 (8.2)	2 (3.3)
'Confident received correct dose' (N = 60)	58 (96.7)	1 (1.7)	1 (1.7)
'Safe disposal of the needle and syringe was not a problem' (N = 61)	58 (96.7)	1 (1.7)	1 (1.7)
'Subcutaneous injection was less painful than intramuscular' (N = 61)	28 (45.9)	28 (45.9)	5 (8.2)

Source: Table 14.2.4.1
Abbreviations: N = Total number of subjects; n = Number of subjects.

Questionnaires regarding satisfaction with self-administration of DMPA-SC or clinic administration of DMPA-IM were completed by the 61 subjects in the SC group and 54 in the IM group for whom follow-up was available at exit. There was no significant difference in the proportion of subjects in each group who reported feeling either 'the same or better' on their chosen injectable preparation. Similar proportions of subjects in each group also agreed that overall, they were satisfied with their chosen injectable method, would recommend their treatment to a friend and would want to continue treatment by self-injection.

Table 10. Satisfaction With Method at End of Study

	DMPA-SC (N = 61)[a] n (%)[b]	DMPA-IM (N = 54)[a] n (%)[b]
'I feel same or better'	56 (94.9)	53 (98.1)
'I am extremely or somewhat satisfied'	56 (91.8)	53 (98.1)
'I would recommend this to a friend'(administered in clinic)	51 (85.0)	53 (100)
'I would recommend this to a friend'(self-administered)	57 (95.0)	-
'I want to continue this method'(administered in clinic)	50 (82.0)	45 (84.9)
'I want to continue this method'(self-administered)	54 (90.0)	-

Source: Table 14.2.4.2
Abbreviations: DMPA-IM = Depot medroxyprogesterone acetate administered intra-muscularly; DMPA-SC = Depot medroxyprogesterone acetate administered subcutaneously; N = Total number of subjects; n = Number of subjects.
a. Total number is the number of subjects who have exit questionnaire data.
b. The denominators of percentages are the numbers of subjects who gave answers to the corresponding questions.

Study A6791035

This was an open-label study of the ability of naïve subjects to correctly interpret the IFU and operate the Sayana® Press delivery system.

Primary Objective:
To assess the proportion of subjects who were able to successfully operate the delivery system on Visit 2 (Day 90) when relying on the Instructions for Use (IFU) provided.

Secondary Objectives:

a) To solicit descriptive information from subjects (directly and via the observers) regarding the ease of use of the Sayana® Press delivery system, in order to inform potential revisions to the IFU for the product;

b) To quantitatively determine the weight of suspension expelled from the Sayana® Press delivery system during the injection attempt.

Study participants

Normal healthy female volunteers aged 18 to 45 years (inclusive) who were able to read and comprehend French or Dutch. Subjects with prior training in the use of a syringe for the purpose of administering parenteral medications to humans (including self-injection) or animals were excluded, as were subjects who had any severe acute or chronic medical or psychiatric condition or laboratory

abnormality that may have increased the risk associated with study participation or could reasonably have precluded the subject from successfully operating the Sayana® Press delivery system.

The study population was chosen to be representative of women who might use DMPA-SC in the Uniject delivery system. Half of the women volunteers were randomised to receive a hands-on training demonstration at visit 1 whereas the remainder were randomised to receive no hands-on training, however all women were provided with the written IFU.

Method

Each participant was assessed after receiving training from a staff member and reading the IFU (for those in the 'trained' group) or after reading the IFU (for those in the 'untrained' group). The participants were told to follow the instructions and perform an injection into a rubber/foam injection trainer designed to simulate distinct layers of skin, subcutaneous fat and muscle.

The test sessions were led by an Observer/Moderator who conducted the session as laid out by the written Observer Assessment Tool (OAT) that was divided into segments corresponding to the individual steps in the IFU. The Observer recorded the participant's ability to perform each step and noted any errors made by the participant.

Endpoints

The primary endpoint was the Delivery System Success Rate (DSSR) which was calculated based on the data recorded in the OAT by the staff member who led the participant through the assessment and observed their performance. An overall success rate whose one-sided 95% lower confidence bound is greater than 80% will support a conclusion that the design of the delivery system, together with the accompanying IFU, are fit for purpose.

The secondary endpoints were: categorical responses to questions 2 to 5 on the PAT, comments provided by subjects as part of the PAT, time to perform each step as recorded by the observer to the nearest second, and weight of suspension expelled from the Sayana® Press delivery system following injection.
The time required to perform each step on the OAT was summarized and presented by visit and for each step.

Statistical Methods:

Assuming an underlying DSSR >91%, a sample size of approximately 120 randomized subjects would provide at least 90% power to conclude that the DSSR at Visit 2 (Day 90) for Sayana® Press exceeds the threshold value of 80%, evidenced by the one-sided 95% lower confidence bound exceeding 80%. This target sample size assumed that at least 80% of randomized subjects would contribute to the DSSR calculation at Visit 2 (Day 90).

Results

Subject Disposition and Demography:

A total of 120 subjects were assigned to the 2 groups (trained and untrained) equally (i.e., 60 subjects in each group).

All subjects in the study were female. The mean age was 32.4 years and 32.6 years for the trained group and untrained group, respectively. The majority of the subjects were White

Table S2. Demographic Characteristics

	Trained Group	Untrained Group
Number of subjects (females)	60	60
Hormonal status: premenopausal, n (%)	60 (100.0)	60 (100.0)
Age (years), n (%)		
18-25	13 (21.7)	12 (20.0)
26-35	26 (43.3)	26 (43.3)
36-45	21 (35.0)	22 (36.7)
Mean (SD)	32.4 (7.3)	32.6 (6.7)
Range	21-45	20-45
Race, n (%)		
White	54 (90.0)	55 (91.7)
Black	1 (1.7)	3 (5.0)
Other	5 (8.3)	2 (3.3)
Weight (kg)		
Mean (SD)	66.4 (12.4)	65.3 (15.4)
Range	43.4-111.0	45.0-117.0
Body mass index[a] (kg/m^2)		
Mean (SD)	24.3 (4.3)	24.1 (4.9)
Range	17.3-37.5	18.7-42.5
Height (cm)		
Mean (SD)	165.2 (6.1)	164.4 (6.9)
Range	153-181	149-180

Abbreviations: n = number of subjects, SD = standard deviation
a. Body mass index = weight/(height × 0.01)^2.

Results:

Primary

The one-sided 95% lower confidence bound for the trained group was >80% for both visits but this was not the case in the untrained group suggesting that training prior to operating the delivery system was important in helping subjects operate the delivery system successfully

Table 26. Study A6791035 – Summary of Delivery System Success Rate (DSSR)

Visit Day	Number of Subjects	Number of Success	Percent Success	One-sided 95% CI[a]
Trained Group				
Day 1	60	54	90.0%	(81.81%, 100%)
Day 90	60	58	96.7%	(90.42%, 100%)
Untrained Group				
Day 1	60	46	76.7%	(66.66%, 100%)
Day 90	60	53	88.3%	(79.81%, 100%)
All Subjects[b]				
Day 1	120	100	83.3%	(77.02%, 100%)
Day 90	120	111	92.5%	(87.54%, 100%)

a. Wilson method was used to calculate the 95% CI.
b. the results for all subjects reflects a population in which half are trained and half are not trained, which may or may not correspond to a real clinical situation.
CI = confidence interval; DSSR = delivery system success rate.
Source: Study A6791035 CSR Table 14.2.1.1.

Secondary

In the trained group, there was no difference between visits in the DSSR (CI contained 0: -2.42%, 15.75%). On the other hand, in the untrained group, prior experience was shown to be effective as reflected in the higher percent success at Visit 2 (CI did not contain 0: 1.24%, 22.09%).

Table 27. Study A6791035 - Summary and Analysis of Delivery System Success Rate for Visit Difference

Percent Success at Visit 1	Percent Success at Visit 2	Difference	95% CI[a]
Trained Group			
90.0%	96.7%	6.7%	(-2.42%, 15.75%)
Untrained Group			
76.7%	88.3%	11.7%	(1.24%, 22.09%)
All Subjects			
83.3%	92.5%	9.2%	(2.24%, 16.09%)

a. The asymptotic method was used to calculate the 95% CI for difference dependent proportions.
CI = confidence interval.

Problems Encountered During Injection Attempts

For most of the IFU steps assessed by the observer, there were no important differences in performance (i.e., numbers of errors) between the trained group and the untrained group. However, the step that requires the participant to 'activate' the Uniject delivery system appeared to have more errors in the untrained group,

Table 28. Study A6791035 - Success Rates for the Uniject Activation Step Based on OAT Data

	Participants Assessed (N)	Participants Unable to Active the Uniject (n)	% Successful [(N-n)/Nx100]
Trained Group – Day 1	58	2	96.6
Trained Group – Day 90	60	0	100.0
Untrained Group – Day 1	59	8	86.4
Untrained Group – Day 90	60	3	95.0

OAT = observer assessment tool; N = total number of subjects participated in study; n = number of subjects with measured characteristic.
Source: Study A6791035 CSR Table 14.2.3.

It was observed that approximately 36% of the subjects in both the groups (trained group: 37.5%, untrained group: 35.3%) faced 'noticeable difficulty' while trying to expel the medicine on Day 1. However, when the simulated injection was repeated on Day 90, the proportion of participants having difficulty expelling the drug was lower: trained group: 16.7%, untrained group: 22.8%.

Completeness of Injection – Weight of Suspension Expelled from Sayana Press

Generally, subjects in the trained group were able to expel more of the suspension from the Sayana® Press delivery system, compared to the untrained group. Visit-wise, all subjects were able to expel more of the suspension from the Sayana® Press delivery system at Visit 2,

There were 13 subjects who were listed as "expelling" <10 mg of the dose. However, this apparent "loss" may be attributed to small differences in weighing accuracy of the injector since the majority of these subjects (12/13 subjects) did not actually proceed to the injection step. A majority (10 subjects) stopped at Step 5 (activating the injector).

Study A6791035 is a usability study of the instruction for use (IFU) for Sayana Press and the subjects in the study did not at any time self-inject. The results suggest that women that received training prior to trying out the Uniject system were more likely to succeed on first attempt compared to the women who relied solely on the IFU. It would also appear that errors can occur during the use of the delivery system.

Relevant literature references (as considered by the applicant)
Apparently to the applicant there have been three studies reported in the literature that involved self-administration of DMPA-SC (104 mg every 3 months) by patients, either independently or under supervision at the clinic. DMPA-SC in the prefilled syringe was apparently used in the studies.

Beasley A, White K and Westhoff C (Contraception, 2014)

This study evaluated the feasibility, acceptability and continuation rates following self-administration of DMPA-SC for up to 1 year. In addition, trough MPA levels in women who self-injected at home and women who received their injections at the clinic. 137 women were enrolled in to the study out of which 91 were allocated to self-administration, and 90 were able to correctly self-administer DMPA-SC. Eighty-seven percent (87%) of the subjects completed follow-up. The continuation rate for DMPA use at 1 year was not different between the 2 groups: 71% for the self-administration group and 63% for the clinic group (p=0.47). Uninterrupted (perfect) DMPA use was 47% and 48% for the self-administration and clinic administration groups at 1 year (p=0.70), respectively, serum trough MPA levels in both groups were similar and all participants had therapeutic trough MPA levels.

Table 29. Beasley et al. Serum Trough MPA Levels at 12 Month Visit		
Serum MPA (pg/mL)	Clinic Injection by HCP	Self-Injection At Home
Median	641.0	640.8
Mean	686.2	695.8
Minimum	236.4	227.0
Maximum	1283.2	1519.5
HCP = health care professional; MPA = medroxy progesterone acetate; Source: Beasley et al (2014) Figure 2.		

Prabhakaran and Sweet (Contraception, 2012)

This prospective, single-arm, non-comparative study assessed the feasibility, continuation rates and patient satisfaction during a 1-year period of self-administration of DMPA-SC using prefilled syringes. The women were taught to self-inject DMPA-SC at the first visit and then supplied with an injection kit containing the subsequent doses for self-administration. DMPA continuation at 1 year was 74% [95% CI; 62%–86%]. Of 150 possible self-injections, documentation was collected for 124 injections. Of these, 121 (98%) were independent self-injections, and 3 (2%) were supervised self-injections. None of the patients requested to have clinic staff inject the subcutaneous formulation.

By Injection 4, 26% (n=13) of subjects either discontinued DMPA-SC or were lost to follow-up. Two (2) subjects discontinued DMPA-SC due to side effects, 1 continued DMPA but discontinued self-administration due to the fear of self-injection, 1 desired pregnancy, and 12 were lost to follow-up.

Following the 3 cycles of self-injections, 87% reported self-injection to be ‘very easy’ or ‘easy,’ whereas 7% found it ‘very difficult’ or ‘difficult’; 3% reported ‘no opinion’ and 3% did not provide an answer.

The most frequent complaint from participants related to the needle used with the prefilled syringe, with 17% reporting that they encountered difficulty getting the drug suspension to flow through the needle.

Williams et al (Contraception, 2013)

This study reported a planned secondary analysis of a randomised controlled trial comparing pain between DMPA-IM and DMPA-SC among adolescent and young adult users of DMPA. 55 subjects were randomised to receive DMPA-IM or DMPA-SC as their first study injection. The participants then received the alternate formulation at the 3-Month follow-up visit (cross-over). At the 9-month visit the participant could elect to learn and perform self-administration of DMPA-SC in the clinic, if desired and the study explored participants attitudes towards home self-administration but none self-administered at home as all self-injections were done in clinic. Proficiency level for overall ability to self-administer DMPA-SC was as follows: 42.1% (8/19) ‘independent’, 21.1% (4/19) ‘independent after repeat education’, 21.1% (4/19) ‘with assistance’ and 15.8% (3/19) ‘not competent to self-administer’. The participants were then questioned in a structured interview

Conclusion

The available clinical and usability data suggest that self-injection of Sayana Press could be feasible and effective as a method for contraception, provided that physicians exercise due care in selecting and training appropriate patients for this option. Under no circumstances should a woman who is either not motivated to self-inject, or not capable of self-injecting, be compelled to do so in order to use the method.

The efficacy of DMPC-SC has been previously demonstrated and is not the subject of this variation application.

The MAH provides data from four studies to support the application to allow self-administration of Sayana Press at home unsupervised**;**

- Studies 267 and 269 (both demonstrated the efficacy of DMPA-SC (the option to self-administer at home was available to a proportion of subjects because of a study protocol amendment). Home self-injection was performed at least once by 15.6% (278/1787) of the subjects in these studies [10% (73/722) Study 267 and 19.2% (205/1065) in Study 269]. Self-injection was obtained from 6,279 woman-cycles however most of the women who self-administered did so in the clinic and approximate to 5,442 woman cycles. The experience with at-home self-injection totalled 837 woman-cycles and it would appear that nearly all the subjects who self-injected at home did so for only one injection. The end of treatment questionnaire (EOTQ) assessed subjects' satisfaction with the self-injection process. Even though the questionnaires were apparently not validated, the results suggest that most subjects who received training prior to self-injecting were happy with the training received and able to self-inject using the instructions provided.

- An independent study which compared the self-injection of DMPA-SC in prefilled syringes with administration of DMPA-IM (depot medroxyprogesterone acetate, intramuscular) by a healthcare professional in the clinic (Study GA67815). 128 subjects participated in this study with 64 randomised to DMPA-SC and 64 to DMPA-IM, the results of the study showed that the 12 month discontinuation rate was similar in both groups with a few more subjects lost to follow up in the DMPA-IM group. A total of 171 self-injections were independently attempted, at the post-baseline time-points (3 months, 6 months, 9 months) for the subjects in the DMPA-S group.
- A usability study assessing the ability of representative users to correctly operate the Uniject injection delivery system (the device Sayana Press is contained in) according to the instructions provided (Study A6791035). The results suggest that women that received training prior to trying out the Uniject system were more likely to succeed compared to the women who relied solely on the IFU**.** It is however crucial to note that the participants in this study did not self-inject. It would also appear that errors can occur during the use of the delivery system.

Overall, it would appear that majority of women included in the studies were able to self-inject when trained appropriately as indicated by the results from studies 267, 269 and GA67815 although subjects in studies 267 and 269 self-injected only on one occasion. In addition, the results from study GA67815 suggest that women can self-inject on repeated occasions on schedule even though the numbers included in the study are quite small. The results from the literature references also suggest that women are able to self-inject.

The only drawback with the data provided is that Sayana Press (the subject of this variation) was not utilised in any of the studies. However, the results from the usability study suggest that with prior and adequate training women are able to use the Uniject system but using the instructions for use (IFU) alone did not appear to be adequate in preparing women on how to use the system.

III.3.3 Clinical safety

The safety profile of DMPA-SC injection was demonstrated in three Phase 3 studies Studies 267 and 269 (contraceptive efficacy studies) and Study 267BMD small 3-year BMD safety study

To support this variation application, the company has provided the summaries of the safety findings from Study 267, Study 269 and Study GA67815.

Patient exposure

1060 subjects received at least one dose of DMPA-SC in study 269 out of which 856 completed 12 months of treatment (4 injections). 656 of the subjects self-injected and home self-injection was performed by 205 of the subjects

In study 267, 720 subjects received at least 1 dose of DMPA-SC out of which 489 completed 12 months of treatment. 384 of the subjects self-injected with 73 receiving 1 home self-injection.

In study GA67815, 64 subjects performed self-injection of DMPA-SC at the baseline visit, overall 235 DMPA-SC injections were performed.

Adverse events
Study 269

At least 1 adverse event was reported by 46.5% (493/1060) of the subjects. The most common adverse events (occurring in at least 5% of subjects) were amenorrhea not otherwise specified (NOS) (8.1%, 86/1060), intermenstrual bleeding (7.9%, 84/1060), and headache NOS (5.0%, 53/1060). Vaginal haemorrhage was reported in 4.6% (49/1060) of the subjects and increased weight was reported in 4.3% (46/1060) of the subjects. Depression (combined preferred terms [PT's], depression not elsewhere classified [NEC] and depressed mood) was reported as an adverse event in only 1.2% (13/1060) of the subjects.

There were 17 injection site reaction events **(**1.6% of the subjects) occurred in this study including injection site atrophy, injection site induration, injection site pain, injection site reaction NOS, and lipodystrophy.

Fifty-one (51) adverse events occurred on or after self-injection and were reported in 38 subjects**, o**f these, 8 adverse events in 7 subjects were considered treatment-related. One occurred (atrophy at site of injection anterior thigh) occurred on or within 7 days after self-injection

Thirty-two percent (31.7%, 336/1060) of the subjects were deemed by the investigator to have at least 1 adverse event related to the study drug. Adverse events leading to discontinuation were reported in 5.3% 56/1060) of the subjects; the most common adverse event leading to discontinuation was intermenstrual bleeding (0.9%, 10/1060). Serious adverse events were reported in 1.4% (15/1060) of the subjects.

Table 31. Study 269 - Treatment-Related Adverse Events with Incidence of ≥1% (ITT Population)

System/Organ Class (MedDRA ver. 2.3)	DMPA-SC N=1065	
	n	%
Total Subjects Reported	1060†	100
General Disorders and Administration Site Conditions		
Hemorrhage NOS	12	1.1
Investigations		
Weight Increased	45	4.2
Nervous System Disorders		
Headache NOS	26	2.5
Psychiatric Disorders		
Libido Decreased	16	1.5
Reproductive System and Breast Disorders		
Amenorrhea NOS	85	8
Intermenstrual Bleeding	84	7.9
Menometrorrhagia	33	3.1
Menorrhagia	23	2.2
Menstruation Irregular	19	1.8
Uterine Hemorrhage	14	1.3
Vaginal Hemorrhage	49	4.6
Skin and Subcutaneous Tissue Disorders		
Acne NOS	16	1.5

DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects participated in study; NOS = Not otherwise specified.
† No follow-up safety data were available for 5 subjects
Source: Study 269 CSR Table 13.

Study 267

At least 1 adverse event was reported by 70.7% (509/720) of the subjects. The most common adverse events (i.e., occurring in ≥5% of subjects) were headache (11.8%, 85/720), weight increased (8.5%, 61/720), intermenstrual bleeding (6.4%, 46/720), amenorrhea (5.8%, 42/720), and libido decreased (5.1%, 37/720). Depression (combined PTs depression NEC and depression aggravated) was reported as an adverse event in 3.5% (25/720) of the subjects.

Injection site reaction was also a common adverse event. A total of 94 injection site reaction adverse events were reported by 9.7% (70/720) of the subjects (some subjects had multiple occurrences of the same adverse event and/or had more than 1 type of injection site adverse event). Most of the events were of mild intensity. 50.0%, 47/94) of the injection site events occurred at the first (enrolment) visit; 74 of 94 events occurred after in-office injection by a professional (78.7% of the events; 4.2% of the 1770 clinic-administered injections in the study); 19 of the 94 events occurred after in-office self-injection (20.2% of the events; 3.4% of the 562 clinic-based self-injections); and 1 of the 94 events occurred after a home self-injection (1.1% of the 94 events; 1.4% of the home self-injections). The location for the majority of the injection site events was the thigh (60.6%, 57/94 events); the remainder were in the abdomen (37.2%, 35/94 events) or were reported as injection site unknown (2.1%, 2/94 events). The most common injection site reactions were injection site pain (2.6%, 19/720 subjects), injection site granuloma (1.9%, 14/720 subjects), and injection site atrophy (1.3%, 9/720 subjects).

A total of 14 treatment-related adverse events were reported by 9 subjects on or after starting self-injections: headache NOS (2 occurrences in 2 subjects); acne NOS, breast pain, mood alteration NOS, vaginitis, pain in limb, menstrual disorder NOS, intermenstrual bleeding, dizziness (excluding. vertigo), proteinuria present, breast neoplasm NOS, dysmenorrhea and depression NEC.

Adverse events leading to discontinuation were reported in 13.9% (100/720) of the subjects; the most common adverse event leading to discontinuation was weight gain (2.5%, 18/720)

Table 33. Study 267 - Treatment-Related Adverse Events with Incidence of ≥1%

System/Organ Class (MedDRA ver. 2.3)	DMPA-SC N=722	
	n	%
Total Subjects Reported	720†	100
Gastrointestinal		
Abdominal Distension	11	1.5
Abdominal Pain NOS	14	1.9
Nausea	8	1.1
General Disorders and Administration Site Conditions		
Fatigue	20	2.8
Injection Site Atrophy	9	1.3
Injection Site Granuloma	12	1.7
Injection Site Pain	19	2.6
Investigations		
Weight Increased	59	8.2
Metabolism and Nutrition Disorders		
Appetite Increased NOS	7	1
Nervous System Disorders		
Dizziness (Excluding Vertigo)	10	1.4
Headache NOS	44	6.1
Insomnia NEC	8	1.1
Psychiatric Disorders		
Anorgasmia	7	1
Depression NEC	12	1.7
Irritability	11	1.5
Libido Decreased	30	4.2
Mood Alteration NOS	8	1.1
Mood Swings	10	1.4
Reproductive System and Breast Disorders		
Amenorrhea NOS	42	5.8
Breast Pain	8	1.1
Breast Tenderness	10	1.4
Intermenstrual Bleeding	44	6.1
Menorrhagia	9	1.3
Vaginal Hemorrhage	19	2.6
Skin and Subcutaneous Tissue Disorders		
Acne NOS	27	3.8
Vascular Disorders		
Hot Flushes NOS	7	1

DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects participated in study; NEC: Not Elsewhere Classified; NOS = Not otherwise specified; MedDRA = Medical Dictionary for Regulatory Activities.
† No follow-up safety data were available for 2 subjects.
Source: Study 267 CSR Table 12.

Study GA67815

21 out of 64 DMPA-SC subjects (32.8%) reported a total of 41 adverse events. In the DMPA-IM group, there was a lower incidence of adverse events reported: 12 subjects (18.8%) reported a total of 15 adverse events.

For treatment-related adverse events, 15 out of 64 DMPA-SC subjects (23.4%) reported a total of 30 adverse events. In the DMPA-IM group, there was a lower incidence of adverse events reported: 6 subjects (9.4%) reported a total of 9 adverse events.

Overall, adverse events were reported more frequently in the DMPA-SC self-injection group in Study GA67815 compared with the DMPA-IM clinic group. The most notable differences in the reported AEs were for injection site reactions (14 reports for DMPA-SC and none for the DMPA-IM group.

Table 35. Study GA67815 – Treatment-Related Treatment Emergent Adverse Events

TE AE (treatment-related)	DMPA-SC (N=64)		DMPA-IM (N=64)	
	n	%	n	%
Gastrointestinal Disorders	4	6.3	1	1.6
Abdominal distension	0		1	1.6
Abdominal mass	1	1.6	0	
Abdominal pain	1	1.6	0	
Diarrhoea	1	1.6	0	
Gastritis	0		1	1.6
Nausea	2	3.1	0	
Vomiting	1	1.6	0	
General Disorders and Administration Site Conditions	10	15.6	0	
Feeling abnormal	1	1.6	0	
Injection site induration	1	1.6	0	
Injection site mass	1	1.6	0	
Injection site pain	4	6.3	0	
Injection site reaction	7	10.9	0	
Injection site vesicles	1	1.6	0	
Infections and Infestations	0		2	3.1
Candida infection	0		2	3.1
Investigations	0		1	1.6
Weight increased	0		1	1.6
Musculoskeletal and Connective Tissue Disorders	1	1.6	0	
Pain in extremity	1	1.6	0	
Nervous System Disorders	1	1.6	0	
Tremor	1	1.6	0	
Psychiatric Disorders	2	3.1	1	1.6
Emotional disorder	2	3.1	0	
Irritability	0		1	1.6
Mood swings	0		1	1.6
Reproductive System and Breast Disorders	3	4.7	1	1.6
Breast tenderness	2	3.1	1	1.6
Premenstrual cramps	1	1.6	0	
Vaginal discharge	1	1.6	0	
Skin and Subcutaneous Tissue Disorders	0		1	1.6
Skin disorder	0		1	1.6
Vascular Disorders	1	1.6	0	
Hot flush	1	1.6	0	
Total Preferred Term Events	30		9	

Abbreviations: DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; DMPA-IM = Depot medroxyprogesterone acetate Intramuscular; ITT = intent-to-treat; N = total number of subjects participated in study; NOS = Not otherwise specified.
Source: Study GA67815 CSR Table 14.3.2.2.6.

Study 267BMD,

Was a 3-year Phase 3 study that randomised women to DMPA-SC (clinic injection) or DMPA-IM (clinic injection) and has been included by the applicant to explore the possibility that there is difference in the incidence of adverse events between DMPA-SC and DMPA-IM in view of the safety results observed in the other studies. For this study also injection site reactions, pain and atrophy occurred in approximately 6.% of the subjects.

Table 36. Study 839-FEH-0012-267BMD (Study 267BMD) – Adverse Events Reported by 1% or More Subjects in Either Group

	DMPA-SC		DMPA-IM	
	n	%	n	%
Total Subjects Reported	263†	100	266†	100
Subjects with at least 1 adverse event	214	81.4	207	77.8
Gastrointestinal Disorders				
Abdominal Distension	6	2.3	6	2.3
Abdominal Pain NOS	6	2.3	16	6
Diarrhea NOS	2	0.8	8	3
Dyspepsia	3	1.1	8	3
Flatulence	3	1.1	2	0.8
Nausea	15	5.7	24	9
Oral Pain	3	1.1	1	0.4
Sore Throat NOS	6	2.3	9	3.4
Vomiting NOS	0	0	7	2.6
General Disorders and Administration Site Conditions				
Chest Pain NEC	3	1.1	1	0.4
Fatigue	9	3.4	4	1.5
Influenza-like Illness	2	0.8	3	1.1
Injection Site Atrophy	7	2.7	0	0
Injection Site Pain	4	1.5	0	0
Injection Site Reaction NOS	6	2.3	0	0
Pyrexia	3	1.1	4	1.5
Immune System Disorders				
Hypersensitivity NOS	10	3.8	2	0.8
Infections and Infestations				
Bronchitis NOS	10	3.8	10	3.8
Ear Infection NOS	3	1.1	2	0.8
Fungal Infection NOS	3	1.1	4	1.5
Helminthic Infection NOS	2	0.8	4	1.5
Herpes Simplex	3	1.1	3	1.1
Influenza	7	2.7	8	3
Kidney Infection NOS	3	1.1	0	0
Nasopharyngitis	25	9.5	34	12.8
Pharyngitis Streptococcal	11	4.2	7	2.6
Sinusitis NOS	19	7.2	14	5.3
Tonsillitis NOS	1	0.4	5	1.9
Upper Respiratory Tract Infection NOS	13	4.9	9	3.4
Urinary Tract Infection NOS	20	7.6	6	2.3
Vaginal Candidiasis	5	1.9	2	0.8
Vaginitis	11	4.2	11	4.1
Vaginitis Bacterial NOS	9	3.4	7	2.6
Vaginosis Fungal NOS	4	1.5	1	0.4

Serious adverse events and deaths

Study 269

Serious adverse events were reported in 1.4% (15/1060) of the subjects.

Study 267

Serious adverse events occurred in 1.3% (9/720) of the subjects. One (1) subject died during the study period as the result of injuries sustained in a motor vehicle accident; unrelated to the study drug.

Laboratory findings

Study 269 and 267

No noteworthy changes were found over the study period in the hematology, chemistry, or urinalysis laboratory assays. Blood pressure (both systolic and diastolic) did not change significantly over the study period.

Safety in special populations
N/A

Assessor's overall conclusion on safety
The safety of DMPA-SC has previously been characterised are there are no particular issues. The occurrence of local injection site reaction has previously been noted and in study A67815 the incidence was approximately 10%. In terms of self-injection, there were no adverse events of note reported.

Product information

III.4.1 Summary of Product Characteristics(SmPC)

Suitable changes have been made to the SmPC, based on the points for clarification made by the member states.

III.4.2 Package leaflet (PIL) and user test

Suitable changes have been made to the PIL, based on the points for clarification made by the member states.

III.4.3 Readability user testing

Suitable results from user testing of the revised PIL have been provided such that they show that users understand the PIL and can act on the information that it contains.

III.4.4 Labelling

Not applicable

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The MAH has submitted a type II variation to introduce the option of home self-injection by patients in section 4.2 of the summary of product characteristics (SmPC) and the PIL. In support of this application, the MAH provides data from four studies (267, 269, GA67815 and A6791035).

Studies 267 and 269 (both have been used previously to demonstrate the efficacy of DMPA-SC. However, the option to self-administer at home was available to a proportion of subjects due to a study protocol amendment). In these two studies home self-injection was performed at least once by 15.6% (278/1787) of subjects. Self-injection was obtained from 6,279 woman-cycles however most of the women who self-administered did so in the clinic and approximate to 5,442 woman cycles. The experience with at-home self-injection totalled 837 woman-cycles and it would appear that nearly all the subjects who self-injected at home did so for only one injection.

Study (GA67815) which compared self-injection of DMPA-SC in prefilled syringes with administration of DMPA-IM (depot medroxyprogesterone acetate, intramuscular) by a healthcare professional in the clinic 128 subjects participated in this study with 64 randomised to DMPA-SC and 64 to DMPA-IM, the results of the study showed that in the DMPA-SC group, the discontinuation rate was 13.8% as compared to the DMPA-IM group were the rate of discontinuation was 25% attributable to 10 subjects being lost to follow up in this group). A total of 171 self-injections were independently attempted, at the post-baseline time-points (3 months, 6 months, 9 months) for the

subjects in the DMPA-S group. This small study provides the bulk of evidence that women are able to self-inject repeatedly on schedule.

Unfortunately Sayana Press which utilises the Uniject system (the subject of this variation) was not used in any of the studies. However, the results of a usability study (A6791035 which assessed the ability of users to correctly operate the Uniject injection delivery suggest that with prior and adequate training women are able to use the Uniject system but using the instructions for use (IFU) alone did not appear to be adequate in preparing women on how to use the system.

Although it would appear that women are able to self-inject when trained appropriately as indicated by the results from studies 267, 269 and GA67815 and in addition, the results from study GA67815 suggest that women can self-inject on repeated occasions on schedule. Unfortunately Sayana Press which utilises the Uniject system and comes with a needle already attached was not used in any of the studies apart from the usability study in which participants did not actually self-inject but the results of the usability study provides some evidence that women are able to inject with adequate training and use of the IFU. Therefore it will be necessary for the MAH to adequately justify that women will be able to self-inject on themselves with the Uniject system. In addition the small numbers of women who have actually self-injected in clinical studies to date is a cause for concern and the MAH should adequately justify that the results obtained will translate into real-life situations.

In terms of safety, the only significant issue to note is the occurrence of local injection reactions with the administration of DMPA-SC.

The benefit risk for Sayana Press remains unchanged and proposal to allow women to self-administer could be approvable if the MAH provides a satisfactory response to the points for clarification and reassurance is provided that women will be adequately trained and counselled.

V. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

V.1 Potential serious risks to public health

None

V.2 Points for clarification

1. Given that Sayana Press was not used in any of the clinical studies and women did not self-inject in the usability study A6791035, the MAH should adequately justify that women will be able to self-inject on themselves with the Uniject system.

2. Only a small number of women have self-injected on multiple occasions to date in clinical studies. The MAH should adequately justify that the results obtained in these studies will translate into real-life situations.

3. The results of the usability study A6791035 suggest that a certain amount of training is needed and reading the IFU alone might not be sufficient for women. The MAH should provide a detailed discussion of the training proposed for women.

4. It is proposed that women self-inject on a regular basis. The MAH should provide a detailed discussion on how women will be followed-up to ensure they don't miss injections. It should also be clarified whether women will have regular medical check-ups and how frequently this will be.

5. An in-depth discussion should be provided on the disposal of Sayana Press after self-administration. In addition the product information should also be updated.

ASSESSMENT OF THE RESPONSES TO THE MEMBER STATE(S) REQUEST FOR SUPPLEMENTARY INFORMATION

Potential serious risks to public health

None

Points for clarification

1. **Given that Sayana Press was not used in any of the clinical studies and women did not self-inject in the usability study A6791035, the MAH should adequately justify that women will be able to self-inject on themselves with the Uniject system.**

MAH's response

This was the central issue that the MAH posed to MHRA when we sought Scientific Advice in September 2012 in order to take a decision about progressing this project. That is, the purpose of the meeting was to determine whether or not the results of the independent Cameron study (Study GA67815), which used only the DMPA-SC pre-filled syringe (PFS), plus the results of the proposed A6791035 device usability study (using DMPA-SC in Uniject) could, together, serve as adequate primary evidence for approval of self-injection labeling for DMPA-SC in Uniject (Sayana Press). At that meeting it was agreed that this approach would be acceptable (as this replicated the original basis of registration of the Sayana Press injector for Healthcare Professionals) and that no additional clinical study would be required at the time of submission if certain required modifications to the proposed approach were implemented. Specifically:

1. While MHRA accepted that the independently-conducted Cameron study could provide acceptable primary evidence that women could successfully self-inject DMPA-SC unsupervised, at home, MHRA stated that the published report of the Cameron study contained insufficient detail regarding the safety of the study participants. MHRA requested that the MAH work with the study's Principal Investigators in order to collect, from patient records, full details of the safety events that occurred during the study and to prepare a final clinical study report (CSR) that would be suitable for in-depth regulatory review. This requirement was accomplished and the CSR for the Cameron study has been included in the submission.

2. In addition, MHRA stated that the originally proposed design for the A6791035 device usability study was inadequate because it only assessed the participants on a single occasion (Day 1), which would be the day that the 'trained' participants would receive their training on the device. While single assessment is standard practice for device usability studies, it was recognized that DMPA-SC is somewhat unusual in that it is administered at a very widely spaced interval (q3 months) and, therefore, it would be important to demonstrate that women retain the ability to correctly operate the device after 3 months had passed. The MAH agreed to incorporate a follow-up testing visit (Day 90) and to re-assess participants at this visit with no additional (i.e., refresher) training to be provided at that visit.

The results of the Cameron study demonstrated that most participants were able to satisfactorily perform subcutaneous self-injection with DMPA-SC at home, over a 1-year period, when they were instructed and knew how to operate the particular injection device they had been given – which in this case was a pre-filled syringe. However, that clinical experience cannot be immediately extrapolated to DMPA-SC in Uniject because the operation of the Uniject device is different to that of a syringe. While all other aspects of the Cameron study are translatable to women who will self-inject with DMPA-SC in Uniject (e.g., general willingness and ability to perform a subcutaneous self-injection; ability to inject on a prescribed schedule; the safety and efficacy profile of subcutaneous DMPA 104 mg), it was agreed that the MAH must provide evidence that women can correctly interpret the Instructions for Use (IFU) for the Uniject, and, as a result, can correctly operate the device from a mechanical perspective, on the day of training and again, at the 90-day follow-up point. If it can be shown that most women can correctly operate the Uniject device, as they were able to correctly operate the PFS in the Cameron study, then the one key difference between the Cameron study and an

otherwise identical study using DMPA-SC in Uniject will have been bridged since the results of the Cameron study are based on the fact that the women could mechanically operate the injection device.

Providing this linkage is very important, in our view, because the fact that women were able to independently operate a PFS 90 days after training, as they did in the Cameron study, does not necessarily mean that they can do the same with Uniject. The operation of a PFS is essentially self-evident. The patient sees the needle and the plunger and intuitively knows that the needle must be inserted into the skin and, even if she has never personally used a syringe, she will have seen one used and it will be obvious that the plunger must be depressed to deliver the medicine. Furthermore, these points will be just as obvious on Day 90 as they were on Day 1. The one critical requirement of the DMPA-SC PFS, however, is the need to depress the plunger slowly because any attempt to rapidly (i.e., with increased force) deliver a solid-in-liquid suspension (such as DMPA-SC) will increase the viscosity of the suspension and make it difficult to deliver through a fine needle; pure solutions do not have this non-Newtonian property, but solid-in-liquid suspensions do have it. Several participants in the Cameron study did report that the syringe required considerable force to inject and they may not have realized that increasing the force on the plunger would only worsen the problem. Although not explicitly reported to have occurred in the Cameron study, excessive force on the plunger can cause the needle hub to detach from the syringe body since it has a friction-fit interface.

In contrast, the Uniject device might be less intuitive than the PFS, at least on the surface, and it is therefore necessary to assess the ability of typical users to successfully operate the device, both initially and after a time gap. Like the PFS, the needle end of the Uniject is self-evident and the need to insert the needle into the skin will be obvious to the patient. However, instead of a plunger, there is a bubble/reservoir that must be pinched in order to expel the medicine. This simple action requires only thumb and forefinger to perform while the PFS requires a somewhat more complex action: the index and middle fingers must hold the syringe body while the thumb simultaneously depresses the plunger.

There are two particular issues for Uniject that users must consider in order to successfully deliver the dose:

1. The DMPA-SC suspension in the Uniject is identical to the suspension used in the PFS, so the injection must be done slowly over 5-7 seconds and excess pressure will decrease the flow of the suspension through the needle, with either device. The problem could, in theory, be slightly less acute with the Uniject since the needle diameter is slightly larger, which decreases pressure, and because a bubble held between two fingers does not allow the patient to develop quite the same mechanical advantage as she would get with a thumb on a plunger, which also lessens the applied force a little. In the A6791035 usability study, >95% of subjects gave Uniject an overall rating of 'somewhat easy' or 'very easy' to use. However, when questioned about specific steps in the procedure, 20% to 30% (depending on cohort and visit) reported that they felt, subjectively, that they had at least some degree of difficulty squeezing the bubble, including comments that they had to squeeze it firmly or repeatedly in order to ensure that the drug was fully delivered. In fact, despite their expressed concerns on the survey, the participants were actually quite successful in delivering the full dose: the median weight of drug delivered was at or above the nominal weight of the prescribed dose (0.65 mL = 0.677 mg) for both trained and untrained participants, at both the Day 1 and the Day 90 Visits. It appears that the subjects' expressed concern was a reflection of their diligence and their initial unfamiliarity with the injector.

2. The Uniject does have one feature that clearly sets it apart from the PFS: it must be mechanically 'activated' in order to operate. With the needle still capped, the user must hold the two ends of the device and push them together along the central axis. When a 'click' is felt (or heard), the activation step is complete: the proximal end of the needle has punctured the internal septum and is now in contact with the suspension in the bubble reservoir. This step is very simple to perform when you know what to do, but it is not at all self-evident how one would activate the device nor even that activation should be needed; the user must be instructed on the need for activation and how to perform the step through the IFU or the training. In Study A6791035, most of the participants who did not receive any hands-on training (they had the IFU available but with no

demonstration, practice or opportunity to ask questions) were able to perform this step successfully (86.4% on Day 1; 95.0% on Day 90). The trained cohort was provided with the IFU plus a demonstration and an opportunity to practice and ask clarifying questions; in this cohort the activation step was performed successfully by 96.6% on Day 1 and by 100% on Day 90. While the differences between the trained and untrained cohorts fell just shy of statistical significance, it is still reasonable to recommend that women who intend to self-inject with DMPA-SC in Uniject should be given a hands-on demonstration of the device, have clarifying questions answered, and have an opportunity to perform the technique under supervision. Given the simplicity of the device, such training should be relatively quick to accomplish and should not be overly burdensome to the clinic staff.

The Cameron study (GA67815) showed that women who are willing to self-inject and have been instructed in the operation of the subcutaneous injection device can successfully self-administer DMPA-SC at home using the device for which they have received instruction (IFU, demonstration, etc.). In order to reasonably conclude that women can successfully self-inject DMPA-SC using an alternative subcutaneous injection device, and to conclude that the clinical outcomes reported in the Cameron study can reasonably be extrapolated to another subcutaneous injection device, we need evidence showing that the alternative device has essentially similar usability to the PFS. More specifically, we need evidence that the alternative device is 'usable' by a very high proportion of women in the same way that the PFS is usable by a very high proportion of women, which then puts the alternative device on a par with the device used in the Cameron study since all other factors remain constant: drug, dose, formulation, site of injection, timing of injections and so forth. Ideally, we would like to be able to directly compare formal usability data for the PFS and for the Uniject (% successful simulated injections based on use error analysis), but, because the Sayana PFS is a common syringe and not a new device, formal usability testing and use error analysis were not required. While the Cameron study did not collect usability data per se on the PFS, Table 16.2.6.1 (GA67815 CSR) shows that 4 (of 64) subjects had difficulty expelling the suspension from the PFS, which can occur since the plunger can generate quite high applied force against the suspension, increasing viscosity. Another common use error with the PFS is the needle hub becoming disconnected from the syringe body, probably again related to the higher pressures that are possible with a syringe plunger. Therefore, even in the absence of formal usability testing and use error analysis for the PFS, we believe it is reasonable to expect that the usability of the PFS is very good and one could anticipate that the PFS used in the Cameron study would generate overall scores at or above the 95% level in a formal usability study, similar to the scores achieved by the Uniject device.

Therefore, the MAH believes that study A6791035 shows that most women are able to successfully use the Uniject device, when given appropriate instruction, and that this demonstration establishes the Uniject device as having essentially similar usability to the PFS that was deployed in the Cameron study, from the perspective of the patient. Hence, if the two devices are similar in this respect, and if all other factors are not different (drug, dose, formulation, route of administration, site of injection, timing of injections, etc.), then we believe that the clinical experience from the Cameron study (GA67815) is relevant and translatable to the clinical experience that is likely to occur if healthcare professionals are afforded the opportunity to select certain of their Sayana Press patients for self-injection, when they and the patient decide that self-injection is a suitable option for the patient. Should any woman experience significant difficulty in performing their initial injections in the home setting, the PIL is explicit in instructing them to return to their Healthcare professional for advice. This would give the opportunity for re-training or re-assessment regarding suitability for continuing with self-injection.

Assessment of response

The applicant considers that the results of Study GA67815) provide evidence that women are able to successfully self-inject DMPA-SC with the pre-filled syringe (PFS) unsupervised and on repeated occasions at home and these results can be extrapolated to the Uniject system since the results of the usability study for the Uniject system (A6791035) showed that approximately 86% of the women who did not receive hands on training were able to follow the instructions for use and correctly inject on day 1 and on day 90, 95% of the women were able to follow the instructions for use.

This is considered acceptable since the objectives of the usability study were met. Even though the ladies did not self-inject it appears that they were able to follow instructions adequately (with or without training). It is reasonable to assume that if women understand the instructions, have been adequately trained and are willing to self-inject they are likely to succeed. If they encounter problems at home there are clear instructions in the PIL.

Overall, taking into consideration that the DMPA-SC suspension in the Uniject is identical to the suspension used in the PFS and the results of the usability study show that women are to follow instructions after training the proposal by the MAH for women to self-inject using Sayana Press is therefore considered acceptable.

Point resolved

2. Only a small number of women have self-injected on multiple occasions to date in clinical studies. The MAH should adequately justify that the results obtained in these studies will translate into real-life situations.

MAH's response
This is, of course, the essential question for any drug product seeking approval for use in the general population – will the results of carefully controlled clinical trials, large or small, accurately predict what will happen in practice? There are several aspects to consider:

1. Study Design: Typically, trial participants must fulfil a long list of inclusion/exclusion criteria, some of which are medically based. Patients may be excluded on the basis of factors related to concurrent medical conditions, baseline laboratory values, physical or psychological status and other factors. Some of these trial restrictions may become part of clinical practice regarding the use of the drug, but many will not, which will create differences between the study population and the general patient population who will use the drug product. Another study design parameter is the duration of study: will a 1- or 2-year study predict the effects that will be seen after a patient has taken a drug for 11 years? These can be characterized as objective or measurable parameters that could create differences in outcomes between trial participants and real patients.

2. Study Participants: Other differences will not be so easily measurable, particularly those related to behaviour and motivation on the part of the participants, which are important considerations for a topic like self-administration since it has a strong behavioural component. Trial participants typically were willing to give up their personal time for study-required testing and for additional clinic appointments that they would not otherwise have needed. Many patients in the general population are not willing to do this, which means that they are different to those who are willing to adhere to the demands of an investigational study, but in ways that are hard to quantify. As an example, one could imagine that these undefined behavioural differences could lead to different rates of adherence to therapy between trial participants and other patients, which could lead to differences in efficacy or safety between the clinical trial results and 'real life' outcomes.

3. Study Investigators: Study subjects are managed by experienced clinical study investigators. There are many very experienced physicians who do not participate in clinical trials, but there are also physicians in practice who may not have the expertise or experience that would qualify them to be a clinical trial investigator. The way in which a prescriber selects a patient for therapy and how that patient is subsequently managed could influence efficacy and safety outcomes and, therefore, create differences between clinical trial results and results achieved in general practice.

We will now examine how these factors are relevant to the Cameron study (GA67815) and to the Usability study (A6791035) and to what extent the results of these studies might not be predictive of real-world experience.

Study Design (Cameron Study)
The inclusion criteria for the Cameron study (GA67815) are listed below, in full:

1. Women aged 18 to 40 years.
2. Currently using DMPA-IM for at least the previous 9 months.
3. Wishing to continue using DMPA for at least 1 more year.
4. No contraindications to DMPA (World Health Organization [WHO] Medical Eligibility Criteria – category 3 or 4).
5. Not wishing to conceive within the next 2 years.
6. Not planning to move out of the area for at least 12 months.
7. Willing to be contacted at work or at home.
8. Willing and able to give informed consent.
9. Without significant preexisting medical conditions.

The exclusion criteria for the Cameron study are also shown below, but they present no additional restrictions because they are simply the inverse of specific inclusion criteria:

1. Contraindications to DMPA (WHO Medical Eligibility Criteria - category 3 and 4 conditions).
2. Wishing to conceive within the next 2 years.
3. Unable to give informed consent to participation.
4. Likely to move out of the area in the next year.
5. Unwilling to be contacted at home or at work.

Overall, the study entry criteria describe a population that is quite close to the general patient population who might perform self-injection. Most will be current DMPA users, either DMPA-IM or DMPA-SC, and most will be intending to practice long-term contraception, as evidenced by their choice of a depot method. While some patients in the general population will have some significant pre-existing medical condition, these would be varied, making it difficult to assess what, if any, impact the condition might have on the ability to self-inject.

The one study requirement that does differentiate study participants from the general population of patients would be the age requirement for the study: 18 to 40 years. In terms of objective medical/clinical factors, the 18 to 40 years study cohort should be representative of typical DMPA users who are under 18 or over 40 since we are primarily dealing with healthy women. Thus, we will examine the behavioural implications of self-injection by women who fall outside the study-defined age range.

Firstly, it is unlikely that women over 40 (up to the peri-menopause) would be unable to successfully self-inject if it is determined that adult women under 40 can do so. With respect to adolescents, the injection technique is simple, and while there should be little doubt that adolescents should be able to learn and physically perform the technique, there is a responsibility that must be assumed by the adolescent to adhere to the 3-monthly schedule, and this deserves some comment.

In a report on compliance with oral contraceptives (OCPs) [Hillard PJ; 1992;], adolescents using oral pills had an annual contraceptive failure rate as high as 18% due to inconsistent adherence to the unsupervised daily dosing regimen they must follow. Therefore, adequate adherence to a 3-monthly unsupervised regimen cannot necessarily be assumed for all adolescents, particularly for adolescents who are unreliable. However, there is an important difference between OCPs and self-injection of DMPA-SC. With OCPs there is no alternative except to require the adolescent to adhere to the unsupervised daily regimen. But, for DMPASC in Uniject, the HCP can decide that a particular patient would be best served by having the product administered in the clinic if they feel that the patient is unlikely to independently adhere to the prescribed regimen at home. The decision to permit self-injection is entirely under the control of the prescriber and the maturity and reliability of the patient will necessarily be important factors for the prescriber to consider when making that decision for each patient.

Study Participants (Cameron Study)
The focus of this section is to examine whether the study population in the Cameron Study differed from typical DMPA users in ways that may be more subtle and may not be readily apparent simply by reviewing the study entry criteria.

As mentioned above, the DMPA patients at the NHS Lothian clinic who self-administered in the Cameron study (GA67815) were approached by the Investigator when she thought the patient might be suitable for self-injection. Those who participated voluntarily agreed to take part, while other patients declined the opportunity. The demands of the study were minimal from the participant's perspective (no additional visits or tests, etc.), so those who declined most likely did so for reasons other than excessive demands on their time. Study participation enabled the participant to self-inject at home, and if the patient perceived value in being allowed to self-inject (e.g., convenience), then this was presumably the motivating factor that led the patient to agree to participate in the study, since self-injection was not available outside of the study.

In general clinical practice, the situation would not be substantially different to that described above. The HCP would approach only those DMPA patients who, in the opinion of the HCP, would be suitable for self-injection. Those patients who find the option interesting would agree to receive the training and attempt self-injection at home, while those who are uninterested for whatever reason (e.g., fear of handling a needle) would decline the offer. Since the dynamics at play here would be very similar to the dynamics that took place during the recruitment of the Cameron study, we conclude that the study population is probably predictive of the patients who would be attempting self-injection in clinical practice. In both situations the decision made by the patient (to try self-administration in the Cameron study, or not; or to try self-administration in general practice, or not) would not affect the treatment the patient received since DMPA treatment could continue regardless, whether self-injected or HCP-injected.

Study Investigators (Cameron Study)
The principal investigators are recognized experts in the field of reproductive health and are highly qualified clinical study investigators and, therefore, it is legitimate to consider whether their expertise might have led them obtain more favourable results in their study than typical practitioners might achieve in medical practice. Such a situation could certainly arise if the disease under study, or the therapy being tested, was very complex and/or required especially skilled management of the patient. But that does not appear to be the case here. For the most part, these are normal healthy women requiring only routine care. The investigator (or the practitioner) who introduces DMPA self-injection into their practice needs to pay attention to a few key points**:**

- Select appropriate patients: among women who use DMPA, there will be those whom the physician judges to be potentially suitable for home self-administration, assuming they can demonstrate competence during the training session, and others who are probably not suitable for various reasons. It is important for any physician to know their patient, which is a skill shared by reproductive health experts and by general practitioners alike.
- Assist the self-injecting patient to keep to the 3-monthly schedule: in most practices it is routine for DMPA patients to receive some type of reminder to ensure they attend their next 3-monthly clinic visit. It is typically an appointment card, a text or voice-mail message or an email. Whatever method is currently used in a practice, the same method can be very simply adapted to remind the patient of her 'at-home appointment' when she will self-inject DMPA-SC in Uniject. This would pose no additional burden on the practice.

- Provide proper follow-up: the physician needs to query the woman about any problems encountered and assess whether self-injection remains a viable option for the patient, going forward. If not, she can revert to getting the injection at the clinic or switch to another contraceptive method.

These requirements on the part of the prescriber were no different in the Cameron study than they would be in general practice. Moreover, expertise in the field, such as that possessed by the principal investigators, is not necessary to fulfil these basic responsibilities of patient care. Thus, we would

expect that the results obtained by the Investigators in their study will be translatable to general medical practice.

With respect to the Cameron study and for the reasons outlined above (study design; patients, investigators), we conclude that the study results should generally be quite predictive of clinical outcomes in general medical practice. We will now examine the Usability study (A6791035) from the same 3 perspectives.

Study Design (A6791035)
As a usability study, the study design is not intended to mirror clinical practice and involves no actual administration of drug to the participants. A usability study is focused solely on the delivery system. The specific purposes of a delivery system usability study are:

- Enrol participants who are appropriately representative of the intended users of the delivery system and provide them with information (about the delivery system) that closely approximates the information that will be made available to actual patients;

- Identify the 'use errors' that occur, including the frequency of the errors and the consequences of the errors; and

- Identify the underlying causes of the identified 'use errors': mistakes made by the participants, misunderstanding of the instructions by participants, design faults of the delivery system itself, lack of clarity in the instructional materials, manufacturing defects in the delivery system, or other.

Therefore, to the extent that the usability study participants are representative of actual patients, and to the extent that the instructions for use (IFU) and/or training represent what would be used in clinical practice, then the errors observed in the study (and their frequency) should be predictive of the use errors that will occur in clinical practice. The instructional materials used in the A6791035 study are appended to the A6791035 CSR and are the basis for the materials to be used in practice. In terms of the study participants, their relevance to actual patients is discussed in the following section.

Study Participants (A6791035)
The Usability was designed to recruit women who are demographically similar to DMPA users. Subjects were included based on gender (female only), age (18-45 years) and the ability to read. Subjects were excluded if they had a severe or chronic condition that would, in the opinion of the investigator, preclude them from successfully participating in the study; one example would be someone with impairment of the hands that would preclude them from operating a small mechanical device. In clinical practice, DMPA subjects are not required to be literate, but the nature of the assessments in the usability study made that requirement necessary. Therefore, in terms of demographics, the study participants were not dissimilar to DMPA patients. However, not all DMPA patients will be deemed suitable for independent self-injection and the study participants were not selected on the basis of their suitability for self-injection, as would happen in clinical practice. While the criteria that physicians may use to select 'suitable' self-injectors from among all their DMPA patients would necessarily be subjective, that additional screen was not applied to the participants in the usability study.

There may be another difference that is also not readily apparent. The study participants were healthy volunteers who were compensated monetarily for their time whether they were successful or not in operating the Uniject; they did not know the purpose of the drug and their primary motivation was to complete the testing. In contrast, a patient self-injecting DMPA-SC in Uniject has a very strong motivation to learn and perform the task correctly because contraceptive efficacy depends on correct injection. In addition, the patient will be trained and will need to demonstrate her proficiency in the clinic, prior to being allowed to attempt unsupervised injection at home. Those patients who are unable to demonstrate proficiency would not be permitted to self-inject at home. Therefore, given the focus and motivation that the patient will have, in addition to the need for the actual patient to

demonstrate proficiency prior to leaving the clinic, we believe it is unlikely that patients self-injecting at home will make errors at a rate higher than that observed with volunteers in the Usability study.

Study Investigators (A6791035)
This study was conducted in a dedicated Phase 1 unit in Brussels and the investigator did not clinically manage the participants. Therefore, the expertise of the investigator would not be relevant to this discussion in the same way that the expertise of the investigators for the Cameron study was relevant to the translatability of their study findings to clinical practice**.**

Conclusions
We believe that these two studies (GA67815 and A6791035) each provide important information that is directly relevant to the ability of patients to self-inject DMPA-SC in Uniject at home, without direct supervision. The usability study carefully assessed each step in the injection process in detail and determined that most women can successfully operate the Uniject device, even when those women had not been pre-selected by a physician as someone who would be 'suitable' for self-injection, as will happen in clinical practice.

The Uniject is a fairly simply device to operate, as shown in the usability study (A6701035), so the central issue will be the ability of women to remember to inject every 3 months, within the 2-week window that is specified in the SmPC. It is important for the self-injecting patient to know that she can contact the clinic if there is a problem. If a woman attempts to inject but cannot activate the device, or encounters some other issue that prevents a proper injection, that situation will be immediately apparent to the patient; it will not go unnoticed. Therefore, the patient would make an appointment to come in and have the injection performed by the nurse, or other, as needed.

The patient would be encouraged to attend to any injection issue promptly, so that the injection occurs within the 2-week window (12-14 weeks after the previous injection). However, it is reassuring that for most women there would be no immediate risk of pregnancy if an injection was to be delayed. The results from study 839 FEH-0012-272 (Jain et al. 2004) showed that subcutaneous DMPA prevented ovulation for a median time of 212 days (30 weeks). While the shortest effective time was observed to be only 15 weeks in this study, hence necessitating a 3-month interval if all women are to be properly protected, the vast majority of women will have a very considerable margin for error in terms of the timing of injections. This property of DMPA largely explains the reason behind there being no contraceptive failures among the >1700 women in the Sayana Phase 3 programme (Studies 839-FEH-0012-267, 839-FEH-0012-267BMD, 839-FEH-0012-269); the method is quite robust.

We anticipate the results of the two studies discussed above to be confirmed in the Phase IV study proposed by the MAH in response to the request for further evidence of efficacy and safety of Sayana Press in a 'real world 'setting as part of the assessment of the Risk Management Plan (please see the accompanying response to RMP Request 9 for further details).

Assessment of response
The applicant's detailed response is noted. However, the crucial issue is whether efficacy is maintained in real-life situations when women self-inject and if efficacy will be comparable to results obtained in clinical studies. It would appear that the MAH intends to address this issue as it is noted from the responses provided to the RMP the intention to conduct a Phase IV interventional, safety and efficacy study of self-injection with Sayana Press.

Point considered resolved

3. The results of the usability study A6791035 suggest that a certain amount of training is needed and reading the IFU alone might not be sufficient for women. The MAH should provide a detailed discussion of the training proposed for women.

MAH's response
We agree with the conclusion stated in the body of this Question. While the difference in the 'proportion of successful injections' between trained and untrained participants in Study A6791035 fell just shy of statistical significance, the result certainly suggests that it is appropriate that women who intend to self-inject at home with Sayana Press should be trained; they should be given a demonstration of the device, have their questions answered, and be asked to perform supervised self-injection at the clinic in order to demonstrate that they are proficient.

The MAH intends to support the Healthcare Professional's (HCP's) efforts by providing, apart from the IFU itself, written and electronic materials that will be directed to the HCP.

The educational plan recognizes that the HCP has two essential tasks: (i) to use their best judgement in selecting patients who are likely to be successful with self-injection and (ii) to properly train the patient to be proficient in the injection technique. The HCP-directed materials will include practical guidance and a demonstration video.

- The guidance will be available to the HCP electronically and can be printed for easy reference.

    - The guidance will first focus the HCP's attention to the matter of selecting appropriate patients for self-injection. It will recommend that appropriate patients should, first, be suitable for treatment with DMPA (desiring long-term contraception; no contraindications; etc.). Secondly, it will advise that the patient should clearly express a desire to attempt self-injection; there is no requirement to self-inject in order to use Sayana Press since clinic injection is available. Finally, the HCP should assess factors which, in their judgment, may bear upon the patient's reliability and make a determination that the patient is likely to be successful (i.e. no physical, social or psychological impediments that would suggest any inability to successfully self-inject at home).

    - The guidance will then provide support to the HCP who will train the women. It will recommend that the Trainer should be someone who

        - has thoroughly read the IFU in detail,
        - has viewed the training video and understands it,
        - has become proficient in operating the Uniject injector, and, importantly,
        - has first-hand experience administering Sayana Press injections to patients in the clinic.

    - The steps to be covered when training a patient are, briefly:

        - Before sitting with the patient, ask her to read the IFU thoroughly.
        - Sit with the patient. Confirm that the patient understands that self-injection is voluntary/optional (injection in the clinic is still available)
        - Confirm that the patient understands that she must commit to keep to the
        - 3-monthly schedule (+/-1 week) or risk a contraceptive failure.
        - Confirm that the patient understands that if she encounters a problem when injecting (failed injection), she must contact the clinic as soon as possible for advice and/or a clinic appointment, as needed.
        - Show her the device, and allow her to hold it. Point out the components of the injection device, such as the needle cap, the reservoir, etc.). Demonstrate in principle how to activate the device, but without actually doing it (the patient will do this later); strongly emphasize that a 'click' must be heard or felt to ensure the device has been properly activated – or the medicine will not come out of the needle.

- Explain how to give a SC injection. Show the patient how to: (a) choose the injection site; (b) grab a good skin fold to ensure an SC injection; (c) insert the needle straight into the skin fold to full depth; and (d) squeeze the reservoir firmly but slowly for 5-7 seconds, until injection is complete.
- Allow the patient to view the brief Sayana Press video, as a review of the process (the video is described below).
- Invite the patient to perform self-injection. Observe that the patient has properly activated the injector, and confirm that the patient did, indeed, feel/hear a 'click'. Observe her as she performs each step and correct any potential or pending errors.
- Based on the HCP's observations, decide if the patient is suitable to perform self-administration. If yes, review the patient-directed materials (described below) with the patient and answer any questions she may have.
- If the clinic will normally provide a 3-month reminder (by post, email, other), inform the patient of this. Also inform the patient of the reminder techniques available the patient-directed materials.
- Ensure that the patient understands that she can decide, at any time, to get her next injection at the clinic if she is not comfortable doing self-injection, and, that she must call the clinic if an attempted self-injection cannot be completed successfully (injection difficulties during the attempt; or any other reason).

The patient-directed materials would typically be available to the patient after she has been trained. These materials are intended to support the 'hands-on' training received from the HCP and are proposed to consist of:

Sayana Press Responsive Website
The Sayana Press website will be the most important resource for patients. The website will provide access to the patient video as described below and this can also be accessed and played on smartphones as well as computer/laptop due to the responsive design. Patients will be able to subscribe to a reminder service (see below). Frequently asked questions may also be added to the website.

Self-injection Training Video
The training video will be a few minutes long and will use simple animation to illustrate the steps in the injection process using information, graphics and language consistent with the IFU. The video could be first used during the training provided by the HCP, and then used at home as a means to reinforce steps that have already been explained and demonstrated to the patient by the HCP. It is expected that the video will increase patients' confidence by providing them with a visual representation of the IFU in a series of small steps.

Reminders
Women who receive the product for self-administration at home will be solely responsible for maintaining compliance with the schedule of administration. As an alternative to traditional manual methods (e.g., use of calendar, diary) and the reminder aide proposed as Step 8 of the revised IFU (see also response to RMP Request 12), the website will provide instruction for patients on how to add calendar reminders on their own electronic calendar, which is a functionality of smartphones. In addition, it will have an option for patients to receive SMS text reminders. Patients will only receive these reminders if they enrol for the service.

Printed materials
It is proposed to supplement the website/video with a printed patient pamphlet in a question and answer format which will reinforce key messages on the following topics:

How to inject Sayana Press and helpful hints for injecting Sayana Press

The pamphlet will give advice on the importance of properly activating the injector, performing the injection slowly over 5-7 seconds and how best to squeeze the reservoir to expel all the medicine. Also we propose to provide a visual representation (e.g. photographs) of what the injector looks like

before use and once the medicine has been expelled. This will help to show the traces of suspension left in the injector reservoir due to the overage and to reassure patients who may be unsure if they have given themselves a full dose.

Messages regarding contacting their HCP if they experience any problems during administration will be reinforced.

Remembering when to inject Sayana Press

Practical advice on alternative methods of remembering when to give the next injection will be given for patients not enrolling in the reminder service.

The importance of injecting at 13 weeks +/-1 week will be emphasized and will reinforce advice in the PIL regarding what action to take if an injection is administered late or missed.

Summary
Taken together, the HCP- and patient-directed educational materials are intended to ensure that the proper patients are selected for this option, that they are properly trained, and that they have the support they need to be successful and minimize the risks of incorrect administration and non-adherence to the injection schedule. Nevertheless, since self-injection is an option and not a requirement for use of the product, women who are not inclined to self-inject, or are not proficient at the technique, may continue to use Sayana Press administered by the HCP at the clinic.

Assessment of response
The MAH has provided details of the training proposed for women. This include guidance for Healthcare Practitioners to aid training, educational videos, pamphlets, a website and reminder aids. The proposals are considered to be appropriate and acceptable subject to appropriate vetting to ensure that promotional material is not included.

Point considered resolved

4. It is proposed that women self-inject on a regular basis. The MAH should provide a detailed discussion on how women will be followed-up to ensure they don't miss injections. It should also be clarified whether women will have regular medical check-ups and how frequently this will be.

MAH's response
The Phase 3 clinical studies for DMPA-SC showed that this product is highly effective. No contraceptive failures occurred amongst 1779 women during 16,023 woman-cycles (excluding cycles during which a barrier method was used and/or no intercourse occurred). But it only works if women use it and are able to inject competently. Since the first dose would take place under supervision, we need to look at compliance after the first dose, which would be 'adherence' to therapy.

We will first examine the various factors that influence how well, or how poorly, patients adhere to a prescribed regimen and then focus on how those factors come into play for Sayana Press. In particular, we will look at the roles of the patient, the physician/HCP and the MAH/manufacturer, and consider how each can contribute to good adherence to the Sayana Press self-injection schedule. At the end of this Response we will address the topic of medical appointments for these women.

For any drug, adherence to an outpatient therapy depends on three things: (i) the degree of difficulty the patient may have in administering the drug properly; (ii) the administration schedule; and (iii) the patient's motivation to adhere to that schedule. In terms of difficulty of administration, an oral pill is certainly very simple (swallow it with water), while an inhaled agent or a subcutaneous injectable requires some basic training on the delivery device in order to insure that the drug is delivered properly. Improper operation of a dry powder inhaler, for example, results in the powder remaining

largely in the patient's mouth, rather than reaching the lungs. In contrast, IV and IM injectables are generally not suitable for self-administration, for various reasons. We would characterise Sayana Press as being of moderate difficulty to administer in that appropriate instruction is required in order to operate the device properly, but suitable for patient administration when the physician has provided training and determined that the patient is proficient in the technique.

The administration schedule is a major determinant of adherence. A 14-day course of antibiotics for an outpatient infection frequently has incomplete adherence even with a once daily drug, but even more so with a more demanding regimen that requires 3 or 4 doses per day [Sorenson, 2009; Pechere, 2007]. Taking a daily oral contraceptive pill (OCP) is certainly not difficult. However, taking a pill every single day without missing any pills over a 1 year period is actually quite demanding. Consequently, unintended pregnancies are not uncommon with OCPs and are reported to be as high as 18% per year in high-risk adolescents [Hillard PJ; 1992;]. In contrast, the Sayana Press regimen requires 4 doses per year. Presuming that the patient knows how to operate the injector and can note the four scheduled dates on their electronic or paper calendar, this regimen is not very demanding of the patient's time and attention compared to a daily regimen, and this feature would tend to promote better adherence.

However, the most important factor for adherence to therapy is really the motivation of the patient to follow the schedule, irrespective of the route of administration or the dosing schedule itself. Oncology patients and other patients with very serious diseases often have quite complex regimens of numerous daily pills, some with on-treatment and off-treatment periods at semi-irregular intervals. However, oncology patients are typically motivated to take steps to ensure proper adherence (e.g., setting up compartmented pill boxes) because they know that poor adherence can have serious consequences. In contrast, an outpatient with a bothersome but non-serious infection is oftentimes less highly motivated because no similar, severe consequence is perceived by the patient. Patients sometimes stop their antibiotic after a few days as symptoms begin to improve, saving the remaining pills for the next time they need them; this would be poor adherence essentially by intention.

Women using contraception, however, are generally quite motivated to adhere to their regimen since they recognize the seriousness of an unintended pregnancy. Unfortunately, it is easy for a patient to think that she took the pill this morning, since she takes it every morning, but sometimes it didn't actually happen. Or, she unintentionally leaves the pill pack at home when travelling for a few days. Or, a gastrointestinal illness causes the pill to not be absorbed properly.

As suggested by these examples, a key factor to consider is the sensitivity of a drug regimen to transient non-adherence, where the patient has not stopped the regimen by intent, but has not perfectly adhered to the schedule. Missing a few days of a cholesterol-lowering pill will not, in all likelihood, acutely precipitate a myocardial infarction nor is it likely that missing one or two doses of a 14-day BID antibiotic regimen, or taking those doses early or late, will lead to a treatment failure.

Oral contraceptive regimens, however, are notoriously sensitive to missed doses and demand consistent adherence, day after day. It is that need for perfect consistency that is makes a once-a-day contraceptive regimen much more demanding than a once-a-day antihypertensive regimen. In contrast, the 3-monthly Sayana Press regimen is relatively insensitive to transient schedule errors. Per the SmPC, there is a 2-week window for the patient to perform the self-injection. This is useful if the woman is away from home, for a few days or a week, on the scheduled injection date; she can do the injection when she returns without any concern for loss of efficacy. If the injection is done later than the allowed window, then there is a possibility that ovulation could occur.

In one study of 39 women receiving a single dose of DMPA-SC [Jain J, et al. 2004], pharmacokinetics, ovulation suppression and return to ovulation were assessed following a single injection of subcutaneous DMPA. The shortest observed interval for ovulation suppression (serum progesterone <4.7 ng/mL) was 15 weeks in that study. However, the mean time for ovulation suppression was 31 weeks (median = 30 weeks; range = 15 weeks to 51 weeks), which represents 18 weeks beyond the recommended 13-week injection interval. Therefore, even if a woman misses the

dosing window by several weeks, there is relatively little chance of contraceptive failure. In that regard, the method is quite robust.

Therefore, the Sayana Press regimen is reasonably forgiving of common circumstances that could cause a patient to be unable to inject precisely on the target date. For example, the patient who goes abroad for two weeks and forgets to bring her Sayana Press can inject when she returns with little chance that a contraceptive failure would occur.

As noted, the motivation of the patient to comply with the schedule is critical, and the physician can enhance that in several ways. The most important way, and the most obvious, is to ensure that only highly motivated patients are selected for self-injection. Self-injection is not required to use Sayana Press, so there should never be an attempt to persuade a woman to try self-injection if she is not comfortable with the concept. The best patients for self-injection should be those who are eager to try – not just those who are willing. Those patients will take the measures needed to ensure that injections are done in a timely manner (marking a calendar; putting an alert into her mobile phone; etc.) – none of which are difficult to do.

Secondly, the physician can ensure that the training is done thoroughly with each patient. Part of the training is how to activate the device and insert the needle, etc. But another part is education about the responsibility that she is taking on – ensuring that the patient understands that she will bear the responsibility to perform the injection every 3 months (+/-1 week), and that she needs to put an alert or reminder in place to ensure that the date is not missed. And, of course, the patient needs to know that she must call the clinic if she runs into any problems with the injection.

Thirdly, the physician can deploy a system for providing reminders to the patients. That is, most clinics already provide appointment cards and/or telephone contact prior to scheduled DMPA appointments, and this simple system generally works well for patients who intend to continue receiving DMPA. The physician can easily adapt the existing system to provide the same reminder to the self-injecting patient – essentially a reminder for her to perform her 'at home injection appointment'.

While encouraging an individual woman to adhere to a prescribed therapy is largely the province of the healthcare provider who knows her and is managing her, the MAH can assist by providing complete and correct information about the product (SmPC, IFU, PIL) along with complementary tools for conducting and supporting the training (such as the aide in Step 8 of the IFU and the electronic reminder system described in the Response to Question #3).

The MAH can also support the patient. In this case, we are fortunate to be dealing with a selected subgroup of motivated patients who have chosen to self-inject of their own accord.
Many DMPA patients will reject this option out of hand because they do not want to handle the needle or other reasons, but those who do attempt it will be those who genuinely want to do this because they have determined that, in their case, it offers an advantage. The primary support the MAH can offer these women is clear and complete information about the dosing schedule: *it is every 13 weeks and there is a 1 week window either side of that date. You need to keep to that schedule because injections beyond that window may not be effective. If your injection will fall outside of that window you should contact your physician for instructions.*

To conclude, self-injection will necessarily take place in a self-selected group of women who have volunteered to try this approach. Given effective training in how to mechanically operate the device and some simple support measures (e.g. appointment reminders), it would be anticipated that they should be quite successful.

Finally, regarding clinical follow-up of otherwise healthy women using a hormonal contraceptive regimen, it is our view that Healthcare professionals will be led by local clinical or contraceptive guidelines available in their country. Although the Czech Republic have withdrawn from this procedure, the CZ assessor revealed in their query that all women using prescribed contraception in CZ visit their physician every 3 months for routine care. In the US, the practice is an annual follow-up

visit. We are also aware that longer follow-up intervals are used in other EU countries, but in light of the CZ practice, we must recognize that there exists wide variation across the EU. That being the case, the MAH would not be best-placed to recommend, in any formal sense, either the interval or the nature of such follow-up because this is the province of those who guide medical practice in each local country. It is important to note that there is no specific rationale by which DMPA use, per se, should require a change in a physician's standard follow-up interval for women using hormonal contraception.

We therefore propose to modify the PIL to remove reference to any specific time interval for routine follow up.
.

Assessment of response
The MAH proposes that follow-up and medical check-up should be based on locally applicable guidelines. It is acceptable but Section 3 of the PIL should remain as it was originally and the section 4.2 of the SmPC should be modified to reflect this information.

Point considered resolvable with SmPC and PIL changes

5. An in-depth discussion should be provided on the disposal of Sayana Press after self-administration. In addition the product information should also be updated.

MAH's response
Precise arrangements for provision and collection of containers for disposal of needles and sharps by a patient injecting at home differs across the EU.

In the UK for example, patients are well provided for in that they may obtain a sharps container on prescription, however arrangements for return of full containers may differ from local authority to local authority, although commonly, full sharps bins are either collected from the patient's home or returned to the pharmacy. Additionally needle clippers to remove the needle may also be available on prescription or for a small charge. However sharps bins collected from home on the local government collection scheme are typically collected when full or every three months, whichever is the soonest. Although this arrangement is suitable for a patient using daily injections (e.g., diabetic) this would not be beneficial for Sayana Press given the one injection every 3 months injection schedule.

A similar arrangement for provision of sharps bins is common in Ireland and the Netherlands

In other EU countries the provision of sharps bins to patients may or may not be common practice and patients are typically expected to return used needles/injectors to the pharmacy. The most pragmatic general practice to adopt would therefore be for patients to return either their sharps containers (if available) or used injectors to their local pharmacy for disposal as this seems to be consistent with practice across all countries surveyed, whereas returning the sharps to a GP/Clinic may or may not be allowed.

We acknowledge that in line with current regulations we wish to discourage the disposal of sharps into household waste and to reinforce messages around prevention of inadvertent injury by reiterating the advice not to attempt to recap the needle once the needle shield has been removed.

A review of Patient Information Leaflets/IFUs for recently approved injectable medicines that may be home administered reveals that there is no set standard text for sharps disposal advice (presumably because of the observed variation in local practice across the EU).

Accordingly, we propose to update the Common PL/IFU text which we believe is consistent with current practices.

Advice on not recapping the needle is already adequately covered in the preceding Step 6 of the IFU.

Assessment of response
The information has been provided.
Point considered resolved

OVERALL CONCLUSIONAND BENEFIT-RISK ASSESSMENT

The benefit risk for SAYANA PRESS remains unchanged and proposal to allow women to self-administer is considered approvable.

Back

Details

Product Name in the RMS: Sayana Press 104 mg/ 0.65 ml

MR Number: UK/H/0960/002
Date of outcome: 22.05.2011

Type of application	
Level 1: Level 2: Level 3: Level 4: Level 5:	Line Extension Initial Application Full Dossier Chemical Substance Prescription Only
Active Substances	medroxyprogesterone acetate 160 mg/ml
Form	Suspension for injection
MA Holder in the RMS	PFIZER LIMITED
RMS	United Kingdom
Date of last change	17.05.2018
ATC-Code	G03AC06 Medroxyprogesterone

CMS Country	Domestic Product Name
Austria	Sayana Press 104 mg/0,65 ml Injektionssuspension
Belgium	
Hungary	Sayana IS 104 mg/0,65 ml szuszpenziós injekció
Netherlands	SAYANA PRESS, 104 mg/0,65 ml suspensie voor injectie
Norway	
Poland	

Documents	
PAR:	http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con126147.pdf (31.08.2011)

Export results to csv
Export results to excel

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-583

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-583

Pfizer, Inc.
Attention: Jennifer Bingaman
Manager, Worldwide Regulatory Strategy
235 East 42nd Street, 150/7/9
New York, NY 10017

Dear Ms. Bingaman:

Please refer to your new drug application (NDA) dated June 30, 2003, received July 02, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for depo-subQ provera 104™ (medroxyprogesterone acetate injectable suspension) 104mg/0.65ml.

We acknowledge receipt of your submissions dated October 22, 2003, 28(2), 29, 30, November 3, December 3, 2003, February 18, 2004, 19, 23, March 1, 10 (2) 15, 29, April 7, 16, 21, 27, May 19, 20, 21, 25, June 15, July 26, 28, October 1, 8, and 21, November 15, December 7, 9, 13, and 14, 2004.

The October 15, 2004 submissions constituted a complete response to our August 2, 2004 action letter.

This new drug application provides for the use of depo-subQ provera 104™ (medroxyprogesterone acetate injectable suspension) 104 mg/0.65 ml for contraception.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and patient package insert) and submitted labeling (immediate container and carton labels submitted December 7, 2004). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-583**". Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are

waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Reproductive and Urologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 827-4266.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Physician Insert and Patient Package Insert

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Donna Griebel
12/17/04 11:00:35 AM

Drugs@FDA: FDA Approved Drug Products

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New Drug Application (NDA): 021583
Company: PHARMACIA AND UPJOHN

EMAIL

Products on NDA 021583

CSV Excel Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route
DEPO-SUBQ PROVERA 104	MEDROXYPROGESTERONE ACETATE	104MG/0.65ML	INJECTABLE;SUBCUTANEOU

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 021583

Labels for NDA 021583

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
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SAYANAJECT

Azienda: PFIZER ITALIA S.R.L.

AIC: 043105

Foglio illustrativo

Riassunto delle Caratteristiche del prodotto

PRINCIPI ATTIVI

Medrossiprogesterone

CONFEZIONI

Denominazione	AIC	Stato
"104 MG SOSPENSIONE INIETTABILE" 1 INIETTORE PRERIEMPITO MONODOSE IN PE DA 0,65 ML CON AGO	043105016	autorizzato

<< < 1 > >>

AGENCIA FEDERAL DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

CERTIFICADO DE PRODUCTO FARMACEUTICO[1]

Este certificado està de acuerdo con el formato recomendado por la Organización Mundial de la Salud.
(Se adjuntan instrucciones generales y notas aclaratorias)

N° de este certificado: 000055 26-01-17
País exportador (certificador): BELGICA
País importador (solicitante): CHILE

1. Nombre y forma farmacéutica del producto: SAYANA PRESS 104 mg/0.65 ml Suspensión inyectable
1.1 Principio(s) y cantidades[2] por unidad de dosis[3] - composición completa incluyendo
excipientes: ver adjunto[4]:
Medroxyprogesterone acetate 104mg

1.2 ¿Está este producto autorizado para su comercialización y uso en el país exportador?[5] sí
1.3 ¿Se comercializa este producto actualmente en el mercado del país exportador? sí
Tiempo de durabilidad: 60 meses
2A.1 Número de la autorización de comercialización[7] y fecha de autorización: BE400075 - 22 septiembre 2011
2A.2 Titular de la Autorización de Comercialización: PFIZER SA, Boulevard de la Plaine 17, 1050 Bruxelles, BELGICA
2A.3 Actividad del Titular de la Autorización de Comercialización[8]: c
2A.3.1 Nombre y dirección del fabricante de la forma farmacéutica[9]:
Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, BELGICA
2A.4 ¿El resumen básico de aprobación se adjunta?[10] no; disponible bajo solicitud.
2A.5 ¿La información autorizada del producto que se adjunta está completa y de acuerdo con la autorización?[11] sí
2A.6 Solicitante del certificado[12]: Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, BELGICA.
2B. No aplicable [6]

3. La autoridad certificadora, dispone la inspección periódica de la planta de fabricación en que se produce la forma farmacéutica[14]: sí (solamente para Bélgica)
3.1 Periodicidad de las inspecciones de rutina: 2 años (solamente para Bélgica)
3.2 ¿Se ha inspeccionado la fabricación de este tipo de forma farmacéutica? Sí (solamente para Bélgica)
3.3 ¿Se adaptan las instalaciones y procedimientos a las GMP recomendadas por la Organización Mundial de la Salud?[15] sí (solamente para Bélgica)

Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
Fedarol Agentschap voor Geneesmiddelen en Gezondheidsproducten
(FAGG)

4. ¿La información presentada por el solicitante satisface a la autoridad de certificación en relación con todos los aspectos de la fabricación del producto?[16]
sí

Dirección de la Autoridad certificadora :	Agencia federal de medicamentos y productos sanitarios - afmps, Eurostation II, Place Victor Horta 40/40, 1060 Bruselas (Belgica)	
Teléfonos : +32 2 528 40 00	www.fagg-afmps.be	certificates@fagg-afmps.be
Sello y fecha : 	26 JAN. 2017 afmps fagg	Nombre de la persona autorizada : Xavier De Cuyper, Administrador General - CEO p.o. Séverine BRASSEUR, Attaché DG Inspection - AFMPS.

B 00045404 B 00045404

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Land/Pays/Land : ***BELGIË – BELGIQUE – BELGIEN.***
2. Deze openbare akte is ondertekend door : / Le présent acte public a été signé par : / Diese öffentliche Urkunde ist unterschrieben von: ***Brasseur, Séverine***
3. Handelend in hoedanigheid van : / Agissant en qualité de : / In seiner/ihrer Eigenschaft als: ***Attaché/Attaché/Attaché***
4. Is voorzien van het zegel van / Est revêtu du sceau de / Sie ist versehen mit dem Siegel des/der: ***FOD Volksgezondheid/SPF Santé publique/FÖD Volksgesundheit Brussels***

Voor echt verklaard / Attesté / Bestätigt

5. ***Te Brussel/A Bruxelles/In Brüssel*** 6. Op/Le/Am : ***06/02/2017***
7. Door FOD Buitenlandse Zaken, Buitenlandse Handel en Ontwikkelingssamenwerking / Par le SPF Affaires étrangères, Commerce extérieur et Coopération au Dévelopement / Durch FOD Auswärtige Angelegenheiten, Außenhandel und Entwicklungszusammenarbeit
8. Onder Nr. /Sous le n°/ Unter Nr. : ***9805279983403547***
9. Stempel/Sceau/Stempel :
10. Ondertekening/Signature/ Unterschrift : Jan Van de Velde

Prijs/Prix/ Preis : *20* EUR

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1. Land/Pays/Land: ***BELGIË - BELGIQUE - BELGIEN***

2. Deze openbare akte is ondertekend door :
Le présent acte a été signé par :
Diese öffentliche Urkunde ist unterschrieben von : ***Brasseur Séverine***

3. Handelend in hoedanigheid van :
Agissant en qualité de :
In seiner/ihrer Eigenschaft als : ***Attaché/Attaché/Attaché***

4. Is voorzien van het zegel van :
Est revêtu du sceau de :
Sie ist versehen mit dem Siegel des/der : ***FAGG/AFMPS/FAGG/FAMPS***

Voor echt verklaard / Attesté / Bestätigt

5. ***Te Brussel/A Bruxelles/In Brüssel*** 6. Op/Le/Am : ***15/07/2020***

7. Door FOD Buitenlandse Zaken, Buitenlandse Handel en Ontwikkelingssamenwerking
Par le SPF Affaires étrangères, Commerce extérieur et Coopération au Développement
Durch FÖD Auswärtige Angelegenheiten, Außenhandel und Entwicklungszusammenarbeit

8. Onder Nr./Sous le n°/Unter Nr. : ***200775880775***

9. Stempel/Sceau/Stempel:

10. Ondertekening/Signature/Unterschrift:

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Belgium

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AGENCIA FEDERAL DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

CERTIFICADO DE PRODUCTO FARMACEUTICO[1]

Este certificado està de acuerdo con el formato recomendado por la Organización Mundial de la Salud.
(Se adjuntan instrucciones generales y notas aclaratorias)

N° de este certificado: 20200713006
País exportador (certificador): BELGICA
País importador (solicitante): CHILE

1. Nombre y forma farmacéutica del producto: SAYANA PRESS 104 mg/0.65 ml Suspensión inyectable

1.1 Principio(s) y cantidades[2] por unidad de dosis[3] - composición completa incluyendo excipientes: ver adjunto[4]:
Medroxyprogesterone acetate 104mg
Methyl parahydroxybenzoate (E218) 1.04mg - Propyl parahydroxybenzoate (E216) 0.0975mg - Sodium chloride 5.2mg - Macrogol (polyethylene glycol) 3350 18.688mg - Polysorbate 80 1.95mg - Monobasic sodium phosphate monohydrate 0.451mg - Disodium phosphate dodecahydrate 0.382mg -
Methionine 0.975mg - Povidone, K 17 PF 3.25mg - Sodium Hydroxide q.s. ** - Hydrochloric acid. q.s. ** - Water for injections q.s. ad 0.65ml
** utilizado para adaptación del pH

1.2 ¿Está este producto autorizado para su comercialización y uso en el país exportador?[5] sí

1.3 ¿Se comercializa este producto actualmente en el mercado del país exportador? sí
Tiempo de durabilidad: 36 meses

2A.1 Número de la autorización de comercialización[7] y fecha de autorización: BE400075 - 22 septiembre 2011

2A.2 Titular de la Autorización de Comercialización**:** PFIZER SA, Boulevard de la Plaine 17, 1050 Bruxelles, BELGICA

2A.3 Actividad del Titular de la Autorización de Comercialización[8]: c

2A.3.1 Nombre y dirección del fabricante de la forma farmacéutica[9]:
Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, BELGICA

2A.4 ¿El resumen básico de aprobación se adjunta?[10] no; disponible bajo solicitud.

2A.5 ¿La información autorizada del producto que se adjunta está completa y de acuerdo con la autorización?[11] sí

2A.6 Solicitante del certificado[12]: Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, BELGICA.

2B. No aplicable [6]

3. La autoridad certificadora, dispone la inspección periódica de la planta de fabricación en que se produce la forma farmacéutica[14]: sí (solamente para Bélgica)

3.1 Periodicidad de las inspecciones de rutina: 2 años (solamente para Bélgica)

3.2 ¿Se ha inspeccionado la fabricación de este tipo de forma farmacéutica? Sí (solamente para Bélgica)

3.3 ¿Se adaptan las instalaciones y procedimientos a las GMP recomendadas por la Organización Mundial de la Salud?[15] sí (solamente para Bélgica)

4. ¿La información presentada por el solicitante satisface a la autoridad de certificación en relación con todos los aspectos de la fabricación del producto?[16]
sí

Dirección de la Autoridad certificadora :	Agencia federal de medicamentos y productos sanitarios - afmps, Eurostation II, Place Victor Horta 40/40, 1060 Bruselas (Belgica)	
Teléfonos : +32 2 528 40 00	www.fagg-afmps.be	certificates@fagg-afmps.be
Sello y fecha : 13-07-2020 		Nombre de la persona autorizada : Xavier De Cuyper, Administrador General – CEO On Behalf, Séverine Brasseur, DG Inspection - File Manager

Instrucciones generales

Favor referirse a la guía para instrucciones completas sobre cómo llenar este formulario e información sobre la implementación del esquema.
Los formularios son adecuados para generarse por computadora. Deben enviarse siempre en original, con respuestas impresas en caracteres en vez de llenados a mano**.**
Hojas adicionales pueden ser anexadas, si son necesarias, para incluir observaciones y explicaciones.

Notas explicatorias

1. Este certificado, que se emite en el formato recomendado por la OMS, establece el estado de un producto farmacéutico y del solicitante del certificado, en el país de exportación. Es únicamente para un solo producto ya que las disposiciones de manufactura y la información aprobada para diferentes formas farmacéuticas y diferentes concentraciones, podrían variar.
2. Usar, cuando sea posible, Nombres Internacionales No Patentados (INNs) o nombres nacionales no patentados.
3. La fórmula (composición completa) de la forma farmacéutica debe especificarse en el certificado o puede ser anexada.
4. Se prefieren detalles de la composición cuantitativa, pero su provisión está sujeta al acuerdo del tenedor de la licencia del producto.
5. Cuando sea aplicable, anexar detalles de alguna restricción aplicable a la venta, distribución o administración del producto que se especifique en la licencia del producto.
6. Secciones 2A y 2B son mutualmente exclusivas.
7. Indicar, cuando sea aplicable, si la licencia es provisional, o si el producto aún no ha sido aprobado.
8. Especificar si la persona responsable de colocar el producto en el mercado:
   (a) manufactura la forma farmacéutica;
   (b) empaca y/o etiqueta la forma farmacéutica manufacturada por una compañía intependiente;
   (c) no está involucrada en ninguno de los dos puntos anteriores
9. Esta información sólo puede ser proporcionada con el consentimiento del tenedor de la licencia del producto o, en el caso de productos no registrados, del solicitante. No completar esta sección indica que la parte interesada no está de acuerdo en incluir esta información.
   Debe anotarse que la información concerniente al lugar de producción es parte de la licencia del producto. Si el lugar de producción es cambiado, la licencia debe actualizarse o ya no será válida.
10. Esto se refiere al documento, preparado por algunas autoridades regulatorias nacionales, que resume la base técnica sobre la cual el producto ha sido licenciado.
11. Esto se refiere a la información del producto aprobada por la autoridad nacional regulatoria competente, tal como Resumen de Características del Producto (SPC).
12. En esta circunstancia, se require permiso del tenedor de la licencia del producto para emitir el certificado. Este permiso debe ser otorgado a la autoridad por el solicitante.
13. Favor indicar la razón que el solicitante ha proporcionado para no solicitar el registro:
   (a) el producto ha sido desarrollado exclusivamente para el tratamiento de condiciones—particularmente enfermedades tropicales—no endémicas en el país de exportación;
   (b) el producto ha sido reformulado con el propósito de mejorar su estabilidad bajo condiciones tropicales;
   (c) el producto ha sido reformulado para excluir excipientes no aprobados para usarse en productos farmacéuticos en el país de importación;
   (d) el producto ha sido reformulado para cumplir con un límite máximo de dosificación diferente para un ingrediente activo;
   (e) cualquier otra razón, favor especificar.
14. No aplicable significa que la manufactura toma lugar en un país diferente del país que emite el certificado del producto y la inspección es conducida bajo el amparo del país de manufactura.
15. Los requerimientos de las buenas prácticas de manufactura y control de calidad de los medicamentos referidos en el certificado, son aquéllos incluidos en el repote treinta y dos del Comité Experto en Especificaciones para Preparaciones Farmacéuticas, Reporte Técnico de la OMS Serie No. 823, 1992, Anexo 1. Recomendaciones específicamente aplicables para productos biológicos han sido formulados por el Comité Experto de la OMS en Estandarización Biológica (Reporte Técnico de la OMS Serie No. 822, 1992, Anexo 1).
16. Esta sección debe completarse cuando el tenedor de la licencia del producto o solicitante se ajuste al status (b) o (c) como se describe en el numeral 8 antes citado. Es de particular importancia cuando contratistas extranjeros están involucrados en la manufactura del producto. En estas circunstancias, el solicitante debe suministrar a la autoridad que certifica, la información para identificar las partes contratantes responsable de cada etapa de la manufactura de la forma farmacéutica terminada, y la extensión y naturaleza de cualquier control ejecutado sobre cada una de estas partes.

BEL 20C12

RESUME DES CARACTERISTIQUES DU PRODUIT

1. DENOMINATION DU MEDICAMENT

SAYANA PRESS 104 mg/0,65 ml suspension injectable.

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

SAYANA PRESS récipient unidose avec 104 mg d'acétate de médroxyprogestérone (AMP) dans 0,65 ml de suspension injectable.

Excipients à effet notoire:

Parahydroxybenzoate de méthyle – 1,04 mg par 0,65 ml
Parahydroxybenzoate de propyle – 0,0975 mg par 0,65 ml
Sodium – 2,47 mg par 0,65 ml

Pour la liste complète des excipients, voir rubrique 6.1.

3. FORME PHARMACEUTIQUE

Suspension injectable.

Suspension homogène de couleur blanche à blanc cassé.

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

SAYANA PRESS est indiqué pour la contraception à long terme chez la femme. Chaque injection sous-cutanée empêche l'ovulation et offre une contraception pendant 13 semaines au moins (± 1 semaine). Toutefois, il faut tenir compte du fait que le délai avant le retour de la fertilité (ovulation) peut aller jusqu'à un an (voir rubrique 4.4).

Dans la mesure où une perte de densité minérale osseuse peut se produire chez des femmes de tous âges qui utilisent SAYANA PRESS à long terme (voir rubrique 4.4), une évaluation risque/bénéfice, tenant compte également de la diminution de la densité minérale osseuse qui se produit pendant la grossesse et/ou l'allaitement, doit être envisagée.

Utilisation chez les adolescentes (de 12 à 18 ans)
Chez les adolescentes, l'utilisation de SAYANA PRESS n'est indiquée qu'après que d'autres méthodes de contraception ont été jugées inappropriées ou inacceptables, en raison d'effets inconnus à long terme de perte osseuse associée à SAYANA PRESS au cours de la période critique d'accrétion osseuse (voir rubrique 4.4).

SAYANA PRESS n'a pas été étudié chez des femmes âgées de moins de 18 ans, mais on dispose de données concernant l'acétate de médroxyprogestérone dépôt (DMPA-IM) intramusculaire 150 mg dans cette population.

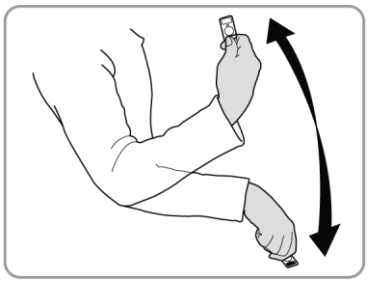
4.2 Posologie et mode d'administration

SAYANA PRESS peut être administré par un professionnel de la santé ou, quand le professionnel de la santé l'estime approprié, par la patiente elle-même, pour autant qu'elle bénéficie du suivi médical nécessaire conformément aux recommandations cliniques locales.

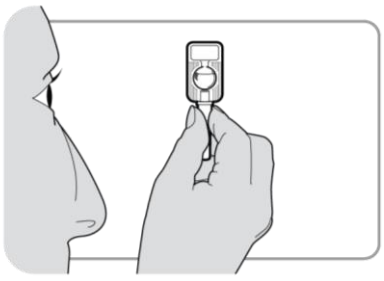
L'administration de SAYANA PRESS doit être instaurée sous la surveillance d'un professionnel de la santé. Après une formation adéquate sur la technique d'injection et sur le schéma d'administration, la patiente peut s'injecter elle-même SAYANA PRESS si son professionnel de la santé estime que c'est approprié et qu'elle bénéficie du suivi médical nécessaire.
Le récipient unidose de SAYANA PRESS doit être à température ambiante. Il doit être agité vigoureusement juste avant l'emploi afin de s'assurer que la dose administrée représente une suspension uniforme. Le contenu est complètement scellé dans le réservoir de l'injecteur. L'injecteur doit être activé avant l'utilisation. La procédure d'activation perce la fermeture interne pour que le médicament puisse passer par l'aiguille lorsque le réservoir est comprimé. Le liquide ne remplit pas complètement le réservoir. Il y a une petite bulle d'air au-dessus du liquide. La dose est administrée par injection sous-cutanée (SC) dans la partie antérieure de la cuisse ou l'abdomen. Lorsque l'injection est administrée, l'injecteur doit être utilisé avec l'aiguille pointant vers le bas. Cela garantit que la dose complète de liquide est délivrée à travers l'aiguille. Le médicament doit être injecté lentement pendant 5-7 secondes.

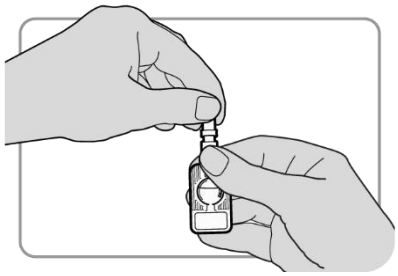
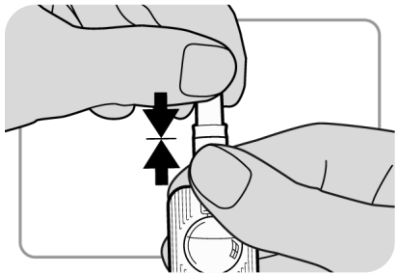
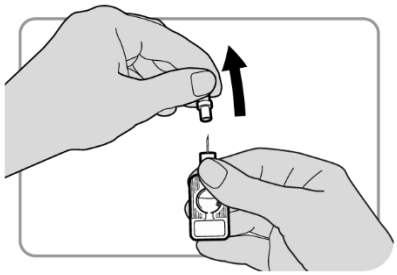
Mélange du médicament

- Assurez-vous que le récipient unidose de SAYANA PRESS est à **température ambiante**.
- Tenez fermement l'injecteur par le porte-aiguille.
- Agitez vigoureusement l'injecteur pendant au moins 30 secondes de manière à mélanger le médicament.



- Le médicament doit avoir un aspect blanc et uniforme. Dans le cas contraire, jetez l'injecteur et utilisez-en un nouveau.
- Si vous voyez du liquide s'écouler ou en cas d'autres problèmes, jetez l'injecteur et utilisez- en un nouveau.
- En cas de délai entre le mélange du médicament et l'injection, il faut répéter la procédure de mélange.



Activation de l'injecteur • Maintenez fermement l'injecteur par le porte-aiguille, en veillant à ce que le cache-aiguille soit dirigé vers le haut. Veillez à ne pas presser le réservoir. • Maintenez le cache-aiguille avec l'autre main.	
• Poussez le cache-aiguille fermement vers le porte-aiguille jusqu'à ce qu'il n'y ait plus d'espace. L'injecteur est maintenant activé.	
• Retirez le cache-aiguille et jetez-le.	

Prière de consulter les **Instructions d'utilisation** comprises dans la notice pour les **instructions détaillées** sur la préparation et l'administration d'une injection.

Adultes

Première injection : Pour obtenir une couverture contraceptive lors du premier cycle d'utilisation, une injection de 104 mg SC doit être administrée pendant les cinq premiers jours d'un cycle menstruel normal. Si l'injection est effectuée selon ces instructions, aucune mesure contraceptive supplémentaire n'est requise.

Doses suivantes : La deuxième injection et les injections suivantes doivent être administrées à intervalles de 13 semaines ; pour autant que l'injection soit administrée dans un délai de sept jours maximum après cette période, aucune mesure contraceptive supplémentaire (p. ex. méthode de barrière) n'est requise. Si le délai écoulé depuis l'injection précédente est supérieur à 14 semaines (13 semaines plus 7 jours) pour quelque raison que ce soit, une grossesse doit alors être exclue avant l'administration de l'injection suivante. L'efficacité de SAYANA PRESS dépend du respect du schéma de traitement recommandé.

Les femmes doivent être réévaluées régulièrement de façon appropriée sur le plan clinique, au moins une fois par an, afin de déterminer si SAYANA PRESS est toujours la meilleure option pour elles.

Post-partum : Si la patiente n'allaite pas, l'injection doit être administrée dans les 5 jours post-partum (pour augmenter la certitude que la patiente n'est pas enceinte). Si l'on choisit d'administrer l'injection à un autre moment, une grossesse doit être exclue.

Si la patiente allaite, l'injection doit être administrée au plus tôt six semaines post-partum, lorsque le système enzymatique du nourrisson est plus développé (voir rubrique 4.6).

Il est démontré que les femmes auxquelles SAYANA PRESS a été prescrit pendant la période puerpérale immédiate peuvent expérimenter des saignements prolongés et abondants. C'est la raison pour laquelle ce médicament doit être utilisé avec précaution pendant la période puerpérale. Les femmes qui envisagent d'utiliser le produit immédiatement après l'accouchement ou l'interruption de grossesse doivent être informées que le risque de saignements abondants ou prolongés peut être augmenté. Il est rappelé aux médecins que l'ovulation peut se produire dès la quatrième semaine chez la patiente en post-partum n'allaitant pas.

Passage d'autres méthodes de contraception à SAYANA PRESS : Lors du passage d'autres méthodes de contraception à SAYANA PRESS, celui-ci doit être administré de manière à garantir une couverture contraceptive continue compte tenu du mode d'action des deux méthodes (p. ex. les patientes qui passent d'un contraceptif oral à SAYANA PRESS doivent recevoir leur première injection de SAYANA PRESS dans les 7 jours après la prise de leur dernière pilule active).

Insuffisance hépatique: L'effet d'une affection hépatique sur le profil pharmacocinétique de SAYANA PRESS n'est pas connu. Puisque SAYANA PRESS subit essentiellement une élimination hépatique, il peut être faiblement métabolisé chez les patientes souffrant d'insuffisance hépatique sévère (voir rubrique 4.3).

Insuffisance rénale: L'effet d'une affection rénale sur le profil pharmacocinétique de SAYANA PRESS n'est pas connu. Etant donné que SAYANA PRESS est éliminé presque exclusivement par métabolisme hépatique, aucun ajustement posologique ne devrait être nécessaire chez les femmes souffrant d'insuffisance rénale.

Population pédiatrique
SAYANA PRESS n'est pas indiqué avant l'apparition des premières règles (voir rubrique 4.1). Des données existent chez les adolescentes (12-18 ans) en ce qui concerne l'administration IM d'acétate de médroxyprogestérone (voir rubriques 4.4 et 5.1). Hormis les préoccupations relatives à la perte de densité minérale osseuse, la sécurité et l'efficacité de SAYANA PRESS devraient être identiques chez les adolescentes après l'apparition des premières règles et chez les femmes adultes.

4.3 Contre-indications

- SAYANA PRESS est contre-indiqué chez les patientes qui ont une hypersensibilité connue à l'acétate de médroxyprogestérone ou à l'un de ses excipients mentionnés à la rubrique 6.1.
- SAYANA PRESS est contre-indiqué en cas de grossesse connue ou suspectée.
- SAYANA PRESS est contre-indiqué chez les femmes qui ont une tumeur maligne connue ou suspectée du sein ou des organes génitaux.
- SAYANA PRESS est contre-indiqué chez les patientes qui présentent des saignements vaginaux non diagnostiqués.
- SAYANA PRESS est contre-indiqué chez les patientes qui souffrent d'insuffisance hépatique sévère.
- SAYANA PRESS est contre-indiqué chez les patientes qui souffrent de maladies osseuses métaboliques.
- SAYANA PRESS est contre-indiqué chez les patientes présentant une maladie thromboembolique active et chez les patientes présentant une maladie cérébrovasculaire actuelle ou antérieure.

4.4 Mises en garde spéciales et précautions d'emploi

Mises en garde :

Perte de densité minérale osseuse:
L'utilisation d'acétate de médroxyprogestérone dépôt sous-cutanée (DMPA-SC) réduit les taux sériques d'œstrogènes et est associée à une perte significative de densité minérale osseuse due à l'effet connu d'un déficit en œstrogènes sur le remodelage osseux. La perte osseuse augmente avec la durée d'utilisation, toutefois la densité minérale osseuse semble augmenter après l'arrêt de DMPA-SC et la production d'œstrogènes d'origine ovarienne augmente.

Cette perte de densité minérale osseuse est particulièrement préoccupante pendant l'adolescence et au début de l'âge adulte, une période critique d'accrétion osseuse. On ignore si l'utilisation de DMPA-SC par les femmes plus jeunes va réduire le pic de masse osseuse et augmenter le risque de fracture à un stade ultérieur de la vie, c.-à-d. après la ménopause.

Une étude destinée à évaluer les effets sur la densité minérale osseuse du DMPA-IM (Depo-Provera) chez les adolescentes a montré que son utilisation était associée à une diminution statistiquement significative de la densité minérale osseuse par rapport au départ. Après l'arrêt du DMPA-IM chez les adolescentes, le retour de la densité minérale osseuse moyenne aux valeurs initiales a nécessité 1,2 an au niveau de la colonne vertébrale, 4,6 ans au niveau de la hanche totale et 4,6 ans au niveau du col du fémur (voir rubrique 5.1). Cependant, chez certaines participantes, la densité minérale osseuse n'est pas entièrement revenue aux valeurs initiales pendant le suivi et les résultats à long terme ne sont pas connus dans ce groupe. Chez les adolescentes, SAYANA PRESS peut être utilisé, mais seulement après que d'autres méthodes de contraception ont été discutées avec les patientes et ont été jugées inappropriées ou inacceptables.

Une vaste étude observationnelle menée en majorité auprès d'utilisatrices adultes de contraceptifs a démontré que l'utilisation du DMPA-IM n'augmentait pas le risque de fractures osseuses. Il est important de savoir que cette étude ne pouvait pas déterminer si l'utilisation du DMPA a un effet sur le taux de fractures plus tard dans la vie (voir rubrique 5.1 – Relation entre l'incidence des fractures et l'utilisation du DMPA-IM chez les femmes en âge de procréer).

Chez les femmes de tous âges, une réévaluation minutieuse des risques et des bénéfices du traitement doit être effectuée chez celles qui souhaitent poursuivre le traitement au-delà de 2 ans. En particulier, chez les femmes qui, au vu de leur mode de vie et/ou pour des raisons médicales, ont des facteurs de risque significatifs d'ostéoporose, d'autres méthodes de contraception doivent être envisagées avant d'utiliser SAYANA PRESS.

Les facteurs de risque significatifs d'ostéoporose comprennent :
- Abus d'alcool et/ou tabagisme
- Utilisation chronique de médicaments qui peuvent réduire la masse osseuse, par ex. anticonvulsivants ou corticostéroïdes
- Indice de masse corporelle bas ou troubles alimentaires, par ex. anorexie mentale ou boulimie
- Antécédent de fracture secondaire à un traumatisme mineur
- Antécédent familial d'ostéoporose

Pour de plus amples informations sur les modifications de la densité minérale osseuse chez les femmes adultes et les adolescentes, veuillez vous référer à la rubrique 5.1. Des apports adéquats de calcium et de vitamine D, soit via l'alimentation, soit via des suppléments, sont importants pour la santé osseuse des femmes, quel que soit leur âge.

Menstruations irrégulières :

La plupart des femmes qui utilisent l'acétate de médroxyprogestérone dépôt par injection sous-cutanée dépôt ont présenté une modification du profil des saignements menstruels. Les patientes doivent être conseillées de façon adéquate au sujet de la probabilité de troubles menstruels et d'un retard potentiel du retour de l'ovulation. Lors de la poursuite du traitement par l'acétate de médroxyprogestérone dépôt par injection sous-cutanée, les femmes étaient moins nombreuses à présenter des saignements irréguliers et plus nombreuses à présenter de l'aménorrhée. Après avoir reçu la quatrième dose, 39 % des femmes présentaient de l'aménorrhée au sixième mois. Au douzième mois, 56,5 % des femmes présentaient de l'aménorrhée. Les modifications du profil menstruel mises en évidence par les trois études menées sur la contraception sont présentées dans les figures 1 et 2. La figure 1 illustre l'augmentation du pourcentage de femmes présentant de l'aménorrhée au fil de l'étude (12 mois). La figure 2 représente le pourcentage de femmes qui ont présenté uniquement du spotting, uniquement des saignements, ou à la fois des saignements et du spotting au cours de cette même période. Outre l'aménorrhée, les modifications du profil menstruel incluaient saignements intermenstruels, ménorragies et métrorragies. Si les saignements anormaux associés à l'injection sous-cutanée d'acétate de médroxyprogestérone dépôt persistent ou sont sévères, des examens et un traitement appropriés doivent être mis en place.

Figure 1. Pourcentage de femmes traitées par l'acétate de médroxyprogestérone dépôt par injection sous-cutanée avec aménorrhée dans les études menées sur la contraception, par mois de 30 jours (population ITT, n = 2053)

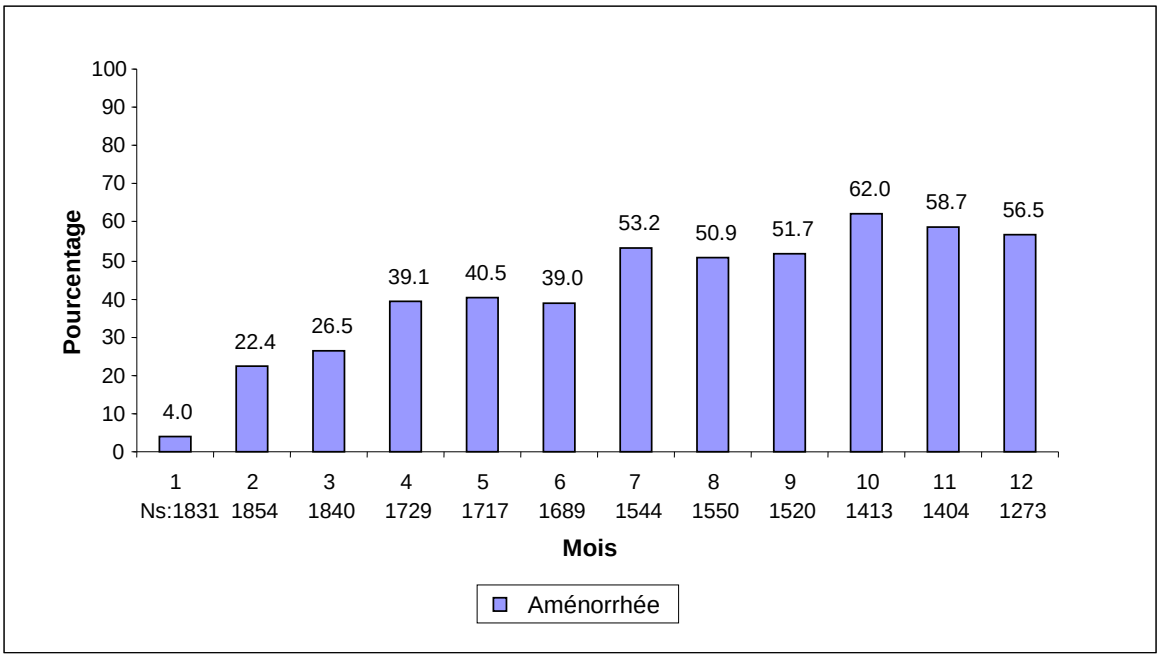
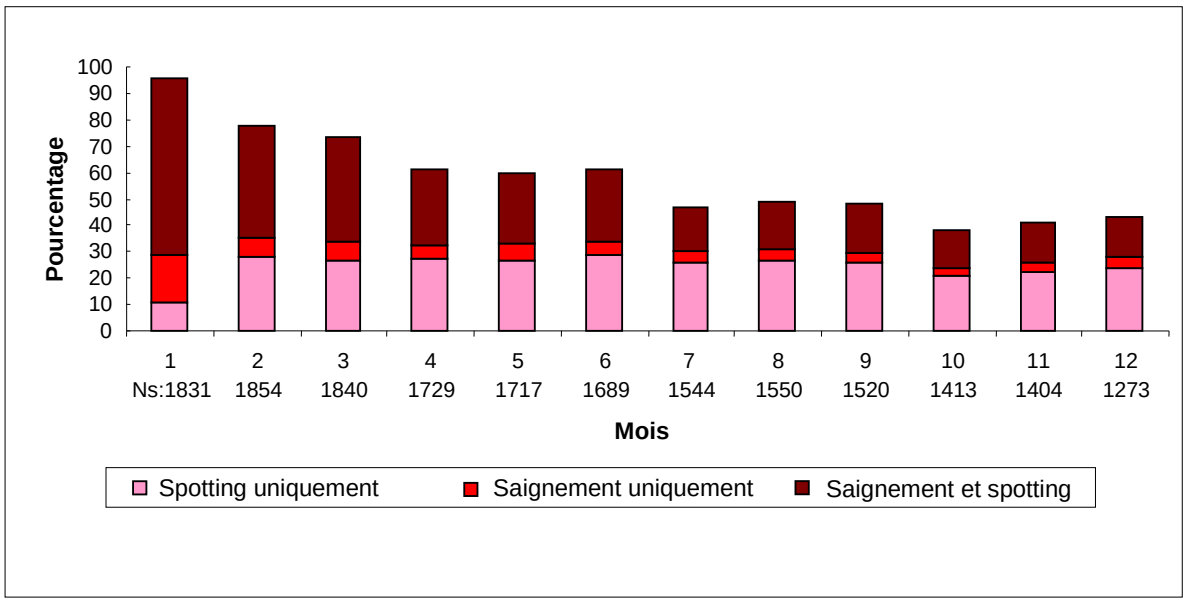


Figure 2. Pourcentage de femmes traitées par l'acétate de médroxyprogestérone dépôt par injection sous-cutanée avec saignements et/ou spotting dans les études menées sur la contraception, par mois de 30 jours (population ITT, n = 2053)



Risques de cancer :
La surveillance des utilisatrices d'injections intramusculaires d'acétate de médroxyprogestérone dépôt à 150 mg dans des études cas-témoins à long terme n'a pas révélé de risque global accru de cancer de l'ovaire, du foie ou du col de l'utérus et a montré un effet protecteur prolongé d'une réduction du risque de cancer de l'endomètre chez les utilisatrices.

Le cancer du sein est rare chez les femmes de moins de 40 ans, qu'elles utilisent ou non des contraceptifs hormonaux.

Les résultats de certaines études épidémiologiques suggèrent une faible différence du risque de contracter la maladie entre les utilisatrices actuelles et récentes d'acétate de médroxyprogestérone dépôt et les femmes n'en ayant jamais utilisé. Chez les utilisatrices actuelles et récentes d'acétate de médroxyprogestérone dépôt, tout risque excédentaire est faible en termes de risque global de cancer du sein, surtout chez les femmes jeunes (voir ci-dessous), et n'est pas apparent 10 ans après la dernière utilisation. La durée d'utilisation ne semble pas importante.

Nombre possible de cas supplémentaires de cancer du sein diagnostiqués jusqu'à 10 ans après l'arrêt de progestatifs injectables*

Âge au moment de la dernière utilisation d'acétate de médroxyprogestérone dépôt	Nombre de cas sur 10.000 femmes n'ayant jamais été exposées	Cas supplémentaires possibles sur 10.000 utilisatrices d'acétate de médroxyprogestérone dépôt
20	Moins de 1	Beaucoup moins de 1
30	44	2-3
40	160	10

*sur la base d'une utilisation de 5 ans

Affections thromboemboliques

Bien qu'un rapport de cause à effet n'ait pas été établi entre l'acétate de médroxyprogestérone et l'induction d'affections thrombotiques ou thromboemboliques, toute patiente qui développe ce type d'événement, notamment embolie pulmonaire, maladie cérébrovasculaire, thrombose rétinienne ou thrombose veineuse profonde, durant un traitement par SAYANA PRESS, ne peut plus recevoir ce médicament. Les femmes ayant des antécédents de maladies thromboemboliques n'ont pas été étudiées dans les études cliniques et aucune information n'est disponible, permettant d'étayer la sécurité de l'utilisation de SAYANA PRESS dans cette population.

Anaphylaxie et réaction anaphylactoïde
Si une réaction anaphylactique se produit, un traitement approprié doit être instauré. Les réactions anaphylactiques sévères requièrent un traitement médical d'urgence.

Affections oculaires
Si une perte de vision soudaine, partielle ou complète, se produit ou en cas d'apparition soudaine de proptose, de diplopie ou de migraine, le médicament ne sera pas ré-administré avant qu'un examen n'ait été réalisé. Si l'examen révèle un œdème papillaire ou des lésions vasculaires rétiniennes, le médicament ne sera pas ré-administré**.**

Précautions

Changements de poids
Les changements de poids sont fréquents mais imprévisibles. Dans les études de phase 3, le poids corporel a été suivi pendant 12 mois. La moitié (50%) des femmes conservait leur poids initial, à 2,2 kg près. 12% des femmes ont perdu plus de 2,2 kg, et 38% des femmes ont pris plus de 2,3 kg.

Rétention aqueuse
Il est démontré que les progestatifs peuvent entraîner un certain degré de rétention aqueuse. Par conséquent, la prudence s'impose lors du traitement de toute patiente qui souffre d'une pathologie médicale préexistante qui pourrait être influencée négativement par une rétention aqueuse.

Retour de l'ovulation
Après l'administration d'une dose unique d'acétate de médroxyprogestérone dépôt par injection sous-cutanée, le taux cumulé de retour de l'ovulation mesuré à l'aide de la progestérone plasmatique était de 97,4 % (38/39 patientes) un an après l'administration. Après la fenêtre thérapeutique de 14 semaines, le retour le plus rapide de l'ovulation était d'une semaine et le délai médian d'ovulation était de 30 semaines. Les femmes doivent être averties de la possibilité d'un retour tardif de l'ovulation après l'utilisation de cette méthode, quelle que soit la durée d'utilisation. Toutefois, il est établi que l'aménorrhée et/ou les irrégularités menstruelles notées après l'arrêt de la contraception hormonale peuvent être dues à une affection sous-jacente associée aux irrégularités menstruelles, en particulier le syndrome des ovaires polykystiques.

Affections psychiatriques
L'état dépressif et la dépression sont des effets indésirables bien connus liés à l'utilisation de contraceptifs hormonaux (voir rubrique 4.8). La dépression peut être grave et constitue un facteur de risque bien connu de comportement suicidaire et de suicide. Il convient de conseiller aux femmes de contacter leur médecin en cas de changements d'humeur et de symptômes dépressifs, y compris peu de temps après le début du traitement.

Protection contre les infections sexuellement transmissibles
Les femmes doivent être averties que SAYANA PRESS ne protège pas contre les infections sexuellement transmissibles (IST), notamment l'infection par le VIH (SIDA), mais l'acétate de médroxyprogestérone dépôt est également une injection stérile qui, si elle est utilisée selon les indications, ne les exposera pas

aux IST. Les pratiques sexuelles sûres, y compris l'utilisation correcte et systématique des préservatifs, réduisent la transmission des IST par contact sexuel, notamment le VIH.

Les avantages des options contraceptives et leurs risques doivent être évalués individuellement pour chaque femme.

Hydrates de carbone/Métabolisme
Certaines patientes qui reçoivent des progestatifs pourraient présenter une diminution de la tolérance au glucose. Les patientes diabétiques doivent faire l'objet d'une surveillance étroite durant ce type de traitement.

Fonction hépatique
Si un ictère se développe chez une femme qui reçoit SAYANA PRESS, le traitement ne sera pas ré-administré (voir rubrique 4.3).

Hypertension et troubles lipidiques
Des données limitées suggèrent qu'il y a une légère augmentation du risque d'événements cardiovasculaires chez les femmes ayant de l'hypertension ou des troubles lipidiques qui ont utilisé des injections uniquement de progestatifs. Si de l'hypertension se produit pendant le traitement par SAYANA PRESS et/ou que l'augmentation de l'hypertension ne peut pas être contrôlée adéquatement par des antihypertenseurs, le traitement par SAYANA PRESS doit être arrêté. Les facteurs de risque additionnels pour les affections thrombotiques artérielles comprennent : l'hypertension, le tabagisme, l'âge, les troubles lipidiques, la migraine, l'obésité, les antécédents familiaux positifs, les troubles valvulaires cardiaques, la fibrillation auriculaire.

SAYANA PRESS doit être utilisé avec précaution chez les patientes avec un ou plusieurs de ces facteurs de risque.

Autres conditions
Les conditions suivantes ont été rapportées à la fois pendant la grossesse et pendant l'utilisation de stéroïdes sexuels, mais une association avec l'utilisation de progestatifs n'a pas été établie : jaunisse et/ou prurit associé à une cholestase ; formation de calculs biliaires ; porphyrie ; lupus érythémateux systémique ; syndrome urémique hémolytique ; chorée de Sydenham ; herpès gestationnel ; perte auditive associée à l'otosclérose.

En présence d'une des affections ou d'un des facteurs de risque mentionné(e)s, il faudra mettre en balance les bénéfices de l'utilisation de SAYANA PRESS par rapport aux risques possibles pour chaque femme individuellement, et il faudra en parler avec la femme avant qu'elle ne décide d'utiliser ce médicament. En cas d'aggravation, d'exacerbation ou de première apparition d'une de ces affections ou d'un de ces facteurs de risque, la femme doit contacter son médecin, qui devra alors décider s'il faut interrompre l'utilisation de SAYANA PRESS.

Epreuves de laboratoire
Le pathologiste sera mis au courant du traitement progestatif lors de la transmission des prélèvements pertinents. Le médecin sera informé que certains tests endocriniens et hépatiques et certains constituants du sang pourraient être affectés par le traitement progestatif :

a) Diminution des stéroïdes plasmatiques/urinaires (p. ex. progestérone, œstradiol, prégnanediol, testostérone, cortisol)
b) Diminution des taux plasmatiques et urinaires de gonadotrophine (p. ex., LH, FSH)
c) Diminution des concentrations de la globuline fixant l'hormone sexuelle (SHBG).

Excipients
Étant donné que ce produit contient du parahydroxybenzoate de méthyle et du parahydroxybenzoate de propyle, il peut entraîner des réactions allergiques (potentiellement retardées), et exceptionnellement un bronchospasme. Ce médicament contient moins de 1 mmol de sodium (23 mg) par 104 mg/0,65 ml, il est donc quasi ‘exempt de sodium’.

4.5 Interactions avec d’autres médicaments et autres formes d’interactions

Aucune étude d’interaction n’a été conduite avec SAYANA PRESS.

Des interactions avec d'autres traitements médicaux (y compris anticoagulants oraux) ont été rarement rapportées, mais un rapport de cause à effet n'a pas été déterminé. Il convient de garder à l'esprit la possibilité d'interactions chez les patientes qui reçoivent un traitement concomitant par d'autres médicaments.

L’acétate de médroxyprogestérone est métabolisé in-vitro principalement par hydroxylation via le CYP3A4. Il n'a pas été mené d’études d'interactions médicamenteuses spécifiques évaluant les effets cliniques avec des inducteurs ou des inhibiteurs du CYP3A4 sur l’acétate de médroxyprogestérone et par conséquent, les effets cliniques des inducteurs ou des inhibiteurs du CYP3A4 sont inconnus.

4.6 Fertilité, grossesse et allaitement

Fertilité
SAYANA PRESS est indiqué pour la prévention de la grossesse.

Les femmes peuvent présenter un retard du retour de la fertilité (conception) après l’arrêt de SAYANA PRESS (voir rubrique 4.4).

Grossesse
SAYANA PRESS est contre-indiqué chez les femmes enceintes. Certains rapports suggèrent une association entre l'exposition intra-utérine aux médicaments progestatifs durant le premier trimestre de la grossesse et des anomalies génitales chez les fœtus de sexe masculin et féminin. Si SAYANA PRESS est utilisé pendant la grossesse ou si la patiente devient enceinte lors de l’utilisation de ce médicament, la patiente sera avertie des risques potentiels pour le fœtus.

Une étude a indiqué que les nourrissons issus de grossesses accidentelles survenant 1 à 2 mois après l'injection du DMPA-IM (150 mg) présentaient un risque accru d'un faible poids de naissance ; ceci a été associé, à son tour, à un risque accru de décès néonatal. Toutefois, le risque global en est très faible parce que les grossesses au cours d'un traitement par DMPA-IM (150 mg) sont peu fréquentes.

Les enfants exposés à l'acétate de médroxyprogestérone in utero et suivis jusqu'à l'adolescence n'ont pas montré de signes d'effets indésirables sur la santé, que ce soit au niveau du développement physique, intellectuel, sexuel ou social.

Allaitement
Des quantités faiblement détectables du médicament ont été identifiées dans le lait de mères recevant l'acétate de médroxyprogestérone. Chez les femmes allaitantes traitées par DMPA-IM (150 mg), la composition, la qualité et la quantité du lait ne sont pas influencées négativement. Les effets développementaux et comportementaux de l'exposition de nouveau-nés et de nourrissons à l'acétate de médroxyprogestérone contenu dans le lait maternel ont été étudiés, et ce jusqu'à la puberté. Aucun effet indésirable n'a été relevé. Toutefois, en raison de données limitées sur les effets de l’acétate de médroxyprogestérone chez les nourrissons de moins de six semaines allaités, SAYANA PRESS devra être

administré au plus tôt six semaines post-partum lorsque le système enzymatique du nourrisson est plus développé.

4.7 Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

SAYANA PRESS n'a aucun effet sur l'aptitude à conduire des véhicules et à utiliser des machines.

4.8 Effets indésirables

Evénements rapportés lors d'essais cliniques :

Le tableau ci-dessous fournit une liste des réactions indésirables au médicament avec leur fréquence, sur base des données de toutes causalités des études cliniques qui ont enrôlé 2 053 femmes traitées par acétate de médroxyprogestérone dépôt par injection sous-cutanée pour la contraception. Les réactions indésirables au médicament les plus fréquemment rapportées (> 5 %) étaient la céphalée (8,9 %), la métrorragie (7,1 %), la prise de poids (6,9 %), l'aménorrhée (6,3 %) et les réactions au site d'injection (tout type, 6,1 %).

Les effets indésirables sont énumérés en fonction des catégories suivantes, à savoir :
Très fréquent (≥ 1/10)
Fréquent (≥ 1/100 à <1/10)
Peu fréquent (≥ 1/1 000 à <1/100)
Rare (≥ 1/10 000 à < 1/1 000)
Fréquence indéterminée (ne peut être estimée sur la base des données disponibles)

Evénements rapportés lors de la surveillance post-commercialisation :

De plus, les événements indésirables médicalement significatifs issus des données post-commercialisation relatives à l'utilisation de l'acétate de médroxyprogestérone dépôt injectable (IM ou SC) sont aussi inclus dans la liste ci-dessous :

Classe de systèmes d'organes	***Très fréquent***	***Fréquent***	***Peu fréquent***	***Rare***	***Fréquence indéterminée***
Tumeurs bénignes, malignes et non précisées (incl. kystes et polypes)				Cancer du sein (voir rubrique 4.4)	
Affections du système immunitaire			Hypersensibilité au médicament (voir rubrique 4.4)		Réaction anaphylactique, réaction anaphylactoïde, angio-œdème (voir rubrique 4.4)

Troubles du métabolisme et de la nutrition			Rétention aqueuse (voir rubrique 4.4), augmentation de l'appétit, diminution de l'appétit		
Affections psychiatriques		Dépression, insomnie, anxiété, troubles affectifs, irritabilité, baisse de la libido	Nervosité, perturbations émotionnelles, anorgasmie		
Affections du système nerveux		Etourdissement, céphalée	Migraine, somnolence		Crise convulsive
Affections de l'oreille et du labyrinthe			Vertiges		
Affections cardiaques			Tachycardie		
Affections vasculaires			Hypertension (voir rubrique 4.4), veines variqueuses, bouffées de chaleur		Embolie pulmonaire, embolie et thrombose (voir rubrique 4.4), thrombophlébite
Affections gastro-intestinales		Douleur abdominale, nausées	Distension abdominale		
Affections hépatobiliaires					Ictère, anomalie de la fonction hépatique (voir rubrique 4.4)
Affections de la peau et du tissu sous-cutané		Acné	Alopécie, hirsutisme, dermatite, ecchymose, chloasma, rash, prurit, urticaire	Lipodystrophie acquise	Vergetures
Affections musculo-squelettiques et systémiques		Douleur dorsale, douleur dans les extrémités	Arthralgie, spasmes musculaires		Ostéoporose, fractures ostéoporotiques

Affections des organes de reproduction et du sein		Ménométrorragie, métrorragie, ménorragie (voir rubrique 4.4), dysménorrhée, aménorrhée, vaginite, douleur mammaire	Kyste ovarien, saignement utérin (irrégulier, augmentation, diminution), pertes vaginales, dyspareunie, galactorrhée, douleur pelvienne, sécheresse vulvo-vaginale, syndrome prémenstruel, sensibilité des seins, augmentation de la taille des seins		
Troubles généraux et anomalies au site d'administration		Fatigue, réaction au site d'injection, atrophie/creux/fossette persistante au site d'injection, nodule au site d'injection, douleur/sensibilité au site d'injection	Pyrexie	Asthénie	
Investigations		Augmentation du poids (voir rubrique 4.4), anomalies du frottis cervical	Diminution de la densité minérale osseuse (voir rubrique 4.4), diminution de la tolérance au glucose (voir rubrique 4.4), anomalies des enzymes hépatiques	Diminution du poids (voir rubrique 4.4)	

Déclaration des effets indésirables suspectés
La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via l'Agence Fédérale des Médicaments et des Produits de Santé – Division Vigilance, Boîte Postale 97, B-1000 Bruxelles, Madou (website: www.afmps.be; e-mail: adversedrugreactions@fagg-afmps.be).

4.9 Surdosage

Aucune action positive n'est requise, si ce n'est l'arrêt du traitement.

5. PROPRIETES PHARMACOLOGIQUES

5.1 Propriétés pharmacodynamiques

Code ATC : G03AC06
L'acétate de médroxyprogestérone est un analogue de la 17 α-hydroxyprogestérone avec des effets anti-œstrogéniques, anti-androgéniques et antigonadotrophiques.

Le DMPA-SC inhibe la sécrétion des gonadotrophines ce qui, à son tour, prévient la maturation folliculaire et l'ovulation, et entraîne un épaississement du mucus cervical qui inhibe l'entrée du sperme dans l'utérus. Ces actions produisent son effet contraceptif.

Modifications de la densité minérale osseuse chez les femmes adultes

Une étude comparant les modifications de la densité minérale osseuse chez des femmes utilisant DMPA-SC et chez des femmes utilisant DMPA-IM a montré une perte de densité minérale osseuse similaire entre les deux groupes après deux années de traitement. Les pourcentages moyens de modification de la densité minérale osseuse dans le groupe avec DMPA-SC sont énumérés dans le tableau 1.

Tableau 1. Modification moyenne en % (Intervalles de Confiance à 95 %) de la densité minérale osseuse par rapport à la valeur initiale chez les femmes adultes utilisant DMPA-SC, par partie du squelette

Temps sous traitement	**Colonne vertébrale**		**Hanche totale**		**Col du fémur**	
	N	Modification moyenne (%)(IC à 95 %)	N	Modification moyenne (%)(IC à 95 %)	N	Modification moyenne (%)(IC à 95 %)
1 an	166	-2,7(-3,1 à -2,3)	166	-1,7(-2,1 à -1,3)	166	-1,9(-2,5 à -1,4)
2 ans	106	-4,1(-4,6 à -3,5)	106	-3,5(-4,2 à -2,7)	106	-3,5(-4,3 à -2,6)

IC = Intervalle de Confiance

Dans une autre étude clinique contrôlée, des femmes adultes ayant utilisé du DMPA-IM pendant une durée maximale de 5 ans ont présenté des diminutions moyennes de la densité minérale osseuse de 5-6 % au niveau de la colonne vertébrale et de la hanche, contre aucun changement significatif de la densité minérale osseuse dans le groupe témoin. La diminution de la densité minérale osseuse était plus marquée durant les deux premières années d'utilisation, avec des diminutions plus faibles au cours des années suivantes. Des modifications moyennes de la densité minérale osseuse au niveau de la colonne lombaire de -2,9 %, -4,1 %, -4,9 %, -4,9 % et -5,4 % après 1, 2, 3, 4 et 5 ans respectivement, ont été observées. Les diminutions moyennes de la densité minérale osseuse au niveau de la hanche totale et du col du fémur étaient similaires. Veuillez vous reporter au tableau 2 ci-dessous pour de plus amples détails.

Après l'arrêt du DMPA-IM, la densité minérale osseuse augmentait vers les valeurs de départ au cours de la période post-traitement. Une durée plus longue de traitement était associée à une récupération plus lente de la densité minérale osseuse.

Dans la même étude clinique, un nombre limité de femmes qui avaient utilisé le DMPA-IM pendant 5 ans ont été suivies pendant 2 ans après l'arrêt de l'utilisation du DMPA-IM. La densité minérale osseuse s'est rapprochée des valeurs initiales au cours de la période de 2 ans suivant le traitement. Deux ans après l'arrêt des injections de DMPA, la densité minérale osseuse moyenne a augmenté au niveau des trois sites squelettiques, mais des déficits ont subsisté (voir tableau 2 ci-dessous).

Tableau 2. Modification moyenne en % (Intervalles de Confiance à 95 %) de la densité minérale osseuse par rapport à la valeur initiale chez des adultes, par site squelettique et par cohorte, après 5 ans de traitement par DMPA-IM et après 2 ans post-traitement ou 7 ans d'observation (témoin)

Durée d'inclusion dans l'étude	Colonne vertébrale		Hanche totale		Col du fémur	
	DMPA	Groupe témoin	DMPA	Groupe témoin	DMPA	Groupe témoin
5 ans* n Moyenne (SD) IC à 95%	 33 -5,4 % (3,57) -6,65; -4,11	 105 0,4 % (3,27) -0,20; 1,06	 21 -5,2 % (3,60) -6,80; -3,52	 65 0,2 % (3,18) -0,60; 0,98	 34 -6,1 % (4,68) -7,75; -4,49	 106 -0,3 % (5,22) -1,27; 0,73
7 ans** n Moyenne (SD) IC à 95%	 12 -3,1 % (3,15) -5,13; -1,13	 60 0,5 % (3,65) -0,39; 1,49	 7 -1,3 % (4,95) -5,92; 3,23	 39 0,9 % (3,81) -0,29; 2,17	 13 -5,4 % (2,73) -7,03; -3,73	 63 0,0 % (5,88) -1,51; 1,45

*Le groupe traité se composait de femmes qui recevaient du DMPA-IM pendant 5 ans et le groupe témoin se composait de femmes qui n'avaient pas utilisé de contraception hormonale pendant cette période.
** Le groupe traité se composait de femmes qui recevaient du DMPA-IM pendant 5 ans et avaient ensuite été suivies pendant maximum 2 ans post-traitement et le groupe témoin se composait de femmes qui n'avaient pas utilisé de contraceptifs hormonaux pendant 7 ans.
SD = Standard Deviation (écart type)
IC = Intervalle de Confiance

Modifications de la densité minérale osseuse chez les adolescentes (12-18 ans)

Les résultats d'une étude clinique ouverte non randomisée portant sur l'utilisation du DMPA-IM (150 mg IM toutes les 12 semaines pendant une période maximale de 240 semaines (4,6 ans), suivis de mesures post-traitement) chez des adolescentes (12-18 ans), ont montré également que les injections intramusculaires d'acétate de médroxyprogestérone étaient associées à une diminution significative de la densité minérale osseuse par rapport à la valeur initiale. Chez les patientes qui recevaient ≥ 4 injections/période de 60 semaines, la diminution moyenne de la densité minérale osseuse au niveau de la colonne vertébrale était de -2,1 % après 240 semaines (4,6 ans) ; les diminutions moyennes au niveau de la hanche totale et du col du fémur étaient de -6,4 % et -5,4 % respectivement. Voir tableau 3.
En revanche, une cohorte non comparable de patientes non traitées et non comparables, avec des paramètres osseux initiaux différents des utilisatrices de DMPA, ont montré des augmentations moyennes de la densité minérale osseuse à 240 semaines de 6,4%, 1,7% et 1,9% au niveau, respectivement, de la colonne vertébrale, de la hanche totale et du col du fémur.

Tableau 3. Modification moyenne en % (Intervalles de Confiance à 95%) de la densité minérale osseuse par rapport à la valeur initiale chez des adolescentes recevant ≥ 4 injections par période de 60 semaines, par site squelettique

Durée du traitement	DMPA-IM	
	N	**Modification moyenne (%) [IC à 95 %]**
Densité minérale osseuse au niveau de la hanche totale		
Semaine 60 (1,2 ans)	113	-2,7 [-3,27; -2,11]
Semaine 120 (2,3 ans)	73	-5,4 [-6,16; -4,64]
Semaine 180 (3,5 ans)	45	-6,4 [-7,38; -5,37]
Semaine 240 (4,6 ans)	28	-6,4 [-8,56; -4,24]
Densité minérale osseuse au niveau du col du fémur		
Semaine 60	113	-2,9 [-3,72; -2,15]
Semaine 120	73	-5,3 [-6,23; -4,37]
Semaine 180	45	-6,0 [-7,31; -4,59]
Semaine 240	28	-5,4 [-7,81; -3,00]
Densité minérale osseuse au niveau de la colonne vertébrale		
Semaine 60	114	-2,5 [-2,95; -1,98]
Semaine 120	73	-2,7 [-3,57; -1,91]
Semaine 180	44	-2,7 [-3,99; -1,35]
Semaine 240	27	-2,1 [-4,16; -0,07]

IC = Intervalle de Confiance

Les résultats d'un suivi après le traitement de participantes adolescentes de la même étude qui ont reçu au moins 1 injection de DMPA et qui ont fait l'objet d'au moins 1 mesure de densité minérale osseuse après l'arrêt de l'utilisation du DMPA-IM, sont représentés dans le tableau 4. Le nombre médian d'injections reçues dans cette cohorte pendant la phase de traitement était de 9. Au moment de l'injection finale de DMPA, les modifications en % de la densité minérale osseuse par rapport aux valeurs initiales dans cette cohorte étaient de -2,7 %, -4,1 % et -3,9 % au niveau de la colonne vertébrale, de la hanche totale et du col du fémur, respectivement. Au fil du temps, ces déficits moyens de densité minérale osseuse se sont résorbés vers les valeurs initiales après l'arrêt du DMPA-IM. La récupération vers les valeurs initiales a exigé 1,2 ans au niveau de la colonne vertébrale, 4,6 ans au niveau de la hanche totale et 4,6 ans au niveau du col du fémur. Il est toutefois important de noter qu'un grand nombre de patientes ont quitté l'étude, par conséquent ces résultats sont basés sur un petit nombre de patientes et quelques patientes présentaient encore des déficits de la densité minérale osseuse au niveau de la hanche totale après 240 semaines. L'allongement de la durée du traitement et le tabagisme ont été associés à une récupération plus lente. Veuillez vous reporter au tableau 4 ci-dessous.

Tableau 4. Modifications moyennes en % (Intervalles de Confiance à 95%) de la densité minérale osseuse par rapport aux valeurs initiales chez des adolescentes après l'arrêt de DMPA

Semaine après l'arrêt de DMPA	N	Nombre médian d'injections	Modification moyenne en % (SE) entre les valeurs initiales et la fin du traitement	IC à 95%	Modification moyenne en % (SE) entre les valeurs initiales et la visite post-DMPA	IC à 95%
Densité minérale osseuse au niveau de la hanche totale						

0	98	9	-4,1 (0,43)	[-4,95; -3,25]	N/A	
24	74	9	-4,1 (0,53)	[-5,15; -3,04]	-4,0 (0,61)	[-5,25; -2,80]
60	71	8	-3,6 (0,46)	[-4,48; -2,66]	-2,8 (0,56)	[-3,97; -1,72]
120	52	10	-4,3 (0,64)	[-5,56; -2,98]	-1,7 (0,72)	[-3,14; -0,26]
180	39	7	-4,1 (0,72)	[-5,55; -2,63]	-1,2 (0,85)	[-2,96; 0,46]
240	25	9	-3,4 (0,67)	[-4,73; -1,98]	0,1 (0,98)	[-1,95; 2,11]
Densité minérale osseuse au niveau du col du fémur						
0	98	9	-3,9 (0,50)	[-4,92; -2,92]	N/A	
24	74	9	-3,8 (0,60)	[-5,01; -2,62]	-4,0 (0,71)	[-5,40; -2,55]
60	71	8	-3,3 (0,56)	[-4,41; -2,18]	-3,6 (0,70)	[-4,99; -2,18]
120	52	10	-3,8 (0,74)	[-5,25; -2,28]	-1,8 (0,82)	[-3,43; -0,13]
180	39	7	-3,9 (0,85)	[-5,62; -2,17]	-1,0 (0,98)	[-3,00; 0,97]
240	25	9	-3,4 (0,80)	[-5,07; -1,78]	-0,7 (1,19)	[-3,20; 1,72]
Densité minérale osseuse au niveau de la colonne vertébrale						
0	98	9	-2,7 (0,39)	[-3,45; -1,91]	N/A	
24	74	9	-2,6 (0,43)	[-3,42; -1,69]	-2,5 (0,51)	[-3,52; -1.48]
60	70	8	-2,8 (0,43)	[-3,66; -1,96]	-0,2 (0,60)	[-1,41; 1,01]
120	52	10	-2,7 (0,61)	[-3,96; -1,50]	2,2 (0,73)	[0,74; 3,67]
180	39	7	-3,0 (0,67)	[-4,35; -1,66]	2,8 (0,79)	[1,16; 4,35]
240	25	9	-2,6 (0,80)	[-4,28; -0,99]	4,5 (1,03)	[2,35; 6,61]

SE = Standard Error (erreur type)
IC = Intervalle de Confiance

Relation entre l'incidence des fractures et l'utilisation du DMPA-IM (150 mg) chez les femmes en âge de procréer

Une vaste étude de cohorte rétrospective utilisant les données de la General Practice Research Database (GPRD) comprenait N = 41 876 femmes ayant utilisé le DMPA pour la contraception et pour lesquelles on disposait de données pendant 6 à 24 mois avant leur première utilisation de DMPA et jusqu'à 5,5 ans en moyenne après leur première injection de DMPA. On a observé que le risque de fracture était, dans l'ensemble, plus élevé dans la cohorte de DMPA que chez les non utilisatrices, tant « avant » qu'« après » l'utilisation du DMPA. Le risque de fracture a été comparé entre la période « après » la première injection de DMPA et la période « avant » la première injection : rapport de risque d'incident = 1,01 (IC à 95 % : 0,92 ; 1,11), ce qui suggère que le DMPA n'augmente pas le risque de fracture osseuse.

Le suivi maximal dans cette étude était de 15 ans ; par conséquent, les effets possibles de DMPA qui pourraient s'étendre au-delà de 15 ans de suivi ne peuvent être déterminés. Il est important de savoir que cette étude ne pouvait pas déterminer si l'utilisation de DMPA avait un effet sur le taux de fractures plus tard dans la vie, c.-à-d. après la ménopause.

5.2 Propriétés pharmacocinétiques

Les paramètres pharmacocinétiques de l'acétate de médroxyprogestérone après une injection sous-cutanée unique d'acétate de médroxyprogestérone dépôt figurent dans le tableau 5.

Tableau 5. Paramètres pharmacocinétiques de l'acétate de médroxyprogestérone suite à une injection sous-cutanée unique d'acétate de médroxyprogestérone dépôt chez des femmes en bonne santé (n = 42)

	C_{max} (ng/ml)	T_{max} (jour)	$C_{91\ (min)}$ (ng/ml)	ASC_{0-91} (ng·jour/ml)	$ASC_{0-\infty}$ (ng·jour/ml)	t½ (jour)
Moyenne	1,56	8,8	0,402	66,98	92,84	43
Min	0,53	2,0	0,133	20,63	31,36	16
Max	3,08	80,0	0,733	139,79	162,29	114

C_{max} = pic sérique ; T_{max} = moment auquel la C_{max} a été observée ; ASC_{0-91} = aire sous la courbe de concentration en fonction du temps pendant 91 jours ; t½ = demi-vie terminale ; 1 nanogramme = 10^3 picogrammes.

Caractéristiques générales

Absorption
L'absorption de l'acétate de médroxyprogestérone du site d'injection sous-cutanée à l'atteinte des taux thérapeutiques est relativement rapide. La T_{max} moyenne était atteinte environ une semaine après l'injection. Les concentrations maximales de l'acétate de médroxyprogestérone (C_{max}) vont généralement de 0,5 à 3,0 ng/ml, la C_{max} moyenne étant de 1,5 ng/ml après une injection sous-cutanée unique.

Effet du site d'injection
L'acétate de médroxyprogestérone dépôt a été administré par injection sous-cutanée dans la partie antérieure de la cuisse ou dans l'abdomen afin d'en évaluer les effets sur le profil concentration-temps de l'acétate de médroxyprogestérone. Les concentrations minimales de l'acétate de médroxyprogestérone (C_{min}; jour 91) étaient similaires pour les deux sites d'injection, ce qui suggère que le site d'injection n'affecte pas négativement l'efficacité contraceptive.

Distribution
La liaison de l'acétate de médroxyprogestérone aux protéines plasmatiques est en moyenne de 86 %. L'acétate de médroxyprogestérone se lie essentiellement à l'albumine sérique ; il ne se fixe pas à la globuline fixant l'hormone sexuelle (SHBG).

Biotransformation
L'acétate de médroxyprogestérone est fortement métabolisé dans le foie par les enzymes P450. Sa métabolisation porte essentiellement sur une réduction de l'anneau A et/ou de la chaîne latérale, une perte du groupe acétyle, une hydroxylation en position 2, 6, et 21 ou une combinaison de ces positions, donnant lieu à plus de 10 métabolites.

Elimination
Les concentrations résiduelles d'acétate de médroxyprogestérone au terme de l'intervalle d'administration sous-cutanée (3 mois) d'acétate de médroxyprogestérone dépôt sont généralement inférieures à 0,5 ng/ml, en accord avec sa demi-vie terminale apparente de ~40 jours après l'administration sous-cutanée. La plupart des métabolites de l'acétate de médroxyprogestérone sont excrétés dans l'urine sous forme de glucuroconjugués, avec seulement de faibles quantités excrétées sous forme de sulfates.

Linéarité/non-linéarité
Les données relatives à l'administration de doses uniques n'ont pas révélé de relation non linéaire pour les doses de 50 à 150 mg après l'administration sous-cutanée. La relation entre l'ASC ou la C_{min} et la dose sous-cutanée d'acétate de médroxyprogestérone s'est révélée linéaire. La C_{max} moyenne ne variait pas de manière substantielle avec l'augmentation de la dose.

Populations particulières

Race
Il n'y avait pas de différences apparentes du profil pharmacocinétique et/ou pharmacodynamique de l'acétate de médroxyprogestérone après l'administration sous-cutanée d'acétate de médroxyprogestérone dépôt chez les femmes de toutes les origines ethniques étudiées. Le profil pharmacocinétique/pharmacodynamique de l'acétate de médroxyprogestérone chez les femmes asiatiques a été évalué dans le cadre d'une étude séparée.

Effet du poids corporel
Aucun ajustement posologique de SAYANA PRESS n'est nécessaire en fonction du poids corporel. L'effet du poids corporel sur les paramètres pharmacocinétiques de l'acétate de médroxyprogestérone a été évalué chez un sous-ensemble de femmes (n = 42, l'indice de masse corporelle [IMC] allait de 18,2 à 46,0 kg/m^2). Les valeurs de l'ASC_{0-91} pour l'acétate de médroxyprogestérone étaient de 68,5, 74,8, et 61,8 ng –jour/ml chez les femmes faisant partie des groupes d'IMC de ≤ 25 kg/m^2, > 25 à ≤ 30 kg/m^2 et > 30 kg/m^2, respectivement. La C_{max} moyenne de l'acétate de médroxyprogestérone était de 1,65 ng/ml chez les femmes ayant un IMC ≤ 25 kg/m^2, de 1,76 ng/ml chez les femmes ayant un IMC > 25 à ≤ 30 kg/m^2 et de 1,40 ng/ml chez les femmes ayant un IMC > 30 kg/m^2, respectivement. L'éventail des concentrations minimales (C_{min}) et des demi-vies de l'acétate de médroxyprogestérone était comparable pour les 3 groupes d'IMC.

Relation(s) pharmacocinétique(s)/pharmacodynamique(s)

D'un point de vue pharmacodynamique, la durée de suppression de l'ovulation dépend du maintien des concentrations thérapeutiques de l'acétate de médroxyprogestérone tout au long des 13 semaines que compte l'intervalle d'administration.

5.3 Données de sécurité préclinique

Les données non cliniques issues des études conventionnelles de pharmacologie de sécurité, toxicologie en administration répétée, génotoxicité et cancérogenèse n'ont pas révélé de risque particulier pour l'homme. L'acétate de médroxyprogestérone a des effets néfastes sur la reproduction des animaux et son utilisation est contre-indiquée pendant la grossesse.

6. DONNEES PHARMACEUTIQUES

6.1 Liste des excipients

Macrogol 3350
Parahydroxybenzoate de méthyle (E 218)
Parahydroxybenzoate de propyle (E 216)
Chlorure de sodium
Polysorbate 80
Phosphate de sodium monobasique monohydraté
Phosphate disodique dodécahydraté
Méthionine
Povidone
Acide chlorhydrique et/ou hydroxyde de sodium pour ajustement du pH
Eau pour préparations injectables.

6.2 Incompatibilités

Sans objet.

6.3 Durée de conservation

Avant ouverture : 3 ans
Après ouverture : utiliser immédiatement, éliminer toute partie non utilisée.

6.4 Précautions particulières de conservation

Ne pas mettre au réfrigérateur et ne pas congeler.

6.5 Nature et contenu de l'emballage extérieur

SAYANA PRESS suspension injectable est fourni dans un récipient unidose sous forme d'un injecteur pré-rempli contenant 0,65 ml. L'injecteur est composé d'un réservoir laminé de polyéthylène linéaire à basse densité avec une aiguille siliconisée à parois fines 23 gauge en acier inoxydable AISI type 304, attachée par le biais d'un porte-aiguille et d'une valve en polyéthylène à basse densité.

Les présentations sont:
- un récipient unidose
- 200 récipients unidose

Toutes les présentations peuvent ne pas être commercialisées.

6.6 Précautions particulières d'élimination et manipulation

A usage unique.

Tout médicament non utilisé ou déchet doit être éliminé conformément à la réglementation en vigueur.

7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

Pfizer NV/SA, Boulevard de la Plaine 17, 1050 Bruxelles, Belgique.

8. NUMERO D'AUTORISATION DE MISE SUR LE MARCHE

BE400075

9. DATE DE PREMIERE AUTORISATION / DE RENOUVELLEMENT DE L'AUTORISATION

Date de première autorisation : 22/09/2011
Date de dernier renouvellement : 21/05/2016

10. DATE DE MISE A JOUR DU TEXTE

03/2020 BEL 20C12

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Land/Pays/Land	***BELGIË - BELGIQUE - BELGIEN***
2. Deze openbare akte is ondertekend door : Le présent acte a été signé par : Diese öffentliche Urkunde ist unterschrieben von :	***Brasseur Séverine***
3. Handelend in hoedanigheid van : Agissant en qualité de : In seiner/ihrer Eigenschaft als :	***Attaché/Attaché/Attaché***
4. Is voorzien van het zegel van : Est revêtu du sceau de : Sie ist versehen mit dem Siegel des/der :	***FAGG/AFMPS/FAGG/FAMPS***
Voor echt verklaard / Attesté / Bestätigt	
5. ***Te Brussel/A Bruxelles/In Brüssel***	6. Op/Le/Am : ***25/09/2020***
7. Door FOD Buitenlandse Zaken, Buitenlandse Handel en Ontwikkelingssamenwerking Par le SPF Affaires étrangères, Commerce extérieur et Coopération au Développement Durch FÖD Auswärtige Angelegenheiten, Außenhandel und Entwicklungszusammenarbeit	
8. Onder Nr./Sous le n°/Unter Nr. : ***200916470836***	
9. Stempel/Sceau/Stempel:	10. Ondertekening/Signature/Unterschrift:

Digitally signed by
FPS Foreign Affairs
Belgium

Prijs/Prix/Preis: ***20.00*** EUR

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AGENCIA FEDERAL DE MEDICAMENTOS Y PRODUCTOS SANITARIOS

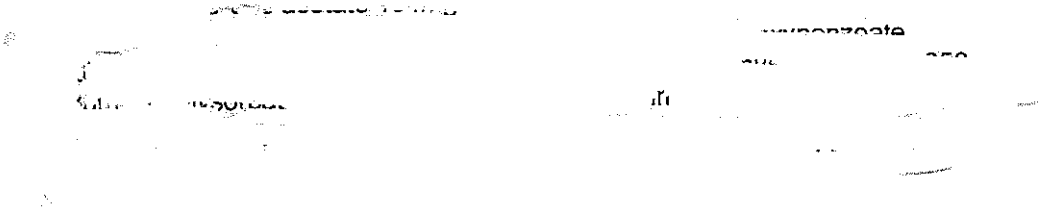
CERTIFICADO DE PRODUCTO FARMACEUTICO[1]

Este certificado està de acuerdo con el formato recomendado por la Organización Mundial de la Salud.
(Se adjuntan instrucciones generales y notas aclaratorias)

N° de este certificado: **20200924008**
País exportador (certificador): BELGICA
País importador (solicitante): CHILE

1. Nombre y forma farmacéutica del producto: SAYANA PRESS 104 mg/0.65 ml Suspensión inyectable

1.1 Principio(s) y cantidades[2] por unidad de dosis[3] - composición completa incluyendo excipientes: ver adjunto[4]



1.2 ¿Está este producto autorizado para su comercialización y uso en el país exportador?[5] sí

1.3 ¿Se comercializa este producto actualmente en el mercado del país exportador? sí
Tiempo de durabilidad: 36 meses

2A.1 Número de la autorización de comercialización[7] y fecha de autorización: BE400075 - 22 septiembre 2011

2A.2 Titular de la Autorización de Comercialización: PFIZER SA, Boulevard de la Plaine 17, 1050 Bruxelles, BELGICA

2A.3 Actividad del Titular de la Autorización de Comercialización[8]: c

2A.3.1 Nombre y dirección del fabricante de la forma farmacéutica[9]: Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, BELGICA

2A.4 ¿El resumen básico de aprobación se adjunta?[10] no; disponible bajo solicitud.

2A.5 ¿La información autorizada del producto que se adjunta está completa y de acuerdo con la autorización?[11] sí

2A.6 Solicitante del certificado[12]: Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, BELGICA.

2B. No aplicable [6]

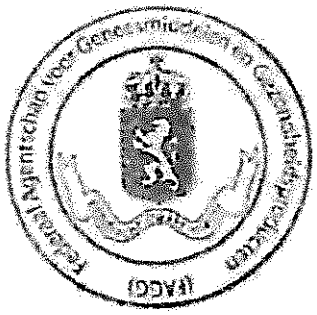
3. La autoridad certificadora, dispone la inspección periódica de la planta de fabricación en que se produce la forma farmacéutica[14]: sí (solamente para Bélgica)

3.1 Periodicidad de las inspecciones de rutina: 2 años (solamente para Bélgica)

3.2 ¿Se ha inspeccionado la fabricación de este tipo de forma farmacéutica? Sí (solamente para Bélgica)

3.3 ¿Se adaptan las instalaciones y procedimientos a las GMP recomendadas por la Organización Mundial de la Salud?[15] sí (solamente para Bélgica)

4. ¿La información presentada por el solicitante satisface a la autoridad de certificación en relación con todos los aspectos de la fabricación del producto?[16]
sí

Dirección de la Autoridad certificadora :	Agencia federal de medicamentos y productos sanitarios - afmps, Eurostation II, Place Victor Horta 40/40, 1060 Bruselas (Belgica)	
Teléfonos : +32 2 528 40 00	www.fagg-afmps.be	certificates@fagg-afmps.be
Sello y fecha : 24/09/2020 	afmps fagg	Nombre de la persona autorizada : Xavier De Cuyper, Administrador General - CEO On Behalf Séverine Brasseur, DG Inspection - File Manager

Instrucciones generales

Favor referirse a la guía para instrucciones completas sobre cómo llenar este formulario e información sobre la implementación del esquema.
Los formularios son adecuados para generarse por computadora. Deben enviarse siempre en original, con respuestas impresas en caracteres en vez de llenados a mano.
Hojas adicionales pueden ser anexadas, si son necesarias, para incluir observaciones y explicaciones.

Notas explicatorias

1. Este certificado, que se emite en el formato recomendado por la OMS, establece el estado de un producto farmacéutico y del solicitante del certificado, en el país de exportación. Es únicamente para un solo producto ya que las disposiciones de manufactura y la información aprobada para diferentes formas farmacéuticas y diferentes concentraciones, podrían variar.
2. Usar, cuando sea posible, Nombres Internacionales No Patentados (INNs) o nombres nacionales no patentados.
3. La fórmula (composición completa) de la forma farmacéutica debe especificarse en el certificado o puede ser anexada.
4. Se prefieren detalles de la composición cuantitativa, pero su provisión está sujeta al acuerdo del tenedor de la licencia del producto.
5. Cuando sea aplicable, anexar detalles de alguna restricción aplicable a la venta, distribución o administración del producto que se especifique en la licencia del producto.
6. Secciones 2A y 2B son mutualmente exclusivas.
7. Indicar, cuando sea aplicable, si la licencia es provisional, o si el producto aún no ha sido aprobado.
8. Especificar si la persona responsable de colocar el producto en el mercado:
   (a) manufactura la forma farmacéutica;
   (b) empaca y/o etiqueta la forma farmacéutica manufacturada por una compañía intependiente;
   (c) no está involucrada en ninguno de los dos puntos anteriores
9. Esta información sólo puede ser proporcionada con el consentimiento del tenedor de la licencia del producto o, en el caso de productos no registrados, del solicitante. No completar esta sección indica que la parte interesada no está de acuerdo en incluir esta información.
   Debe anotarse que la información concerniente al lugar de producción es parte de la licencia del producto. Si el lugar de producción es cambiado, la licencia debe actualizarse o ya no será válida.
10. Esto se refiere al documento, preparado por algunas autoridades regulatorias nacionales, que resume la base técnica sobre la cual el producto ha sido licenciado.
11. Esto se refiere a la información del producto aprobada por la autoridad nacional regulatoria competente, tal como Resumen de Características del Producto (SPC).
12. En esta circunstancia, se require permiso del tenedor de la licencia del producto para emitir el certificado. Este permiso debe ser otorgado a la autoridad por el solicitante.
13. Favor indicar la razón que el solicitante ha proporcionado para no solicitar el registro:
   (a) el producto ha sido desarrollado exclusivamente para el tratamiento de condiciones—particularmente enfermedades tropicales—no endémicas en el país de exportación;
   (b) el producto ha sido reformulado con el propósito de mejorar su estabilidad bajo condiciones tropicales;
   (c) el producto ha sido reformulado para excluir excipientes no aprobados para usarse en productos farmacéuticos en el país de importación;
   (d) el producto ha sido reformulado para cumplir con un límite máximo de dosificación diferente para un ingrediente activo;
   (e) cualquier otra razón, favor especificar.
14. No aplicable significa que la manufactura toma lugar en un país diferente del país que emite el certificado del producto y la inspección es conducida bajo el amparo del país de manufactura.
15. Los requerimientos de las buenas prácticas de manufactura y control de calidad de los medicamentos referidos en el certificado, son aquéllos incluidos en el repote treinta y dos del Comité Experto en Especificaciones para Preparaciones Farmacéuticas, Reporte Técnico de la OMS Serie No. 823, 1992, Anexo 1. Recomendaciones específicamente aplicables para productos biológicos han sido formulados por el Comité Experto de la OMS en Estandarización Biológica (Reporte Técnico de la OMS Serie No. 822, 1992, Anexo 1).
16. Esta sección debe completarse cuando el tenedor de la licencia del producto o solicitante se ajuste al status (b) o (c) como se describe en el numeral 8 antes citado. Es de particular importancia cuando contratistas extranjeros están involucrados en la manufactura del producto. En estas circunstancias, el solicitante debe suministrar a la autoridad que certifica, la información para identificar las partes contratantes responsable de cada etapa de la manufactura de la forma farmacéutica terminada, y la extensión y naturaleza de cualquier control ejecutado sobre cada una de estas partes.

BEL 20C12

RESUME DES CARACTERISTIQUES DU PRODUIT

1. DENOMINATION DU MEDICAMENT

SAYANA PRESS 104 mg/0,65 ml suspension injectable.

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

SAYANA PRESS récipient unidose avec 104 mg d'acétate de médroxyprogestérone (AMP) dans 0,65 ml de suspension injectable.

Excipients à effet notoire:

Parahydroxybenzoate de méthyle – 1,
Parahydroxybenzoate de propyle –
Sodium

Pour la liste complète des excipients, voir rubrique 6.1.

3. FORME PHARMACEUTIQUE

Suspension injectable.

Suspension homogène de couleur blanche à blanc cassé.

4. DONNEES CLINIQUES

4.1 Indications thérapeutiques

SAYANA PRESS est indiqué pour la contraception à long terme chez la femme. Chaque injection sous-cutanée empêche l'ovulation et offre une contraception pendant 13 semaines au moins (± 1 semaine). Toutefois, il faut tenir compte du fait que le délai avant le retour de la fertilité (ovulation) peut aller jusqu'à un an (voir rubrique 4.4).

Dans la mesure où une perte de densité minérale osseuse peut se produire chez des femmes de tous âges qui utilisent SAYANA PRESS à long terme (voir rubrique 4.4), une évaluation risque/bénéfice, tenant compte également de la diminution de la densité minérale osseuse qui se produit pendant la grossesse et/ou l'allaitement, doit être envisagée.

Utilisation chez les adolescentes (de 12 à 18 ans)
Chez les adolescentes, l'utilisation de SAYANA PRESS n'est indiquée qu'après que d'autres méthodes de contraception ont été jugées inappropriées ou inacceptables, en raison d'effets inconnus à long terme de perte osseuse associée à SAYANA PRESS au cours de la période critique d'accrétion osseuse (voir rubrique 4.4).

SAYANA PRESS n'a pas été étudié chez des femmes âgées de moins de 18 ans, mais on dispose de données concernant l'acétate de médroxyprogestérone dépôt (DMPA-IM) intramusculaire 150 mg dans cette population.